FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS. THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS

Maria Biosca Brull

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ROVIRA i VIRGILI

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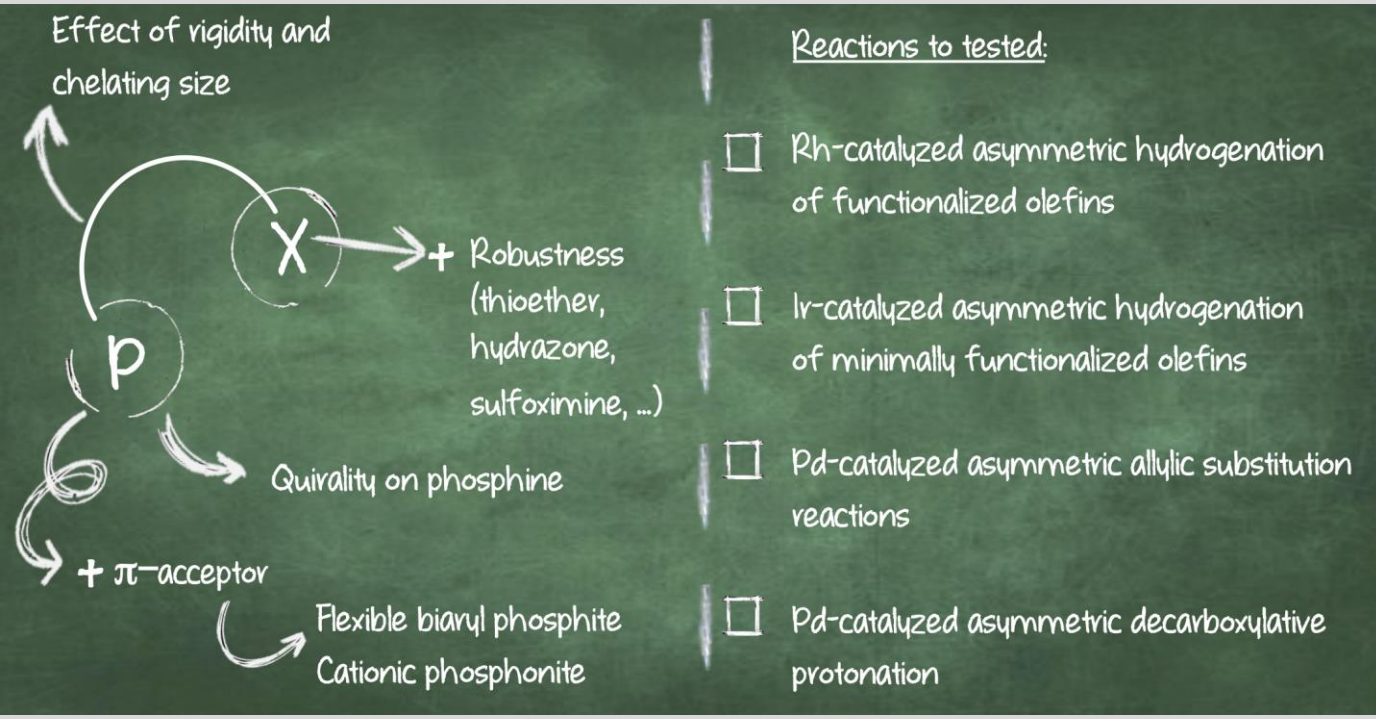

DOCTORAL THESIS
2018

Maria Biosca Brull

Fitting the catalysts for effective enantioselective C-X bond forming reactions. Theoretically guided ligand design and mechanistic investigations

PhD-Thesis

Supervised by Prof. Montserrat Diéguez and Dr. Oscar Pàmies

Departament de Química Física i Inorgànica

UNIVERSITAT ROVIRA I VIRGILI

TARRAGONA

September 2018

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FEM CONSTAR:

Que aquest treball, titulat "Fitting the catalysts for effective enantioselective C-X bond forming reactions. Theoretically guided ligand design and mechanistic investigations", que presenta MARIA BIOSCA BRULL per l'obtenció del títol de Doctor, ha estat realitzat sota la nostra direcció al Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili i que acompleix els requeriments per poder optar a la Menció Europea.

Tarragona, Septembre de 2018

Prof. Montserrat Diéguez Fernández Dr. Oscar Pàmies Ollé

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Acknowledgments/Agraïments

Al llarg d'aquests anys han estat moltes les persones que directament o indirectament, ja sigui d'una manera professional o bé personal, han fet possible el desenvolupament d'aquesta tesi i ha arribat el moment d'agrair-los el seu ajut inavaluable, ja que sense elles no hauria estat possible.

En primer lloc començaré donant les gràcies als meus supervisors la Prof. Montserrat Diéguez i el Dr. Oscar Pàmies, responsables de tot el que científicament sóc. Gràcies per confiar en mi i per oferir-me la oportunitat de fer la tesis al vostre grup, sense vosaltres ara no estaria escrivint aquestes línies. Gràcies també pels vostres consells i el vostre suport, sempre heu sabut donar-me la empenta necessària per continuar.

També voldria agrair a tot el personal de la universitat, professors, tècnics i secretaries, qui amb un simple somriure o amb un paraula amable sempre ajuden a millorar el dia. Especialment, m'agradaria donar les gràcies a la Elisenda i al José, que sempre m'han ajudat a solucionar tots els problemes informàtics que m'han sorgit. També al Josep, qui sempre està disposat ajudar sigui quin sigui el problema i sobretot a la Raquel, que és una de les persones més important pel bon funcionament del nostre laboratori, sense ella seria una caos. I no vull oblidar-me del Ramón, a qui aquests últims mesos he atabalat molt amb els canvis de sonda i les sintonies, però tot i així sempre ha solucionat tots els meus problemes eficientment i amb un somriure.

A més, voldria agrair a tots aquells amb qui he tingut l'oportunitat de col·laborat en algun projecte d'aquesta tesis. Especialment, al Dr. Xisco Caldentey i al Dr. Carles Rodríguez del grup del Prof. Pericàs amb qui he quedat més d'un cop per rebre o recollir lligands/mostres i a la Dr. Maria Besora del grup del Prof. Maseras, qui m'ha resolt molts dubtes sobre química computacional. I sobretot, voldria reconèixer la tasca que el Prof. Per-Ola Norrby a fet amb mi, m'ha guiat durant el meu aprenentatge en la química computacional. Prof. Per-Ola Norrby thank you so much for your tips and your patience in solving all my doubts during these years, without them it would be extremely difficult arrive here.

I would like to thank Prof. Manuel Alcarazo for accepting me in his group at University of Göttingen in 2017. It was a great pleasure working in your group during those four months. I would also like to thank the people there for their kindness help but specially to Leo Nicholls, who teach me about their chemistry. Many thanks for your help in everything.

També a totes aquelles persones de la facultat que en algun moment s'han creuat en aquest trajecte. Als orgànics i als de polímers (Carmen, Lorena, Isma, Macarena, Irene, Jordi, ...), gràcies pels moments compartits i per estar disposats ha ajudar en tot moment. També a la Irina i a l'Albert, a qui ja vaig conèixer durant la carrera i tot i que en àrees diferents hem seguit camins similars i ens seguim tenint al dia a dia.

Ara és l'hora d'agrair a tota la gent que ha passat pel Tecat-OMICH. M'agradaria començar pels laboratoris 216 i 218. Els que ja no esteu, Laia, Alberto, Claudio, Nanette, Itziar, Marc G., Jordi C., Xavi, Thierry, Jèssica C., Enrico, Albert i Lorena un plaer haver coincidit amb vosaltres, espero que tingueu molta sort en el vostre camí. Ana B., gracias por estar siempre dispuesta a ayudar a todo el mundo. Eli, amb el teu somriure i la teva alegria omplies de vida el grup. Fran, gràcies per ser com ets, trobo a faltar les teves preguntes, que creaven tanta controvèrsia i riures. Núria, gràcies pels teus consells i per la teva ajuda en tot moment, ets una persona genial.

Als que encara esteu i que feu que el dia a dia sigui una mica més fàcil. Riccardo, Elliot, Alex, Ricardo, Jordi R., gràcies perquè un simple gest en el moment adequat, et pot canviar el dia. Jorge, gracias por los momentos compartidos y por ayudarme siempre con una sonrisa. Myriam, it was a pleasure working close, you are a hardworking and kind person, I hope the future will provide you the best. Jana, fa poc que has arribat però m'alegro d'haver pogut coincidir amb tu, ets una persona encantadora. I sobretot al Toni, amb qui més moments he passat, qui sempre esta disposat a escoltar-me i donar-me bons consells (ja siguin químics o no). Gràcies Toni, fas que el dia a dia sigui més amè.

Finalment, als que han passat pel laboratori 217: Mercè, Zahra, Fàtima, Carla i Carles, gràcies per tots els moments compartits, m'alegro d'haver pogut treballar amb vosaltres. Al Jordi, et desitjo molta sort en l'etapa que ara comences, tot i que saben com ets segur que no la necessites. Al Pol, ets una persona molt especial, espero que el futur només et depari coses bones, perquè te les mereixes. Al Efrem, vaig aprendre molt amb tu, gràcies per creuar-te en el meu camí. Al Joan, la persona que més m'ha trasbalsat durant aquest temps, tot i les nostres diferències (que no són poques), al final he acabat gaudint de les discussions de química amb tu. A la Jèssica, agrair-te tots els bons consells que hem vas donar durant el temps que vam treballar juntes, també tots els bons moments viscuts, en guardo un molt bon record. Al Marc, gràcies per tot el que hem vas ensenyar durant els anys que vam compartir laboratori i per estar sempre disposat a escoltar els meus problemes i intentar resoldre'ls, tant durant aquest temps com les vegades que t'he molestat després. Dir-te que he trobat molt a faltar les teves cançons i l'alegria que transmeties al laboratori 217, el buit que vas deixar és insubstituïble. I finalment, donar-te les gràcies a tu, Carlota! Pel temps compartint vitrina, per ajudar-me en tot el que has pogut, per els riures i els bons consells, per escoltar cada un dels meus problemes per molt ridículs que semblessin i fer-los teus i sobretot perquè gràcies a tu aquesta recta final se m'ha fet molt més fàcil.

Ara voldria agrair a les persones que no formen part de la vida a la universitat però que no per això són menys importants en el desenvolupament d'aquesta tesis.

Als meus amics (Joana, Laura M., Angels, Mireia, Blanca, Franc, Oscar, Nadia, Arantza, Gisela, Laura S., Nuria, Sarai i els corresponents "remolquets"), tot sabeu com sóc i tot i així sempre que us necessito us trobo al meu costat. Encara que a vegades

passi molt temps sense veure'ns, sempre que estic amb vosaltres és com si aquests intervals de temps no haguessin passat i tot segueix com sempre. Gràcies per cada moment viscut junts, cada un d'ells és únic. Cadascú de vosaltres ha posat el seu granet d'arena en aquesta tesis. Sou extraordinaris i espero poder comptar sempre amb vosaltres.

También quiero agradecerles a Manuela y Rafael por haberme echo sentir desde el primer momento parte de su familia. Gracias por acogerme siempre en vuestra casa con los brazos abiertos y por el apoyo que me habéis dado durante estos años.

I no vull oblidar-me de la meva família, que sempre ha estat al meu costat, tant a les bones com a les dolentes. Mama i papa, gràcies per motivar-me, per intentar entendrem sempre, per fer que aquests anys fossin una mica més fàcils, per donar-me suport en tot el que decideixo i per mil coses més. Gràcies Judit per estar sempre, en uns anys canviarem els rols i m'agradarà ajudar-te igual que tu ho has fet amb mi. També agrair a "ma iaia", perquè tot i "remugant, remugant" sempre m'ha donat suport en les meves decisions i m'ha ajudat en tot el que ha pogut i més. I sobretot, sobretot, no vull oblidar-me de tu; gràcies iaio. Gràcies per estar en tot moment, tot i ja no estar. Sempre sereu el meu model a seguir.

I per últim i no per això menys important, sinó tot al contrari, vull donar-te les gràcies a tu, Adri, la persona que m'ha acompanyat en tot aquest camí, el que ha viscut en mi cada pas. Gràcies per aguantar-me inclús quan jo mateixa no sóc capaç de fer-ho i per fer-me la vida tant i tant fàcil. Sé que aquests quatre anys no han sigut senzills i que probablement tampoc ho seran els que venen però si una cosa estic segura (perquè no ho estic de res més) és de que els vull passar amb tu!

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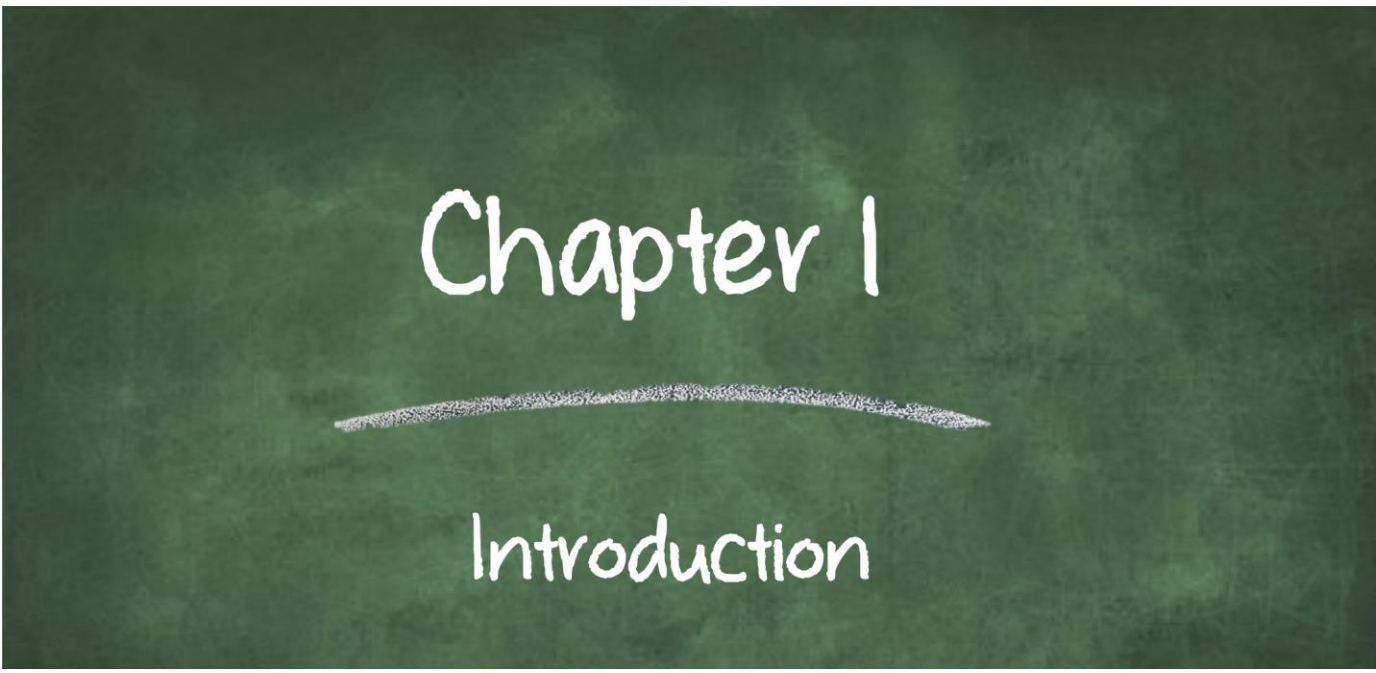
Chapter 1
Introduction

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1. Introduction

Enantiopure compounds play an important role in the production of pharmaceutical, natural and fine chemical products.[1] An obvious reason for this fact is that in many applications only one of both enantiomers has the desired properties while the opposite enantiomer is inactive or has undesirable side effects.[1] The growing demand for enantiopure products has stimulated the development of highly efficient asymmetric processes that show high selectivity and activity, minimum consumption of energy and minimum generation of byproducts. Therefore, the discovery of new synthetic pathways to prepare optically active compounds is one of the most pursued goals in chemistry. Particularly, asymmetric catalysis is one of the most applied technologies in the formation of chiral molecules because it exhibits very high activity and selectivity, and is environmentally friendly.[1] Usually with this strategy, a transition-metal complex with a chiral ligand catalyzes the transformation of a prochiral substrate to one of the enantiomers as major product. The importance of asymmetric catalysis is demonstrated by the many publications in this field and the Nobel Prize award in 2001 to W.S. Knowles, K.B. Sharpless and R. Noyori, for their work in metal-catalyzed asymmetric hydrogenation and oxidation reactions; and in 2010 to E. Negishi, R.F. Heck and A. Suzuki for their work in Pd-catalyzed cross coupling reactions in organic synthesis.[1]

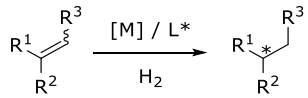
In order to achieve high levels of reactivity and selectivity in catalytic enantioselective reactions, several reaction parameters need to be taken into account. The design and choice of the chiral ligand is perhaps one of the most fundamental step. For this reason, the synthesis of new chiral ligands is essential for the development of new catalytic systems which provide successful results in asymmetric catalysis.[1] In this regard the use of highly modular ligand scaffolds is advantageous because it allows the synthesis and screening of series of chiral ligands in the quest to achieve the highest activities and selectivities for each particular asymmetric catalytic reaction.

In this context, this thesis focuses on the development of several chiral ligands libraries and their application in three different metal-catalyzed asymmetric processes. In this respect, a series of P-N, P-S, and P-P' families of ligands have been applied in the Rh- and Ir-catalyzed asymmetric hydrogenation, Pd-catalyzed asymmetric allylic substitution and Pd-catalyzed decarboxylative protonation. In the following sections, we describe the background of each of the asymmetric catalytic reactions studied in this thesis.

1.1. Asymmetric hydrogenation of olefins

Due to its high efficiency, atom economy and operational simplicity, the asymmetric hydrogenation of olefins can be a sustainable and direct synthetic tool for preparing enantiomerically pure compounds.[1-2] Usually in this strategy, a chiral metal-complex

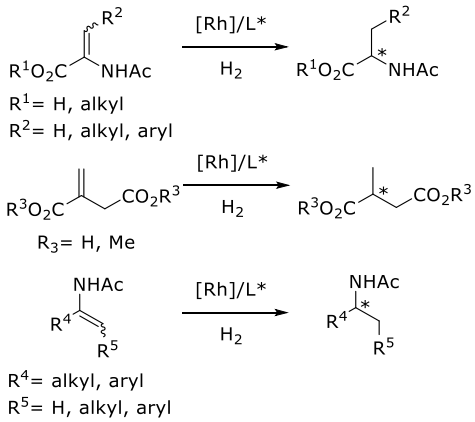
catalyzes the addition of hydrogen to a prochiral substrate containing a double bound giving rise to a new chiral C-H bond (Scheme 1.1).



Scheme 1.1. Asymmetric M-catalyzed hydrogenation of olefins.

1.1.1. Asymmetric hydrogenation of functionalized olefins

The hydrogenation of functionalized olefins is a widely used tool for the preparation of high value compounds that can be used as building blocks in asymmetric synthesis (Scheme 1.2). For example, the production of unnatural amino acids and amines used as intermediates for the pharmaceutical and agrochemical industries rely on catalytic asymmetric hydrogenation of dehydroamino acid derivatives and esters.[1,3] This catalytic reaction is one of the most studied transformations in asymmetric catalysis and is typically used for evaluating the performance of new types of ligands. The most successfully applied catalysts for the hydrogenation of this class of substrates are based on Rh- and Ru-complexes containing chiral ligands with phosphorus and nitrogen donor centers. With this kind of catalysts, excellent activities and enantioselectivities have been achieved for the asymmetric hydrogenation of α-dehydroamino acids and their derivatives and for the reduction of itaconates.[1-3] However, the enantioselective hydrogenation of β-dehydroamino acids still suffers from the low enantioselectivity or reaction efficiency although enantiomerically pure β-amino acids and their derivatives are very attractive targets for the asymmetric synthesis.[4] In general, for this class of substrates, the *E*-isomer have been hydrogenated with higher enantioselectivity than the corresponding *Z*-isomer.



Scheme 1.2. Hydrogenation of dehydroamino acids, itaconates and enamides.

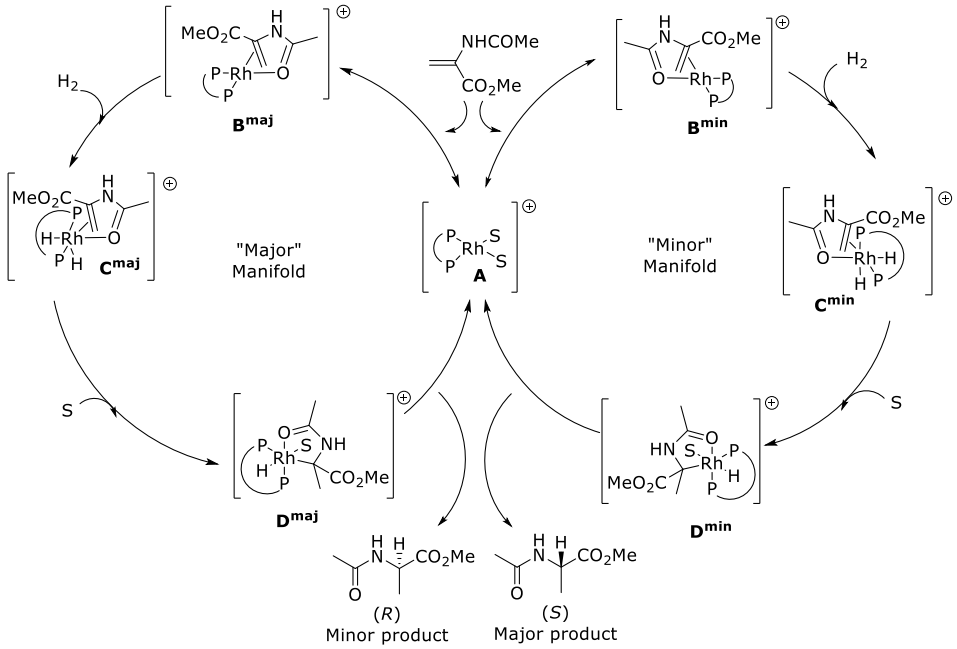
The enantioselective hydrogenation of carbon-nitrogen bounds is a simple and convenient way to synthetize chiral amines. However, their hydrogenation has some serious drawbacks which often provide lower catalytic activities. The main problems in this catalytic reaction are: a) coordination can take place through the nitrogen atom and the double bound; b) the substrate and the catalyst intermediates are unstable under catalytic conditions; and c) homogeneous catalyst can complex both the imine substrate and the amine product.[1] In this context, an alternative to imines is the use of enamides for the synthesis of chiral amines. The reduction of enamides with Rh-complexes have shown to be extremely effective and avoided the problems associated with imines hydrogenation.[3-4] In this field, several efficient catalytic systems have been developed for the hydrogenation of aryl enamides and cyclic enamides. However, until few years ago, the asymmetric hydrogenation of cyclic enamides has been mainly focused on α-enamides, and less extended to β-enamides.[5] Nowadays, the reduction of cyclic β-enamides derived from 2-tetralones and 3-chromanones is highly persuaded due to their hydrogenated products have therapeutic properties.[6]

1.1.1.1. Mechanism

Scheme 1.3 shows the mechanism for the asymmetric hydrogenation of dehydroamino acids and their esters with cationic Rh-precursors containing diphosphines ligands.[7] This mechanism has also proved to be valid for other phosphorus-based ligands (i.e. diphosphinites, diphosphites, etc).[8] The catalytic cycle consists in two coupled diastereomeric manifolds. The cycle starts with the reaction of the substrate with the intermediate **A**, a square planar Rh(I) complex containing the chelating diphosphine and two molecules of solvent. In this first step, the substrate displaces the solvent molecules to give rise the square planar diastereomeric adducts $\mathbf{B^{maj}}$ and $\mathbf{B^{min}}$, where the substrate acts as a bidentate ligand bonded via the olefinic double bond and the oxygen atom of the acetyl group. The next step is the irreversible oxidative addition of hydrogen, which converts the square planar diatereoisomers **B** into the octahedral *cis*-dihydridorhodium complex **C**. Then, the coordinated olefin is inserted to one of the Rh-H bonds to produce the two diastereomeric alkyl complexes **D**. By reductive elimination, they generate the enantiomeric forms of the hydrogenated product and regenerate the catalytically active square planar species **A**.[7]

It is accepted that the oxidative addition of hydrogen is the rate- and enantioselective determining step. In this catalytic cycle, the reactivity of the minor diastereoisomer $\mathbf{B^{min}}$ is much higher than that of the major diastereoisomer $\mathbf{B^{maj}}$, so the minor isomer is the product determining. In order to explain this phenomenon, Brown, Landis, *et al*. have conducted mechanistic studies which showed that the oxidative addition of both major and minor adducts requires the substrates to be rotated in the opposite direction of the rhodium phosphine axis. In the minor adduct, which is less stable, there is a more

hindered configuration that will rotate more easily. Therefore, the minor species is much more reactive towards dihydrogen than the major species.[4-9]



Scheme 1.3. Catalytic cycle for the Rh-catalyzed asymmetric hydrogenation of methyl α-acetamidoacrylate (S= solvent molecule).

1.1.1.2. Ligands

The first advances in asymmetric hydrogenation of olefins arose in the decade of 1960s, after the discovery of Wilkinson's hydrogenation catalyst [$RhCl(PPh_3)_3$],[10] when Knowles,[11] Horner,[12] *et al*. reported the earliest examples of enantioselective hydrogenation, although with poor enantioselectivities. They replaced the triphenylphosphine of Wilkinson's catalyst by a resolved chiral monophosphines. Afterwards, two advances were made in asymmetric hydrogenation. Kagan *et al*. reported the first successful asymmetric hydrogenation using a diphosphine ligand (DIOP, Figure 1.1).[13] On the other hand, Knowles *et al*. made his significant discovery of the C_2-symmetric chelating diphosphine ligand (DIPAMP, Figure 1.1).[14] Due to its high catalytic efficiency, DIPAMP was used in the industrial production of L-Dopa, a drug used to treat Parkinson's disease.[15] For this work, Knowles was awarded the Nobel Prize in 2001.[16]

Following the significant contributions by Kagan, Knowles, *et al*. came the development of hundreds of successful chiral diphosphorus ligands for asymmetric hydrogenation. In the early 1980s the research was mainly focused on developments of Rh-based catalysts. Some of the most representative ligands applied are Bonisch's

CHIRAPHOS and PROPHOS, Kumada's ferrocenes ligands BPPFA and BPPFOH, Achiwa's BPPM, Rhode Poulenc's CBD and Giogo's bis(aminophosphine) ligand PNNP (Figure 1.1).[2,17] However, the substrate scope of these catalysts was limited to α-dehydroamino acids. Later, Noyori's research on the Ru-BINAP catalyst opened up opportunities for the efficient hydrogenation of various substrates (Figure 1.1).[18] Several prochiral olefins and ketones were hydrogenated with excellent enantioselectivities. For this work, Noyori was also awarded the Nobel Prize in 2001. With Ru-BINAP catalytic system, also *E*-β-dehydroamino acid could be successfully hydrogenated.[19] Afterwards, several diphosphine ligands such as DUPHOS,[20] BICP,[21] *o*-HexaMeO-BIPHEP,[22] TCFP,[23] TangPHOS,[24] BPMPI,[25] among others,[26] have been found to be effective for the hydrogenation of *E*-β-dehydroamino acids (Figure 1.1). However, only few chiral diphosphine ligands such as BDPMI,[25] ThangPHOS[24] and TCFP[23] (Figure 1.1) provided high enantioselectivites in the reduction of *Z*-β-dehydroamino acids.

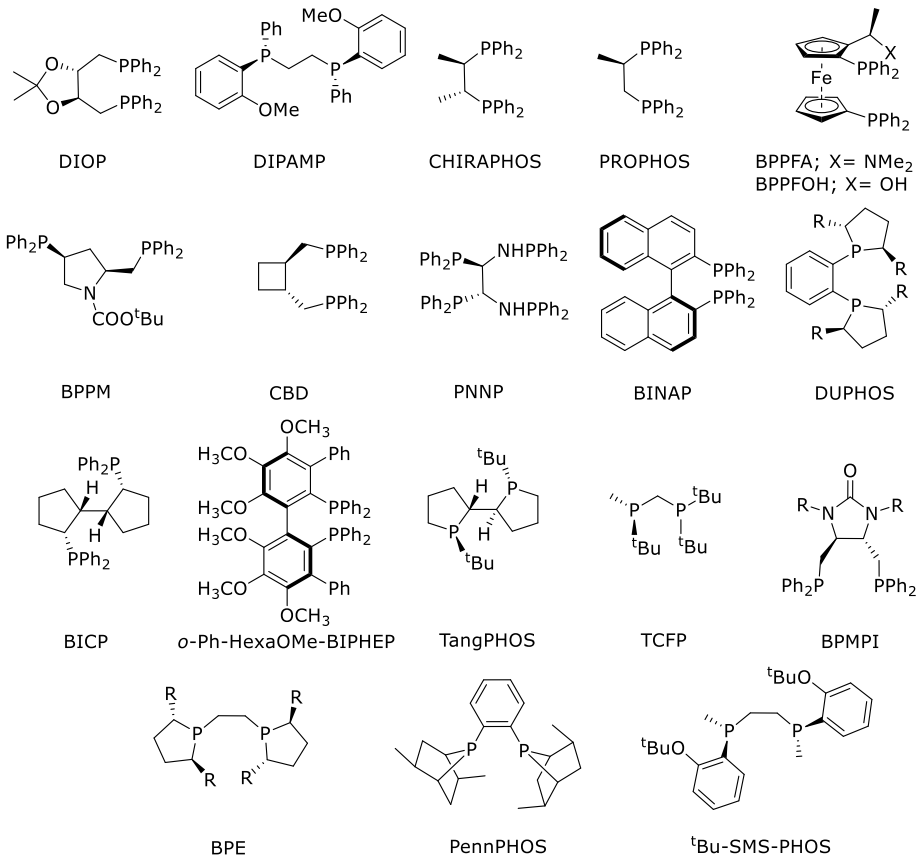


Figure 1.1. Successful diphosphine ligands in asymmetric hydrogenation.

Then, the scope of asymmetric hydrogenation was significantly expanded by the introduction of some efficient chiral diphosphorus ligands, such as BPE developed by

Burk *et al*. (Figure 1.1), which successfully hydrogenate various functionalized olefins, including cyclic α-enamides.[27] Concerning the reduction of cyclic α-enamides, Zhang *et al*. developed conformationally rigid chiral bisphosphanes PennPhos (Figure 1.1) which was successfully applied in Rh-catalyzed asymmetric hydrogenation of 5- and 6-membered cyclic α-enamides.[28] Also, ^{t}Bu-SMS-Phos[29] and *o*-Ph-hexaOMe-BIPHEP[22] ligands (Figure 1.1) provided satisfactory results in the reduction of this class of substrates.

Nowadays, many chiral ligands, mainly phosphorus ligands, with either C_2- or C_1-symmetry have been successfully applied in the asymmetric hydrogenation of functionalized olefins. Catalysts containing diphosphine and diphosphinite have played a dominant role.[1-3,17] Although it has been generally accepted that bidentate ligands are the most appropriate ligands for metal-catalyzed enantioselective hydrogenation, in recent years, it has been shown that some monophosphorus ligands are very efficient for this process.[30] Moreover, some catalysts containing a group of less electron-rich phosphorus compounds, such as phosphite and phosphoroamidite ligands, have also demonstrated their potential utility in Rh-catalyzed asymmetric hydrogenation.[4,31] More recently, ligands containing heterodonor atoms have also received attention. Among the heterodonor ligands, mixed phosphorus ligands have proved to be very effective for this process.[3b,32]

In the next section, we collect the most relevant catalytic data published for Rh-catalyzed asymmetric hydrogenation with the most representative classes of heterodonodor mixed P,P'-ligands.

1.1.1.2.1. Heterodonor mixed P,P'-ligands

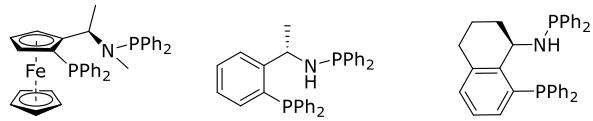
Heterodonor mixed P,P'-ligands have emerged as an efficient class of chelating ligands for Rh-catalyzed hydrogenation of functionalized olefins due to their singular electronic and steric properties conferred by the two different coordinating functionalities.

Phosphine-aminophosphine ligands

The first successful phosphine-aminophosphine (AMMP) ligand for Rh-catalyzed asymmetric hydrogenation was reported in 2002 by Boaz *et al.*, who developed BoPhoz ligand based on a ferrocenylethyl backbone (Figure 1.2). BoPhoz-type ligands showed excellent enantioselectivities in the reduction of α-dehydroamino acid derivatives, itaconates and α-keto esters.[33]

Following this work, Yip, Chan, *et al*. developed and applied the fluorinated BoPhoz-type ligands which increased the substrate scope with the successful reduction of α-aryl enamides.[34] Also, Chen *et al*. modified BoPhoz ligands introducing a stereogenic phosphorus atom in the ligand design. The comparative results demonstrated that P-

chirality improves the enantioselectivity when acting cooperatively with the planar chirality at the carbon center.[35] Zheng *et al*. also applied this BoPhoz-type ligands in the challenging hydrogenation of γ-phthalimido-substituted α,β-unsaturated carboxylic acid esters[36] and in the reduction of α-aryl and α-alkyl substituted vinylphosphonates and 3-aryl-4-phosphonobutenoates[37], achieving satisfactory results (ee's up to 98%).



BoPhoz *S*-HH-Phos *R*-HW-Phos

Figure 1.2. Representative phosphine-aminophosphine ligands.

In 2008, Zheng *et al*. reported a new class of phosphine-aminophosphine ligand, so-called (*S*)-HH-Phos, derived from inexpensive (*S*)-1-phenylethylamine (Figure 1.2). Ligands based on (*S*)-HH-Phos provided good enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of various dimethyl (*R*)-benzoyloxyethenephosphonates bearing β-aryl, β-alkyl and β-alkoxy substituents and *N*-benzyloxycarbonyl α-enamido phosphonates (ee's up to 97%).[38]

Later, Zheng, Hu, *et al*. reported a modification of (*S*)-HH-Phos based ligands introducing different aryl groups in the aminophosphine moiety. These ligands were successfully used in the Rh-catalyzed asymmetric hydrogenation of various α-aryl enamides, β-dehydroamino acid esters, and dimethyl itaconate (ee's up to 99%). The results show that the ligand structure plays an important influence on both the reactivity and enantioselectivity.[39]

Ongoing in this line, Zhuo *et al*. reported a modification of this ligand backbone obtaining the phosphine-aminophosphine ligand (*R*)-HW-Phos prepared from (*R*)-1,2,3,4-tetrahydro-1-naphthylamine (Figure 1.2).[40] Phosphine-aminophosphine ligands based on (*R*)-HW-Phos successfully hydrogenated a broad range of functionalized olefins including α-enol ester phosphonates, α-enamido phosphonates and in the more challenging *Z*-β-(acylamino)acrylates (ee's up to >99%). These new phosphine-aminophosphine ligands were more efficient than previous ligands derived from (*S*)-1-phenylethylamine, suggesting that the increased rigidity conferred by a cyclohexyl fragment in (*R*)-HW-Phos based ligands has a positive effect in the asymmetric induction.[40]

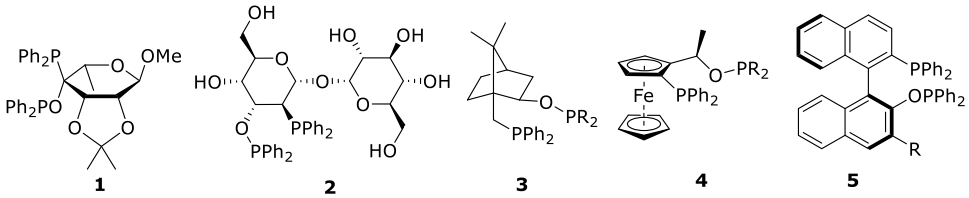
Phosphine-phosphinite ligands

Phosphine-phosphinite ligands have been successfully applied in the hydrogenation of benchmark substrates, the 2-acetamido-3-aryl acetate derivates. However, the asymmetric hydrogenation of topologically distinct prochiral alkenes is very scare.

Yamashita *et al*. reported the first phosphine-phosphinite ligand for Rh-catalyzed asymmetric hydrogenation. However, the enantioselectivity obtained in the reduction of α-acetylaminocinnamic acid using sugar-based ligand **1** (Figure 1.3) was unsatisfactory (5% ee).[41]

In this field, the second application of phosphine-phosphinite ligands was reported by Uemura *et al*., who obtained moderate enantioselectivities (ee's up to 73%) in the reduction of α-dehydroamino acid derivatives using α,α-trehalose derived ligand **2** (Figure 1.3).[42]

Later, Monsees and Laschat developed camphor-derived phosphine-phosphinite ligands **3** (Figure 1.3, R= Ph, Mes, Cy) and applied them in the hydrogenation of α-dehydroamino acids, obtaining good enantioselectivities (ee's up to 89%).[43] The results indicated that further reduction of the conformational flexibility is required in order to further optimize the enantioselectivity.



1 **2** **3** **4** **5**

Figure 1.3. Phosphine-phosphinite ligands **1**-**5**.

In this sense, Chan *et al*. developed ligands **4** (Figure 1.3, R= Ph, 3,5-$(CF_3)_2$-C_6H_3) containing a ferrocene unit for the successful reduction of α-dehydroamino acid derivatives (ee's up >99%) and α-aryl enamides (ee's up to 91%).[44]

On the other hand, Zhang *et al*. applied BINOL-based ligands **5** (Figure 1.3, R= H, Ph) in the hydrogenation of α-*N*-acetoamidoacrylate and several α-dehydroamino acid derivatives obtaining excellent enantioselectivities (ee's up to >99%).[45] Remarkably, these ligands also tolerates the free acid in this type of substrates without any loss of enantioselectivity.

After that, other phosphine-phosphinite ligands were tested but none of them fulfilled the steric and electronic requirements around the rhodium center to achieve such high enantioselectivities.[46]

Aminophosphine-phosphinite ligands

In 1982, Cesarotti *et al*. reported the first application of aminophosphine-phosphinite ligands (AMPP). They synthetized and applied ligands **6** and **7** (Figure 1.4) in the reduction of α-*N*-acetaminocinnamic acid, α-*N*-acetaminoacrylic acid, and itaconic acid, achieving poor-to-moderate enantioselectivities (10-80% ee).[47] Later, the same authors applied ligands **6** and **7** in the hydrogenation of *N*-acetyl amino acids, α-dehydro-*N*-

benzoyl amino acid and itaconic acid with poor-to-good enantioselectivities (10-96% ee).[48]

Pracejus *et al*. developed ligands **8** (Figure 1.4, R^1= Me, Ph, H; R^2= Me, H and R^3= Ph, H) based on optically active β-aminoalcohols and applied them in the hydrogenation of some benchmarks substrates obtaining moderate enantioselectivities (ee's up to 80%).[49] The same authors also developed diastereomeric AMPP ligands **9** (Figure 1.4) based on a norbornane skeleton with which enantioselectivities up to 90% ee were achieved in the hydrogenation of α-acetamidocinnamic acid, methyl-α-acetamidocinnamate, and acetamidoacrylic acid.[50]

Following this works, Petit *et al.* further modified ligands **7** and **8** and synthetized new ligands **10** (Figure 1.4, **10**; R= H, Me). They applied these ligands libraries in the reduction of α-dehydroamino acid derivatives.[51] From the results, they found that the best enantioselectivities were obtained with ligands **10** which forms a more rigid chelating ring with the metal.

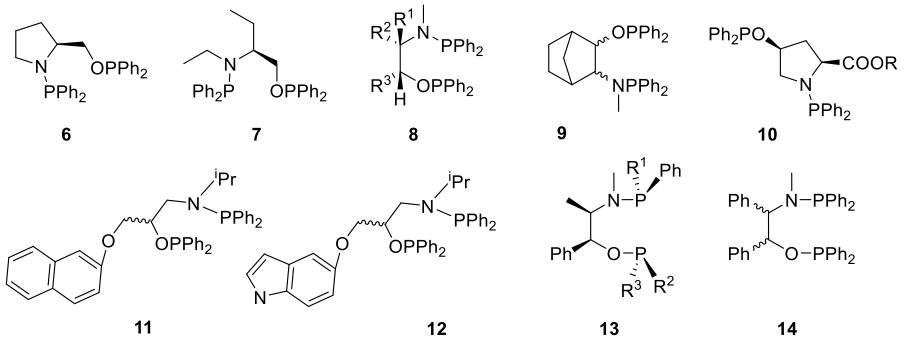


Figure 1.4. Aminophosphine-phosphinite ligands **6**-**14**.

Expanding significantly the substrate scope, Krause, Döbler, Kreuzfeld, *et al*. applied aminophosphine-phosphinite ligands **11** and **12** (Figure 1.4) in the hydrogenation of a wide range of dehydroamino acids including unusual *Z*-2-*N*-benzoylamino-3-(fluorophenyl)-acrylic acids, *Z*-2-*N*-acylamino-3-thienyl-acrylic acids, Z-2-*N*-acylamino-3-pyridyl-acrylic acids and their esters with enantioselectivities up to 95% ee.[52] Ligands **12** showed more efficiency in terms of activity and enantioselectivity than ligands **11**.

Then, Jugé *et al*. reported the synthesis of ephedrine-based aminophosphine-phosphinite ligands **13** with chirality in both phosphorus centers (Figure 1.4, R^1= Ph, Me, *o*-An, 1-Naph, 2-Naph, ^{t}Bu; R^2= Ph, Cy and R^3= Ph, *o*-An, Me, Cy). They applied the corresponding Rh-catalysts in the asymmetric hydrogenation of methyl α-acetamidocinnamate, yielding enantioselectivities up to 99% ee.[53] The results showed that the chirality on the phosphorus centers plays an important role, it could either amplify or cancel out the asymmetric induction resulting from the ephedrine backbone.

Chan *et al*. developed and successfully applied aminophosphine-phosphinite ligands **14** (Figure 1.4) in the reduction of α-dehydroamino acids (ee's up to 98%).[54] Also, Jiang *et al*. applied ligands **14** for the synthesis of L-homophenylalanine with >99.9% ee, a key intermediate of a commercially important ACE (angiotensin-converting-enzyme) inhibitor, a pharmaceutical drug used primarily for the treatment of hypertension.[55]

Phosphine-phosphite ligands

The catalytic activity of rhodium complexes bearing enantiopure phosphine-phosphites (P-OP) in asymmetric hydrogenation has been evaluated against a wider variety of alkenes than for their phosphinite counterparts.

In this field, the first demonstration of the efficiency of P-OP ligands has been provided by Ruiz *et al*., who used ligands **15** based on a xylofuranoside backbone (Figure 1.5) in the hydrogenation of α-*N*-acetadocinnamate and methyl α-*N*-acetaminoacrylate, achieving excellent enatioselectivities.[56]

Alternatively, Leiner *et al*. reported the application of fluorinated BINAPHOS ligand **16** in the hydrogenation of α-*N*-acetamidoacrylate and dimethyl itaconate in supercritical CO_2 (Figure 1.5, R= $CH_2CH_2(CF_2)_5CF_3$).[57]

On the other hand, van Leeuwen *et al*. reported the hydrogenation of α-*N*-acetadocinnamate and methyl α-*N*-acetaminoacrylate using Rh-catalysts containing ligands **17** and **18** (Figure 1.5, **17**; R^1= Ph, ^{t}Bu; R^2= Ph, *o*-An, ^{t}Bu and R^3= (*S*)-Ph, (*S*)-Me, (*R*)-Ph; and **18**; R^1= ^{t}Bu and R^2= (*S*)-Ph, (*R*)-Ph).[58] Interestingly, with ligands **17** they were able to obtain both enantiomers of the hydrogenated product by changing the configuration of the stereogenic center of the backbone. Moreover, the best enantioselectivities were obtained with ligand **17** possessing two phenyl substituents in the phosphine moiety which avoid the chirality in this fragment. This fact indicates the high importance of the phosphite fragment in this process. Also, remarkably, for ligands **18** with a shorter backbone, an important matching/mismatching effect between the stereogenic center of the backbone and the chiral phosphine is observed which is attributed to the closer proximity of both stereogenic elements.

Later, Pizzano *et al.* applied ligands based on atropisomeric phosphite moieties and a simple oxyphenylene backbone **19** in the hydrogenation of dimethyl itaconate and α-*N*-acetadocinnamate (Figure 1.5, R^1= Me, Ph, ^{i}Pr and R^2= Me, Ph, ^{i}Pr).[59] In this case, the product configuration was determined by the biphenyl phosphite group and the enantioselectivity was dependent on the nature of the phosphine moiety. Catalysts based on ligands **19** have been also applied in the hydrogenation of vinyl phosphonates achieving high enantioselectivities.[60] They also studied using ligands **19** the reduction of β-acyloxyvinyl phosphonates.[61] The hydrogenation of this kind of substrates could produce an elimination product. However, by carefully selecting the ligand parameters they minimize the amount of this undesired product. The same authors also reported

the application of ligands **18** and **19** (Figure 1.5, R^1= Ph, *o*-Tol, *m*-Xyl, ^{t}Bu and R^2= Ph, *o*-Tol, *m*-Xyl, Me) in the hydrogenation of 1-alkylvinyl esters. They successfully reduced substrates with different alkyl substituents under very mild conditions.[62] Moreover, these catalysts also hydrogenate with satisfactory results diverse aryl enol esters and phthalimido enol benzoates.[63] More recently, they successfully applied ligands **18** and **19** in the asymmetric hydrogenation of trisubstituted enol esters.[64] The set of substrates comprises α,β-dialkyl, α-alkyl-β-aryl and α,β-diarylvinyl esters. The same authors also applied ligands **18** (Figure 1.5, R^1= Ph, R^2= *S*-Me, *R*-Me) and **20** (Figure 1.5) in this process.[65] They obtained high enantioselectivities in the hydrogenation of dimethyl itaconate and α-*N*-acetadocinnamate (ee's up to 99%) observing small mismatching effects between stereogenic centers.

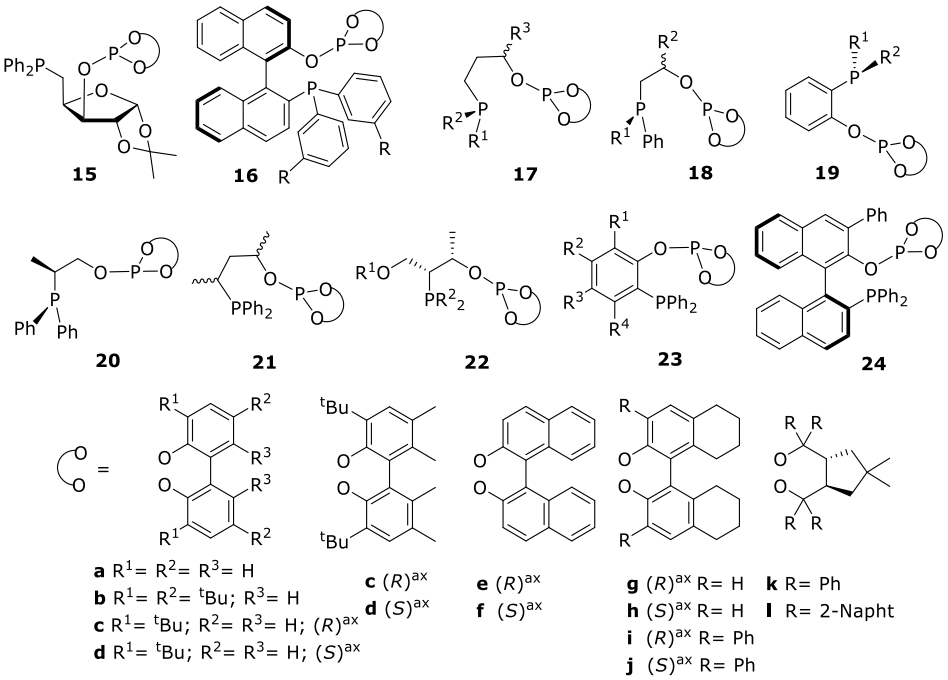


Figure 1.5. Phosphite-phosphine ligands **15**-**24**.

In 2011, Bakos *et al*. successfully applied diastereomeric ligands **21** (Figure 1.5) in Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acids and itaconates.[66] These ligands provided high enantioselectivities with small mismatching effects and again the product configuration was determined by the biaryl phosphite fragment.

Bigger mismatching effects were observed when Vidal-Ferran *et al*. applied diasterioisomeric ligands **22** in the hydrogenation of α-*N*-acetadocinnamate and methyl α-*N*-acetaminoacrylate (Figure 1.5, R^1= Me, $(CH_2)_2OMe$, Bn, Tr, Me, CPh_3 and R^2= Ph, ^{t}Bu, Cy).[8a] In this case, the use of both configuration of the biaryl phosphite group provided the diastereomeric ligands and also controls the configuration of the

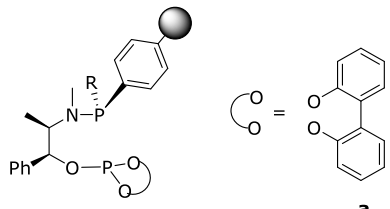
hydrogenated product. More recently, Vidal-Ferran *et al*. reported a second generation of ligands **22** which incorporate more sterically bulky phosphite moieties (**i**-**j**). This increase of the bulkiness of the phosphite group led to higher enantioselectivities in the hydrogenation of benchmark olefins, including several α-dehydroamino acids with different N-protecting groups. Moreover, these Rh-catalysts also showed to be effective in the hydrogenation itaconic acid derivatives, aryl amides, cyclic α-enamides, enol esters and in the preparation of related Weinreb-type amides.[8a,67] Ligands **22** were also applied in the synthesis of the Roche ester, an important precursor in industry.[68] In the latter reaction, Schmalz *et al*. also reported good enantioselectivities using ligand **23** (Figure 1.6, R_1= Me, ^{i}Pr, ^{t}Bu, Ph; R_2= Me; R_3= ^{t}Bu and R_4= Me).[69]

Zhang *et al*. applied Rh-catalysts based on ligands **24** (Figure 1.5) in the hydrogenation of a broad range of α-dehydroamino acids and their corresponding methyl esters, achieving excellent enantioselectivities under very mild conditions.[45]

Aminophosphine-phosphite ligands

In contrast to phosphine-phosphite ligands, the development of aminophosphine-phosphite ligands is much less developed. To best of our knowledge, only one ligand library of aminophosphine-phosphite ligands for application in Rh-catalyzed asymmetric hydrogenation of functionalized olefins was reported.

In this report, Kamer *et al*. showed the efficient parallel solid-phase synthesis of a series of resin-bound P*-stereogenic aminophosphine-phosphite ligands **25** (Figure 1.6, R= ferrocenyl, o-An, 2-biPh, Me, 2-Naph, Ph). The ligands form active hydrogenation catalysts, displaying moderate-to-good enantioselectivities in the reduction of methyl α-acetamidocinnamate, methyl α-acetamidoacrylate and dimethyl itaconate.[70]



25 **a**

Figure 1.6. Aminophosphine-phosphite ligand **25**.

Phosphine-phosphoroamidite ligands

The first successful application of this kind of ligands was reported by Leitner *et al*., who developed ligands **26** (Figure 1.7, R^1= (*S*)-^{n}Bu, (*R*)-^{n}Bu, (*S*)-^{t}Bu, (*R*)-^{t}Bu and R^2= Ph, 3-$(CH_2)_2(CF_2)_6F$) for the hydrogenation of dimethyl itaconate and methyl 2-acetoamidoacrylate, achieving enantioselectivities up to >99% ee. The asymmetric

induction using ligands **26** is mainly determined by the chiral center in the 2-position of the quinoline.[71]

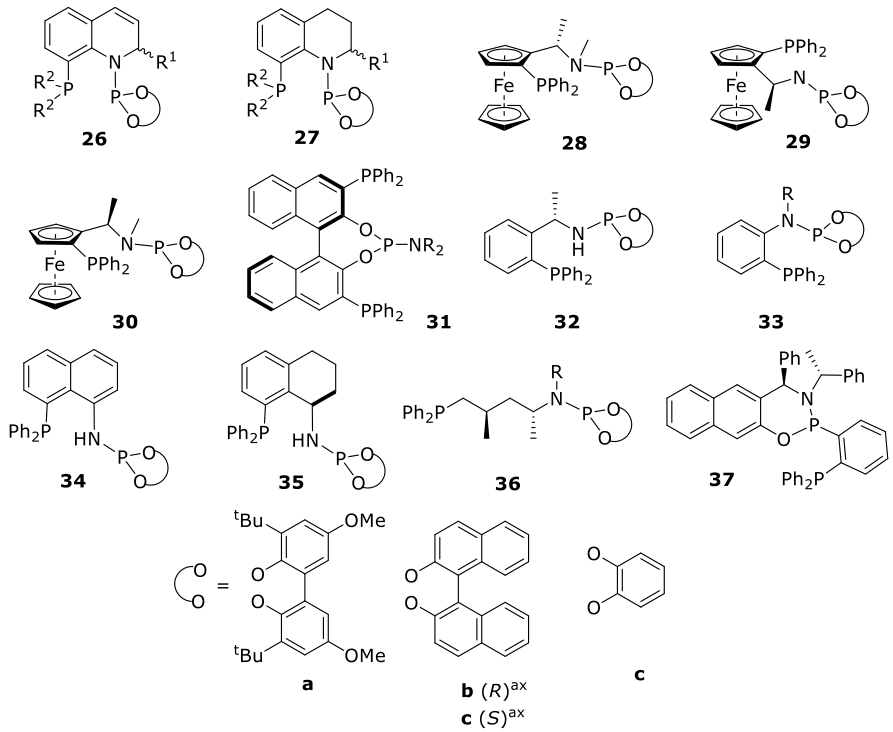


Figure 1.7. Phosphine-phosphoroamidite ligands **26**-**37**.

In 2010, Leitner *et al*. reported the application of new derivatives of Quinaphos and dihydroQuinaphos ligands **26** and **27** (Figure 1.8, **26** and **27**, R^1= (*S*)-^{n}Bu, (*R*)-^{n}Bu, (*S*)-Ph, (*R*)-Ph, (*S*)-1-Naph, (*R*)-1-Naph and R^2= Ph, 3,5-Xyl), obtaining excellent enantioselectivities in several α-dehydroamino acids, itaconates, and aryl enamides.[72]

In 2004, Zheng *et al*. reported the synthesis and application of a new family ferrocene-based phosphine-phosphoroamidite ligands **28** and **29** (Figure 1.7). These ligands exhibited excellent enantioselectivities (ee's up to 99%) in the Rh-catalyzed asymmetric hydrogenation of aryl enamides, dimethyl itaconate, and methyl *Z*-acetamidocinnamate. The binaphthyl moiety is crucial in terms of activity and enantioselectivity and its absolute configuration plays a dominant role in determining the chirality of the hydrogenation products.[73]

In the same year, Chan *et al*. applied ligand **30** (Figure 1.7) with a ferrocene unit in the reduction of α-dehydroamino acid derivatives and α-aryl enamides.[44] This phosphine-phosphoroamidite ligand **30** provide similar enantioselectivities than their related phosphine-phosphinite counterparts **4** (Figure 1.3, R= Ph, 3,5-$(CF_3)_2$-C_3H_6).

Zhang *et al*. reported a new pseudo-C_2-symmetric triphosphorus bidentate phosphine-phosphoroamidite ligands **31** (Figure 1.7). They obtained high

enantioselectivities in the reduction of aryl enamides including *ortho*-substituted aryl enamides (ee's up to 99%) and 1-naphthylenamide (98% ee).[74]

On the other hand, Zheng *et al.* reported the application of ligands **32** (Figure 1.7), analogues of (*S*)-HH-Phos ligand (Figure 1.2). Excellent enantioselectivities were obtained using ligands **32** in the hydrogenation of α-dehydroamino acid esters, α-aryl enamides, and dimethyl itaconate (ee's up to >99%). Interestingly, the central chirality in the phenylethylamine backbone decided the absolute configuration of the hydrogenation product no matter the configuration of binaphthyl moiety.[75]

In 2006, Börner *et al*. developed a novel chiral phosphine–phosphoroamidite ligand **33** (Figure 1.7, R= Me) based on 2-diphenylphosphino-*N*-methylaniline and (*R*)-BINOL moieties. Remarkably, the corresponding Rh-complexes provided high activity and enantioselectivity in the asymmetric hydrogenation of challenging methyl *Z*-α-acetamidocinnamate (100% conversion after 10 min, 98% ee) and dimethyl itaconate (100% conversion after 26 min, 96% ee).[76] Later, Franciò, Leitner, *et al.* introduced an additional chiral center (Figure 1.7, R=(*S*)-1-phenylethyl, (*S*)-1-(1-naphtyl)ethyl) in the amine moiety which led to higher enantioselectivities than previous ligand **33** (ee's up to >99.9%).[77]

Then, Zheng *et al*. prepared a chiral phosphine-phosphoroamidite ligands **34** and **35** (Figure 1.7) which were successfully applied in the Rh-catalyzed asymmetric hydrogenation of various functionalized C=C double bonds including α-(acetamido)cinnamates, α-aryl enamides, and α-enol ester phosphonates.[78] Despite the absence of the central chirality, ligands **34** showed excellent enantioselectivities in the hydrogenation of α-(acetamido)cinnamates and α-enol ester phosphonates, comparable to those obtained with ligands **35**. In the hydrogenation of disubstituted enamides, ligands **34** gave somewhat lower enantioselectivity than ligands **35**. However, higher enantioselectivities were observed in the hydrogenation of trisubstituted enamides using ligands **34** instead of ligands **35**.

Afterwards, Bakos *et al*. applied phosphine-phosphoroamidite ligands **36** (Figure 1.7, R= ^{i}Pr, Me, Bn, Ph), containing 2,4-pentanediyl backbone and BINOL moieties, in the asymmetric hydrogenation of dimethyl itaconate and α-dehydroamino acid derivatives in propylene carbonate.[79] High enantioselectivities were obtained independently of the substituents introduced in the nitrogen moiety.

In 2017, Leitner, Franciò, *et al.* synthetized a new phosphine–phosphoroamidite ligands **37** (Figure 1.7) bearing a chiral phosphorus atom at the phosphoroamidite moiety. Ligands **37** have been applied in the asymmetric hydrogenation of several functionalized olefins, yielding satisfactory enantioselectivities (91-97% ee).[80] Interestingly, whereas the configuration of the stereogenic phosphorus atom was mainly responsible for configuration of the hydrogenated product, the configuration in the ligand backbone had a major influence on the catalyst activity.

Phosphite-phosphoroamidite ligands

In 2001, our group applied for the first time a series of novel phosphite–phosphoroamidite ligands **38** (Figure 1.8), derived from readily available *D*-xylose, in the asymmetric Rh-catalyzed hydrogenation of a series of α,β-unsaturated carboxylic acid derivatives with excellent enantioselectivities (ee's up to >99%).[81] Later, they expanded this family of ligands introducing ligands **39** and different biaryl phosphite/phosphoroamidite moieties (Figure 1.8).[82] These modifications provided high enantioselectivities in the reduction of dimethyl itaconate (ee's up to >99%), α-dehydroamino acid esters (ee's up to 99%), and several α-aryl enamides (ee's up to 92%). Moreover, the authors performed kinetic and NMR studies on the intermediates of the catalytic cycle of the reaction which indicated that the $[Rh(P_1–P_2)(substrate)]^+$ species is the resting state of the reaction, and that the rate dependence is first order in rhodium and hydrogen pressure and zeroth order in the substrate.

Following this work, Cesarotti *et al.* developed phosphoroamidite-phosphite ligands **40** (Figure 1.8, R^1= Et, R^2= H and R^1= R^2= $(CH_2)_2$). Ligands **40** provided enantioselectivities up to 70% in asymmetric hydrogenation of α-acetamidocinnamic acid derivatives.[83]

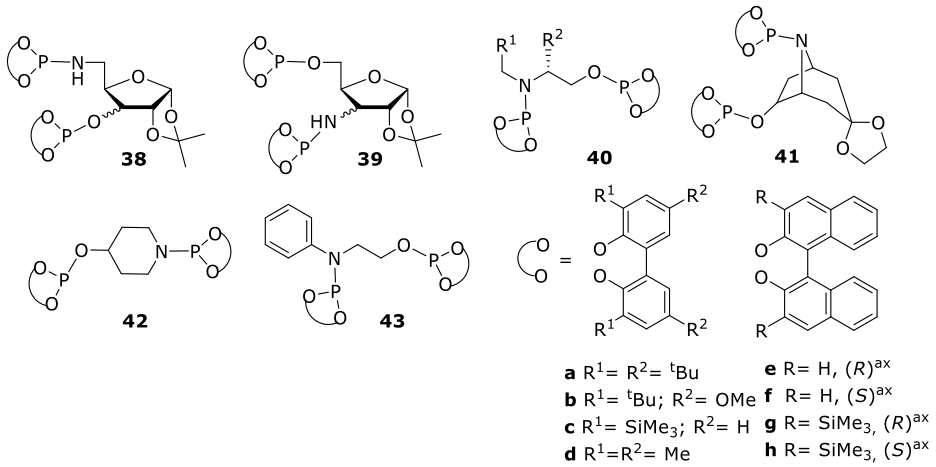


Figure 1.8. Phosphite-phosphoroamidite ligands applied in Rh-catalyzed hydrogenation.

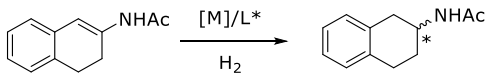
Then, Laschat *et al.* tested ligands **41** (Figure 1.8) with a pure tropane scaffold in the reduction of dimethyl itaconate and methyl acetamidocinnamate, obtaining satisfactory results (ee's up to 85% and 95%, respectively).[84]

In 2006, Reetz *et al*. reported the development phosphite-phosphoroamidite ligand **42** (Figure 1.8) and its application in the Rh-catalyzed hydrogenation of dimethyl itaconate and α-dehydroamino acid esters with enantioselectivities up to 96% ee.[85]

Later, Kostas, Börner, *et al*. synthesized a novel chiral phosphite–phosphoroamidite ligand **43** based on 2-anilinoethanol and (*R*)-BINOL moieties (Figure 1.8). Ligand **43** was evaluated in the enantioselective hydrogenation of α- and β-dehydroamino acid derivatives and dimethyl itaconate.[86] Unfortunately, the enantioselectivities obtained were lower than the ones obtained with previous ligands (ee's up to 63%).

1.1.1.2.2. Ligands for asymmetric hydrogenation of cyclic β-enamides

As previously mentioned, until very recently, the asymmetric hydrogenation of cyclic enamides has been mainly focused on α-enamides, and less extended to β-enamides (Scheme 1.4). Most of the catalysts for hydrogenation of β-enamides are based on Rh- and Ru-catalysts, and the complete control of stereoselectivity with these catalysts has remained elusive.[31f,87]



Scheme 1.4. Hydrogenation of *N*-(3,4-dihydronaphthalen-2-yl)acetamide an example of typical β-cyclic enamides.

With Ru-catalysts, the most relevant ligands were diphosphines BINAP[87a] and **44**[87f,g] (Figure 1.9) reported by Bruneau *et al*. and Rotovelomanona-Vidal *et al*., respectively. These ligands were successfully applied in the hydrogenation of enamides derived from both 2-tetralones and 3-chromanones with ee's up to 96%.

In the field of Rh-catalytic systems, Pizzano *et al*. developed a P*-stereogenic phosphine-phosphite ligand **18d**[87j] (Figure 1.9, R^1= *o*-An and R^2= H) achieving high enantioselectivities in the reduction of β-enamides derived from 2-tetralones (ee's up to 93%). Also, Reek *et al*. applied ligands **45**[87c] (Figure 1.9) in the hydrogenation of enamides derived from 2-tetralones with enantioselectivities up to 96%. In the same field, Tang *et al*. developed ligand **46**[87k] (Figure 1.9) for the hydrogenation of cyclic β-enamides derived from both 2-tetralones and 3-chromanones achieving enantioselectivities up to 96%.

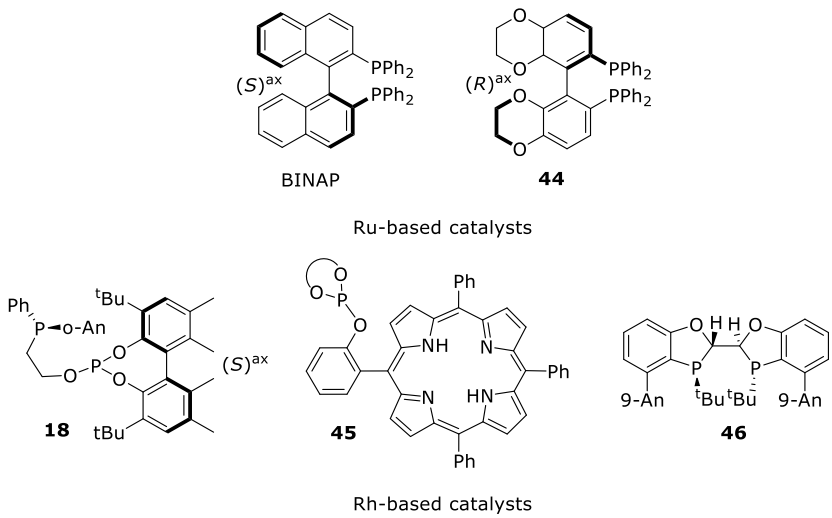


Figure 1.9. Most relevant ligands applied in the hydrogenation of cyclic β-enamides.

A breakthrough in this field came when for the first time Verdaguer *et al*. successfully applied Ir-P,N catalysts in the hydrogenation of cyclic β-enamides. They developed P*-stereogenic phosphine-oxazoline ligands **47** (Figure 1.10, R= ^{i}Pr, ^{t}Bu) which provided enantioselectivities up to 99% ee for those derived from 2-tetralones.[88] Shortly thereafter, our group showed that Ir-catalytic systems with PHOX-based phosphite-oxazoline ligands **48** (Figure 1.10, R= Ph, ^{t}Bu; n= 0, 1) can also be successfully used to reduce cyclic β-enamides derived from both 2-tetralones and 3-chromanones.[89]

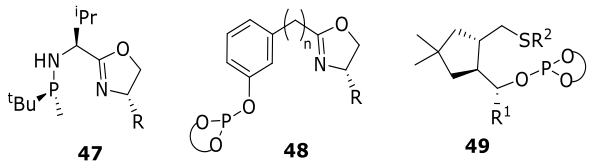


Figure 1.10. P,N- and P,S-ligands applied in the hydrogenation of cyclic β-enamides with Ir-catalytic systems.

More recently, our group also applied P,S-ligands in the reduction of cyclic β-enamides. Ligands **49** (Figure 1.10, R^1= H, Me, $CH_2OTBDMS$ and R^2= Ph, 2-Naph) can be successfully applied in the hydrogenation of cyclic β-enamides (ee's up to 99%).[90] Moreover, it was found that both enantiomers of the hydrogenated products could be obtained by simply switching from Ir to Rh.

1.1.2. Asymmetric hydrogenation of minimally functionalized olefins

Whereas the hydrogenation of olefins containing an adjacent polar group by Rh(I) and Ru(II) complexes bearing phosphorus ligands has a long history,[1,3] the reduction of unfunctionalized olefins is by far less developed. The high stereoselectivity obtained in the asymmetric hydrogenation of alkenes by Rh/Ru-phosphorus ligands rely on the presence of a coordinating group in a close proximity to the double bond which works as a secondary complexation function in addition to the alkene functionality forming a chelate which limits the set of available conformations.[2] In contrast, iridium complexes with chiral heterodonor P,N-ligands have become established as efficient catalysts for asymmetric hydrogenation of minimally functionalized olefins since the iridium catalysts do not require the presence of an extra coordinating group, this fact makes their scope complementary to those of Rh- and Ru-complexes with phosphorus ligands.[91]

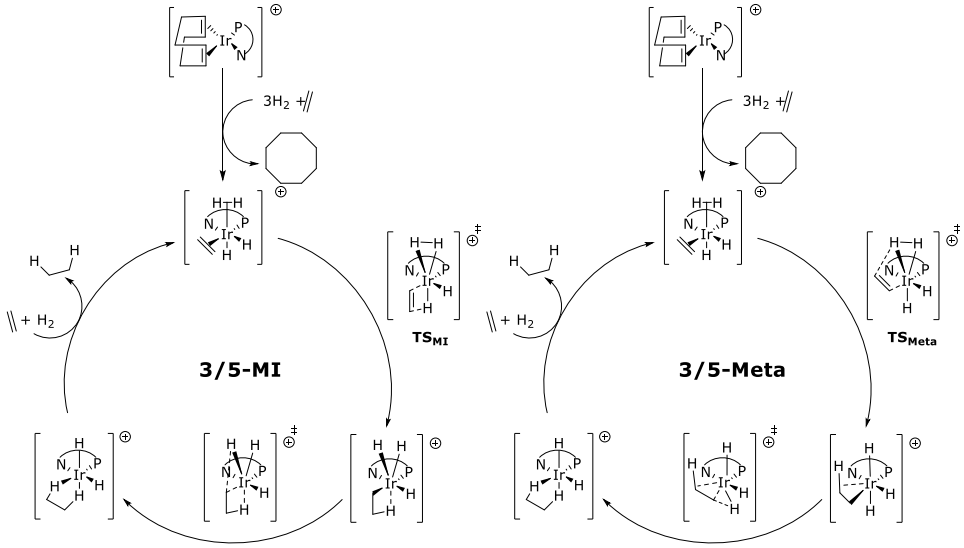
1.1.2.1. Mechanism

Although the mechanism for the Rh-catalyzed asymmetric hydrogenation of olefins containing an adjacent polar group is well understood,[7-8] the mechanism for the Ir-catalyzed hydrogenation of minimally functionalized olefins has been less studied. As mentioned before, in the first case, there are evidences that supports a Rh(I)/Rh(III) mechanism in which the rate of the reaction is determined by the oxidative addition of H_2 and the chelation of the substrate to the metal plays a pivotal role in the stereodiscrimination, but for the asymmetric hydrogenation of minimally functionalized olefins four different mechanisms have been proposed (two of them involving Ir(I)/Ir(III) species[92] and the other two Ir(III)/Ir(V) intermediates[93]).

In 2010, Andersson *et al*. have used DFT (Density Functional Theory) calculations and a full, experimentally tested combination of ligands and substrates to study all possible diastereomeric pathways of the four different proposed mechanisms.[94] They concluded that the catalytic cycle passed through Ir(III)/Ir(V) intermediates, but they failed to distinguish between the two Ir(III)/Ir(V) mechanisms. One of the mechanisms includes the migratory insertion of one hydride onto the olefin followed by a reductive elimination (mechanism 3/5-MI, Scheme 1.5)[93a] whereas the second mechanism involves a σ-metathesis also followed by a reductive elimination (mechanism 3/5-Meta, Scheme 1.5)[93b,c]. For both catalytic pathways, it has been demonstrated that the transition states for the migratory insertion in 3/5-MI (**TS_{MI}**) and the σ-metathesis in 3/5-Meta (**TS_{Meta}**) are responsible for the enantiocontrol in the process.[94]

In 2011, Hopmann *et al*. performed a computational study using a phosphine-oxazoline(PHOX)-based iridium catalysts.[95] At the same time our group in collaboration with Norrby's and Andersson's group performed a study with DFT calculations using iridium catalysts with phosphite-oxazoline ligands.[96] Both studies confirm that the

hydrogenation of minimally functionalized olefins follows the 3/5-MI pathway, but energetic barriers between both catalytic cycles do not differ a lot to discriminate directly 3/5-Meta.



Scheme 1.5. Proposed catalytic cycles 3/5-MI and 3/5-Meta for asymmetric hydrogenation of minimally functionalized olefins.

More recently, in 2014, Pfaltz *et al*. reported a NMR study where they were able to synthetize and characterize the elusive catalytically competent intermediates Ir-dihydride alkene complexes ($[Ir(H)_2(alkene)(L)]^+$).[97] After studying the reactivity of these complexes, it was concluded that an extra molecule of H_2 was needed to convert the catalyst bond-alkene into the hydrogenated product but no signals of a dihydride complex with an additional coordinated H_2 could be detected, thus indicating that these Ir-dihydride alkene complexes corresponds to the resting state. This observation further supports the Ir(III)/Ir(V) mechanism via an $[Ir(H)_2(alkene)(H_2)(L)]^+$ intermediate. They also found that there are two dihydride-alkene intermediates in equilibrium via dissociation/association process, resulting from an enantioface exchange of the coordinated olefin. The configuration of the hydrogenated product corresponds to the one that should lead to the minor isomer. So, the minor intermediate, which is less stable, is converted to the major intermediate, similar to the mechanism of the Rh-catalyzed asymmetric hydrogenation.[7]

1.1.2.2. Ligands

During the 1970s, Crabtree *et al.* studied the catalytic performance in the alkene hydrogenation of metal complexes of the type $[M(cod)L_2]X$ (M=Rh or Ir; cod= 1,5-cyclooctadiene; L= phosphine ligand; X= Cl, BF_4 or PF_6). After carefully ligand-screening

experiments, they discovered that replacing one of the phosphine ligands by a pyridine lead to a significant improvement of the catalytic performance of the Ir-catalyst. Thus, $[Ir(cod)(Py)(PCy_3)]PF_6$ catalytic precursor (Figure 1.11), so-called Crabtree's catalysts, is faster than the corresponding diphosphine catalyst and able to efficiently reduce tri- and tetrasubstituted nonfunctionalized olefins.[98]

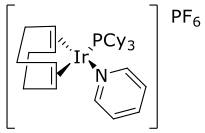


Figure 1.11. Crabtree's catalyst.

A breakthrough in the hydrogenation of minimally functionalized olefins came in 1997 when Pfaltz *et al.* used phosphine-oxazoline ligands PHOX (Figure 1.12) to design $[Ir(cod)(PHOX)]PF_6$,[99] a chiral mimic of the Crabtree's catalyst, that enantioselectively hydrogenated prochiral imines.[100] Although this catalyst was also able to hydrogenate prochiral olefins highly enantioselectively, it was unstable to the reaction conditions. Pfaltz *et al.* overcome this problem by changing the catalyst anion hexafluorophosphate by a less coordinative anion, tetraquis[3,5-bis(trifluoromethyl)phenyl] borate ([3,5-$(F_3C)_2$-$(C_6H_3)_4B]^-$; BAr_F^-). The result was the $[Ir(cod)(PHOX)]BAr_F$ an active, enantioselective, and stable catalyst for hydrogenation of minimally functionalized olefins. Despite this success, the scope of these PHOX ligands was limited (mainly *E*-trisubstituted olefins).[99,101]

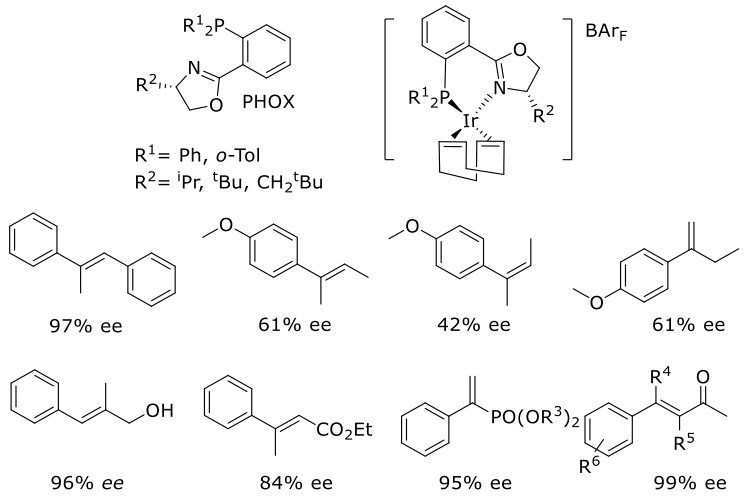


Figure 1.12. Selected Ir-hydrogenation results using PHOX ligands.

Since then, the research in this field has been mainly focused in the design and synthesis of new chiral P,N-ligands.[91] The composition of these P,N-ligands has been extended by replacing the phosphine moiety by a phosphinite, phosphite or carbene group, and the oxazoline moiety by other N-donor groups (such as pyridine, imidazole, thiazole, thiazoline or oxazole).[91] The backbone structure of the ligand has been also modified. More recently, the nature of the N-donor group has been replaced by S-[102] and O-donor[103] groups. An important innovation in the ligand design was the introduction of π-acceptor biaryl phosphite moiety, which provides greater substrate versatility than previous Ir-P,N systems.[91e,96,104] All these modifications have led to the discovery of new catalytic systems that have increase the scope of the hydrogenation of minimally functionalized olefins.

In the next sections we summarized the most relevant catalytic systems reported for Ir-catalyzed hydrogenation of trisubstituted, 1,1'-disubtituted, and tetrasubstituted minimally functionalized olefins with P,N- and P,S-ligands. As mentioned, most of the successful ligands are P,N-ligands but it has been proved that the introduction of most robust group such as thioether was also efficient in process.

1.1.2.2.1. Phosphorus-oxazoline ligands

Phosphine-oxazoline ligands

Inspired by the work of Pfaltz *et al.* using PHOX ligands, several other phosphine-oxazoline ligands have been developed for this process. Künding *et al.* reported a modification in the oxazoline moiety with the development of phosphine-benzoxazine analogues **50** (Figure 1.13, R= ^{t}Bu, ^{i}Pr).[105] The presence of bulky substituents such as *tert*-butyl at the oxazine group provided high enantioselectivities (ee's up to 89% and 55% ee for *E*- and *Z*-trisubstituted olefins, respectively) but these enantioselectivities were lower than those obtained with PHOX ligands.

After these ligands, the rest of new developments in the ligand design were based on modifications of the ligand backbone. Ligands **51**, developed by Burgess *et al.*, were applied in the hydrogenation of several aryl-alkyl alkenes (Figure 1.13, R^1= Ph, *o*-Tol and R^2= Me, ^{t}Bu, 1-Ad, CPh_3).[101b] These ligands proved to be superior to the PHOX ligands in the hydrogenation of *Z*-trisubstituted alkenes while ee's for the reduction of *E*-trisubstituted alkenes were lower. This development promoted a further modification of ligands **51** by introducing again the *ortho*-phenylene motif of the PHOX ligands. In this respect, the new ligands **52** (Figure 1.13, R^1= Ph, Cy and R^2= ^{t}Bu, 1-Ad, $CHPh_2$, 3,5-$^{t}Bu_2$-C_6H_3), developed by Zhang *et al*., proved to be excellent in the hydrogenation of *trans*-α-methylstilbene derivates (ee's up to 99%).[101f]

In 2003, Cozzi *et al.* reported the development of ligands **53**, in which the phenyl ring of the PHOX ligands was replaced by a thiophene group (Figure 1.13, R^1= Ph, *o*-Tol,

Cy and R^2= ^{i}Pr, ^{t}Bu).[101e] This modification also led to high enantioselectivities in the hydrogenation of *trans*-α-methylstilbene (ee's up to 99%).

Then, in 2007, Pfaltz *et al*. synthesized a series of simple and readily accessible phosphine-oxazoline ligands **54** which form a 5-membered chelate ring when coordinated to iridium (Figure 1.13, R^1= Ph, *o*-Tol, Cy, ^{t}Bu and R^2= ^{i}Pr, ^{t}Bu, Ph, Bn).[106] Interestingly, this family of ligands has proved to be one of the most efficient in the hydrogenation of challenging tetrasubstituted alkenes. High enantioselectivities were obtained in a wide range of cyclic tetrasubstituted substrates (ee's up to 96%). Nevertheless, ee's diminished for non-cyclic olefins and specially for 1,2-dihydro-napthalenes (ee's between 89–97% and up to 77%, respectively).

In 2008, on the basis of PHOX ligands, Hou *et al*. developed new phosphine-oxazoline ligands **55** in which the flat *ortho*-phenylene group was replaced by benzylic type group (Figure 1.13, R^1= Ph, *o*-Tol, *p*-Tol and R^2= Me, ^{i}Pr, ^{t}Bu).[107] These ligands were successfully applied in the Ir-catalyzed asymmetric hydrogenation of range of *E*-trisubstituted aryl/alkyl alkenes, allylic alcohols and α,β-unsaturated esters and ketones (ee's up to 98%).

Pfaltz *et al.* also further modified PHOX ligands by replacing the *ortho*-phenylene tether by a branched alkyl chain (ligands **56**; Figure 1.13, R^1= Ph, *o*-Tol, Xyl and R^2= ^{i}Pr, ^{t}Bu, Bn).[101g] These ligands provided higher enantioselectivities in the hydrogenation of trisubstituted *E*- and *Z*-aryl alkenes than the PHOX ligands (ee's up to 98%). The authors demonstrated the potential of ligands **57** with the synthesis of (*R*)-7-demethyl-2-methoxycalamenene, an antitumor natural product.

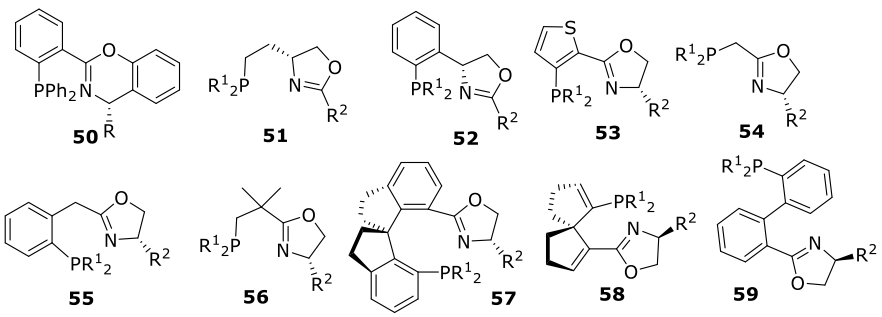


Figure 1.13. Most relevant phosphine-oxazoline ligands.

Zhou *et al.* reported a new family of spiro phosphine-oxazoline ligands **57** (Figure 1.13, R^1= Ph, 3,5-Me_2-C_6H_3, 3,5-$^t Bu_2$-C_6H_3 and R^2= Bn, Ph, Me, H).[108] These ligands were extremely effective in the hydrogenation of both α-aryloxy and α-alkoxy α,β-unsaturated carboxylic acids. Remarkably, excellent enantioselectivities were obtained in the reduction of more challenging α,β-unsaturated carboxylic acids (ee's up to 99%).[109] Other spirocyclic phosphine-oxazoline ligands **58** (Figure 1.13, R^1= *o*-Tol, Ph and R^2= Ph, Bn) were used in the asymmetric hydrogenation of α-aryl-substituted

unsaturated carboxylates,[110] α,β-unsaturated amides,[111] and β,β-disubstituted enones[112].

Afterwards, Zhang *et al.* developed phosphine-oxazoline ligands **59** with an axis-unfixed biphenyl backbone (Figure 1.13, R^1= Ph, 3,5-^{t}Bu$_2$-C$_6$H$_3$, 3,5-^{t}Bu$_2$-4-MeO-C$_6$H$_2$ and R^2= ^{i}Pr, ^{t}Bu, Ph, Me) which successfully hydrogenated exocyclic α,β-unsaturated carbonyl compounds (including ketones, lactones, and lactams),[113] α,β-unsaturated carboxylic acids,[113] 3-substituted 2,5-dihydropyrroles,[114] and 2,5-dihydrothiophene 1,1-dioxides[114].

Aminophosphine-oxazoline ligands

Aminophosphine-oxazoline ligands also have been reported as efficient ligands in the Ir-catalyzed hydrogenation of minimally functionalized olefins. In this context, Pfaltz *et al.* modified the PHOX ligands by replacing the *ortho*-phenylene group by a pyrrole group as linker to the phosphorus leading to ligands **60** (Figure 1.14, R^1= Ph, *o*-Tol, Cy and R^2= ^{i}Pr, ^{t}Bu).[115] Enantiomeric excesses surpassed those previously obtained with the PHOX ligands. Nevertheless, the enantioselectivities for *Z*-trisubstituted olefins were not above 80% ee.

Later, Gilbertson *et al*. developed the proline-based aminophosphine-oxazoline ligands **61** (Figure 1.14, R^1= Ph, *o*-Tol and R^2= ^{i}Pr, ^{t}Bu) that provided lower enantioselectivities than previous pyrrole-based ligands **60**.[116]

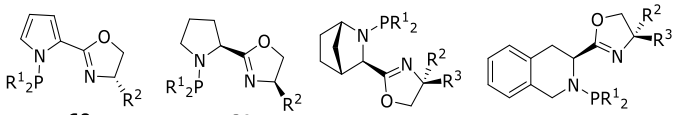


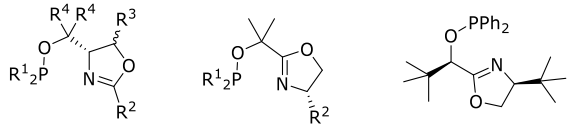
Figure 1.14. Most relevant aminophosphine-oxazoline ligands.

Andersson *et al*. developed ligands **62** and **63** for this process (Figure 1.14, **62**; R^1= Ph, *o*-Tol, Cy; R^2= H, ^{t}Bu, Ph and R^3= H, Ph; and **63**; R^1= Ph; R^2= H, ^{i}Pr, Ph and R^3= H, ^{i}Pr, Ph).[117,118] Ligands **62**,[117] which are based on a rigid bicyclic backbone, provided higher enantioselectivities than ligands **63**,[118] with a more flexible backbone. [Ir(**62**)(cod)]BAr$_F$ catalyst precursors afforded, for first time, high enantioselectivities in the hydrogenation of enol phosphinates,[117b,c] vinyl silanes,[117d] fluorinated olefins,[117e] vinyl boronates,[117f] α,β-unsaturated lactones and α,β-unsaturated acryclic esters[117g].

Phosphinite-oxazoline ligands

For this class of ligands, only three ligands libraries have been developed for the Ir-asymmetric hydrogenation of minimally functionalized olefins.[119]

The first family of phosphinite-oxazoline ligands (ligands **64**, Figure 1.15, R^1= Ph, *o*-Tol, Cy; R^2= ^{t}Bu, Ph, ferrocenyl, 2-Naph; R^3= H, Me, 3,5-Me_2-C_6H_3 and R^4= Me, ^{i}Pr, ^{t}Bu, Bn) was reported by Pfaltz *et al*.[119a-e] Ligands **64** constitute one of the most privileged ligands for this process. These ligands therefore provided excellent enantioselectivities in the hydrogenation of a broad range of both *E*- and *Z*-trisubstituted olefins, including α,β-unsaturated esters and a limited range of more challenging terminal olefins as well as in the reduction of 1,1'-disubstituted enamines.[119a-d] More recently, Ir-catalysts containing ligands **64** have also been successfully applied in the hydrogenation of α,β-unsaturated nitriles.[119e]



64 **65** **66**

Figure 1.15. Most relevant phosphinite-oxazoline ligands.

The second family of ligands (ligands **65**, Figure 1.15, R^1= Ph, *o*-Tol and R^2= ^{i}Pr, ^{t}Bu) is based in the previous one but in this case the alkyl chain is bonded in the carbon 2 instead of the carbon 4 of the oxazoline moiety, which shifts the chirality from the alkyl chain to the oxazoline moiety.[119f] The scope of these ligands is narrower in comparison with the privileged phosphinite-oxazoline ligands **64**, however, they are complementary. Therefore, ligands **65** provided high enantioselectivities for allylic alcohols and alkenes bearing heteroaromatic substituents.

The last family of phosphinite-oxazoline ligands has been developed by Kazmeier *et al.* (ligands **66**, Figure 1.15). The Ir-catalyst containing ligand **66** have provided excellent enantioselectivities for linear and cyclic α,β-unsaturated ketones (ee's up to >99%).[119h]

Phosphite/phosphoroamidite-oxazoline ligands

Despite the advantages of phosphite/phosphoroamidite ligands in asymmetric catalysis,[30a,30c,31b,120] only few families of phosphite/phosphoroamidite-oxazoline ligands have been applied in Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins.

In this context, ligands **67** and **68** (Figure 1.16, **67**; R^1= Ph, *o*-Tol, Cy, 3,5-Xyl-$(CH_2)_4$; R^2= SO_2R, 3-OMe-C_6H_4, 4-OMe-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 2-Naph and R^3= ^{t}Bu, Ph; and **68**; R= Ph, ^{t}Bu) provided lower enantioselectivities and activities than their related phosphinite-oxazoline ligands **65** (Figure 1.15).[121] They also required higher catalyst loadings (4 mol%) and higher pressures (100 bar) to achieve full conversions.

In 2008, our group reported the first successful application of phosphite-oxazoline ligands for this process. Pyranoside phosphite-oxazoline ligands **69** (Figure 1.16, R=

Me, ^{i}Pr, ^{t}Bu, Ph, Bn) provided excellent enantioselectivities in the hydrogenation of a wide range of *E*- and *Z*-trisubstituted olefins, including triaryl-substituted alkenes and 4-methyl-1,2-dihydronaphthalenes (ee's up to >99%).[96] Interestingly, ligands **69** also provided excellent enantioselectivities for the more challenging 1,1'-disubstituted olefins and also for α,β-unsaturated ketones and esters, allylic alcohols and vinyl silanes (ee's up to >99%).

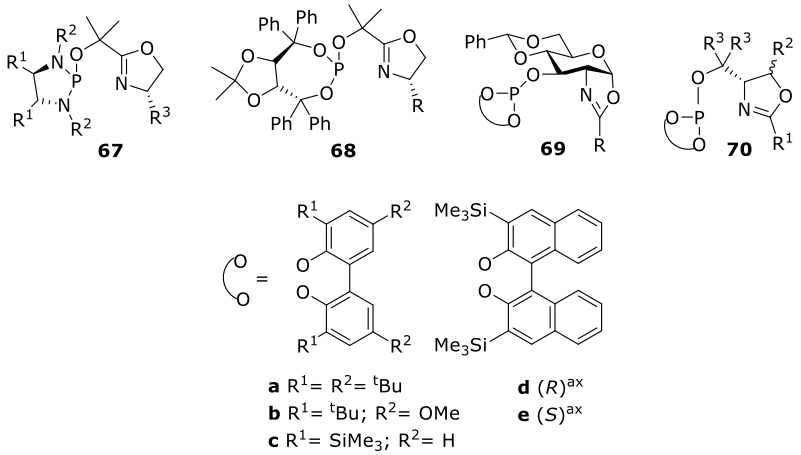


Figure 1.16. Most relevant phosphoroamidite/phosphite-oxazoline ligands.

Biaryl phosphite-oxazoline ligands **70** (Figure 1.16, R^1= Ph, 4-Me-C_6H_4, 4-CF_3-C_6H_4; R^2= H, Me and R^3= H, Me), which are based on privileged phosphinite-oxazoline ligands **64**, have been successfully applied in the hydrogenation of a range of *E*- and *Z*-trisubstituted olefins, 1,1'-disubstituted alkenes, and alkenes containing a neighboring polar group (ee's up to >99%).[104a,104c] These results clearly indicated that introducing a biaryl-phosphite moiety in the ligand design was highly advantageous in terms of catalytic activity and substrate versatility.

1.1.2.2.2. Phosphorus-other nitrogen donor ligands

As mentioned above, Ir-complexes containing phosphorus-oxazoline ligands emerged as powerful tools in the asymmetric hydrogenation of minimally functionalized olefins.[91] However, in the recent years, the research has focused on the design of ligands containing more robust group than oxazolines. In this section, a collection of the most representative phosphorus-other nitrogen donor ligands will be presented.

As an alternative to P-oxazoline ligands, pyridine-containing ligands has attracted interest due to the robustness and the easy incorporation of pyridine group. Although these advantages, only few pyridine-containing ligands have provided outstanding results in terms of enantioselectivity and substrate versatility.

In this respect, Knochel *et al*. designed and applied phosphine-pyridine ligands **71** which mimic the coordination sphere of Crabtree's catalyst (Figure 1.17, R^1= Ph, Cy; R^2= H, Ph, CH-CH=CH-CH and R^3= H, CH-CH=CH-CH). With ligands **71**, they obtained moderate-to-high enantioselectivities in the reduction of *E*-stilbenes derivatives (ee's up to 96%).[122]

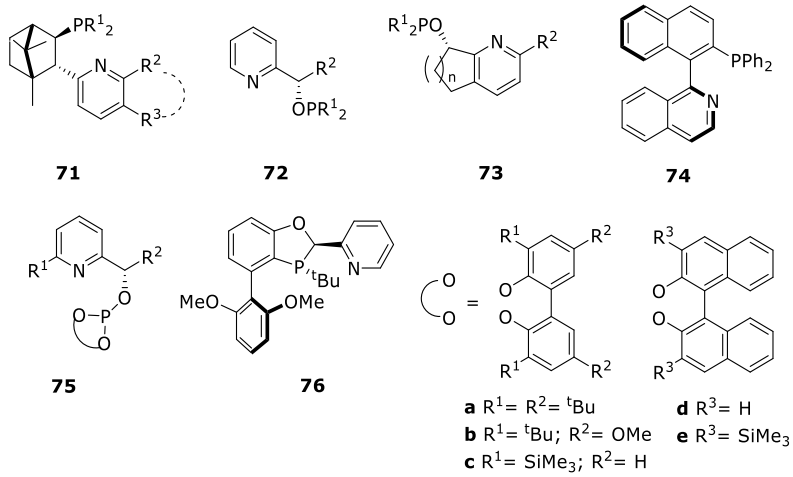


Figure 1.17. Most relevant phosphorus-pyridine ligands.

Then, Pfaltz *et al.* developed the first generation of phosphinite-pyridine ligands **72** (Figure 1.17, R^1= Ph, *o*-Tol, Cy, ^{t}Bu and R^2= Me, ^{t}Bu, Ph, CPh_3), which was successfully used in a limited range of alkenes.[123] In order to increase the rigidity in the alkyl bridge moiety ligands **73** were developed (Figure 1.16, R^1= Ph, *o*-Tol, Cy, ^{t}Bu; R^2= H, Ph, Me and R^3= H, Me).[124] This ligand family with high rigidity in the alkyl bridge moiety demonstrated its high efficiency in the hydrogenation of several kinds of trisubstituted olefins, including purely alkyl trisubstituted alkenes, furans, and benzofurans as well as trisubstituted pinacol derivates, α,β-unsaturated lactones, and N-protected indoles.[119g,124-125]

In 2007, Li *et al*. developed phosphine-quinoline ligands **74** with axial chirality (Figure 1.17).[126] These ligands provided satisfactory results in the hydrogenation of trisubstituted olefins (ee's up to 95% for both *E*-and *Z*-isomers).

Later, our group reported a modular library of readily available phosphite-pyridine ligands **75** (Figure 1.17, R^1= H, Me, Br, Ph and R^2= Me, ^{t}Bu, Ph).[104e] Ligands **75** showed higher substrate versatility than related phosphinite-based ligands **72**. Excellent enantioselectivities (ee's up to 99%) were therefore obtained in a wide range of *E*- and *Z*-trisubstituted alkenes, including more demanding triarylsubstituted olefins and dihydronaphthalenes. Moreover, this phosphite-pyridine family extends its good performance to the very challenging class of terminal disubstituted olefins and to alkenes containing neighboring polar groups.

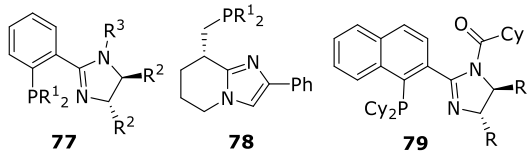
Recently, Qu *et al*. developed a P*-stereogenic phosphine-pyridine ligand **76** (Figure 1.17). This ligand was applied in the hydrogenation of tri- and tetrasubstituted olefins, providing full conversions and promising enantioselectivities (ee's up to 90% and 80%, respectively).[127]

Another interesting change in the nitrogen donor group is the replacement of the oxazoline by imidazole, oxazole, thiazole or thiazoline groups.

In this sense, Pfaltz *et al*. reported the first application of phosphine-imidazole ligands **77** (Figure 1.18, R^1= Ph, *o*-Tol; R^2= ^{i}Pr, ^{t}Bu and R^3= ^{i}Pr, ^{t}Bu, Cy, Ph, Bn, *p*-Tol).[101c] Ligands **77** provided better enantioselectivities in the hydrogenation of *Z*-trisubstituted olefins (ee's up to 88%) than PHOX ligands (ee's up to 42%).

Afterwards, Andersson *et al*. developed phosphine-imidazole ligands **78** (Figure 1.18, R= Ph, *o*-Tol, 3,5-Me_2-C_6H_3) which provide enantioselectivities up to 98% ee in the reduction of unfunctionalized olefins.[128] Interestingly, these Ir-catalyst precursors have also been applied in the hydrogenation of di- and trisubstituted cycloalkenes with high enantioselectivities.[129]

Busacca *et al*. developed phosphine-imidazole ligands **79** (Figure 1.18, R= Ph, 3,5-Me_2-C_6H_3) which could hydrogenate two tetrasubstituted cyclic substrates with ee's up to 96% at low catalyst loading.[130] However, low temperature (0 °C) was required and the preparation of the 1,8-disubstituted naphthalene core of the ligand is not straightforward.



77 **78** **79**

Figure 1.18. Phosphine-imidazole ligands **77**-**79**.

Regarding the oxazole/thiazole-containing ligands, Andersson *et al*. developed phosphine-oxazole ligands **80** (Figure 1.19, R= Ph, *o*-Tol, 3,5-Me_2-C_6H_3)[131] and phosphine-thiazole ligands **81** (Figure 1.19, R^1= Ph, *o*-Tol and R^2= H, Ph)[132]. Both families of ligands provided high enantioselectivities in the hydrogenation of both *E*- and *Z*-aryl/alkyl trisubstituted olefins becoming valuables ligands in the hydrogenation of minimally functionalized olefins. Ligands **81** have also proved to be optimal for the hydrogenation of cyclic alkenes, dienes, and 1,1'-diaryl trisubstituted olefins.

Also, Andersson *et al*. developed aminophosphine-thiazole ligands **82**[133] (Figure 1.19) and **83**[134] (Figure 1.19, R^1= Ph, *o*-Tol and R^2= Me, ^{t}Bu, Ph). Ir-catalyst precursors with ligands **82** allowed to expand the substrate versatility of the catalytic system providing high enantioselectivities in the reduction of fluorinated olefins, diphenylphosphine oxides and vinyl phosphonates. Ligands **83**, with a rigid bicyclic backbone, allows achieving high enantioselectivities in the reduction of *E*-trisubstituted

olefins (ee's up to 97%) but enantioselectivities for *Z*-olefins decreased to 83% ee. Moreover, this ligand library **83** provided excellent enantioselectivities in the hydrogenation of vinyl boronates and in the reduction of vinylic, allylic and homoallylic sulfones.[134]

In 2010, our group in collaboration with Andersson's group reported a library of phosphite-oxazole/thiazole ligands -**84** and **85**- for this process (Figure 1.19, **84**; R= Ph, 4-CH_3-C_6H_4, 4-CF_3-C_6H_4, ^{t}Bu and **85**; R= H, Me).[104d] Enantioselectivities were excellent (ee's up to 99%) for a wide range of *E*- and *Z*-trisubstituted and 1,1'-disubstituted terminal alkenes.

The replacement of oxazoline moiety by other N-donor group than imidazole, oxazole and thiazole is less developed, however some successful examples were reported.

In this context, our group applied phosphite-thiazoline ligand **86** (Figure 1.19) in the reduction of a wide range of *E*- and *Z*-trisubtituted and 1,1'-disubsituted terminal olefins, including examples with neighboring polar groups.[104f] Replacing the oxazoline moiety by a thiazoline group showed to be beneficial in terms of substrate scope due to the high performance of these Ir-catalysts was extended to more challenging *Z*-trisubstituted olefins, α,β-unsaturated ketones, and trifluoromethyl alkenes.

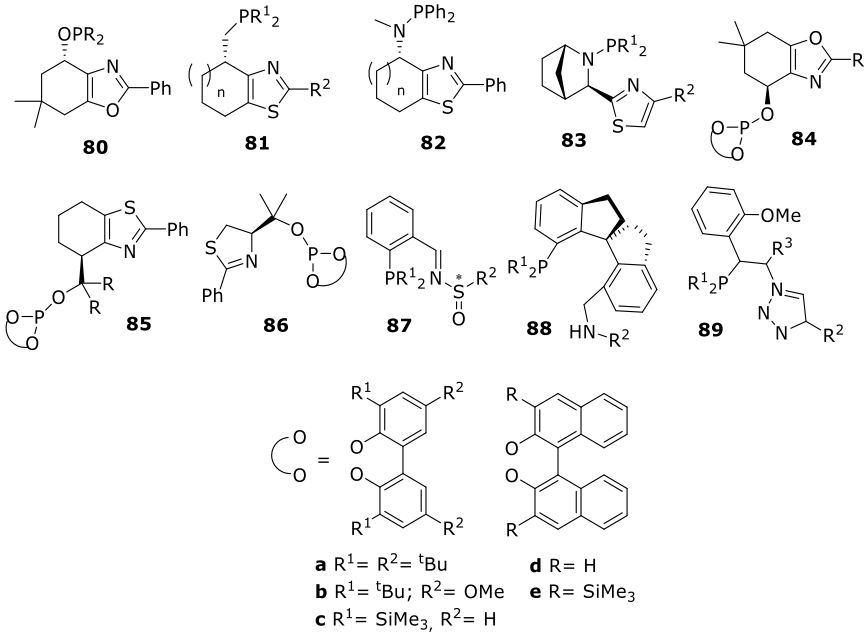


Figure 1.19. Most representative phosphorus-other nitrogen donor ligands.

Ellman *et al*. developed chiral sulfonyl imine ligands **87** (Figure 1.19, R^1= Ph, *o*-Tol, Mes and R^2= ^{t}Bu, 1-Ad, *p*-Tol).[135] These ligands were only able to hydrogenate in high enantioselectivities the standard trisubstituted olefin.

The effect of the replacement of the oxazoline moiety by an amino group was also studied by Zhou *et al*. who modified the spiro ligands **57** (Figure 1.13), leading to ligands **88** (Figure 1.19, R^1= Ph, 3,5-^{t}Bu$_2$-C_6H_3 and R^2= H, Me).[136] Ligands **88** have been successfully applied in the reduction of a wide range α-substituted acrylic acids where secondary amines allows to achieve higher enantioselectivities than primary amines.

Another interesting change of the N-donor groups is the introduction of a triazole moiety instead of a oxazoline group. In this respect, Reek *et al*. applied ligands **89** (Figure 1.19, R^1= Ph, ^{i}Pr; R^2= Ph, Bn and R^3= Ph, *p*-MeO-C_6H_4, 2-Naph) in the Ir-catalyzed hydrogenation of di-, tri-, and tetrasubstituted olefins with moderate-to-good enantioselectivities.[137]

1.1.2.2.3. Phosphorus-thioether ligands

Despite the large amount of Ir-complexes with chiral P,N-ligands developed for the asymmetric hydrogenation of minimally functionalized olefins, there are still important substrate classes that give unsatisfactory results with known catalysts. Great efforts have been made to fine tune the ligand parameters in P,N-ligands, however the possibility of changing the nature of the N-donor atom in these heterodonor ligands has not been contemplated until very recently. In this sense, the presence of a thioether moiety in the ligand could be beneficial in terms of enantioselectivity due to when sulfur atom coordinates to the iridium a new stereocenter with a substituent in close proximity to the metal center is generated, strongly shielding one of the faces of the coordination sphere. Compared to the oxazoline moiety, thioether group has an additional advantage due to its robustness.

The first application of phosphorus-thioether ligands were reported by our group who applied phosphine/phosphinite/phosphite-thioether ligands **90** and **91** (Figure 1.20, **90**; R= Ph, Me, ^{i}Pr, ^{t}Bu, 4-Me-C_6H_4, 4-CF_3-C_6H_4, 2,6-Me_2-C_6H_3 and **91**; R= Ph, Me).[102a,102c] The high modularity of these ligands allows to achieve excellent enantioselectivities in a wide range of *E*- and *Z*-trisubstituted olefins. The Ir-catalysts containing ligands **90** and **91** also successfully hydrogenated a broad range of substrates containing neighboring polar groups such as allylic alcohols, acetates, α,β-unsaturated esters, and vinylboronates. Moreover, they provided high enantioselectivities in the reduction of more challenging terminal disubstituted aryl/alkyl olefins. Remarkably, for this latter class of substrates, both enantiomers of the hydrogenated product could be obtained by simply changing the configuration of the biaryl phosphite moiety.

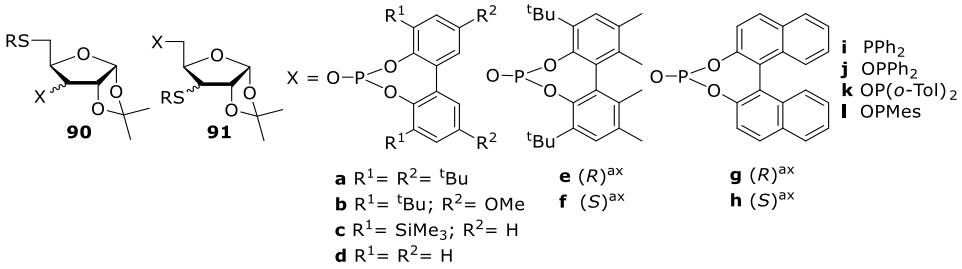


Figure 1.20. Phosphine/phosphinite/phosphite-thioether ligands **90** and **91**.

More recently, our group in collaboration with Pericàs's group reported the application of novel phosphinite/phosphite-thioether ligands **92** in the Ir-catalyzed hydrogenation of minimally functionalized olefins (Figure 1.21, R^1= Ph, 2-Naph, 1-Naph, ^{t}Bu, Ad, 2,6-Me_2-C_6H_3 and R^2= Me, CPh_3, Bn).[102b] The modular ligand design was crucial in finding highly selective catalysts for each substrate. Excellent enantioselectivities (ee's up to 99 %) were obtained for a wide range of substrates, including *E*- and *Z*-trisubstituted and disubstituted olefins, α,β-unsaturated enones, tri- and disubstituted alkenylboronic esters, and olefins with trifluoromethyl substituents.

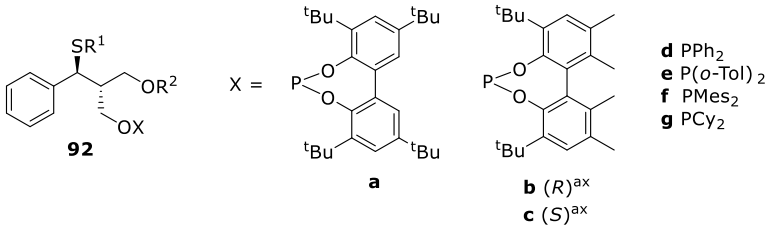


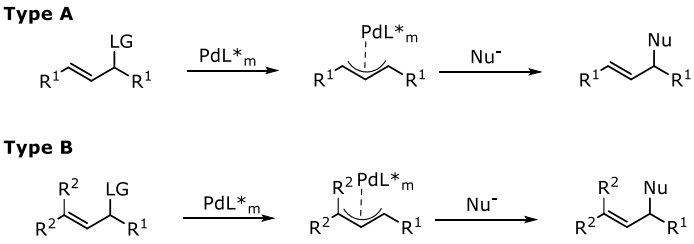
Figure 1.21. Phosphinite/phosphite-thioether ligands **92**.

1.2. Asymmetric Pd-allylic substitution reactions

One of the most important challenges in organic synthesis is the formation of stereoselective C-C, C-N, and C-O bonds. Due to its mild reaction conditions, its tolerance to a wide range of functional groups and the often high level of asymmetric induction achieved, Pd-catalyzed asymmetric allylic substitution has proved to be an efficient synthetic strategy for the synthesis of optically active compounds.[1,138]

This process consists in the attack of a nucleophile (Nu; typically, a carbon or a nitrogen nucleophile) to an allylic racemic substrate which contains a leaving group (LG; normally a malonate or acetate). Scheme 1.6 shows two important classes of asymmetric allylic substitution depending on the type of substrate used. When symmetric substrates (linear or cyclic) is employed (**Type A**), the reaction proceeds via a symmetrical π-allyl intermediate. In this case, the enantioselectivity is determined by the regioselectivity of the nucleophilic attack, and therefore depends on the ability of

the chiral ligand to differentiate between the two allylic termini.[138] On the other hand, when racemic or prochiral substrate with two identical substituents at one of the allyl termini (**Type B**) is used, it reacts via the π-allyl intermediate which can isomerize via well-established π-σ-π-mechanism.[138] In this case, enantioselection can occur either in the ionization step, leading to the allyl intermediate, or in the nucleophilic addition. For these latter substrates, not only the enantioselectivity of the process need to be controlled, but also the regioselectivity is a problem because a mixture of regioisomers may be obtained.[138]



Scheme 1.6. Asymmetric allylic substitution reaction with two different type of substrates.

The range of allylic substrates tested in this reaction (linear or cyclic) is quite wide (Figure 1.22). Among them, 1,3-diphenylprop-2-enyl acetate (Figure 1.22) is widely used as a benchmark substrate for testing the new catalytic systems. For this process the most widely used catalysts are palladium complexes. Most Pd-catalysts developed to date favor the nucleophilic attack towards the less substituted carbon, attaining the linear product. However, a variety of other transition metal complexes derived from Ni, Ru, Ir, Mo, W and other elements are known to catalyze allylic substitution and some of them provide very high selectivity towards the attack at the most substituted carbon, giving the desired branched product.[1,138] In this context, the synthesis of highly regio- and enantioselective Pd-catalysts is still a challenge.

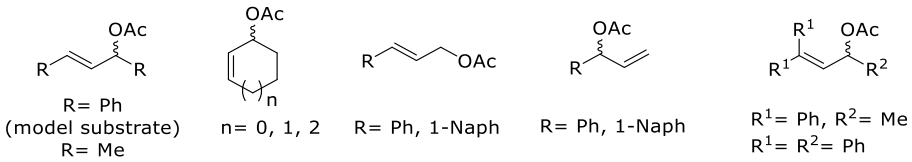


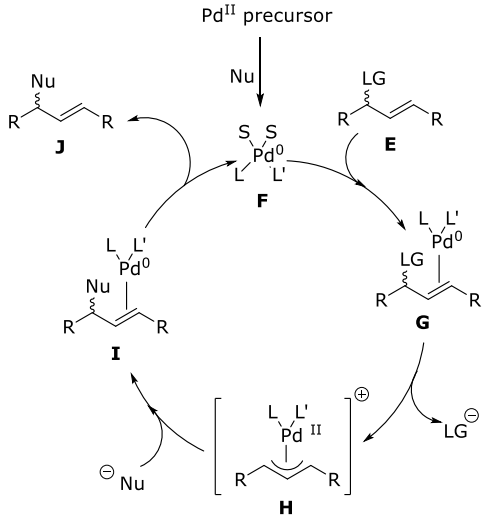
Figure 1.22. The most common substrates used in the enantioselective allylic substitution.

Regarding the nucleophiles, dimethyl malonate has become the standard nucleophile for testing processes. However, many other carbon-stabilized nucleophiles bearing carbonyl, sulfone, nitrile, or nitro groups have been also used.[138] There are only few examples of enantioselective reactions with non-stabilized carbon-nucleophiles such as diorganozinc or Grignard reagents.[139] Amination and etherification have been also studied. While several amines such as primary and secondary alkyl amines, aryl amines,

or nitrogen heterocycles have been extensively employed as nucleophiles (being benzylamine the model N-nucleophile).[138d,138j] Pd-catalyzed allylic etherification has only been efficiently performed in the presence of benzylic alcohols. Aliphatic alcohols have found to be poor nucleophiles for this reaction. Therefore, Pd-catalyzed asymmetric etherification is still a challenge.[138l]

1.2.1. The mechanism

During the last decades, the catalytic cycle for Pd-catalyzed asymmetric allylic substitution with stabilized nucleophiles has been widely studied. The established mechanism involves four steps (Scheme 1.7).[138] The first step is the coordination of the allylic substrate **E** to the catalytic active specie **F**, which enters to the cycle at the Pd(0) oxidation level. Both Pd(II) and Pd(0) can be used as catalyst precursors due to Pd(II) will be reduced *in situ* by the nucleophile to Pd(0). The most widely used catalyst precursors are $Pd_2dba_3{\cdot}CHCl_3$ (dba= dibenzylidenacetone), $Pd(OAc)_2$ and $[Pd(\eta\text{-}C_3H_5)(\mu\text{-}Cl)]_2$. Then, the cycle continues with the oxidative addition of complex **G** to form the π-allyl intermediate **H**. The next step is the nucleophilic attack, the product of the oxidative addition has two positions which are susceptible to nucleophilic attack (two terminal carbons of the allyl system). After the nucleophilic attack, an unstable Pd(0) olefin complex **I** is produced, which rapidly undergoes dissociation, releasing product **J**.



L,L'= mono- or bidentate ligand; S= solvent or vacant; LG= leaving group; Nu= nucleophile

Scheme 1.7. Accepted mechanism for Pd-catalyzed asymmetric allylic substitutions.

For this process, the rate-determining step can be either the oxidative addition or the nucleophilic attack, since both pathways are close in energy. It is known that in the case of benchmark substrate (Figure 1.22), which forms the more stable Pd-π-allyl

complex upon oxidative addition, the nucleophilic attack is the rate determining step of the process.[138]

Concerning to the enantiocontrol of the reaction, it is accepted that the enantioselectivity is controled by the out-sphere nucleophilic attack on the most electrophilic allylic terminal carbon of the π-allyl intermediate **H**. This itermediate, which plays an important role in the catalytic cycle, can be isolated in absence of nucleophile and it can show a dynamic behavior in solution, which leads in a mixture of isomers (Figure 1.23). Among the best known processes, the η^3-η^1-η^3 isomeritzation leads to the *syn*/*anti* interconversion and the apparent "allyl rotation" leads to an *endo*/*exo* isomeritzation. The palladium-allyl exchange results in an inversion of the configuration on all three allyl carbon, however this process is usually slow compared to the other mechanisms.[138]

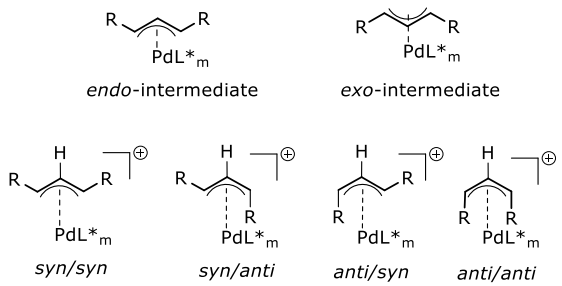
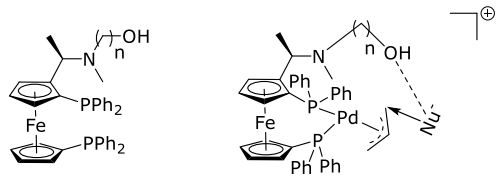


Figure 1.23. Possible isomers adopted by π-allyl palladium complex **H**.

If we assume that the reactions rates are similar for all possible isomers, a single isomer needs to be formed to achieve high enantioselectivities. Both oxidative addition and nucleophilic attack take place stereoselectivily with inversion of congifuration. In that case, if the intermediate **H** does not undergo any isomeritzation that changes its configuration, the overall process proceeds with the retention of configuration; for instance, the nucleophile is introduced on the same side of the allyl plane that was occupied by the leaving group (LG).[138]

1.2.2. Ligands

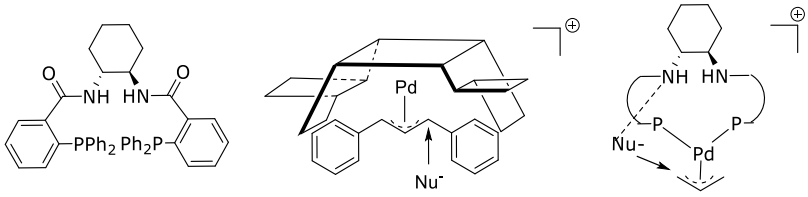
Most of the successful ligands reported to date for this process have been designed using three main strategies. The first one, developed by Hayashi, Ito, *et al*., was based on the use of secondary ligand-nucleophile interaction. They designed ligand **93** with a side chain which is able to direct the approach of the nucleophile to one of the allylic terminal carbon atoms, providing high levels of enantioinduction (Figure 1.24).[140]



93

Figure 1.24. Ferrocene-base phosphine ligand **93**.

The second strategy consists in increase the ligand's bite angle in order to create a chiral pocket between the metal center and the chiral ligand, where the π-allyl complex is perfectly embedded. The enantioselectivity obtained is high due to the differentiation of both allyl termini due to steric hindrance. An example of this strategy is the diphosphine ligand **94** developed by Trost *et al*. (Figure 1.25). This idea paved the way for the successful application of ligands with large bite angles for the allylic substitution of sterically undemanding substrates.[141] Despite historically this rationalization has being generally accepted, in 2009, Norrby in collaboration with Lloyd-Jones reported a DFT calculation analysis which determined that the 13-memebered ring of Pd-**94** not only make a perfect chiral pocket for embedding the substrate but also a secondary interaction which directs the nucleophilic attack (Figure 1.25) as in the case of ligand **93**.[142] This interaction is based on an H-bonding interaction between the enolate oxygen of the dimethyl malonate and the amide group of the ligand backbone and guided the enolate carbon to the proximal (pro-(*S*)) terminus of the η^3-carbon of the allyl with a perfect selectivity. Therefore, the enantiocontrol obtained with Trost's ligand (**94**) would be also consequence of an interaction between the nucleophile and the ligand, as in the case of Hayashi's ligand (**93**), and not just because of the chiral cavity provided by the ligand scaffold.



94

Figure 1.25. Chiral pocket and secondary interactions of Trost ligand **94**.

The last strategy consists on the use of heterodonor ligands, which create an electronic differentiation between both allylic carbon terminal atoms due to the different *trans* influences of the donor groups (Figure 1.26). The first ligand based on this strategy was the phosphine-oxazoline PHOX (Figure 1.26, R= Me, Ph, ^{i}Pr, ^{t}Bu) ligand developed by the groups of Helmchen, Pfaltz and Williams.[143]

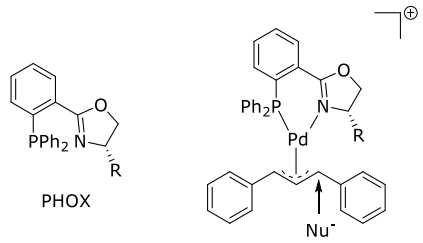


Figure 1.26. PHOX ligand, an example of electronic differentiation ligand.

Unfortunately, this pioneering ligand only provided high enantioselectivities (ee's up to 99%) when model substrate 1,3-diphenylprop-2-enyl acetate was used. When less sterically hindered linear or cyclic substrates were studied, enantioselectivities decreased up to 71% ee or to racemic mixtures. After this work, a wide range of heterodonor ligands have been successfully applied in allylic substitution.[1,138a-k] Among them, P,N-ligands have been the most widely used, however other mixed bidentate donor ligands, such as P,S-[144] and P,P'-[31b,32a,32c] ligands, are emerging as alternative to P,N-based ligands.

More recently, our group found that the use of biaryl phosphite-containing heterodonor ligands is highly advantageous by overcoming the most common limitations of this catalytic process, which are low reaction rates, high substrate specificity and low nucleophile scope.[145] Introducing a biaryl phosphite in the ligand design was beneficial because of its large π-acceptor ability, which increase the reaction rates, and because of its flexibility that allows the catalyst chiral pocket to adapt to both hindered and unhindered substrates. Moreover, the presence of biaryl phosphite moiety increase the regioselectivity to the branched isomer when more challenging monosubstituted substrates were used, thanks to its π-acceptor ability and bulkiness, phosphite moiety increase the density of the most substituted allylic terminal carbon atom via *trans* influence, favoring the nucleophilic attack to this carbon.[145]

In the following sections, we collected the most successful P,N-, P,S- and P,P'-ligands for this process.

1.2.2.1. Phosphorus-nitrogen ligands

Inspired by the early work of the groups of Pfaltz, Helmchen and Williams, several modifications of that PHOX ligands have been made: replacing the phosphine moiety by more electronically deficient phosphinite or phosphite and also replacing oxazoline by other sp^2- and sp^3-nitrogen donor groups. Among phosphorus-sp^2-nitrogen ligands, phosphorus-oxazoline and phosphorus-imine have been the most studied in this process. In the next sections, the most important phosphorus-sp^2- and sp^3-nitrogen donor ligands will be presented.

1.2.2.1.1. Phosphorus-oxazoline ligands

Phosphine-oxazoline ligands

The first modification was reported by Kunz *et al*. in 1998. They developed phosphine-oxazoline ligand **95** (Figure 1.27) derived from *D*-glucosamine. Good to high enantioselectivities were obtained with the benchmark substrate (ee's up to 98%) and trisubstituted substrates (ee's up to 88%), however only moderate enantioselectivities were achieved for unhindered linear and cyclic substrates (ee's up to 69%).[146]

Then, Moyano *et al*. introduced a ferrocenyl substituent in the oxazoline moiety of PHOX ligand, developing ligand **96** (Figure 1.27).[147] The enantioselectivities obtained with ligand **96** were comparable to those obtained with PHOX ligands, but the activity of Pd-**96** complexes were much lower.

Moberg *et al*. reported the application of ligand **97** in which they introduced an additional stereogenic center on the oxazoline ring (Figure 1.27, R^1= Me, Ph and R^2= H, Me).[148] This modification provide higher enantioselectivities in the allylic substitution of cyclic substrates than the PHOX ligands, but still low (ee's up to 59%).

In 2005, Zhang *et al.* developed the conformationally rigid ligand **52** (Figure 1.27) which provided excellent results in terms of enantioselectivity for hindered model substrate (ee's up to 98%), but low enantioselectivities for cyclic substrates (ee's up to 36%).[149]

The effect of replacing the oxazoline ring by oxazine moiety was studied by Zehnder *et al.* with the development of ligand **98** (Figure 1.27). The results with the benchmark substrate were comparable to those obtained with PHOX ligands but activities were much lower.[150]

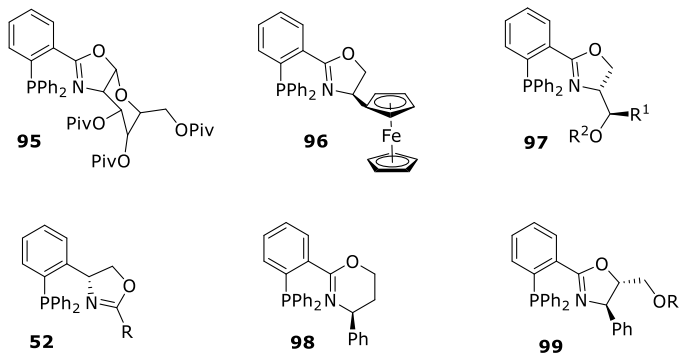


Figure 1.27. Most representative phosphine oxazoline-ligands with modifications in the oxazoline ring.

Later, Pericàs, Vidal-Ferran *et al*. synthesized ligand **99** with two stereocenters in the oxazoline moiety (Figure 1.27, R= Me, Bn, $CHPh_2$, CPh_3, CH_2CH_2OMe).[151] These ligands provide excellent results in the Pd-allylic substitution of the benchmark 1,3-

diphenylprop-2-enyl acetate (ee's up to 97%), trisubstituted substrates (ee's up to 94%), as well as for monosubstituted substrates (regio's up to 93% towards branched isomer and ee's up to 82%). However, for less sterically hindered substrates and cyclic substrates lower enantioselectivities were obtained (ee's up to 43% and 56%, respectively).

Apart from modifying oxazoline ring of PHOX-type ligands, the modification of the ligand backbone has also been studied (Figure 1.28). In this sense, Tietze *et al*. reported the replacement of the benzene ring by a benzothiophene or benzofuran moiety with ligands **100** (Figure 1.28, X= S, O).[152] Unfortunately, these modifications provided lower enantioselectivities than PHOX ligands. Ongoing this work, Iamamoto *et al*. reported ligand **101** in which they replaced the benzene ring by a methylene bridge and also introduced a stereogenic phosphine in the ligand design (Figure 1.28, R^1= Cy, ^{t}Bu, Ph, 1-Ad, CpFeCp; R^2= Me, Cy; R^3= H, Me and R^4= H, Me, ^{i}Pr, ^{t}Bu).[153] These modifications had a negative effect on both activity and enantioselectivity.

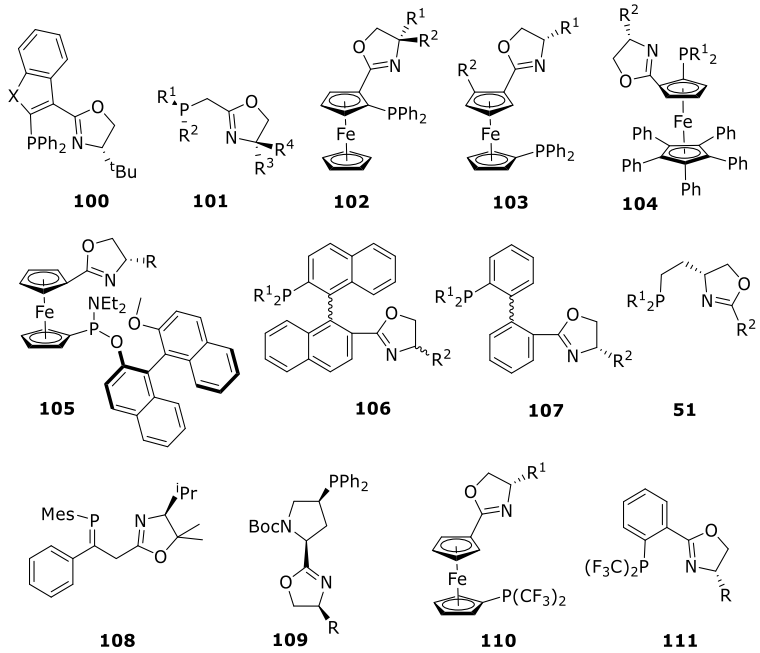


Figure 1.28. Most representative phosphine oxazoline-ligands with modifications in the ligand backbone.

The next modification was the introduction of a ferrocene moiety in the ligand backbone. In this context, ligands **102** (Figure 1.28, R^1= H, Me, Bn and R^2= H, Me, ^{t}Bu, Bn) were developed and successfully applied in the allylic alkylation of model 1,3-diphenylprop-2-acetate substrate (ee's up to 99%).[154] In these ferrocene-based ligands, the effect of varying the positions of the phosphine moiety was also studied with ligands **103** (Figure 1.28, R^1= ^{i}Pr, ^{t}Bu and R^2= H, Me, Bn, $SiMe_3$).[155] Results were similar to

those obtained with ligands **103**. The results indicated that the planar chirality was decisive to control both absolute configuration of the product and enantioselectivity.

Remarkably, ferrocenyl-based phosphine-oxazoline ligand **104** (Figure 1.28) has been applied in the allylic alkylation of cyclic substrates with high enantioselectivities (ee's up to 91%).[156]

Following with ferrocenyl-based ligands, Dai *et al.* synthesized ferrocene phosphine-oxazoline ligands **105** (Figure 1.28, R= ^{i}Pr, Bn, Ph, ^{t}Bu).[157] Excellent enantioselectivities were obtained in the allylic alkylation and amination of monosubstituted substrates (regio's up to 99% towards branched product and ee's up to 97%)

Next, the groups of Ikeda and Pregosin reported the development of ligands **106** (Figure 1.28, R^1= Ph, 3,5-Me_2-C_6H_3 and R^2= ^{i}Pr, ^{t}Bu) which introduce an enantiomerically pure binaphthyl moiety.[158] This modification provided lower enantioselectivities than PHOX ligands and the configuration of the final product was determined by the configuration of the binaphthyl moiety. Following a similar trend, Zhang *et al*. developed phosphine-oxazoline ligand **107** with an axial-unfixed biphenyl backbone (Figure 1.28).[159] When this ligand was coordinated to Pd, only (*S*)-conformer was formed but high enantioselectivity (ee's up to 92%) was only achieved using the standard substrate and dimethylmalonate as nucleophile.

Burguess *et al*. reported the application of ligands **51** that contains an alkyl chain in the ligand backbone which was bonded to carbon 4 of the oxazoline moiety (Figure 1.28, R^1= Ph, *o*-Tol and R^2= Me, ^{t}Bu, 1-Ad, CPh_3).[160] This kind of ligands provided excellent enantioselectivities for the benchmark substrate 1,3-diphenylprop-2-enyl acetate (ee's up to 98%) and moderate enantioselectivities for cyclic substrates (ee's up to 79%).

Another modification was carried out by Gates *et al*. who reported the application of phosphaalkene-oxazoline ligand **108** (Figure 1.28) in the allylic alkylation of the standard substrate using a wide range of nucleophiles with enantioselectivities up to 92%.[161] The enantiopure products obtained were derivatized to cycloalkanes and other synthetically interesting products without losing enantioselectivity.

Giberston *et al*. reported a series of proline-based phosphine-oxazoline ligands **109** (Figure 1.28, R= Ph, ^{i}Pr, ^{t}Bu, Bn).[162] Ligands **109** have been applied in the allylic alkylation of unhindered cyclic substrates. The catalytic results showed that the enantioselectivities increased when reducing the size of the cyclic substrate.

The last modification in the ligand design in this kind of ligands was the replacement of the arylphosphine by a bistrifluorophenyl phosphine. These fluorinated phosphines with a more π-acceptor character were designed for monosubstituted substrates with the aim of favoring the branched substitution. In this respect, You *et al*. synthetized ferrocene-based ligands **110** (Figure 1.28, R= ^{i}Pr, Bn, Ph, ^{t}Bu) that provided excellent regio- (up to 99%) and enantioselectivities (up to 92% ee) for monosubstituted substrates.[163] Also, Shen *et al*. designed ligands **111** (Figure 1.28, R= ^{t}Bu, Ph, Bn, ^{i}Pr),

an electronic modification of PHOX ligand, which provide similar results in terms of regio- and enantioselectivity for monosubstituted substrates than **110**.[164]

Phosphinite-oxazoline ligands

Despite phosphinite-oxazoline ligands showed their efficiency in several metal-catalyzed processes, only two families of this kind of ligands have been successfully applied in the asymmetric Pd-catalyzed allylic alkylation (Figure 1.29).

112 **64**

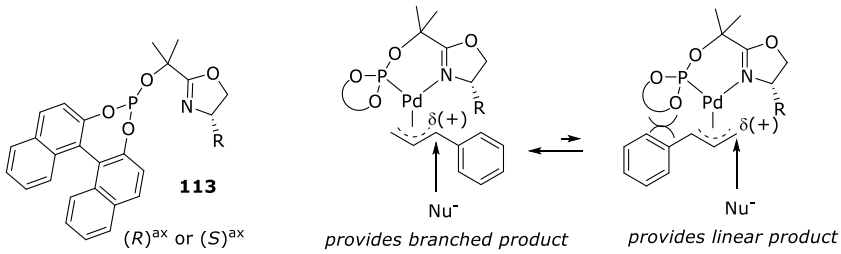
Figure 1.29. Phosphinite-oxazoline ligands **112** and **64**.

The first family of phosphinite-oxazoline ligands have been reported by Uemura *et al*. in 1999. They synthetized phosphinite-oxazoline ligands **112** with pyranoside backbone (Figure 1.29, R= Me, ^{i}Pr, ^{t}Bu, Ph, Bn).[165] These ligands provided high enantioselectivities for the model substrate (ee's up to 96%), but only moderate for unhindered linear and cyclic substrates (ee's up to 74%).

The second family of ligands was phosphinite-oxazoline ligands **64** applied by Richards *et al.* (Figure 1.29, R^1= Ph, *o*-Tol, Cy; R^2= ^{t}Bu, Ph, Ferrocenyl, 2-Naph; R_3= H, Me and R_4= Me, ^{i}Pr, ^{t}Bu, Bn).[166] Ligands **64** provided enantioselectivities up to 96% ee for the benchmark substrate 1,3-dipenylprop-2-enyl acetate.

Phosphite-oxazoline ligands

As previously mentioned, the introduction of phosphite moiety in the ligand design showed to be beneficial in this process. In 1997, Pfaltz *et al*. reported the first successful application of phosphite-oxazoline ligands **113** in the Pd-allylic alkylation (Figure 1.30, R= ^{i}Pr, ^{t}Bu, Ph).[167] These ligands provided high regio- and enantioselectivities in monosubstituted linear substrates (regio's up to 95% towards the branched products and ee's up to 94%).



113

$(R)^{ax}$ or $(S)^{ax}$ *provides branched product* *provides linear product*

Figure 1.30. Phosphite-oxazoline **113** and its effect on regioselectivity.

The authors found that regio- and enantioselectivities were affected by the substituents on the oxazoline moiety and by the substituents and configuration of biaryl phosphite group. Moreover, they attributed the excellent results obtained with monosubstituted substrates to the combination of two ligand parameters that direct the nucleophilic attack to the most substituted allyl carbon (Figure 1.30). The first one is the π-acceptor ability of the phosphite moiety, which decreases the electron density of the allylic terminal carbon atom via *trans* influence, making the electrondensity difference between both allylic terminal atoms. The second one is the introduction of a bulky biaryl-phosphite moiety which switches the equilibrium towards the desired Pd-π-allyl intermediate, which has the bulky substituents of the allyl substrate in the opposite side of the phosphite moiety, favoring nucleophilic attack to the most substituted carbon *trans* to the phosphite moiety (Figure 1.30).

The same authors also developed TADDOL-phosphite-oxazoline ligands **114** (Figure 1.31, R= ^{i}Pr, ^{t}Bu, Ph).[121b] They obtained similar results whether using ligands **113**. High regio- and enantioselectivities were obtained for monosubstituted substrates (regio's uo to >99% and ee's up to 99%) but low enantioselectivities for the benchmark substrate 1,3-diphenylprop-2-enyl acetate and unhindered linear substrates (ee's up to 56%).

On the other hand, Gladiali *et al*. reported the application of chiral (*S*)-binaphthalene-based phosphine-oxazoline ligands **115** (Figure 1.31).[168] Unfortunately, moderate enantioselectivities were achieved using the model substrate (ee's up to 43%).

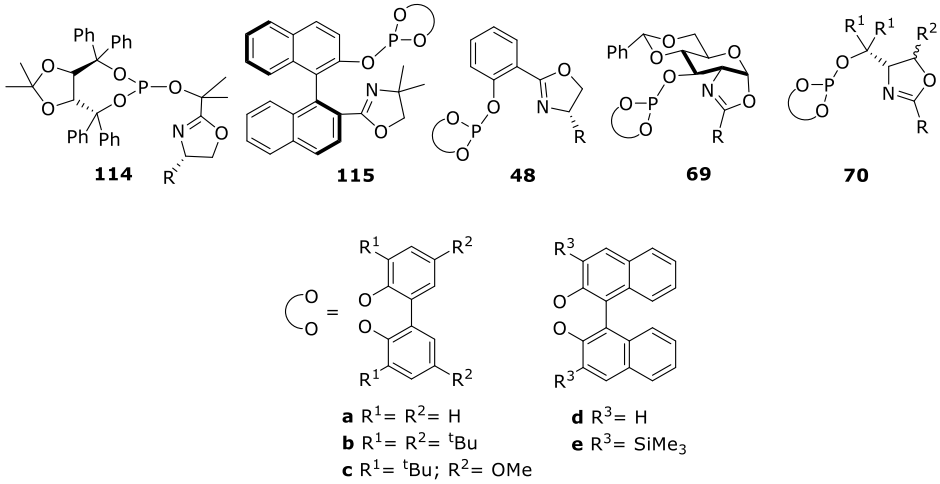


Figure 1.31. Phosphite-oxazoline ligands applied in Pd-catalyzed allylic alkylation.

Later, our group developed phosphite-oxazoline ligands **48**, which are analogous of phosphine-oxazoline ligands (PHOX) (Figure 1.31, R= Et, ^{i}Pr, Ph, ^{t}Bu).[169] The simply replacement of the phosphine moiety by a cheap and simple biphenyl phosphite group showed high activities. Moreover, ligands **48** provide high versatility, thus excellent enantioselectivities have been obtained for the hindered benchmark substrate (ee's up

to >99%), for unhindered linear disubstituted substrates (ee's up to 93%), for cyclic substrates (ee's up to 99%) and monosubstituted substrates (regio's up to 99% and ee's up to 92%). After these significant results, more phosphite-oxazoline ligands libraries have been developed.

The same authors applied pyranoside phosphite-oxazoline **69** (Figure 1.31, R= Me, ^{i}Pr, ^{t}Bu, Ph, Bn)[170] a modification of Uemura's phosphinite-oxazoline ligands **112** (Figure 1.31). Again, the replacement of the phosphinite by a phosphite moiety provided higher enantioselectivities not only for the standard substrate (ee's up to 99%), but also for unhindered linear (ee's up to 81%) and cyclic substrates (ee's up to 95%, respectively). High regio- and enantioselectivities were also achieved in monosubstituted substrates (80% regioselectivity and 90% ee).

They also reported the application of ligands **70** (Figure 1.31, R^1= ^{t}Bu, Ph, *o*-Tol, *p*-Tol, 2,6-Me_2-C_6H_3 and R^2= H, Me, Ph)[171], analogous of phosphinite-oxazoline ligands **64** (Figure 1.29). Ligands **70** provided excellent regio- and enantioselectivities for a wide range of disubstituted (ee's up to 96%), cyclic (ee's up to 83%), and monosubstituted substrates (regio's up to >95% and ee's up to 96%).

1.2.2.1.2. Phosphorus-imine ligands

Although most of P,N-ligands applied in asymmetric Pd-catalyzed allylic substitution contain an oxazoline as nitrogen donor group, heterodonor ligands with imino groups have also played an important role in this process.

Phosphine-imine

The most applied phosphorus-imine ligands are phosphine-imine based ligands. In this respect, Chung *et al*. successfully applied ligand **116** (Figure 1.32, R^1= Me, Ph; R^2= H, Me, Ph and R^3= H, Me) in the Pd-allylic alkylation of the benchmark substrate 1,3-diphenylprop-2-enyl acetate (ee's up to 98%).[172] The same group also developed a manganese derivative ligands **117** (Figure 1.35, R= ^{t}Bu, Ph, Bn, $CHPh_2$)[173] and ferrocene derivatives **118** (Figure 1.32, R^1= Me, Cy, Ph and R^2= H, *p*-OMe, *p*-Cl, *p*-Me, *p*-NO_2, *o*-NO_2)[174]. These ligands provided excellent results, which were comparable to those achieved with ligand **116**. Following this line, Attar *et al*. developed a second generation of ferrocene-imine ligands **119** (Figure 1.32), but they provided lower enantioselectivities than ligands **116**-**118**.[175]

Inspired by these works, van der Eycken *et al*. applied phosphine-imine ligands **120** (Figure 1.32, R= H, *p*-Cl, *p*-Br) in the Pd-catalyzed allylic alkylation.[176] Excellent enantioselectivities were achieved with the model substrate with a wide range of carbon nucleophiles (ee's up to 99%). Moderate-to-high enantioselectivities were achieved with less sterically hindered linear and cyclic substrates (74-90% ee).

Also, Iwao *et al.* reported the synthesis of ferrocenyl-based phosphine-imine ligands **121** (Figure 1.32), and its application in this process, achieving enantioselectivities up to 97% ee for the benchmark substrate 1,3-diphenylprop-2-enyl acetate.[177] Moreover, by DFT calculations they could determine that the *exo*-isomer was more stable than the *endo*-isomer and they could also predict the absolute configuration of the outcome product.

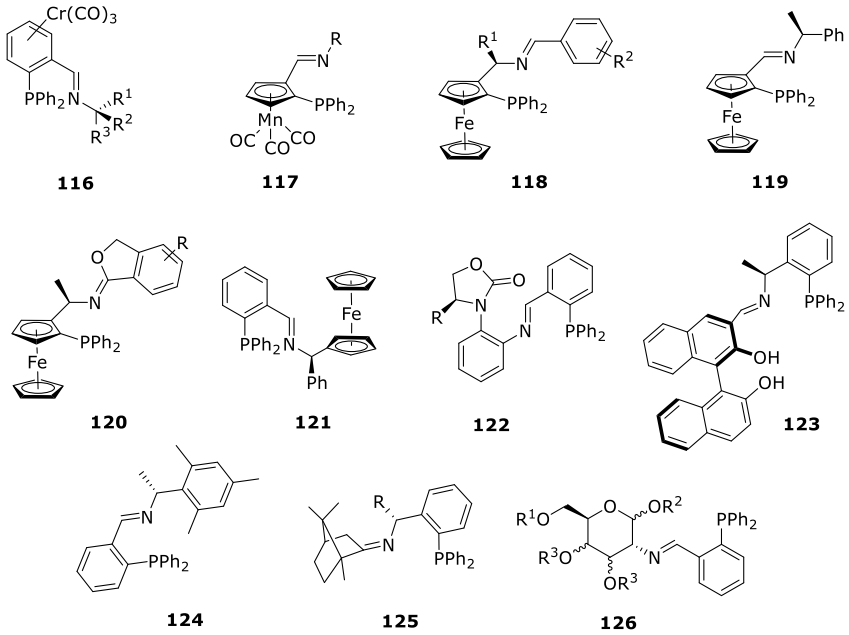


Figure 1.32. Most relevant phosphine-imine ligands.

Later, Jiang *et al*. developed phosphine-imine ligands library **122** (Figure 1.32, R= Ph, ^{i}Pr) which contains an Evans auxiliary as chiral moiety.[178] Ligands **122** provided moderate-to-good enantioselectivities (ee's up to 87%) in the benchmark substrate.

Xu *et al.* applied phosphine-imine ligands **123** (Figure 1.32) with binaphthol as chiral moiety in the enantioselective Pd-catalyzed allylic alkylation of hindered substrates with a broad range of cianoesters, achieving excellent diastereo- and enantioselectivities (99:1 dr and 99% ee).[179]

Another successful example of phosphine-imine ligands is ligand **124** (Figure 1.32) developed by Saigo *et al.*, which provided excellent enantioselectivities in the alkylation of the benchmark substrate with a wide range of α-substituted dimethyl malonates nucleophiles (ee's up to 98%).[180]

Chen, Xu, *et al.* developed a *D*-camphor-based phosphine-imine ligands **125** (Figure 1.32, R= Me, Et).[181] The results showed that the presence of *D*-camphor in combination with a methyl substituent in the ligand backbone was beneficial for the catalyst performance. Excellent enantioselectivities were obtained in the standard substrate and

several modifications of this diphenylated substrate with a broad range of dialkyl malonates and α-substitued dialkyl malonates (ee's up to 99%). These ligands extended their excellent catalytic behavior in the Pd-catalyzed allylic amination with different aryl, benzyl and alkyl amines as nucleophiles. Moreover, ligands **125** provided enantioselectivities up to >99% ee in a wide range of benzyl- and alkylalcohols, providing excellent results for allylic etherification in terms of both enantioselectivities and nucleophile versatility.

Very recently, Zawisza *et al*. reported the application of a family of phosphine-imine ligands **126** based on saccharides (Figure 1.32, R^1= TMS, TBDMS, TBDPS, Ac; R^2= TMS, TBDPS and R^3= TMS, Ac).[182] Ligands **126** provided enantioselectivities up to >99% ee in the Pd-allylic alkylation of the model substrate 1,3-diphenylprop-2-enyl acetate using dimethyl malonate as nucleophile.

Among phosphine-imine ligands, we could also find ligands with hydrazone groups. In this sense, Yamashita, Mino, *et al.* synthetized phosphine-hydrazone ligands **127** (Figure 1.33, R^1= H, Me, Et and R^2= 3-CF_3, 4-CF_3, 4-OMe, 4-Me, 5-CF_3, 5-OMe, 5-Me, 6-CF_3, 6-OMe).[183] These ligands provided excellent enantioselectivities in the allylic alkylation of the model substrate with dimethyl and diethyl malonate (ee's up to 98%), and good enantioselectivities with α-substituted malonates (ee's up to 83%).

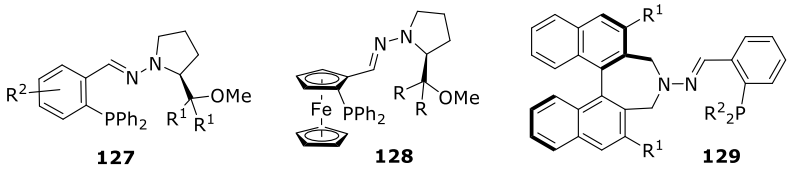


Figure 1.33. Most relevant phosphine-hydrazone ligands.

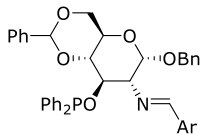
Later, the same authors developed ferrocene-based ligands **128** (Figure 1.33, R= H, Me, Et).[184] Ligands **128** showed their efficiency in the Pd-catalyzed asymmetric allylic alkylation and amination reactions with the benchmark substrate and using dimethyl malonate and benzylamine as nucleophiles (ee's up to 96% and 93%, respectively).

Widhalm *et al.* applied phosphine-hydrazone ligands **129** with a pendant binaphthyl unit as a chiral modifier in the allylic substitution reaction (Figure 1.33, R^1= $SiMe_3$, Cl, I, SPh and R^2= Ph, *m*-An).[185] High enantioselectivities (up to 95% ee) were achieved in the alkylation of the model substrate. However, low enantioselectivities were obtained for cyclic and monosubstituted substrates.

Phosphinite-imine ligands

Only one family of phosphinite-imine ligands have been successfully applied in the Pd-allylic alkylation which have been developed by Zhang *et al*. in 2010. They reported a family of carbohydrate-based phosphinite-imine ligands **130** (Figure 1.34, Ar= Ph, *p*-

Cl, *p*-OMe, *p*-NO_2, *o*-CF_3, *m*-Cl, *m*-NO_2) which provided high enantioselectivities in the Pd-allylic substitution of the benchmark substrate with different carbon and nitrogen nucleophiles (ee's up to 92%).[186]



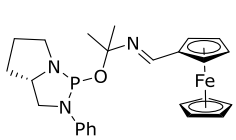
130

Figure 1.34. Phosphinite-imine ligands **130**.

Phosphoroamidite/phosphite-imine ligands

Phosphoroamidite/phosphite-imine ligands have been less developed than their phosphine analogous. There are only two families of this kind of ligands reported which provided good results for this process, both have been developed by Gavrilov *et al*.

In 2005, they reported the application of P-chiral ferrocenyl diaminophosphite-imine ligand **131** (Figure 1.35) in Pd-allylic substitution reaction of the model substrate 1,3-diphenylprop-2-enyl acetate with enantioselectivities up to 98% ee.[187] Later, they applied phosphite-imine ligands **132** (Figure 1.35) in the allylic alkylation of the benchmark substrate with somewhat lower enantioselectivities (up to 94% ee).[188]



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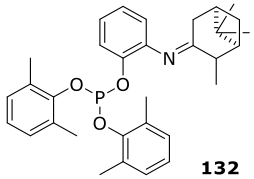


132

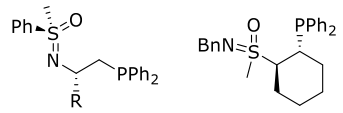
Figure 1.35. Phosphoroamidite/phosphite-imine ligands **131** and **132**.

1.2.2.1.3. Phosphorus-other sp^2-nitrogen ligands

Apart from phosphorus-oxazoline and phosphorus-imine, other phosphorus-sp^2 nitrogen ligands have emerged as efficient ligands for this process.

Phosphine-other sp^2-nitrogen ligands

In this context, Reggelin *et al*. designed phosphine-sulfoximine **133** (Figure 1.36) which provided high enantioselectivities for the benchmark substrate (ee's up to 95%) and low enantioselectivities for cyclic substrates (ee's up to 35%).[189] Regarding sulfoximine-based ligands, Gais *et al.* reported the development of ligand **134** (Figure 1.36), and its application in the allylic alkylation of the model substrate with enantioselectivities up to 97%.[190]



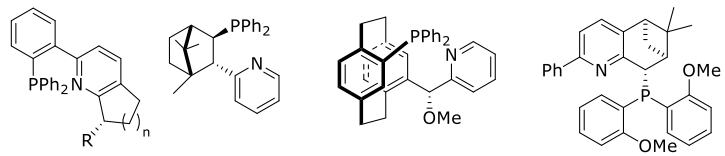
133 **134**

Figure 1.36. Phosphine-sulfoximine ligands **133** and **134**.

The introduction of pyridine group instead of an oxazoline or imine moiety is also an alternative for synthetizing more robust P,N-ligands. In this sense, Knochel *et al.* developed phosphine-pyridine ligands **135** (Figure 1.37, R= Ph, ^{i}Pr, $CMe_2OSiMe_2{}^{t}Bu$ and n= 1, 2).[191] Ligands **135** have been found to be effective for the alkylation of the hindered model substrate and unhindered linear substrates (ee's up to 98% and 96%, respectively).

Phosphine-pyridine ligands **71** (Figure 1.37) have also been evaluated in the Pd-catalyzed allylic alkylation and amination of the benchmark substrate 1,3-diphenylprop-2-enyl acetate, achieving enantioselectivities up to 96% ee and 87% ee, respectively.[192]

Jiang *et al.* developed a phosphine-pyridine ligand **136** derived from [2,2]-paracyclophane which possesses planar and central chirality (Figure 1.37).[193] Enantioselectivities up to 97% ee were obtained using the model substrate and dimethyl malonate as nucleophile.



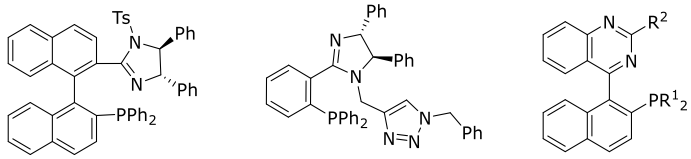
135 **71** **136** **137**

Figure 1.37. The most relevant phosphine-pyridine ligands.

Then, Li *et al.* reported the synthesis of tetrahydroquinone-based phosphine-pyridine ligand **137** (Figure 1.37), and its successful application in the allylic alkylation of the model substrate using a wide range of dialkyl malonates as nucleophiles, obtaining enantioselectivities up to 95% ee.[194]

Another sp^2-nitrogen donor group used instead of the oxazoline moiety is the imidazole. In this context, Shi *et al.* developed ligand **138** (Figure 1.38), achieving high enantioselectivities for the benchmark substrate (ee's up to 98%).[195]

In 2011, Pericàs and Claver *et al*. presented a phosphine-remote triazole **139** (Figure 1.38).[196] Using DFT calculations, they determined that the most stable Pd-**139** complex was the one in which the triazole moiety has been coordinated. High enantioselectivities have been achieved in the allylic alkylation with malonates and in the allylic amination with several N-nucleophiles, using in both cases the model substrates (ee's up to 99%).



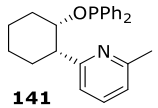
138 **139** **140**

Figure 1.38. Phosphine-other sp^2-nitrogen ligands **138**-**140**.

Later, Guiry *et al.* developed a series of quinazolap ligands **140** (Figure 1.38, R^1= Ph, 3,5-Xyl and R^2= Ad, ^{c}Bu, ^{i}Pr).[197] The catalytic results showed that enantioselectivity in the allylic alkylation of the model substrates decreased when bulky substituents such as adamantyl were present in quinazoline moiety, however good enantioselectivities were obtained when substituent in 3-position of quinazoline was an isopropyl group (ee's up to 92%).

Phosphinite-other sp^2-nitrogen ligands

Only one family of phosphinite-sp^2 other nitrogen ligands has been successfully applied in the Pd-allylic alkylation which has been developed by Zhou *et al.* It consists on a cyclohexyl-based phosphinite-pyridine ligand **141** (Figure 1.39).[198] Ligand **141** provided enantioselectivities up to 95% ee in the alkylation of the benchmark substrate.



141

Figure 1.39. Phosphinite-pyridine ligand **141**.

Phosphoroamidite/phosphite-other sp^2-nitrogen ligands

Phosphoroamidite/phosphite-other sp^2-nitrogen ligands have been less developed than their phosphine analogous. However, there are some examples in the literature of their application in the asymmetric Pd-catalyzed allylic substitution.

Li *et al.* developed phosphite-pyridine ligand **142** (Figure 1.40) which provided high enantioselectivities for the model diphenylated substrate (ee's up to 95%) and good enantioselectivities for cyclic substrates (ee's up to 80%).[199]

Also, our group has contributed in extending the study of this kind of ligands. They developed phosphite-pyridine **75**, phosphite-thiazoline **86**, phosphite-oxazole **84** and phosphite-thiazole **85** ligands (Figure 1.40). Phosphite-pyridine ligands **75** provided excellent results in several substrates (hindered and unhindered) using a broad range of C-, N-, and O- nucleophiles with enantioselectivities up to 99% ee.[200] Remarkably, with these ligands the authors could also achieved enantioselectivities up to 99% ee in trisubstituted substrates.[200] Phosphite-thiazole ligand **86** provided excellent results for

cyclic substrates (ee's up to 94%) and excellent regio- and enantioselectivities for monosubstituted substrates (regio's up to 90% towards branched product and ee's up to 95%).[201] Phosphite-oxazole **84** provided excellent enantioselectivities for the benchmark substrate (ee's up to 92%) and trisubstituted substrates (ee's up to 95%), whereas phosphite-thiazole ligand **85** was good for more challenging linear unhindered substrates (ee's up to 92%).[202]

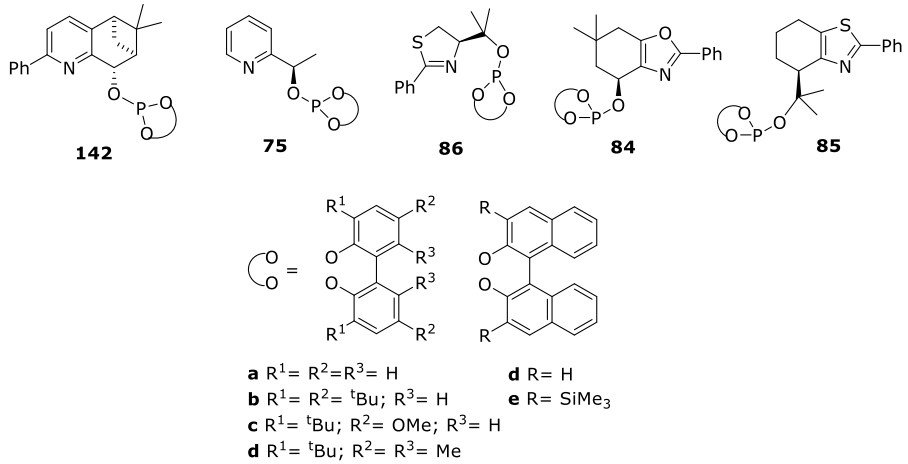


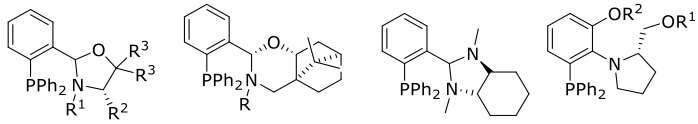
Figure 1.40. Most representative phosphite-other sp^2-nitrogen ligands.

1.2.2.1.3. Phosphorus-sp^3-nitrogen ligands

Although most of the phosphorus-nitrogen ligands applied in enantioselective Pd-allylic substitution have been phosphorus-sp^2-nitrogen ligands, some heterodonor phosphorus-sp^3-nitrogen ligands have been also successfully applied.

Phosphine-sp^3-nitrogen ligands

The first class of phosphine-sp^3 nitrogen ligands applied in this process consist on modifications of PHOX ligands, where the oxazoline moiety has been replaced by sp^3-nitrogen heterocycles such as oxazolidines (ligands **143**; Figure 1.41, R^1= Me, Bu; R^2= ^{i}Pr, Ph and R^3= H, Ph),[203] oxazinanes (ligands **144**; Figure 1.41, R= Et, Pr, Bu, Bn),[204] and imidazolidines (ligands **145** and **146**; Figure 1.41, **146**; R_1= H, $SiMe_3$ and R_2= Me, Et, Ph, OMe)[204,205]. All of them provided similar enantioselectivities in the Pd-catalyzed allylic substitution of the benchmark substrate (ee's up to 99%).

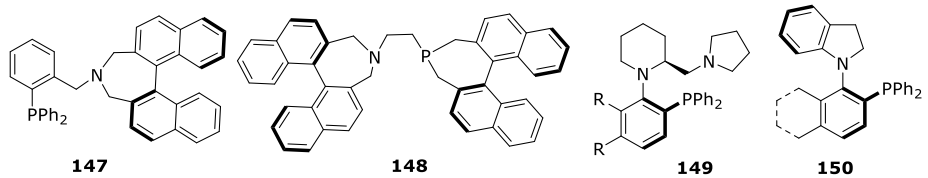


143 **144** **145** **146**

Figure 1.41. PHOX-type phosphine-sp^3-nitrogen ligands.

Later, azepine-type ligands **147** and **148** (Figure 1.42) with axial chirality have been developed.[206] With these ligands high enantioselectivities were achieved in the allylic alkylation of the model substrate 1,3-diphenylprop-2-enyl acetate (ee's up to 97%), but poor results were obtained for unhindered substrates.

In this context, Mino *et al*. developed amino-phosphine ligands **149** (Figure 1.42, R= OMe, 1-Naph) which also presented axial chirality.[207] High enantioselectivities were obtained in the allylic alkylation of the benchmark substrate with a wide range of C-nucleophiles derived from dimethyl malonate (ee's up to 99%). The same authors also developed ligand **150** (Figure 1.42) which provided excellent results (ee's up to 97%) for the standard substrate.[208] Remarkably, using these ligands they observed kinetic resolution, obtaining also the enantioenriched model substrate from the reaction mixture (ee's up to 98%).

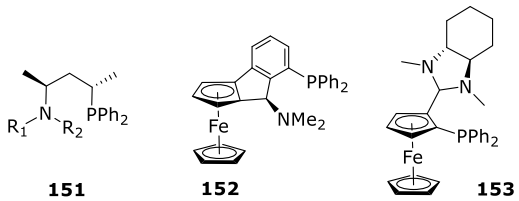


147 **148** **149** **150**

Figure 1.42. Axially chiral phosphine-amine ligands.

Also, P,N-ligands with stereogenic N-donor secondary amines have been successfully applied in this process. Bakos *et al.* developed pentane-2,4-diyl based aminoalkyl-phosphine ligands **151** (Figure 1.43, R^1= H; R^2= Me, ^{i}Pr, ^{t}Bu, Cy, Bn, Ph, 2-Me-C_6H_4, 1-Ad and R^1= R^2= -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_2O(CH_2)_2$-).[209] These ligands were applied in Pd-catalyzed asymmetric allylic alkylation and amination of the benchmark substrate with several C- and N-nucleophiles giving high activities and enantioselectivities (up to 95% ee in alkylation and 90% ee in amination processes). The results showed that the enantioselectivity increase with the steric bulk of the amino substituents.

In this field, ligands with planar chirality has been also developed. In this sense, Fukusawa *et al*. synthetized ferrocene-based phosphine-amine ligand **152** (Figure 1.43).[210] This ligand provided excellent enantioselectivities in the allylic alkylation and amination of the standard substrate (ee's up to 96% and 90%, respectively). On the other hand, ligand **153** (Figure 1.45), developed by Kim, Jin, *et al.*, provided excellent enantioselectivities for the alkylation of the model substrate (ee's up to >99%).[211]



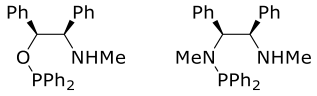
151 **152** **153**

Figure 1.43. Selected phosphine-stereogenic sp^3-amine and ferrocene-based phosphine-sp^3-nitrogen ligands.

Phosphinite/aminophosphine-sp^3-nitrogen ligands

Concerning phosphinite/aminophosphine-sp^3-nitrogen ligands*, o*nly two successful examples are reported in the literature. The first one is ligand **154** (Figure 1.44), developed by Chan *et al*. which have been successful applied in the allylic alkylation of the model substrate with enantioselectivities up to 95% ee.[212] Authors found that secondary amines provided better enantioselectivities that tertiary amine-based ligands.

The second one is the aminophosphine-amino based ligand **155** (Figure 1.44) also based on secondary amine moiety, developed by Bujoli and Petit. Ligand **155** exhibited enantioselectivities up to 93% ee in the allylic alkylation of the benchmark substrate 1,3-dipenylprop-2-enyl acetate.[213]



154 **155**

Figure 1.44. Selected phosphinite/aminophosphine-sp^3-nitrogen ligands.

Phosphoroamidite/phosphite-sp^3-nitrogen ligands

Phosphite-sp^3-nitrogen ligands have been poorly studied as in the case of phosphinite-based ligands. However, few successful examples are present in the literature.

First example, reported by Zhang *et al*. is based on chincona alkaloid. Amino-phosphite ligand **156** (Figure 1.45) provided excellent enantioselectivities in allylic alkylation of the model substrate with a variety of C-nucleophiles such as malonates and acetylacetones.[214]

The second example, developed by Nemoto and Hamada, is ligand **157** (Figure 1.45).[215] This ligand is peculiar as the actual active scpecies binding to the palladium is generated *in situ*. Ligand **157** comes from P(V) analogue, which is reduced to P(III) by BSA, achieving P-stereogenic phosphite-type ligand. This ligand provided high

enantioselectivities in the allylic alkylation and amination of the benchmark substrate as well as for cyclic substrates (ee's up to 99%).

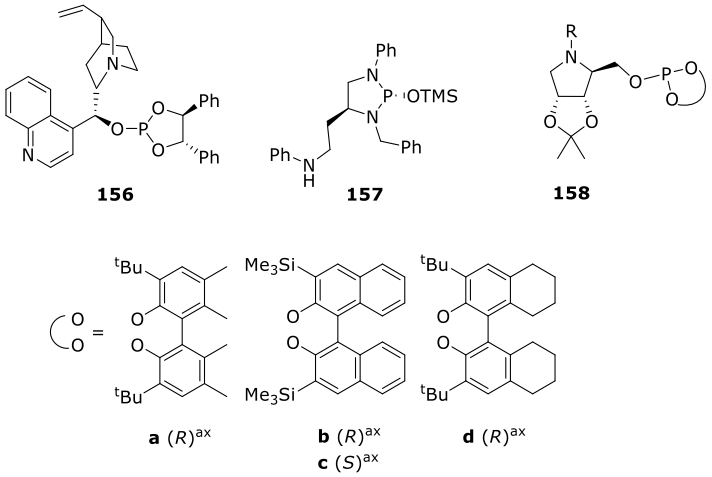


Figure 1.45. Phosphoroamidite/phosphite-sp^3-nitrogen ligands.

Very recently, our group in collaboration with Robina's group reported the application of iminosugars based ligands **158** (Figure 1.45, R= Me, Bn, ^{i}Pr) in Pd-allylic substitution.[216] They attained good results in a wide range of linear and cyclic substrates with several electronic and steric properties using a variety of C- and N-nucleophiles (ee's up to 93%).

1.2.2.2. Phosphorus-thioether ligands

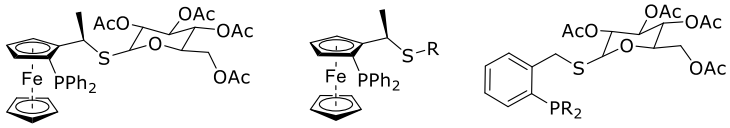
Although P,S-ligands have been less studied compared to P,N-ligands, there are some successful examples of their application in the literature. In this next section, the most successful P,S-ligands reported to date will be discussed.

Phosphine-thioether ligands

Among P,S-ligands, the combination of phosphine-thioether ligands have been the most widely studied in the enantioselective Pd-catalyzed allylic substitutions.

The first phosphite-thioether ligand applied in the Pd-allylic alkylation has been the ferrocene-based ligand **159** (Figure 1.46), developed by Albinati, Pregosin, *et al*. in 1996.[217] Ligand **159** bearing a thyoglicose functionality afforded the alkylated product of the model substrate 1,3-diphenylprop-2-enyl acetate with an enantioselectivity of 88% ee. They also studied the change of the carbohydrate substituent of ligand **159** for alkyl substituents, leading to ligands **160** (Figure 1.46, R= Cy, Et), which resulted in a dramatic decrease in the enantioselectivity (67% ee and 34% ee, respectively). The same authors also studied the replacement of the ferrocene group by a phenyl ring

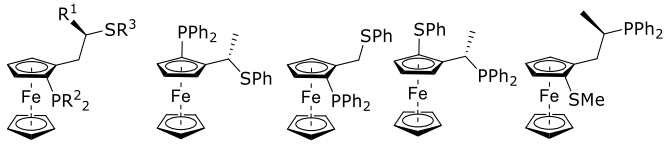
with ligands **161** (Figure 1.46, R= Ph, Cy).[218] This modification also results in a low asymmetric induction (ee's up to 64%). Thus, the combination of the two stereogenic fragments and the substituents of the thioether moiety was crucial for achieving good levels of enantioselectivity.



159 **160** **161**

Figure 1.46. Chiral phosphine-thioether ligands **159**-**161**.

Later, other ferrocenyl-based phosphite-thioether ligands have been developed (Figure 1.47, ligands **162**-**166**; **162**; R^1= Me, Et; R^2= Ph, ^{i}Pr and R^3= Me, ^{i}Pr).[219] The catalytic results using these ligands indicated that enantioselectivity is better when the phosphine group is attached to the Cp ring rather than when is attached to the thioether unit (Figure 1.47, ligands **162**-**164** vs ligands **165**-**166**). From the results, it could be also concluded that enantioselectivities are not affected by the presence of an additional stereogenic unit or by the length of the thioether chain (Figure 1.47, comparison between ligands **162**-**164**). Thus, the highest enantioselectivities of the series was achieved using ligand **164** (ee's up to 93%). Furthermore, the structural studies of a 1,3-diphenylallyl palladium intermediates ([Pd($^3\eta$-1,3-PhC_3H_3Ph)(**162**)]PF_6) indicated that the presence of small substituents on thioether moiety favors the nucleophilic attack in the *cis* position to the S-donor group.[219]

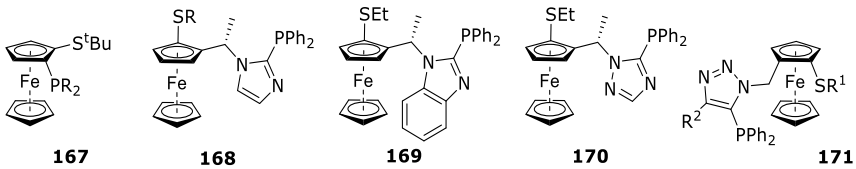


162 **163** **164** **165** **166**

Figure 1.47. Ferrocene-based ligands **162**-**166**.

Afterwards, Carretero *et al*. developed a readily available enantiopure phosphine-thioether ferrocenes ligands **167** which have exclusively planar chirality (Figure 1.48, R= Ph, 4-F-C_6H_4, 4-CF_3-C_6H_4, 2-Fur, Cy, *o*-Tol, 1-Naph).[220] Ligands containing electronwithdrawing phosphines provided high enantioselectivities in shorter reaction times (20 min) with the model diphenylated substrate (ee's up to 97%). High enantioselectivities were also obtained in the Pd-catalyzed allylic amination of the benchmark substrate with ligands containing bulky phosphines (ee's up to >99%). The authors also performed NMR studies of these P,S-bidentated ligands which concluded that the nucleophilic attack takes place *trans* to the phosphorus moiety and the bulky

thioether substituent plays an important role in enhancing the reactivity of the *endo*/*exo* intermediate.



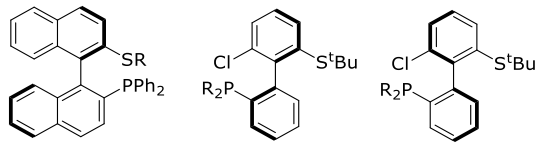
167 **168** **169** **170** **171**

Figure 1.48. Phosphine-thioether ligands **167**-**171**.

Recently, Chan *et al*. reported a new class of ferrocenyl phosphine-thioether ligands **168**-**170** with heterocyclic scaffolds (Figure 1.48, **168**; R= Ph, *p*-Tol, Me, Et, ^{i}Pr, Cy, ^{t}Bu).[221] These ligands provided satisfactory results in the Pd-catalyzed indole alkylation of the benchmark substrate and using several malonates and indoles as nucleophiles (ee's up to 96%). Moreover, ligand **169** provided good enantioselectivities in the Pd-catalyzed allylic alkylation of cyclic substrates and unsymmetrical allylic substrates (ee's up to 87%).

Fukuzawa *et al*. developed a novel phosphine-thioether ligands **171** based on a triazoleferrocenylethyl backbone (Figure 1.48, R^1= Ph, *p*-Tol, *p*-Cl-C$_6$H$_4$, Cy, Et and R^2= Ph, H).[222] Ligands **171** were successfully applied in asymmetric Pd-catalyzed allylic alkylation, amination, and etherification of the benchmark substrate 1,3-diphenylprop-2-enyl acetate (ee's between 74% to 99%).

The axially chiral 1,1'-binaphtyl backbone has been also widely used in the ligand design for the asymmetric Pd-catalyzed allylic substitution reactions. In this respect, several groups reported the application of ligands **172** with different alkyl groups on the sulfur atom. Kang *et al.* applied ligand **172** (Figure 1.49, R= Me) in the allylic alkylation of the model substrate 1,3-diphenylprop-2-enyl acetate with 91% ee.[223] Gladiali *et al.* tested the isopropyl derivative of **172** (Figure 1.49, R= ^{i}Pr), which led to the corresponding compound in quantitative yields and 60% ee.[224] Later, Shi *et al.* applied ligand **172** (Figure 1.49, R= Bn, CHPh$_2$) obtaining enantioselectivities up to 77% ee.[225] Interestingly, they obtained reversal of enantioselectivity depending on the sulfur substituent used ((*R*)-product for R=Me, Bn and (*S*)-product for R= ^{i}Pr, CHPh$_2$), thus the steric bulkiness of alkyl group on the sulfur atom seems to be the responsible for the configuration of the product. Moreover, by X-ray analysis and NMR studies they confirmed a P,S-coordination as a metallocycle in a pseudo-boat-seven-membered arrangement. More recently, Hagiwara *et al.* reported the synthesis of the aryl-thioether analogues of **172** (Figure 1.49, R= Ph, 2-^{i}Pr-C$_6$H$_4$, 2-Naph, 3,5-Xyl, Cy).[226] These latter ligands provided enantioselectivities (up to 95% ee) in the Pd-catalyzed allylic alkylation of the model substrate using dimethyl malonate and several indoles as C-nucleophiles.

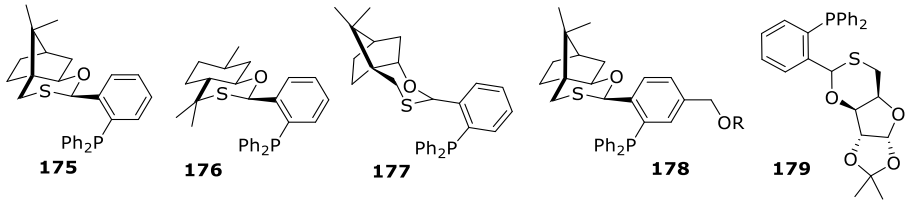


172 **173** **174**

Figure 1.49. Axially chirality phosphine-thioether ligands **172**-**174**.

More recently, the application of others axially chiral thioether-phosphine ligands **173** and **174** (Figure 1.49, R= Ph, Cy) in the Pd-catalyzed allylic substitution has been reported by Leroux *et al*.[227] Ligands **173** and **174** provided similar enantioselectivities (up to 94% ee) than **172** in the alkylation of the model substrate using dimethyl malonate and indoles.

Another class of phosphine-thioether ligands applied in this process are based on oxathiane. The first example was reported by Nakano and Hongo who synthetized ligands **175**-**179** (Figure 1.50) and successfully used them in alkylation and amination reactions of substituted allyl acetates.[228] Ligand **175** with norbornane core gave the highest levels of enantioselectivity (ee's up to 94%).



175 **176** **177** **178** **179**

Figure 1.50. Phosphinooxathiane ligands **175**-**179**.

Inspired by this work, Nakano *et al*. also reported a novel polymer-supported P,S-type ligands **178** (Figure 1.50, R= TES, Ac, PS-DES, PS-Et-CO, Tenta Gel-MB-CO) and applied them in Pd-catalyzed asymmetric alkylations and amination, obtaining high enantioselectivities in both processes (96% ee and 99% ee, respectively).[229] Additionally, the same authors developed a new xylofuranoside-based phosphinoxathiane ligand **179** (Figure 1.50) which provided also high enantioselectivities in the asymmetric Pd-catalyzed allylic substitution of the model substrate (ee's up to 91%).[230]

Cyclopropane-based ligands **180**-**184** (Figure 1.51, **180**; R= Me, Ph; **181**; R^1= ^{t}Bu, 1-Ad, Et, Ph, 3,5-Me_2-C_6H_3, 2,6-Me_2-C_6H_3, 4-CF_3-C_6H_4, 4-MeO-C_6H_4, 2,4,6-Me_3-^{i}Pr and R^2= Ph, Cy, ^{i}Pr; and **184**; R= ^{t}Bu, 2,6-Me_2-C_6H_3, Et) were applied in the Pd-catalyzed allylic alkylation of the benchmark substrate with dimethyl malonate. Varying the ligand substituents on the phosphorus, sulfur, and carbon chain revealed ligand **181** (R^1= ^{t}Bu and R^2= Ph) to have the optimal configuration for this process, giving the product in high yield and with good enantioselectivity (ee's up to 93%).[231]

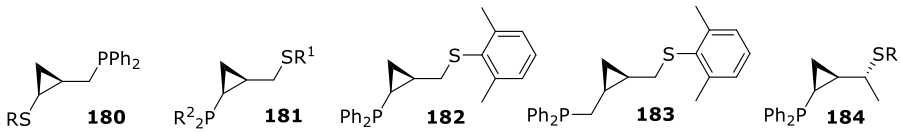


Figure 1.51. Cyclopropane-based thioether-phosphine ligands **180**-**184**.

A series of (*S*)-proline-derived phosphine-thioether ligands **185**-**187** were prepared and used in the Pd-catalyzed allylic alkylation of the model substrate with ee's up to 84% (Figure 1.52, R= Me, Ph, Et, Pr, ^{i}Pr, Bn, 1-NaphMe).[232] The catalytic results showed that an increase of the steric hindrance around the sulfur atom resulted in higher values of enantioselectivity.

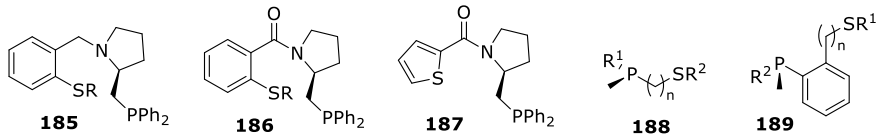
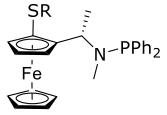


Figure 1.52. (*S*)-Proline-based and P-stereogenic thioether-phosphine ligands **185**-**189**.

Also, P-stereogenic phosphine-thioether ligands have been successfully applied in this process. In this respect, two families of ligands could be found in the literature. The first example are ligands **188** (Figure 1.52, R^1= ^{t}Bu, Ad; R^2= Ph, *o*-Tol, Bn and n= 1, 2) which were reported by Imamoto *et al.*[233] By changing the substituents on the phosphorus and sulfur atom, enantioselectivities up to 90% ee were achieved the with model substrate and different malonates. More recently, a second family of this kind of ligands has been developed, ligands **189** (Figure 1.52, R^1= Ph, Et, ^{t}Bu, Bn, *p*-Anth, *o*-Anth, 3,5-Me_2-C_6H_3, 4-CF_3-C_6H_4; R^2= *o*-An, *o*-Tol, *o*-biPh, Fc, *m*-Xyl, *o*-Anth and n= 0, 1, 2).[234] Ligands **189** provided excellent enantioselectivities in the allylic alkylation and amination of the model substrate (ee's up to 96%) but low-to-moderate enantioselectivities for less sterically hindered linear and cyclic substrates (ee's up to 66%).

Aminophosphine-thioether ligands

In 2006, Chan *et al*. developed a series of ferrocene aminophosphine-thioether ligands **190** (Figure 1.53, R= Et, ^{t}Bu, Ph, ^{i}Pr, Cy) and successfully applied them in the asymmetric Pd-catalyzed allylic substitution of the benchmark substrate 1,3-diphenylprop-2-enyl acetate (ee's up to 93%).[235] Moreover, ligands **190** provided high yields and enantioselectivities in Pd-catalyzed etherification of the model substrate with a broad range of aliphatic alcohols (ee's up to 96% ee).

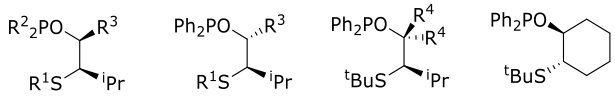


190

Figure 1.53. Aminophosphine-thioether ligand **190**.

Phosphinite-thioether ligands

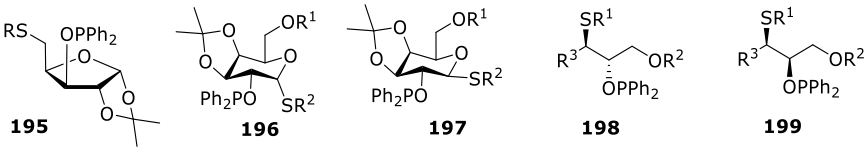
Phosphinite-thioether ligands are less studied than their phosphine analogues, but some examples have been reported. The first application in the Pd-catalyzed allylic substitution of a family of mixed thioether-phosphinite ligands was reported by Evans *et al.* who synthetized ligands **191**-**194** (Figure 1.54, R^1= Ph, 4-MeO-C_6H_4, 3,5-Me_2-C_6H_3, 1-Naph, Bn, Cy, ^{t}Bu, 2,3,5,6-F_4-C_6H_1, 4-^{t}Bu-C_6H_4, 3,5-$^t Bu_2$-C_6H_3, 2-Naph, 2-MeO-C_6H_4, 4-F-C_6H_4, 3,5-$(CF_3)_2$-C_6H_3; R^2= Ph, 1-Naph; R^3= Ph, ^{i}Pr, Me and R^4= H, Me).[236] Ligands **191**-**194** have been successful applied in the Pd-catalyzed allylic substitution of several linear and cyclic substrates. Enantioselectivities up to 98% ee were achieved for the model substrate using dimethyl malonate and benzyl amine as nucleophiles. Also, high enantioselectivities were achieved with cycloalkenyl acetates (ee's up to 97%) and sulfur and nitrogen containing heterocyclic substrates (ee's up to 94%). These ligands were also able to induce high levels of enantioselectivity in trisubstituted substrates (ee's up to 94%). The authors could furthermore prove the contribution of sulfur in the coordination of the palladium by X-ray analysis.



191 **192** **193** **194**

Figure 1.54. Phosphinite-thioether ligands **191**-**194**.

Our group developed a series of furanoside phosphinite-thioether ligands **195** (Figure 1.55, R= Me, Ph, ^{i}Pr, ^{t}Bu, 4-Me-C_6H_4, 4-CF_3-C_6H_4, 2,6-Me_2-C_6H_3).[237] These thioether based ligands have been applied in the Pd-catalyzed allylic substitution of mono- and disubstituted linear and cyclic substrates with enantioselectivities up to 95% ee. The thioether substituent has an important role on the catalytic performance when bulkiest thioether groups are present in the ligand design, the enantioselectivities were higher.



195 **196** **197** **198** **199**

Figure 1.55. Phosphinite-thioether derived from furanoside and arylglicidol.

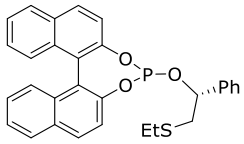
At the same time, Fernández *et al*. reported the application of phosphite-thioether ligands **196** and **197** (Figure 1.55, R^1= Ac, H, TBDMS and R^2= 4-Me-C_6H_4, ^{t}Bu) in the Pd-catalyzed allylic substitution of the model substrate 1,3-diphenylprop-2-enyl acetate (ee's up to 96%).[238]

More recently, Pericàs *et al.* developed phosphinite-thioether ligands **198** and **199** (Figure 1.55, R^1= Ad, Cy, ^{t}Bu, Ph, 4-^{t}Bu-C_6H_4, 2,6-Me_2-C_6H_3, 3,5-Me_2-C_6H_3, 2-Naph, 4-MeO-C_6H_4, 4-Br-C_6H_4, ^{i}Pr; R^2= Bn, Bzh, Tr, Me and R^3= Ph, Mes).[239] After an iterative optimization of four different structural parameters (the skeletal aryl group, the thioether substituent, the ether moiety and the relative configuration of the chiral centers), highly active and enantioselective ligands were identified for this process. In this way, excellent enantioselectivities were obtained in the reaction of the benchmark substrate with dimethyl malonate (ee's up to 99%), benzyl amine (ee's up to 95%), and a much less common O-nucleophile (ee's up to 94%), in very short reaction times.

Phosphoroamidite/phosphite-thioether ligands

Several phosphine-thioether and phosphite-thioether ligands have been studied and proved to be effective in this process, however less attention has been paid to phosphoroamidite/phosphite-thioether ligands.

In this sense, Pregosin *et al.* developed BINOL-based phosphine-thioether ligand **200** (Figure 1.56) and applied them in the Pd-allylic alkylation.[240] Ligand **200** provided yields up to 95% for monosubstituted substrates, however the regio- (up to 68%) and enantioselectivities (up to 74% ee) obtained were moderate.



200

Figure 1.56. Binaphthylphosphinite-thioether ligand **200**.

Phosphite-thioether ligands **90**-**91** with a furanoside backbone were also applied in Pd-catalyzed allylic substitution (Figure 1.57, **90**; R= Me, ^{t}Bu, 4-Me-C_6H_4, 4-CF_3-C_6H_4, 2,6-Me_2-C_6H_3, Ad, 1-Naph; **91**; R= Ph, Me).[241] The ligand screening indicated that the best enantioselectivities were achieved with xibofuranoside ligand scaffold **90**. High enantioselectivities were obtained with hindered and unhindered substrates with a broad range of C-, N-, and O-nucleophiles (ee's up to >99%). The authors also carried out a combination of NMR studies and DFT calculations which allows them to better understand the origin of enantioselectivity with this kind of ligands.

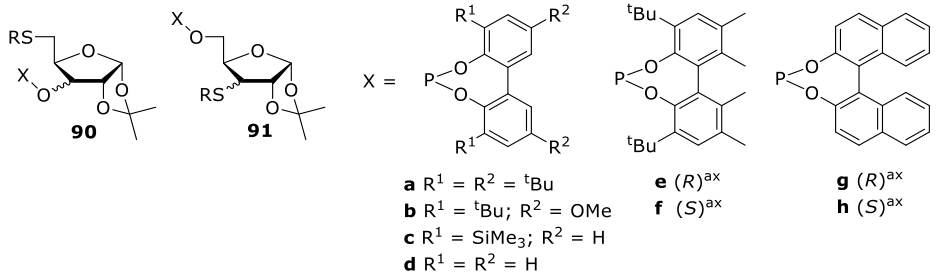


Figure 1.57. Phopshite-thioether ligands **84**-**85**.

Very recently, Xiao *et al*. successfully applied phosphoroamidite-thioether ligand **201** and **202** (Figure 1.58; **201**, R= Ph, H, Me, I) in the Pd-catalyzed allylic amination of linear diphenylated substrates with different steric and electronic requirements using a wide range of hydrazones (ee's up to 99%).[242] These ligands were also applied in the allylic amination of monosubstituted substrates with moderated regioselectivities.

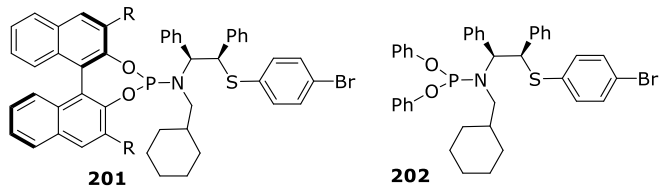


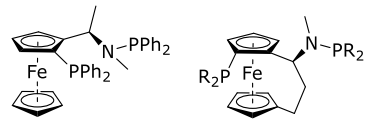
Figure 1.58. Phosphoroamidite-thioether ligand **201-202**.

1.2.2.4. Heterodonor mixed P,P'-ligands

Considering that Pd-catalyzed allylic substitutions have been studied for a long time and that it has become benchmark reaction for evaluating new chiral ligands, it is quite surprising that there not many reports concerning the use of heterodonor mixed phosphorus ligands compared to other classes of ligands. In the next sections, there is a collection of the most representative combinations of P,P'-ligands developed for this process.

Phosphine-aminophosphine ligands

For this kind of ligands, only one report could be found in the literature which consists in the application of ferrocenyl ligands BoPhoz and **203** (Figure 1.59, **203**; R= Ph, Cy) in the Pd-catalyzed allylic alkylation of the model substrate acetate.[243] Enantioselectivities up to 55% ee were obtained with bridged ligand **203** compared to 33% ee with analogous non-bridged BoPhoz ligand. Both ligands were also applied in allylic alkylation reaction of symmetrical cyclic and unsymmetrical substrates, but the enantioselectivities obtained were poor.

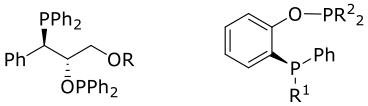


BoPhoz **203**

Figure 1.59. Phosphine-aminophosphine ligands applied in Pd-catalyzed allylic alkylation.

Phosphine-phosphinite ligands

Also, the study of phosphine-phosphinite ligands for this process is limited. In this field, Vidal-Ferran *et al.* tested palladium complexes containing phosphine-phosphinite ligands **204** (Figure 1.60, R= Me, CPh_3) in the allylic alkylation of the benchmark substrate using dimethyl malonate. Although full conversions were achieved, the enantioselectivities were low (ee's up to 21%).[244]



204 **205**

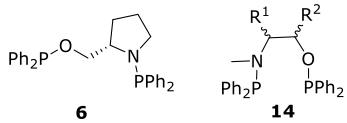
Figure 1.60. Phosphine-phosphinite ligands applied in Pd-catalyzed allylic alkylation.

Later, Grabulosa *et al*. developed ligands **205** (Figure 1.60, R^1= Me, ^{t}Bu and R^2= ^{i}Pr, Ph) and applied them in the Pd-catalyzed allylic alkylation of the model substrate, but again the enantioselectivities were poor (ee's up to 18%).[245]

Aminophosphine-phosphinite ligands

The first example of aminophosphine-phosphinite ligands have been reported by Cessarotti *et al*. in 1991.[246] They developed ligand **6** (Figure 1.61) and applied it in the allylic alkylation of the model substrate and with other less sterically hindered substrates, obtaining in all cases low enantioselectivities (up to 30% ee).

Then, Chan *et al*. applied aminophosphine-phosphinite ligands **14** (Figure 1.61, R^1= Ph, Me and R^2= Ph, H) in the Pd-catalyzed asymmetric allylic alkylation of the benchmark substrate with dimethyl malonate.[247] The chirality of the carbon bonded to O-PPh_2 in the ligands was found to be very important to the enantioselectivity of the catalysts. Introduction of this stereogenic center has led to significantly improved enantioselectivities (ee's up to 60%).



6 **14**

Figure 1.61. Aminophosphine-phosphinite ligands applied in Pd-catalyzed allylic alkylation.

Phosphine-phosphite ligands

In contrast to the previously mentioned type of P,P'-ligands, several phosphine-phosphite ligands were evaluated for this process and with better results. The first example in the application of phosphine-phosphite ligands was reported by van Leeuwen *et al*. in 2000.[248] They developed ligands **17** and **18** (Figure 1.62, **17**; R^1= ^{t}Bu, Ph, 1-Naph, *o*-An; R^2= Ph, ^{t}Bu and R^3= Ph, H, Me) and applied them in the reaction of the model substrate with dimethyl malonate, achieving enantioselectivities up to 82% ee. From the catalytic results and with the help of X-ray structure, the authors conclude that the attack of the nucleophile takes place *trans* toward the phosphine moiety. Therefore, the phosphine moiety has little effect on the chiral induction. The biaryl moiety induces the enantioselectivity controlled by the stereogenic center next to the phosphite moiety and a larger bite angle improves the enantioselectivity.

In the same year, Faraone *et al.* developed ligands **206** containing different biaryl phosphite moieties (Figure 1.62).[249] These new ligands were tested in the Pd-catalyzed enantioselective alkylation of the model substrate, achieving acceptable enantioselectivities up to 71% ee. Again, the authors conclude that the nucleophilic attack of the malonate occurred preferentially at allylic carbon far from the binaphthalene moiety, namely *trans* to the phosphite group.

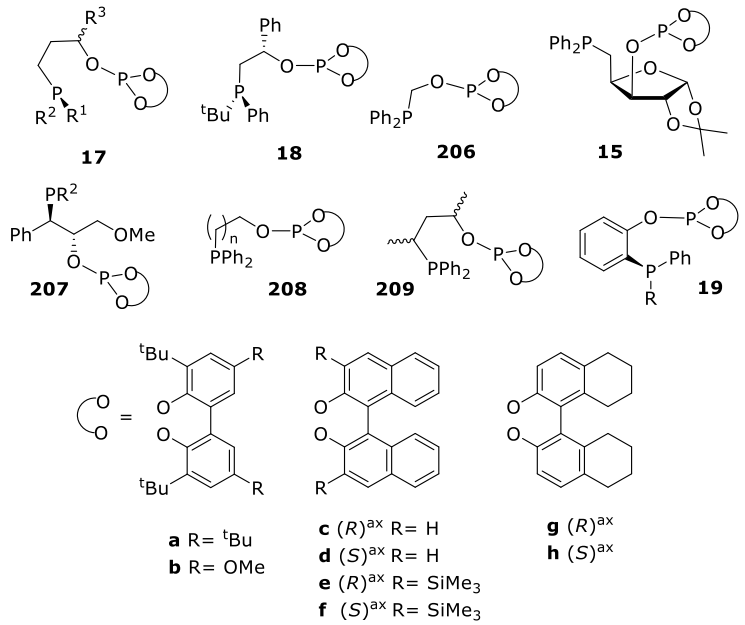


Figure 1.62. Most relevant phosphine-phosphite ligands.

Following this work, our group applied furanoside-based phosphine-phosphite ligands **15** (Figure 1.62) in the Pd-catalyzed allylic alkylation of the model substrate with dimethyl malonate.[241a] Unfortunately, the enantioselectivities achieved with these ligands were lower than the ones obtained with previous ligands of this class.

Later, Vidal-Ferran *et al*. described the synthesis of new phosphine-phosphinite ligands **207** which incorporate substituents with different electronic properties on the phosphino group (Figure 1.64, R= Ph, *p*-CF_3-C_6H_4, *p*-OMe-C_6H_4).[244] Ligands **207** have been evaluated in palladium-catalyzed allylic substitutions, affording enantioselectivities ranging from low-to-good for all combinations of substrates and nucleophiles. From the catalytic results, they observed an increase of enantioselectivity when more electrodonating groups are present on aryl groups of the phosphine moiety (ee's of 64%, 80%, and 80% for the *p*-CF_3, *p*-H, and *p*-MeO substituted phosphino groups, respectively) in the allylic alkylation of the benchmark substrate with dimethyl malonate.

Bakos *et al*. tested phosphine–phosphite ligands **208** and **209** (Figure 1.62, **208**; n=0, 1, 2, 3) in the asymmetric allylic alkylation of the benchmark substrate, achieving moderate enantioselectivities (ee's up to 69%).[250] The results obtained showed that activity was strongly sensitive to the chain length of the ligands and that the conformation of the chelate ring controlled by the stereogenic elements of the backbone plays an important role in determining the enantioselectivity.

In 2016, Grabulosa *et al*. applied ligands **19** (Figure 1.62, R= Me, ^{t}Bu, Ph), analogous of ligands **205** (Figure 1.60), in the Pd-catalyzed allylic alkylation of the model substrate using dimethyl malonate as nucleophile. The introduction of phosphite moiety in the ligand design dramatically increase the enantioselectivity obtained (ee's up to 94% compared to 18% ee obtained with phosphine-phosphinite ligands **205**).[245]

Phosphine-phosphoroamidite ligands

Only three families of phosphine-phosphoroamidite ligands have been successfully applied in the Pd-catalyzed allylic substitution reaction. The first family was phosphine-phosphoroamidite ligands **210** and **211** (Figure 1.63, **210**; R= Ph, ^{i}Pr, Cy, *o*-Tol; and **211**; R^1= Ph, H and R^2= H, Me) which was developed by Reek *et al*.[251] High enantioselectivities (ee's up to 90%) were achieved with the model diphenylated substrate, but moderate-to-low enantioselectivities (ee's up to 50%) were obtained with less sterically hindered linear and cyclic substrates, and monosubstituted substrates. By NMR studies, the authors concluded that due to steric effects on the phosphine moiety, a selective isomerization was found in ligands **210**. This selectivity was not observed in ligands **211** which led to not discrimination of both allylic terminal carbon atoms during the nucleophilic attack, thus providing lower enantioselectivities compared to ligands **210**.

The second family was developed by Bakos *et al*. and consists on phosphine-phosphoroamidite ligands **212** (Figure 1.63, R= ^{i}Pr, Me, Bn, Ph).[79b] Ligands **212** provided moderate enantioselectivities in the allylic alkylation of the benchmark substrate 1,3-diphenylprop-2-enyl acetate with dimethyl malonate (ee's up to 64%).

Later, Grabulosa *et al*. applied ligands **213** (Figure 1.63, R= Me, ^{t}Bu, Ph), which are based on the same backbone than ligands **205** and **19** (Figure 1.60 and 1.62).[245] The introduction of phosphoroamidite moiety showed to be benefical in the allylic amination of the model substrate (ee's up to 70%) where the two other combinations of P,P'-ligands (**205** and **19**) failed.

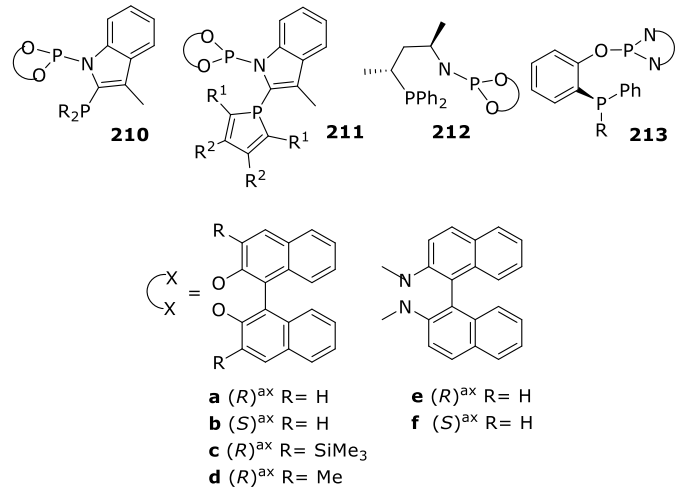


Figure 1.63. Phosphine-phosphoroamidite ligands applied in the Pd-catalyzed asymmetric allylic substitution.

Phosphite-phosphoroamidite ligands

In this field, our group successfully applied the first family of phosphite-phosphoroamidite ligands in this process.[252] They synthetized ligands **214** (Figure 1.64) derived from *D*-glucosamine and applied them in the allylic alkylation of several substrates. They obtained good enantioselectivities (ee's up to 89%) with linear and cyclic substrates as well as for monosubstituted substrates. For these latter class of substrates, ligands **214** proved to be inadequate in terms of regioselectivity.

The same authors also reported the application of ligands **215** (Figure 1.64, R_1= H, Me, Et, ^{i}Pr, ^{t}Bu, Ph; R_2= H, Ph and R_3= H, Me), analogous of phosphinite-aminophosphine ligands **14** (Figure 1.4), which provided enantioselectivities up to 99% ee in the allylic substitution of both linear and cyclic substrates with a range of C- and N-nucleophiles.[253] The introduction of phosphoroamidite moiety in the ligand design showed to be beneficial.

Afterwards, they also reported the development of ligands **38**-**39** and applied them in the allylic alkylation of a broad range of substrates.[254] After ligand screening, xylofuranoside ligands **38** were found to be optimal, achieving high enantioselectivities (ee's up to 98%) for a range of disubstituted linear and cyclic substrates. High ee's (up to 90% ee) were also obtained in the alkylation of monosubstituted substrates, albeit with moderate regioselectivities (up to 75%) towards the desired branched isomer.

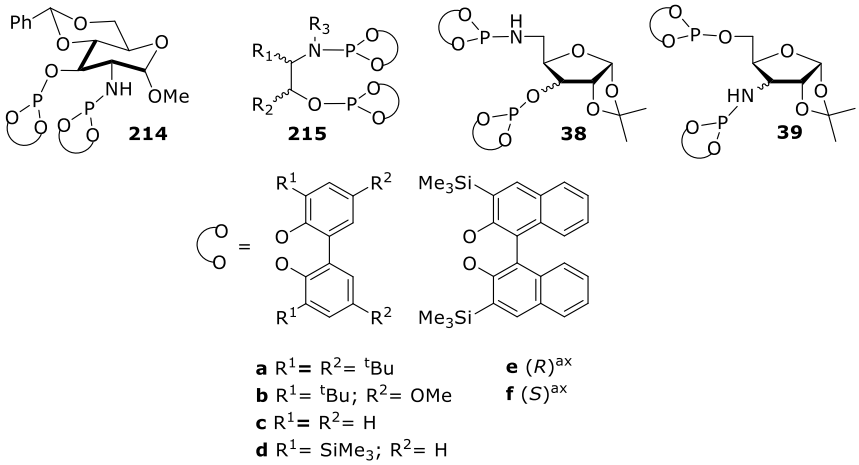


Figure 1.64. Phosphite-phosphoroamidite ligands applied in asymmetric Pd-catalyzed allylic alkylation.

1.3. Asymmetric Pd-decarboxylative protonation reaction

One of the most challenging problems in organic chemistry which need to be overcome is the formation of stereoselective C-C bond between an aromatic carbon and a carbon α- to a carbonyl group. In the last decade, transition metal catalyzed α-arylation has attracted considerable attention due to the versality and utility of these α-aryl carbonyl-containing frameworks in many medicinal targets.[255] As example, oxindoles are endogenous aromatic organic compounds that are found in the tissues and body fluids of mammals. Oxindoles constitute an important heterocyclic subunit present in various natural products which exhibits a wide range of biological properties such as anti-viral, anti-bacterial and anti-carcinogenic activities (Figure 1.65).[255]

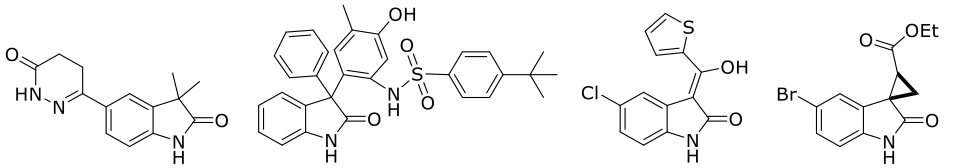
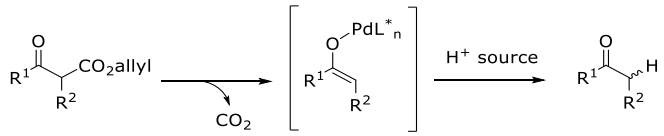


Figure 1.65. Examples of oxindole-based biologically active products.

Owing the importance of C-3 substituted oxindoles, great efforts have been made to find synthetic methods for accessing to this class of scaffolds. Among enantioselective α-substituted oxindoles, α-aryl oxindoles has been less developed.

The enantioselective protonation of achiral metal enolates or enol equivalents involving chiral proton sources is an efficient route to access carbonyl compounds with tertiary carbon stereocenters at α-position. However, most of the reported methods presents some limitations, such as limited substrate scope, only few of them are catalytic and they do not provide a general solution for the enantioselective protonation of enolates.[256]

An alternative to this synthetic route is the Pd-catalyzed decarboxylative protonation. In this reaction a prochiral enolate formed from the decarboxylation of the substrate was intercepted by a proton source, leading the tertiary α-substituted carbonyl compound (Scheme 1.8).



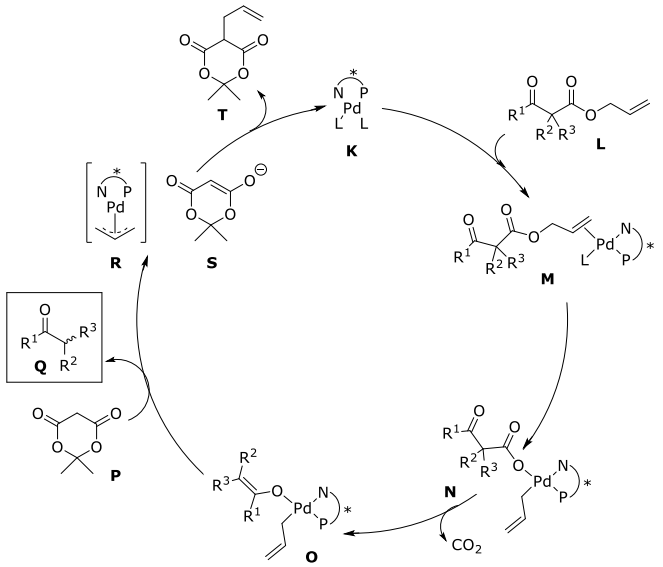
Scheme 1.8. Asymmetric Pd-catalyzed decarboxylative protonation.

1.3.1. The mechanism

Despite the mechanism for the Pd-catalyzed asymmetric decarboxylative allylation of allyl β-ketoesters has been investigated both experimentally and computationally, the mechanism for the decarboxylative protonation is still not understood.[257] The actual mechanism proposal for decarboxylative protonation mainly relies on some preliminary kinetic experiments developed by Stoltz *et al*. with allyl β-ketoesters.[258]

The proposed catalytic cycle consists in five steps (Scheme 1.9), where first is obtained the Pd(0) active species **K** by complexation of P,N-based ligands to Pd catalyst precursor. Then, olefin coordination occurs and this new Pd(0) complex **M** undergoes an oxidative addition forming an alkoxy intermediate **N**. After that, decarboxylation take place leading the formation of a prochiral enolate **O** which will attack to the acid proton of the proton source **P** by a proton transfer step providing the α-substituted compound **Q**. Finally, a reductive elimination will provide the regeneration of the active species **K** and the formation of the side product monoarylated-H^+ source **T**.

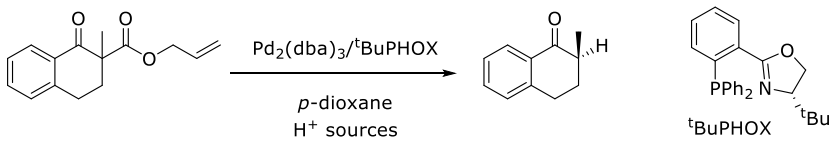
By kinetic studies, Stoltz *et al*. studied the variation of the substrate concentration over the time by NMR spectroscopy and found a zero-order dependence on substrate concentration which suggests that the substrate reacts very fast.[259] Although these results give some information regarding the first two steps of the catalytic cycle (the coordination and oxidative addition), further studies are required to elucidate the mechanism and the origin of the enantioselectivity.



Scheme 1.9. Proposed catalytic cycle for the enantioselective Pd-catalyzed decarboxylative protonation of β-ketoesters.

1.3.2. Previous work

Pd-catalyzed decarboxylative protonation was first introduced by Stoltz *et al*. in 2006.[260] They reported the successful enantioselective protonation of a wide scope of racemic β-ketoesters to obtain chiral α-tertiary cyclic ketones with high enantioselectivities (up to 92% ee) using PHOX-based ligand (Scheme 1.10). Several achiral organic proton sources were tested and the proton source which provide the best results was the commercially available Meldrum's acid. Concerning to the ligand, bulky substituents on the oxazoline moiety provided the best enantioselectivities for the decarboxylative protonation of β-ketoesters.

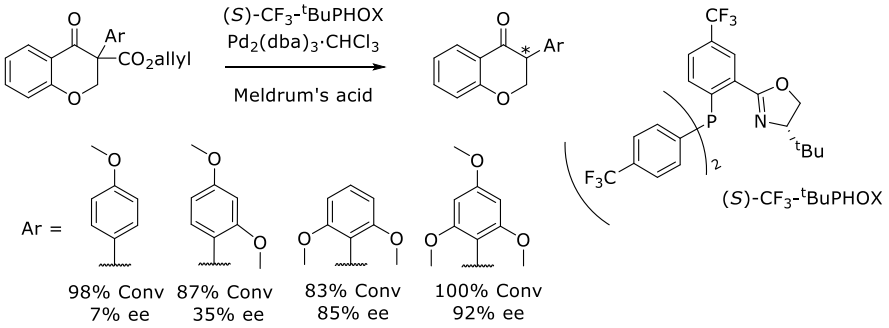


Scheme 1.10. Pd-catalyzed decarboxylation protonation of β-ketoesters.

This transformation provides α-tertiary ketones with various alkyl groups in excellent yields and enantioselectivities, however α-aryl examples are not reported. In this line, more recently, Guiry *et al*. reported the Pd-decarboxylative protonation of three different type of α-aryl substituted carbonyl-containing compounds.[257a,261]

First, they reported the catalytic synthesis of isoflavanones from α-aryl-β-ketoesters achieving high enantioselectivities (up to 97% ee) for a wide range of sterically hindered

aryl groups. They applied different PHOX-based ligands in the Pd-decarboxylative protonation of α-aryl-β-ketoesters. They found that the use of electron deficient (*S*)-CF_3-^{t}BuPHOX ligand (Scheme 1.11) increased the enantioselectivities obtained compared to ^{t}BuPHOX ligand (92% ee compared to 78% ee, respectively). In this study, the authors used several aromatic substituted-moieties to determine their influence on the enantioselectivity (Scheme 1.11). They found that the bulky substituents on the aryl group and, also on the oxazoline moiety, play an important role in the enantioselectivity of the reaction.



Scheme 1.11. Asymmetric catalyzed decarboxylative protonation of isoflovanones.

Based on their catalytic results, the authors propose an intermediate for the enantiodetermining step of the process. This key intermediate consists in a prochiral palladium enolate where one of the *ortho*-methoxy groups and the ^{t}Bu group of the oxazoline blocks the *Re*-face of the enolate and ensures the protonation through the *Si*-face (Figure 1.66).

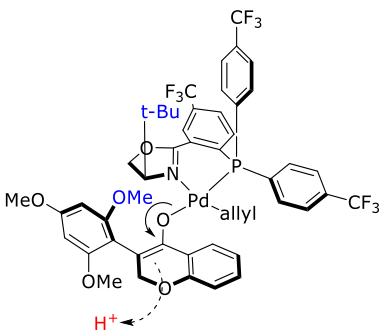
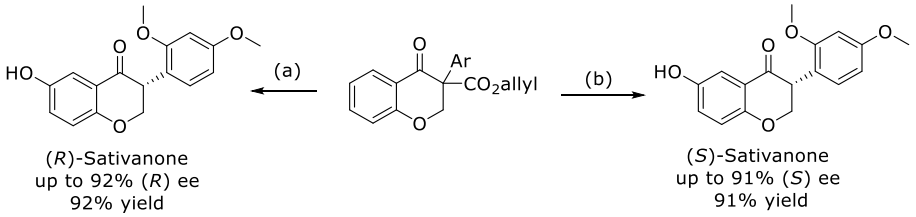


Figure 1.66. Proposed transition state in asymmetric protonation.

Working on the synthesis of Sativanone,[261b] Guiry *et al*. found that changing the proton source, using formic acid instead of Meldrum's acid, also provides excellent enantioselectivities, but leading to the opposite enantiomer. This phenomenon indicated that the enantiodetermining step could be the proton transfer, and changing the proton

source, the key intermediate would be different, and so will allow the switch of the enantioselectivity of the reaction (Scheme 1.12).[261b]



Scheme 1.12. Enantiodivergence observed in the preparation of Sativanone with different proton sources. (a) Meldrum's acid used as proton source. (b) Formic acid used as proton source.

The ability to obtain both enantiomers of a chiral molecule using the same chiral ligand is a valuable methodology in organic synthesis and represents a significant challenge. Previously, dual stereocontrol has been achieved by variation of catalyst substituents and changing the metal center or precursor. In this instance they have shown that these factors are not the cause of the observed switch in enantioselectivity. Interestingly, the rates of the reactions are significantly different; such that the Meldrum's acid reaction is complete in 30 min, whereas the formic acid reaction takes up to 10 h.

In 2014, Guiry *et al*. were able to generate enantiomerically enriched α-aryl tertiary stereocenters in cyclic ketones via Pd-decarboxylative protonation approach using the same methodology as for the synthesis of isoflavanones (Figure 1.70).[261c] They could also see the influence of the substituents in the aryl group on the enantioselectivity: the more sterically hindered, the highest enantiodiscrimination is obtained.

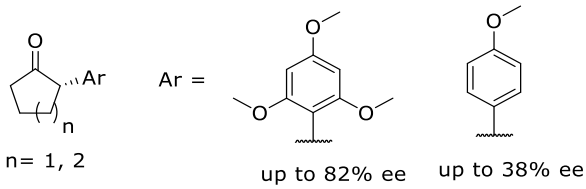
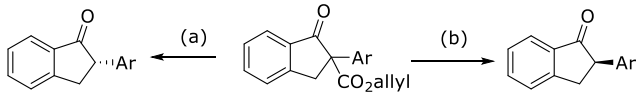


Figure 1.70. Asymmetric Pd-decarboxylative protonation. Generation of α-tertiary stereocenters in cyclic ketones.

Later, they described the development of an efficient enantiodivergent synthesis of sterically hindered tertiary α-aryl-1-indanones from the corresponding α-aryl-β-keto allyl esters (Scheme 1.13).[257a] Again, by switching the achiral proton source, both enantiomers of a series of tertiary α-aryl-1-indanones are readily accessed from the corresponding α-aryl-β-keto allyl esters. Enantioselectivities up to 94% (*S*) and 92% (*R*) were achieved using Meldrum's acid and formic acid, respectively.



Scheme 1.13. Enantiodivergence synthesis of tertiary α-aryl-1-indanones. (a) Meldrum's acid used as proton source. (b) Formic acid used as proton source.

Based on the experimental evidence of this studies, they suggest that the decarboxylative protonation reaction with formic acid may occur via an alternative catalytic cycle, where an hydridopalladium enolate is involved resulting in an inner-sphere-type protonation to a different face of the enolate than with Meldrum's acid.

1.5. References

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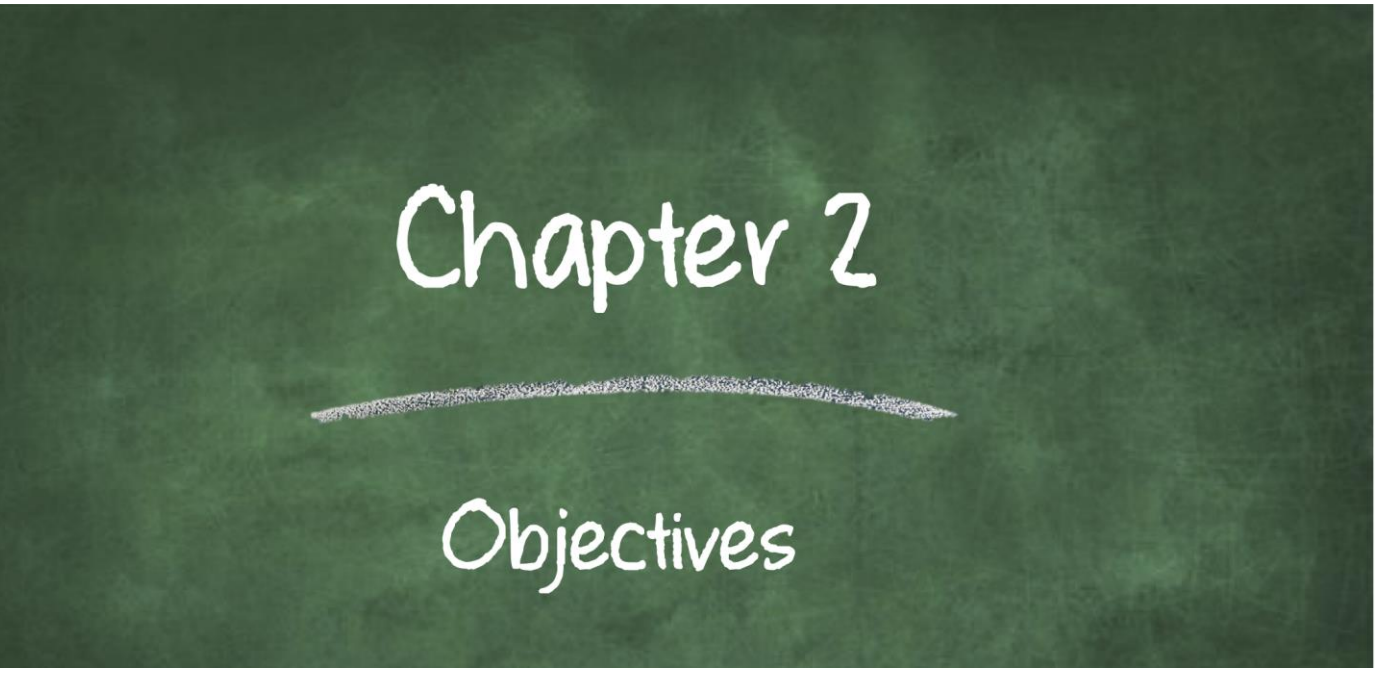
UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull


Chapter 2
Objectives

UNIVERSITAT ROVIRA I VIRGILI
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2. Objectives

The objective of this thesis was focused on the development of several modular chiral ligand libraries in order to apply them in three main relevant asymmetric catalytic transformations: (1) Rh- and Ir-catalyzed hydrogenation, (2) Pd-catalyzed allylic substitution and (3) Pd-catalyzed decarboxylative protonation. Next, we compile for each catalytic reaction the ligands developed.

1. For the Rh- and Ir-catalyzed asymmetric hydrogenation twelve families of heterodonor ligands have been synthesized. Seven of them are P-oxazoline/thiazole/sulfoximine/pyridine ligand libraries (P= phosphine, phosphinite, phosphonite, phosphite and phosphoroamidite), four are P-thioethers (P= phosphine, phosphinite and phosphite) and one is a *N*-phosphine-phosphite ligand library. The specific ligand libraries are collected below.

1.1. Heterodonor P-oxazoline/thiazole/sulfoximine/pyridine ligand libraries

1.1.1. The bicyclic phosphoroamidite-oxazoline/thiazole ligands **L1**-**L2a**-**b** (Figure 2.1) for application in the Ir-catalyzed hydrogenation of minimally functionalized olefins. The design of ligands **L1**-**L2** derives from a previous successful generation of bicyclic *N*-phosphine-oxazoline/thiazole ligands, by replacing the *N*-phosphine group with π-acceptor biaryl phosphoroamidite moiety (**a**-**b**).

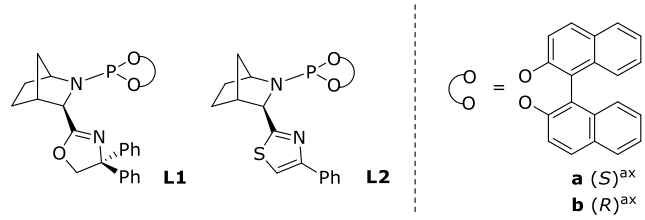


Figure 2.1. Phosphoroamidite-oxazoline/thiazole ligands **L1**-**L2a**-**b**.

1.1.2. The PHOX-based phosphite-oxazoline ligands **L3**-**L9a**-**g** (Figure 2.2) for application in the Rh- and Ir-catalyzed hydrogenation of minimally functionalized olefins and cyclic β-enamides. Ligands **L3**-**L6** are based on privileged phosphine-oxazoline PHOX ligands in which the phosphine was replaced with several biaryl phosphite moieties (**a**-**g**). Ligands **L7**-**L9** differ from previous ligands by a methylene group spacer between the oxazoline and the phenyl ring of the ligand backbone.

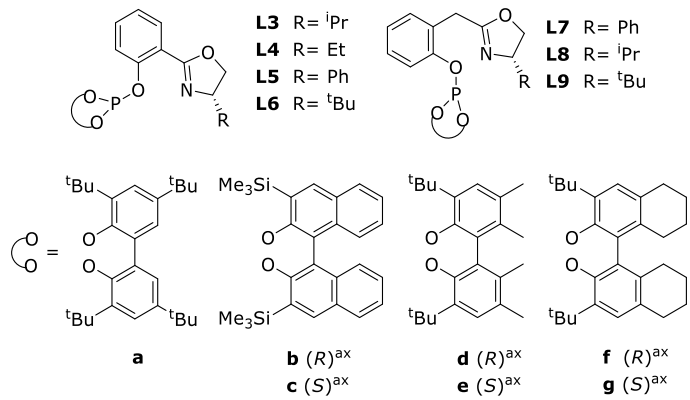


Figure 2.2. PHOX-based phosphite-oxazoline ligands **L3**-**L9a**-**g**.

1.1.3. The phosphite/phosphinite-oxazoline ligands **L10**-**L16a**-**i** (Figure 2.3) for application in the Ir-catalyzed hydrogenation of minimally functionalized olefins. They differ from phosphite-oxazoline PHOX-based ligands **L3**-**L9**, previously presented in Figure 2.2, in the presence of a chiral alkyl chain instead of the flat *ortho*-phenylene tether. We have also studied the effect of several phosphinite moieties (**g**-**i**).

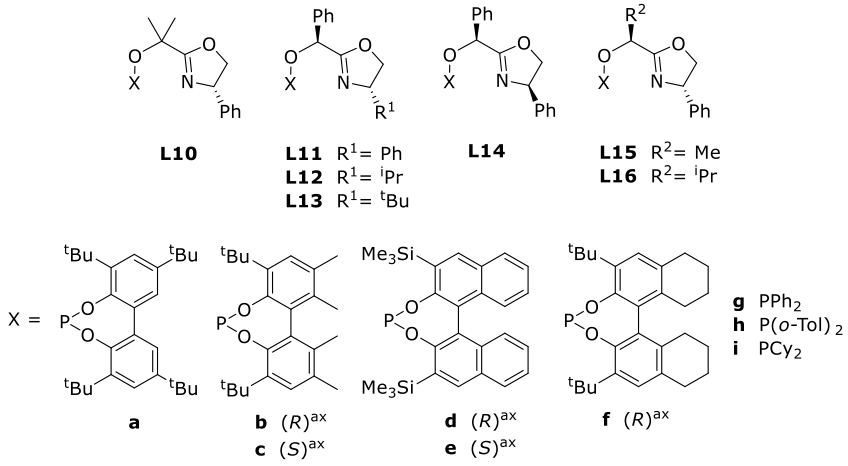
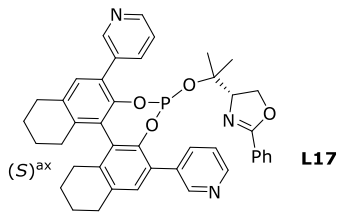


Figure 2.3. Phosphite/phosphinite-oxazoline ligands **L10**-**L16a**-**i**.

1.1.4. The synthesis of **L17** (Figure 2.4) for further inclusion in a supramolecular cage. This ligand contains a modified biaryl phosphite moiety with *meta*-pyridine groups which interact with Zn-porphyrins building blocks of the supramolecular cage.



L17

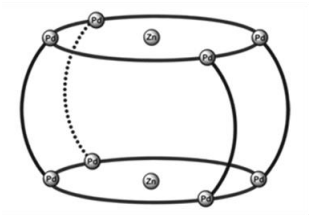
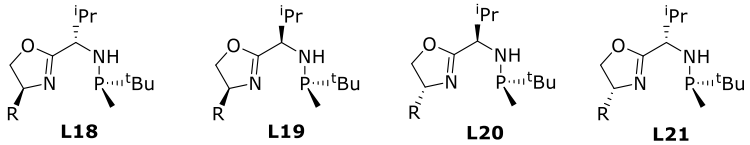


Figure 2.4. Phosphite-oxazoline ligand **L17** and a representation of the supramolecular cage.

1.1.5. The chiral aminophosphine-oxazoline ligands **L18**-**L21a**-**c** (Figure 2.5) for application in the Ir-catalyzed hydrogenation of minimally functionalized olefins. This family of ligands introduce a P*-stereogenic moiety instead of phosphinite/phosphite groups.

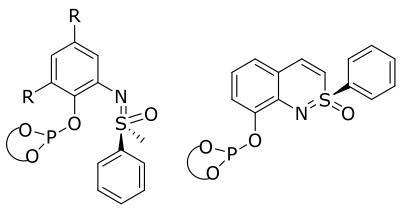


L18 **L19** **L20** **L21**

a R= Ph; **b** R= ^{i}Pr; **c** R= ^{t}Bu

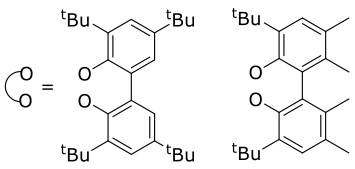
Figure 2.5. Chiral aminophosphine-oxazoline ligands **L18**-**L21a**-**c**.

1.1.6. The phosphite-sulfoximine ligands **L22**-**L24a**-**c** (Figure 2.6) for application in the Ir-catalyzed hydrogenation of minimally functionalized olefins. With these ligands we studied the effect of replacing the oxazoline moiety by a sulfoximine functionality while maintaining the π-acceptor biaryl phosphite moiety.



L22 R= H
L23 R= ^{t}Bu

L24



a

b $(R)^{ax}$
c $(S)^{ax}$

Figure 2.6. Phosphite-sulfoximine ligands **L22**-**L24a**-**c**.

1.1.7. The synthesis of novel cationic phosphonite-pyridine ligands **L25** and **L26** (Figure 2.7; Dipp= 2,6-diisopropylphenyl). The architecture of the cationic phosphonite moiety confers to the resulting ligand strong acceptor properties which usually surpass those of traditional acceptor ligands such as phosphites.

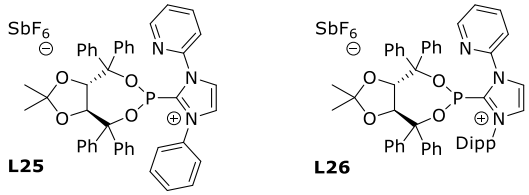
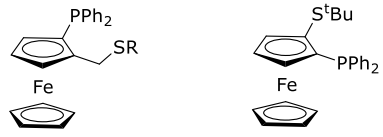


Figure 2.7. Cationic phosphonite-pyridine ligands **L25** and **L26**.

1.2. Heterodonor P-thioether ligand libraries

1.2.1. The chiral ferrocene-based P,S-ligand library **L27**-**L38** (Figure 2.8) for application in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Ligands **L27**-**L38** incorporate the advantages of ferrocenes and the robustness of the thioether moiety.



L27 R= Et **L32** R= Ph
L28 R= ^{i}Pr **L33** R= Bn
L29 R= Cy **L34** R= 1-Naphthyl
L30 R= ^{t}Bu **L35** R= 2,6-Me_2-C_6H_3
L31 R= Ad

L36

L37 R= Ph
L38 R= 2,6-Me_2-C_6H_3

Figure 2.8. Chiral ferrocene-based P,S-ligand library **L27**-**L38**.

1.2.2. The cyclohexane-based P-thioether ligands **L39**-**L40a**-**g** (Figure 2.9) for application in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Ligands **L39**-**L40a**-**g** combine the robustness of the thioether group with the high modularity of the phosphite/phosphinite moiety. Moreover, the simplicity of these ligands facilitates the performance of a combination of HP-NMR spectroscopy and theoretical studies to identify the catalytically competent intermediates.

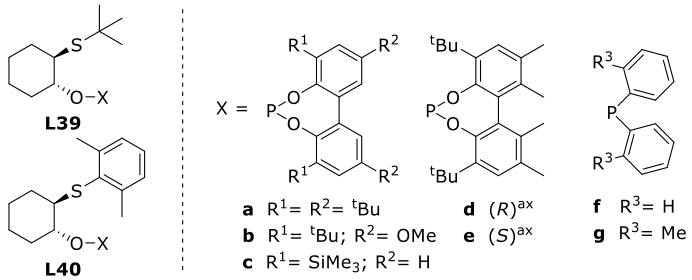


Figure 2.9. Cyclohexane-based P-thioether ligands **L39**-**L40a**-**g**.

1.2.3. The phosphite/phosphinite-thioether ligands **L41**-**L48a**-**g** (Figure 2.10) for application in the Ir-catalyzed hydrogenation of minimally functionalized olefins. This ligand library **L41**-**L48a**-**g** was synthetized in only three steps from inexpensive indene and has high modularity in both thioether and P-moiety.

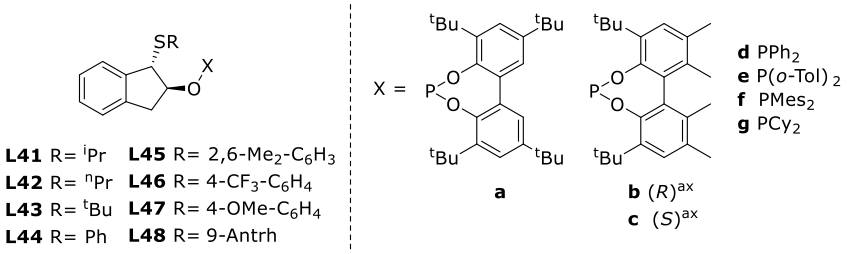


Figure 2.10. Phosphite/phosphinite-thioether ligands **L41**-**L48a**-**g**.

1.2.4. The phosphite/phosphinite-thioether ligands **L49**-**L50a**-**e** (Figure 2.11; Ad= 1-adamantyl) for application in the Ir-catalyzed hydrogenation of minimally functionalized olefins. Ligands **L49**-**L50** differ from the previous phosphite/phosphinite-thioether ligands **L41**-**L48** (Figure 2.10) by the increase of the flexibility in the ligand backbone.

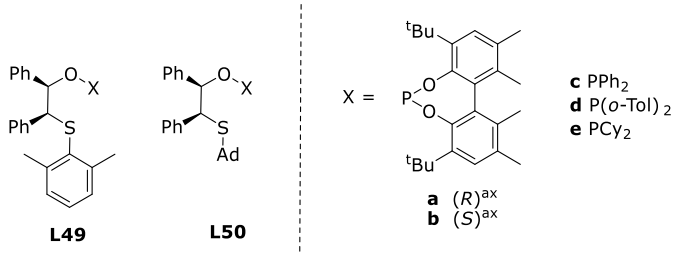


Figure 2.11. Phosphite-phosphinite-thioether ligands **L49**-**L50a**-**e**.

1.3. The P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**L54a**-**c** (Figure 2.12) for application in the Rh-catalyzed hydrogenation of functionalized olefins. These ligands possess two highly modular functionalities (phosphite and phosphine moieties). Ligands **L54** have a more rigid backbone than ligands **L51**-**L53**.

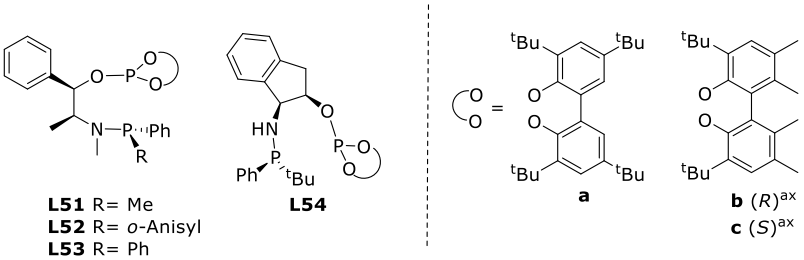


Figure 2.12. P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**L54a**-**c**.

2. For the Pd-catalyzed asymmetric allylic substitution six families of ligands have been developed. Four of them are P-oxazoline/amino/hydrazone ligand libraries (P= phosphinite and phosphite), one is a P-thioether ligand libraries (P= phosphinite and phosphite) and one is a *N*-phosphine-phosphite ligand library. The specific ligand libraries are listed below.

2.1. Heterodonor P-oxazoline/amino/hydrazone ligand libraries

2.1.1. The previously described PHOX-based phosphite/phosphinite-oxazoline ligands **L3a**-**g** (Figure 2.2) and **L10**-**L16a**-**e** (Figure 2.3). In this work, a DFT study to identify the relevant intermediates of the catalytic cycle has been performed in to better understand the enantioselectivities obtained.

2.1.2. The phosphite-hydrazone ligand library **L55a**-**c** (Figure 2.13) which differs from the previous presented phosphite-oxazoline PHOX-based ligands **L3**-**L9** (Figure 2.2) by the replacement of the oxazoline group by a hydrazone moiety.

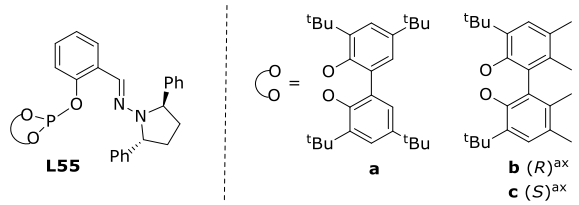


Figure 2.13. Phosphite-hydrazone ligands **L55a**-**c**.

2.1.3. The phosphite-amino ligand library **L56**-**L61a**-**g** (Figure 2.14). This ligand library combines the robustness of the amino group with a highly modular skeleton. In this work, a DFT study has been performed and used for further optimization of the ligand backbone.

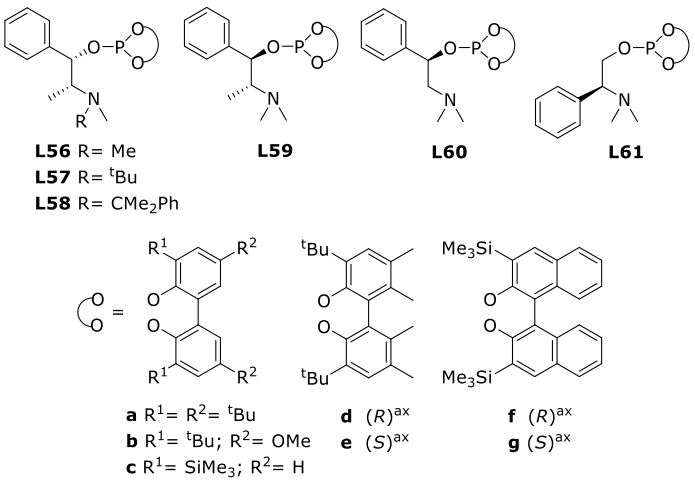


Figure 2.14. Phosphite-amino ligand library **L56**-**L61a**-**g**.

2.2. Heterodonor P-thioether ligand libraries

2.2.1. The previously described phosphite/phosphinite-thioether ligands **L41**-**L48a**-**g** (Figure 2.10). A DFT study has been carried out to help in the optimization process of the ligand backbone.

2.3. The previously described P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**L54a**-**c** (Figure 2.12).

3. For the asymmetric Pd-catalyzed decarboxylative protonation three P,N-ligand libraries (Figure 2.15) have been applied in order to synthetize α-aryl oxindoles from α-aryl-β-amido allyl esters. The first ligand library is the PHOX-based phosphite-oxazoline ligand library **L3**-**L6a** previously presented in Figure 2.2. In the second ligand library (**L62**-**L65a**-**c**) the flat *ortho*-phenylene tether in **L3**-**L6** has been replaced by an alkyl chain bonded to carbon 4 of the oxazoline moiety. In the third one (ligands **L66**-**L73a**-**e**) the oxazoline group has been replaced by a more robust pyridine group. In this part, experimental and theoretical mechanistic investigations have been performed.

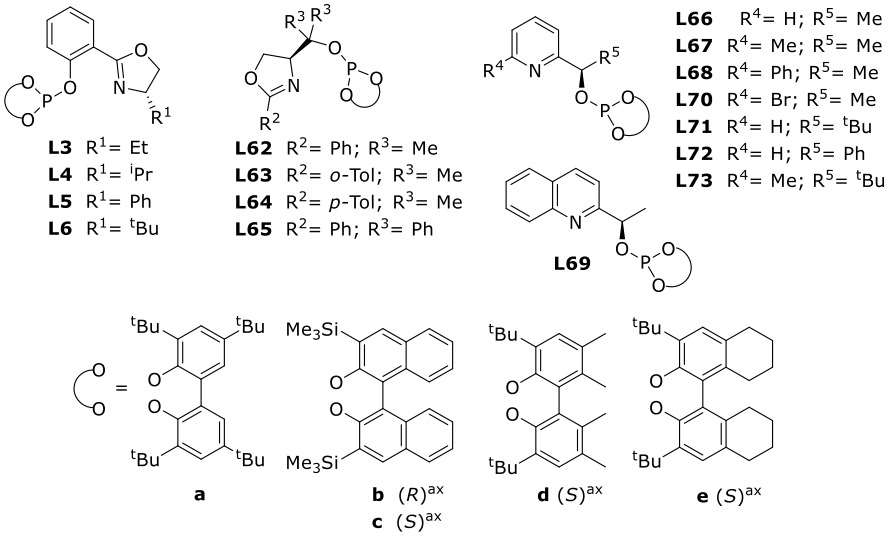
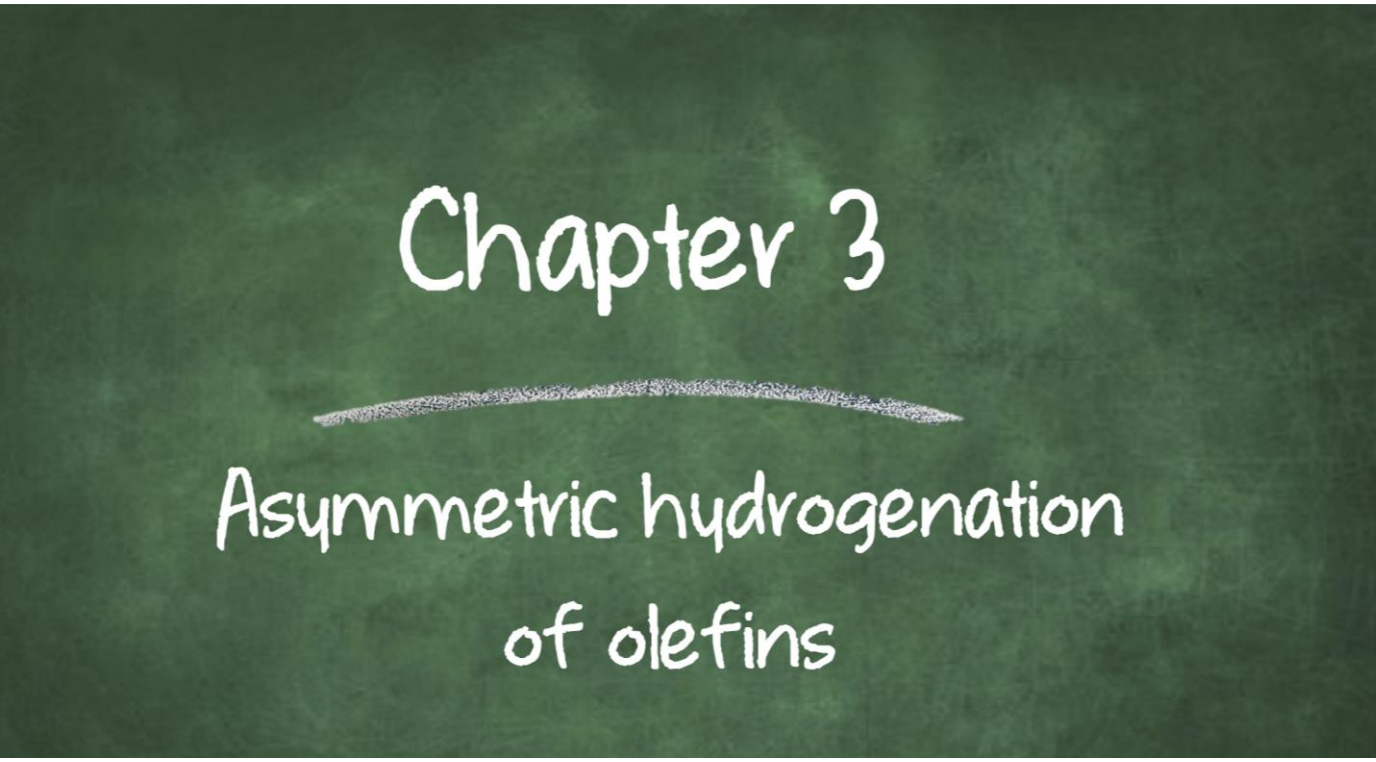


Figure 2.15. Phosphite-nitrogen ligand families.


Chapter 3
Asymmetric hydrogenation
of olefins

UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull

3.1. Extending the substrate scope of bicyclic P-oxazoline/thiazole ligands for Ir-catalyzed hydrogenation of unfunctionalized olefins by introducing a biaryl phosphoroamidite group

Biosca, M.; Paptchikhine, A.; Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem. Eur. J.* **2015**, *21*, 3455.

In collaboration with the group of Prof. P. G. Andersson (Stockholm University).

Abstract: This study identifies a series of Ir-bicyclic phosphoroamidite-oxazoline/thiazole catalytic systems that can hydrogenate a wide range of minimally functionalized olefins (including *E*- and *Z*-tri- and disubstituted substrates, vinylsilanes, enol phosphinates, tri- and disubstituted alkenylboronic esters and α,β-unsaturated enones) in high enantioselectivities (ee values up to 99%) and conversions. The design of the new phosphoroamidite-oxazoline/thiazole ligands derives from a previous successful generation of bicyclic *N*-phosphine-oxazoline/thiazole ligands, by replacing the *N*-phosphine group with a π-acceptor biaryl phosphoroamidite moiety. A small but structurally important family of Ir-phosphoroamidite-oxazoline/thiazole precatalysts has thus been synthesized by changing the nature of the N-donor group (either oxazoline or thiazole) and the configuration at the biaryl phosphoroamidite moiety. The substitution of the *N*-phosphine by a phosphoroamidite group in the bicyclic *N*-phosphine-oxazoline/thiazole ligands extended the range of olefins that can be successfully hydrogenated.

3.1.1. Introduction

Chirality is a fundamental property of a wide variety of technologically and biologically interesting products. Enormous efforts are being made to discover enantioselective routes that can be used to create stereogenic centers.[1] Of these routes, asymmetric hydrogenation is one of the most efficient, sustainable, and straightforward. This approach can be used to achieve high selectivity, has perfect atom economy, and is operational simple.[1-2] For this process, the use of Rh/Ru-P,P based catalysts is well known, but it normally requires substrates with a good coordination group close to the C=C double bond to achieve high selectivity.[1,3] To address this limitation, the asymmetric reduction of olefins with chiral Ir-P,N catalysts has emerged as an effective method for producing complex chiral compounds from simple olefins.[4] In 1998, Pfaltz *et al*. reported the first successful application of an [Ir(P,N)(cod)]BAr_F chiral catalysts library (P,N= phosphine-oxazoline ligands (PHOX); cod= 1,5-cycloocatadiene) to a limited range of minimally functionalized olefins.[5] Pfaltz and other groups then focused on Ir-catalysts based on a wide range of new ligands (mainly P,N compounds), which

significantly broadened the substrate scope. Most of ligand designs were based on replacing the phosphine moiety in previous PHOX ligands with a phosphinite or a carbene group,[6] and the oxazoline moiety with other nitrogen groups such as pyridine,[7] thiazole,[6o,8] oxazole[9], and imidazole.[10,11] The latest breakthrough in the design of ligands for Ir-catalyzed hydrogenation was the substitution of the phosphinite/phosphine group by a π-acceptor biaryl phosphite moiety. In this context, it was recently shown that the presence of biaryl-phosphite groups in the ligand increases activity and substrate versatility.[12] Several mixed phosphite-nitrogen compounds have thus emerged as extremely effective ligands that provide better substrate versatility than earlier Ir-phosphinite/phosphine-N systems and higher activities and enantioselectivities for many largely unfunctionalized *E*/*Z*-trisubstituted and 1,1'-disubstituted olefins. Although Ir-P,N catalysts are powerful tools for reducing minimally functionalized olefins and they complement Rh/Ru-catalysts, their activity and selectivity for some significant substrates still need to be improved if they are to be used to synthetize more complex molecules. Therefore, novel, easy to handle, readily accessible, and highly efficient chiral ligands that enhance the application range still need to be found. Here, we report the successful application of a small but structurally valuable library of phosphoroamidite-oxazoline/thiazole ligands **L1**-**L2a**-**b** (Figure 3.1.1) in the Ir-catalyzed hydrogenation of a large number of minimally functionalized alkenes, with the addition of concrete examples with neighboring polar groups.

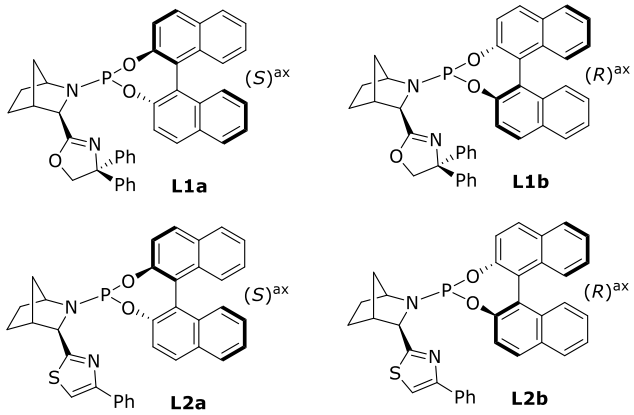


Figure 3.1.1. Phosphoroamidite-oxazoline/thiazole ligands **L1**-**L2a**-**b**.

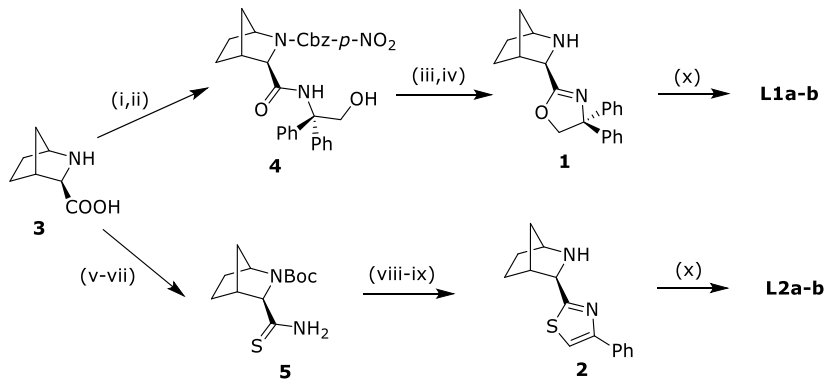
The new ligands are based on a first successful generation of bicyclic *N*-phosphine-oxazoline/thiazole ligands[6h,8e] in which the *N*-phosphine group is replaced by a π-acceptor biaryl phosphoroamidite moiety. The previous generation of bicyclic *N*-phosphine-oxazoline/thiazole ligands was one of the best-performing ligand families developed for Ir-catalyzed hydrogenation, and they proved to be highly efficient in the hydrogenation of many minimally functionalized aryl-alkyl *E*-trisubstituted olefins.[6h,8e,13] Despite this, the enantioselectivity achieved by using these ligands for such important

substrates as *Z*-analogues, 1,1'-disubstituted olefins, and some compounds containing weakly coordinating groups still needs to be improved. With the simple biaryl phosphoroamidite-oxazoline/thiazole design introduced here (Figure 3.1.1), we expect to increase substrate versatility in the hydrogenation of largely unfunctionalized olefins. Interestingly, in addition to having the fundamental advantages of the π-acceptor properties of the phosphoroamidite moiety, ligands **L1**-**L2a**-**b** are also more robust to air and other oxidizing agents than phosphines and phosphinites and they are easily synthesized from readily available alcohols. Although phosphoroamidite-based ligands have been successfully used in other enantioselective reactions,[14] their potential as a source of highly effective chiral ligands in Ir-catalyzed hydrogenation remains unexplored.[15]

3.1.2. Results and Discussion

3.1.2.1. Synthesis of ligands

The sequence of ligand synthesis is summarized in Scheme 3.1.1. Ligands **L1**-**L2a**-**b** were synthesized very efficiently from the appropriate, easily accessible amino-oxazoline **1** and amino-thiazole **2** compounds.[8e,16] Compounds **1** and **2** were prepared in four and five steps, respectively, by following previously reported procedures from (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (**3**),[17] which is readily available on a multigram scale from a stereoselective aza-Diels-Alder reaction. The last step of the synthesis is the same for all ligands (step x). Treating compounds **1** and **2** with one equivalent of the appropriate phosphorochloridite formed *in situ*[18] in the presence of triethylamine provided direct access to the desired phosphoroamidite-oxazoline/thiazole ligands **L1**-**L2a**-**b**.

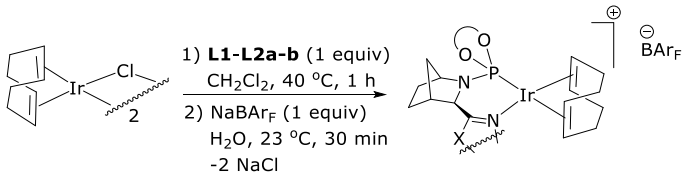


Scheme 3.1.1. Synthetic route for the synthesis of new phosphoroamidite-oxazoline/thiazole ligands **L1**-**L2a**-**b**: (i) *p*-NO_2-CbzCl, NaOH, dioxane/H_2O, rt; (ii) EDC, HOBt, 2-amino-2,2-diphenylethanol, CH_2Cl_2, rt; (iii) MsCl, NEt_3, CH_2Cl_2, 0 °C; (iv) Pd/C, H_2, EtOH, rt; (v) Boc_2O, THF/H_2O, rt; (vi) NH_4HCO_3, Py, dioxane; (vii) Lawesson's reagent, THF, rt; (viii) phenacyl bromide, $CaCO_3$, MeOH, reflux; (ix) HCl, THF, rt; (x) $ClP(OR)_2$, NEt_3, toluene, 80 °C.

All ligands were stable during purification on neutral silica under an atmosphere of argon and all were isolated as white solids. The ligands were stable in air and very stable to hydrolysis, so further manipulation/storage was carried out in air. Elemental analyses and HRMS-ESI spectra were consistent with the assigned structures. The ligands were also characterized by $^{31}P\{^{1}H\}$, ^{1}H, and $^{13}C\{^{1}H\}$ NMR spectroscopy. The spectral assignments, based on ^{1}H-^{1}H and ^{13}C-^{1}H correlation measurements, were as expected for these C_1-symmetric ligands.

3.1.2.2. Synthesis of Ir-catalyst precursors

The Ir-catalyst precursors were prepared in a two-step, one-pot procedure (Scheme 3.1.2). First, $[Ir(\mu\text{-}Cl)(cod)]_2$ reacts with one equivalent of the appropriate ligand. Then, Cl^-/BAr_F^- counterion exchange was achieved by reaction with $NaBAr_F$ in the presence of water.



Scheme 3.1.2. Synthetic route used for the synthesis of catalyst precursors [Ir(cod)(**L1**-**L2a**-**b**)]BAr_F.

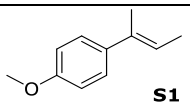
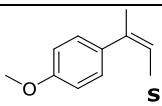
The iridium catalyst precursors were isolated in pure form as air-stable orange solids in excellent yields (92-96%) after simple extraction workup. No further purification was required. The elemental analyses were consistent with the assigned structures. The HRMS-ESI spectra of [Ir(cod)(**L1**-**L2a**-**b**)]BAr_F displayed the m/z signals for the heaviest ions that correspond to the loss of the BAr_F anion from the molecular species. The ^{1}H, ^{13}C, and ^{31}P NMR spectra show the expected pattern for these C_1-complexes. Variable-temperature (VT) NMR spectra in CD_2Cl_2 (+35 to -85 °C) showed that only one isomer was present in solution. In all cases, one singlet in the $^{31}P\{^{1}H\}$ NMR spectra was observed.

3.1.2.3. Asymmetric Ir-catalyzed hydrogenation of trisubstituted substrates

The asymmetric hydrogenation of minimally functionalized trisubstituted olefins is highly dependent on the olefin geometry.[4] In this respect, *Z*-trisubstituted olefins are commonly hydrogenated less enantioselectivity than the corresponding *E*-isomers. To evaluate the efficiency of ligands **L1**-**L2a**-**b** in the hydrogenation of olefins with different geometry, we initially tested the ligands in the asymmetric reduction of the model

substrate **S1** and the hydrogenation of *Z*-substrate **S2** (Table 3.1.1). In general, the enantioselectivities were found to be highly dependent on the configuration of the biaryl phosphoroamidite group. Reactions conducted with ligands containing a (*S*)-binaphthyl phosphoroamidite group proceeded with the highest enantioselectivities for both substrates (Table 3.1.1, entry 1 vs. 2). However, whereas for substrate **S1** the nature of the N-donor group had a little effect on enantioselectivity, for the more demanding substrate **S2**, the presence of the thiazole group had a positive effect on enantioselectivity. Of the four ligands, phosphoroamidite-thiazole ligand **L2a** provided excellent activities and enantioselectivities for both substrate types (ee values up to 83%[19]). We also studied these reactions at a low catalyst loading (0.25 mol%) using ligand **L2a**, which had provided the best results, and the excellent enantioselectivities were maintained (Table 3.1.1, entry 5).

Table 3.1.1. Ir-catalyzed hydrogenation of **S1** and **S2** using **L1**-**L2a**-**b**.[a]

		 **S1**		 **S2**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L1a**	100	92 (*R*)	100	82 (*S*)
2	**L1b**	100	37 (*R*)	100	3 (*S*)
3	**L2a**	100	95 (*R*)	100	97 (*S*)
4	**L2b**	100	95 (*R*)	100	56 (*S*)
5	**L2a**	100	95 (*R*)	100	97 (*S*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (50 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^1H NMR spectroscopic analysis after 2 h; [c] Enantiomeric excesses determined by GC analysis; [d] Reaction carried out at 0.25 mol% of Ir-catalyst precursor for 3 h.

To further establish the versatility of the reaction with the new ligands **L1**-**L2a**-**b**, we selected a representative family of substrates, some of which contained poorly coordinative groups; the most noteworthy results are shown in Figure 3.1.2 (for a complete series of results, see Table SI-1 in Supporting Information at the end of this chapter). We again found that the ligand components must be selected to suit each substrate to obtain the highest enantioselectivity. With the aim of comparing these results with the first generation of ligands and the state-of-art catalytic systems for each substrate, we have collected the results in Table SI-3 in the Supporting Information at the end of this chapter.

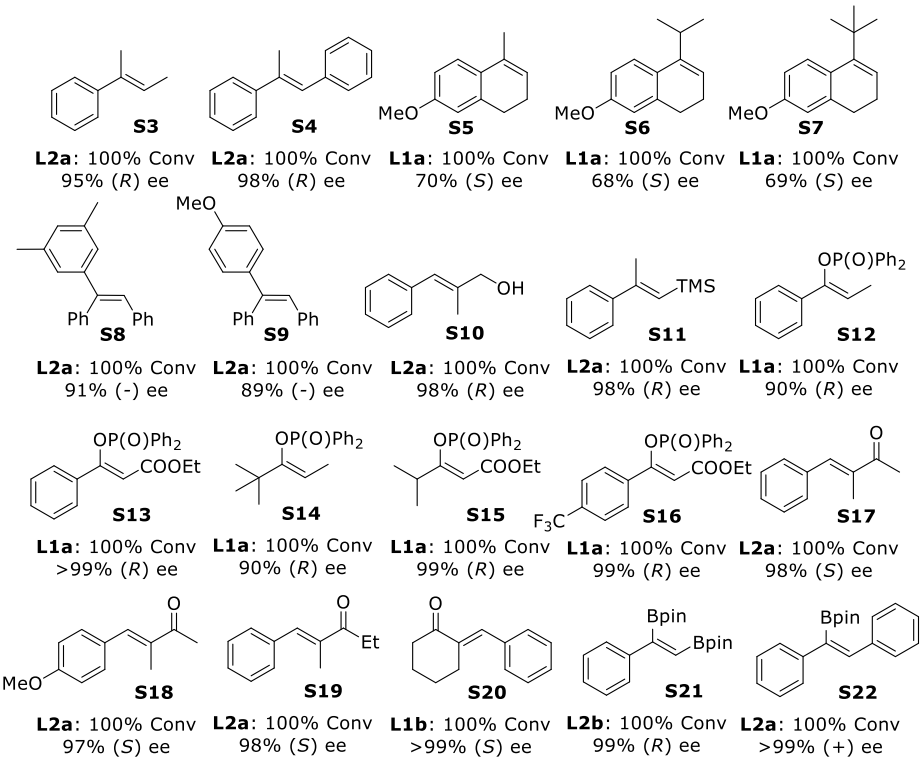


Figure 3.1.2. Selected results for the hydrogenation of trisubstituted olefins **S3**-**S22** by using [Ir(cod)(**L1**-**L2a**-**b**)]BAr_F catalyst precursors. Reaction conditions: Catalyst precursor (2 mol%), CH_2Cl_2, H_2 (50 bar), 4 h.

We first considered the reduction of substrates **S3** and **S4**, which differ from **S1** in the substituent in the aryl ring and the substituents *trans* to the aryl group. For both substrates, Ir/**L2a** also provided excellent enantioselectivities (up to 98%). For the more demanding dihydronaphthalenes **S5**-**S7**, enantioselectivities were as high as 70% but, unlike *Z*-**S2**, using the Ir/**L1a** catalytic system. Remarkably, the Ir/**L2a** catalyst also provided high enantioselectivities in the reduction of triaryl-substituted substrates **S8** and **S9** (ee values up to 91%), surpassing the enantioselectivities obtained by using the first-generation ligands. This latter substrate class has received little attention,[8f,11b,12c] although it provides an easy entry point to diarylmethine chiral centers, which are present in many important drugs.[20] We then looked into the hydrogenation of a broad range of key trisubstituted olefins with neighboring polar groups. Hydrogenation of these olefins is of particular interest because they can be further functionalized and become important intermediates for more complex chiral molecules. Interestingly, the reduction of allylic alcohol **S10** and vinylsilane **S11** with Ir/**L2a** proceeded with higher enantioselectivities than those achieved when the first generation of bicyclic *N*-phosphine-oxazoline/thiazole ligands was used.[8e,13c] The Ir/**L1a** catalytic system can also hydrogenate the sterically demanding enol phosphinates **S12**-**S16** with high

enantioselectivities that were comparable to those achieved with the first generation of ligands, which constitute the state-of-art for this substrate class.[13b] The effective hydrogenation of this type of substrates opens up an appealing route to chiral organophosphinates, which can be easily transformed into high-value compounds such as alcohols and phosphines. The excellent results obtained up to this point encouraged us to test the hydrogenation of α,β-unsaturated enones **S17**-**S20**, for which the related *N*-phosphine-oxazoline/thiazole counterparts provided low enantiocontrol.[21] Although hydrogenation of this type of substrate is an elegant path to ketones with a stereogenic center in the α-position to the carbonyl moiety, such substrates have been less studied and less successfully hydrogenated than other trisubstituted olefins.[6i,6x] We found that a range of enones could be hydrogenated with excellent enantioselectivities that were comparable to the best values previously reported. Interestingly, all four of the tested ligands provided similar high enantioselectivities (96-98% ee for substrate **S17**; see the Supporting Information at the end of this chapter) irrespective of the configuration of the biaryl phosphoroamidite group and the nature of the N-donor group. This indicates that the backbone of the bicyclic phosphoroamidite-N ligand is particularly well suited to the specific electronic and steric requirements of α,β-unsaturated enones. We also found that hydrogenation of **S17**-**S20** yields products with opposite configuration to those achieved with the other *E*-trisubstituted olefins studied. This behavior has been observed previously and has been attributed to the strong polarization of the double bond.[4a,6o]

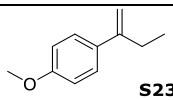
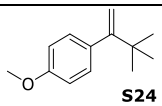
We finally turned our attention to the asymmetric reduction of alkenylboronic esters. Among the existing methods for preparing chiral organoboron compounds, this is one of the most sustainable and most straightforward. The synthesis of chiral organoboron compounds has recently received considerable attention; they are valuable organic intermediates because the C-B bond can be readily transformed into chiral C-N, C-O and C-C bonds. In this field, the reduction of alkenylboronic esters has been less investigated, and only a few catalytic systems have been used effectively.[11a,13a,22] Our results show that by correctly choosing the N-donor group (thiazole rather than oxazoline) and the configuration of the biaryl group ((*R*) for **S21** and (*S*) for **S22**) of the ligand, excellent enantioselectivities can be achieved for the reduction of two types of alkenylboronic esters containing either one or two (pinacolato)boron groups. The enantioselectivities achieved are among the best reported and they surpass those obtained with the first generation of ligands.[11a,13a,22]

In summary, the simple substitution of the *N*-phosphine by a phosphoroamidite group in the bicyclic *N*-phosphine-oxazoline/thiazole ligands extended the range of hydrogenated trisubstituted olefins and led to enantioselectivities that, for most of the substrates, were among the best reported so far (see Table SI-3 in the Supporting Information at the end of this chapter).[23]

3.1.2.4. Asymmetric Ir-catalyzed hydrogenation of 1,1'-disubstituted substrates

Unlike trisubstituted olefins, 1,1'-disubstituted olefins have not been successfully hydrogenated until very recently.[4a,4d] This is because the catalyst has the added difficulty of controlling not only the face selectivity coordination (only two substituents compared with the three of trisubstituted olefins), but also the isomerization of the olefins to form the more stable *E*-trisubstituted substrates, which are hydrogenated to form the opposite enantiomer.[4a,4d] To estimate how effective systems with ligands **L1**-**L2a**-**b** are at reducing this type of substrate, we first studied the hydrogenation of substrates **S23** and **S24**, which have different steric requirements at the alkyl chain (Table 3.1.2). In addition, whereas substrate **S23** is prone to isomerization, **S24** cannot isomerize. In all cases, full conversions were achieved by using 1 bar of H_2.[24]

Table 3.1.2. Ir-catalyzed hydrogenation of **S23** and **S24** using ligands **L1**-**L2a**-**b**.[a]

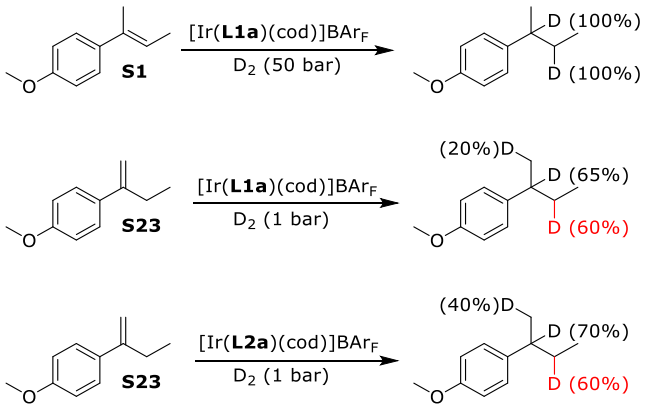
		 **S23**		 **S24**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L1a**	100	13 (*R*)	100	93 (*S*)
2	**L1b**	100	3 (*S*)	100	69 (*S*)
3	**L2a**	100	65 (S)	100	76 (*S*)
4	**L2b**	100	40 (*S*)	100	68 (*S*)
5	**L1a**	100	12 (*R*)	100	93 (*S*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (1 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^{1}H NMR spectroscopic analysis after 2 h; [c] Enantiomeric excesses determined by GC analysis; [d] Reaction carried out at 0.25 mol% of Ir-catalyst precursor for 3 h.

We found that the effect of the ligand parameters on enantioselectivity is different for the two substrates. Whereas for **S23** the effect is like that observed for **S1** and **S2** (the enantioselectivity was highest with phosphoroamidite-thiazole ligand **L2a**), the enantioselectivity for **S24** was best with the phosphoroamidite-oxazoline ligand **L1a**. We also found that enantioselectivity are highly dependent on the nature of the alkyl chain of the substrate (Table 3.1.2). Whereas enantioselectivities up to 93% ee can be achieved with **S24**, only moderate enantiocontrol was obtained in the reduction of **S23** (up to 65% ee). This suggests that competition between isomerization and direct hydrogenation may be responsible for the moderate enantioselectivities achieved by using **S23**. However, face selectivity issues cannot be excluded.

To address this point, we performed deuterium labelling experiments (Scheme 3.1.3). For this purpose, we performed the reduction of **S1** and **S23** with deuterium. In contrast to **S1**, the reduction of **S23** with deuterium led to the incorporation of

deuterium not only at the expected positions (direct addition to the double bond) but also at the allylic position, which is indicative of the presence of a competing isomerization process.



Scheme 3.1.3. Deuterium labeling experiments with substrates **S1** and **S23**. The percentage of incorporation of deuterium atoms is shown in parentheses. The results of the indirect addition of deuterium due to the isomerization process are showed in red.

It has been suggested that this isomerization process can proceed either through the formation of the Ir-π-allyl intermediates or through protonation of the double bond at the terminal position, which gives a stabilized carbocation.[6d,25] Accordingly, the mass spectra data of the resulting deuterated products, in the deuterium addition to **S23**, indicated the presence of reduced species with more than two deuterium atoms incorporated into the product.

We also studied these reactions at low catalyst loading (0.25 mol%) and found that the catalytic performance was maintained (Table 3.1.2, entry 5).

In line with the observed isomerization, similar moderate enantioselectivities were achieved in the hydrogenation of substrates **S25**-**S28** irrespective of the steric demands of the alkyl substituents (Figure 3.1.3).

We then focused on evaluating how the electronic and steric properties of the aryl group of the substrate affected the catalytic performance. For this purpose, a wide range of α-*tert*-butylstyrene type substrates (**S29-S35**) were tested (Figure 3.1.3). Advantageously, we found that enantioselectivity (ee values up to 98%) is relatively insensitive to changes in the electronic and steric properties of the aryl group. However, the highest enantioselectivity of the series was achieved in the hydrogenation of substrates containing either electron-withdrawing groups at the *para*-position (**S29**) or substituents at the *ortho*-position (**S34** and **S35**) of the aryl group.

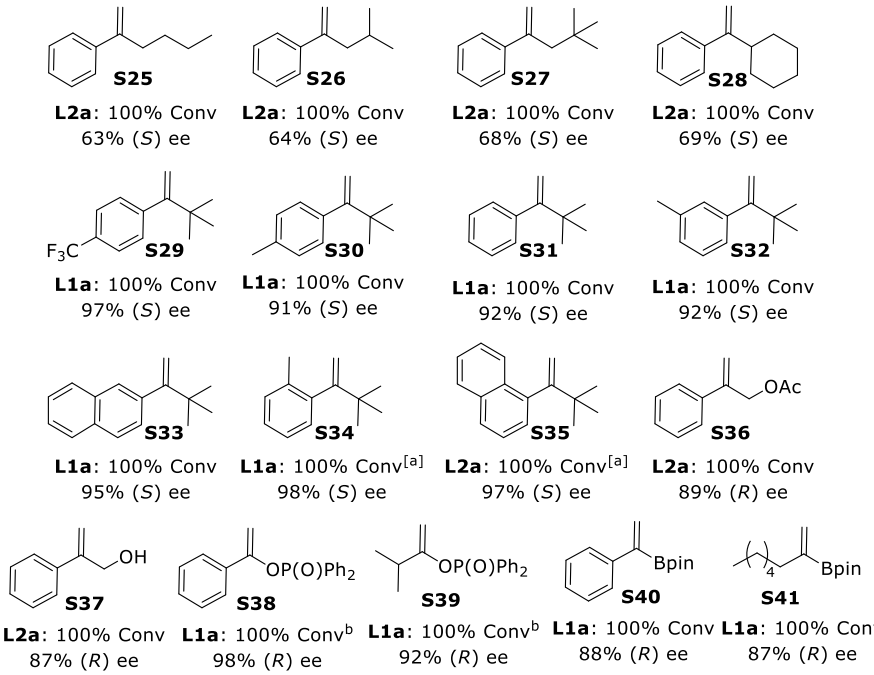


Figure 3.1.3. Selected results for the hydrogenation of 1,1'-disubstituted olefins **S25**-**S41** by using [Ir(cod)(**L1**-**L2a**-**b**)]BAr_F catalyst precursors. Reaction conditions: Catalyst precursor (2 mol%), CH_2Cl_2, H_2 (1 bar), 4 h. [a] Reactions carried out for 8 h; [b] Reactions carried out at 50 bar H2 for 12 h.

Finally, we also investigated the hydrogenation of relevant 1,1'-disubstituted olefins containing neighboring polar groups (Figure 3.1.3, substrates **S36**-**S41**). We were again able to fine tune the ligand to obtain high to excellent enantioselectivities (ee values up to 98%). The results are among the best reported for each substrate, even in the reduction of such highly appealing substrates as enol phosphinates **S38** and **S39**[26] and pinacolatoboron-containing substrates **S40**[27] and **S41**[28], for which only very few catalytic systems have provided high enantioselectivities. It should be noted that although **S41** is prone to isomerization, it has been hydrogenated with high enantioselectivity.

In summary, although isomerization was not completely suppressed by introducing a biaryl phosphoroamidite group, the face coordination mode of the substrate was successfully controlled, thus facilitating the reduction of a broad range of 1,1'-disubstituted substrates with high enantioselectivities that were comparable for most of the substrates (except for olefins prone to isomerization) to the best reported so far. Once again, the introduction of the biaryl phosphoroamidite group was also advantageous compared with related bicyclic *N*-phosphine-oxazoline/thiazole counterparts that have been efficiently applied in the hydrogenation of very few 1,1'-disubstituted substrates.[8e,13a,b,26a] See Table SI-4 in the Supporting Information at the

end of this chapter to compare these results with the first generation of ligands and the state-of-art systems for each substrate.

3.1.3. Conclusions

We have identified new Ir-bicyclic phosphoroamidite-oxazoline/thiazole catalytic systems that can hydrogenate a wide range of minimally functionalized olefins (including *E*- and *Z*-tri- and disubstituted substrates, vinylsilanes, enol phosphinates, tri- and disubstituted alkenylboronic esters and α,β-unsaturated enones) with enantioselectivities up to 99% ee and with high conversions. These catalytic systems were derived from a previous successful generation of Ir-bicyclic *N*-phosphine-oxazoline/thiazole catalysts, by replacing the *N*-phosphine group of the ligand with a π-acceptor biaryl phosphoroamidite moiety. The simple substitution of the *N*-phosphine by a phosphoroamidite group extended the range of olefins that could be successfully hydrogenated and furnished enantioselectivities that were comparable, for most of the substrates, to the best reported so far. In this respect, the new Ir-phosphoroamidite-oxazoline/thiazole catalysts have been able to efficiently hydrogenate not only minimally functionalized model olefins (i.e., **S1**, **S2**, **S4** and **S10**), but also a wide range of demanding olefins (**S5**-**S9** and **S11**-**S41**) that have recently received a great deal of attention because the resulting hydrogenated compound can be easily stereoselectively transformed into high-value organic compounds. Therefore, the effective hydrogenation of these substrates with the Ir-bicyclic phosphoroamidite-oxazoline/thiazole catalysts reported in the present study opens up an appealing route that is more efficient, straightforward, sustainable, and selective than alternative methods.[29] Another important advantage of the new ligands over previous bicyclic *N*-phosphine-oxazoline/thiazole ligands, is that they are solid and stable to air. The ligands are therefore easier to handle and can be manipulated and stored in air.

3.1.4. Experimental Section

3.1.4.1. General considerations

All reactions were carried out by using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites were easily prepared in one step from the corresponding binaphthols.[18] Substrates **S1**-**S2**,[30] **S3**,[31] **S5-S7**,[32] **S8**,[8f] **S9**,[33] **S10**,[34] **S11**,[35] **S12**-**S16**,[13b] **S17**,[36] **S18**-**S19**,[6i] **S20**,[37] **S23**,[38] **S25**,[39] **S26**,[40] **S27**,[41] **S28**,[42] **S36**-**S37**,[43] **S38**-**S39**,[13b] and **S41**[22] were prepared following the reported procedures and **S4**, **S21**-**S22** and **S40** were commercially available. Intermediate amine-oxazoline/thiazole compounds **1**[16] and **2**[8e] were prepared as reported previously. Neutral silica (pH 7,

0.040-0.063 mm) was purchased from Merck. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded with 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H and ^{13}C assignments were made based on the results of ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments.

3.1.4.2. General procedure for the preparation of phosphoroamidite-oxazoline/thiazole ligands L1-L2a-b

The corresponding phosphorochloridite (0.55 mmol) produced *in situ* was dissolved in toluene (2 mL), and triethylamine (0.3 mL, 2.15 mmol) was added. The amino-oxazoline/thiazole compound (0.50 mmol) was azeotropically dried with toluene (3x3 mL) and then dissolved in toluene (2 mL) to which triethylamine (0.3 mL, 2.15 mmol) was added. The phosphorochloridite solution was then transferred slowly to the amino-oxazoline/thiazole solution. The reaction mixture was stirred at 80 °C for 2 h, after which the triethylamine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography on neutral silica (CH_2Cl_2 as eluent) to produce the corresponding ligand as a white solid.

L1a: Yield: 118 mg (37%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 153.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.70 (d, 1H, CH_2, $^{2}J_{H-H}$= 10.0 Hz), 0.75 (m, 1H, CH_2), 1.0 (m, 2H, CH_2), 1.65 (m, 1H, CH_2), 1.9 (b, 1H, CH_2) 2.40 (b, 1H, CH), 3.35 (b, 1H, CH), 3.80 (a, 1H, CH), 4.47 (d, 1H, CH_2, $^{2}J_{H-H}$= 8.4 Hz), 4.56 (d, 1H, CH_2, $^{2}J_{H-H}$= 8.4 Hz), 6.80-8.81 (m, 12H, C=H). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 27.6 (CH_2), 34.4 (CH_2), 36.8 (CH_2), 42.1 (CH), 53.5 (C), 58.2 (CH), 61.4 (d, CH, $^{2}J_{C-P}$= 20.4 Hz), 80.6 (CH_2), 122.3-167.4 (aromatic carbons). $[\alpha]^{23}_{D}$=+102.41 (c= 0.1 in CH_2Cl_2). MS HR-ESI [found 633.2307, $C_{41}H_{33}N_2O_3P$ $(M+H)^+$ requires 633.2307]. Elemental analysis calcd (%) for $C_{41}H_{33}N_2O_3P$: C 77.83, H 5.26, N 4.43; found: C 77.81, H 5.4, N 4.39.

L1b: Yield: 114 mg (36%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 146.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.56 (d, 1H, CH_2, $^{2}J_{H-H}$= 10.0 Hz), 0.85 (m, 1H, CH_2), 1.10 (m, 2H, CH_2), 1.72 (m, 1H, CH_2), 1.82 (b, 1H, CH_2), 2.46 (b, 1H, CH), 3.63 (b, 1H, CH), 3.97 (s, 1H, CH), 4.47 (d, 1H, CH_2, $^{2}J_{H-H}$= 8.8 Hz), 4.56 (d, 1H, CH_2, $^{2}J_{H-H}$= 8.8 Hz), 6.86-7.67 (m, 12H, C=H).^{13}C NMR (100.6 MHz, C_6D_6): δ= 28.7 (CH_2), 33.6 (CH_2), 43.6 (CH), 46.1 (CH_2), 54.1 (C), 57.6 (CH), 62.5 (d, CH, $^{2}J_{C-P}$= 19.2 Hz), 81.4 (CH_2), 123.1-168.5 (aromatic carbons). $[\alpha]^{23}_{D}$= -112.24 (c= 0.1 in CH_2Cl_2). MS HR-ESI [found 633.2304, $C_{41}H_{33}N_2O_3P$ $(M+H)^+$ requires 633.2307]. Elemental analysis calcd (%) for $C_{41}H_{33}N_2O_3P$: C 77.83, H 5.26, N 4.43; found: C 77.80, H 5.24, N 4.37.

L2a: Yield: 182 mg (64%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 155.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.65 (d, 1H, CH_2, $^{2}J_{H-H}$= 10.0 Hz), 0.80 (m, 1H, CH_2), 1.10 (m, 1H, CH_2), 1.22 (m, 1H, CH_2), 1.80 (b, 2H, CH_2) 2.45 (b, 1H, CH), 3.40 (b, 1H, CH), 4.63 (d, 1H,

CH, $^3J_{H-P}$= 4.0 Hz), 6.82-7.98 (m, 13H, C=H). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 28.3 (CH_2), 32.5 (CH_2), 36.2 (CH_2), 46.4 (CH), 59.1 (CH), 66.3 (d, CH, $^2J_{C-P}$= 24.2 Hz), 133.7-176.4 (aromatic carbons). $[\alpha]^{23}_D$= +188.18 (c= 0.11 in CH_2Cl_2). MS HR-ESI [found 571.1599, $C_{35}H_{27}N_2O_2PS$ $(M+H)^+$ requires 571.1609]. Elemental analysis calcd (%) for $C_{35}H_{27}N_2O_2PS$: C 73.67, H 4.77, N 4.91, S 5.62; found: C 73.69, H 4.76, N 4.87, S 5.27.

L2b: Yield: 163 mg (57%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 147.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.76 (d, 1H, CH_2, $^2J_{H-H}$= 10.0 Hz), 1.10 (m, 1H, CH_2), 1.23 (m, 1H, CH), 1.78 (m, 1H, CH_2), 1.98 (d, 1H, CH_2, $^2J_{H-H}$= 10.0 Hz), 2.40 (b, 1H, CH), 3.84 (b, 1H, CH), 4.78 (d, 1H, CH, $^3J_{H-P}$= 3.2 Hz), 6.86-8.07 (m, 13H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 28.2 (CH_2), 33.5 (CH_2), 36.7 (CH_2), 46.7 (CH), 58.7 (CH), 65.4 (d, CH, $^2J_{C-P}$ = 17.4 Hz), 113.3-175.8 (aromatic carbons). $[\alpha]^{23}_D$= -133.64 (c= 0.11 in CH_2Cl_2). MS HR-ESI [found 571.1602, $C_{35}H_{27}N_2O_2PS$ $(M+H)^+$ requires 571.1609]. Elemental analysis calcd (%) for $C_{35}H_{27}N_2O_2PS$: C 73.67, H 4.77, N 4.91, S 5.62; found: C 73.64, H 4.75, N 4.87, S 5.59.

3.1.4.3. General procedure for the preparation of [Ir(cod)(L1-L2a-b)]BAr$_F$

The corresponding ligand (0.074 mmol) was dissolved in CH_2Cl_2 (5 mL), and [Ir(μ-Cl)(cod)]$_2$ (25.0 mg, 0.037 mmol) was added. The reaction mixture was heated at 40 °C for 1 h. After 5 min at rt, $NaBAr_F$ (77.2 mg, 0.080 mmol) and water (5 mL) were added and the reaction mixture was stirred vigorously for 30 min at rt. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ filtered through a plug of Celite and the solvent was evaporated to give the product as an orange solid.

[Ir(cod)(L1a)]BAr$_F$: Yield: 127 mg (96%). ^{31}P NMR (161.9 MHz, $CDCl_3$, 25 °C): δ= 112.0 (s). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ= 1.26 (s, 7H, CH_2 and CH), 1.56 (m, 4H, CH_2, cod), 1.90 (m, 2H, CH_2, cod), 2.04 (m, 1H, CH_2, cod), 2.27 (m, 1H, CH_2, cod), 2.43 (m, 1H, CH), 3.91 (m, 1H, CH=, cod), 4.35 (m, 1H, CH), 4.49 (b, 1H, CH=, cod), 4.61 (d, 1H, CH=, cod, $^2J_{H-H}$= 9.2 Hz), 5.21 (d, 2H, CH_2, $^2J_{H-H}$= 9.2 Hz), 6.68-8.02 (m, 32H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ= 22.9 (b, CH_2, cod), 27.2 (CH_2), 27.4 (b, CH_2, cod), 29.9 (CH), 30.6 (CH_2), 31.0 (b, CH_2, cod), 34.1 (CH_2), 38.7 (b, CH_2, cod), 57.6 (CH=, cod), 58.5 (CH), 62.0 (CH=, cod), 62.4 (CH), 82.6 (CPh_2), 86.6 (CH_2), 97.7 (CH=, cod), 101.3 (CH=, cod), 119.5-133.0 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136.1-149.2 (aromatic carbons), 162.0 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz), 173.0 (C=N). MS HR-ESI [found 933.2795, $C_{81}H_{57}BF_{24}IrN_2O_3P$ $(M-BAr_F)^+$ requires 933.2797]. Elemental analysis calcd (%) for $C_{81}H_{57}BF_{24}IrN_2O_3P$: C 54.16, H 3.20, N 1.56; found: C 54.13, H 3.16, N 1.53.

[Ir(cod)(L1b)]BAr$_F$: Yield: 123 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 102.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.21 (s, 7H, CH_2 and CH), 1.59 (m, 4H, CH_2, cod),

1.85 (m, 2H, CH_2, cod), 2.01 (m, 1H, CH_2, cod), 2.35 (m, 1H, CH_2, cod), 3.50 (m, 1H, CH), 3.69 (m, 1H, CH), 4.27 (b, 1H, CH=, cod), 4.58 (b, 1H, CH=, cod), 4.68 (b, 1H, CH=, cod), 4.95 (d, 1H, CH_2, $^2J_{H-H}$= 9.2 Hz), 5.22 (d, 1H, CH_2, $^2J_{H-H}$= 9.2 Hz), 5.29 (b, 1H, CH=, cod), 7.05–8.35 (m, 32H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 24.5 (b, CH_2, cod), 25.7 (CH_2), 28.7 (b, CH_2, cod), 29.4 (CH), 31.7 (CH_2), 32.0 (b, CH_2, cod), 38.3 (CH_2), 39.3 (b, CH_2, cod), 57.5 (CH=, cod), 58.5 (CH), 62.3 (CH=, cod), 65.9 (CH), 82.9 (CPh_2), 86.3 (CH_2), 93.8 (CH=, cod), 100.5 (CH=, cod), 117.7 (b, CH=, BAr_F), 119.1-131.2 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136.2-150.0 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz), 173.3 (C=N). MS HR-ESI [found 933.2792, $C_{81}H_{57}BF_{24}IrN_2O_3P$ (M-BAr_F)$^+$ requires 933.2797]. Elemental analysis calcd (%) for $C_{81}H_{57}BF_{24}IrN_2O_3P$: C 54.16, H 3.20, N 1.56; found: C 54.12, H 3.16, N 1.52.

[Ir(cod)(L2a)]BAr_F: Yield: 119 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 114.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.26 (s, 7H, CH_2 and CH), 1.36 (m, 2H, CH_2, cod), 1.63 (m, 2H, CH_2, cod), 1.73 (m, 2H, CH_2, cod), 2.11 (m, 1H, CH_2, cod), 2.25 (m, 1H, CH_2, cod), 2.77 (m, 1H, CH), 2.98 (m, 1H, CH), 3.36 (m, 1H, CH=, cod), 4.39 (b, 1H, CH=, cod), 4.47 (b, 1H, CH=, cod), 4.84 (b, 1H, CH=, cod), 5.00 (s, 1H, CH=), 6.72-8.26 (m, 27H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 25.3 (b, CH_2, cod), 28.3 (CH_2), 29.8 (b, CH_2, cod), 31.3 (CH), 31.7 (CH_2), 32.9 (b, CH_2, cod), 37.7 (CH_2), 40.9 (b, CH_2, cod), 53.7 (CH), 60.0 (CH), 62.3 (CH=, cod), 65.2 (CH=), 65.4 (CH=, cod), 94.5 (d, CH=, cod, J_{C-P}= 21.3 Hz), 103.6 (b, CH=, cod, J_{C-P}= 11.4 Hz), 116.7 (C=), 117.7 (b, CH=, BAr_F), 119.1-131.0 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136.1-158.2 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz), 170.8 (C=N). MS HR-ESI [found 871.2087, $C_{75}H_{51}BF_{24}IrN_2O_2PS$ (M-BAr_F)$^+$ requires 871.2090]. Elemental analysis calcd (%) for $C_{75}H_{51}BF_{24}IrN_2O_2PS$: C 51.94, H 2.96, N 1.62; found: C 54.89, H 2.94, N 1.59, S 1.81.

[Ir(cod)(L2b)]BAr_F: Yield: 122 mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 102.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.27 (s, 7H, CH_2 and CH), 1.39 (m, 2H, CH_2, cod), 1.56 (m, 2H, CH_2, cod), 1.89 (m, 2H, CH_2, cod), 2.07 (m, 1H, CH_2, cod), 2.23 (m, 1H, CH_2, cod), 3.41 (m, 1H, CH=, cod), 4.46 (b, 1H, CH=, cod), 3.62 (m, 1H, CH), 4.03 (b, 1H, CH=, cod), 4.93 (m, 1H, CH), 5.00 (b, 1H, CH=, cod), 5.35 (s, 1H, CH=), 7.12-8.34 (m, 27H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 24.9 (b, CH_2, cod), 27.0 (CH_2), 28.1 (b, CH_2, cod), 29.9 (CH), 31.2 (CH_2), 32.8 (b, CH_2, cod), 37.6 (CH_2), 42.2 (b, CH_2, cod), 58.7 (CH), 65.5 (CH), 65.9 (CH=), 66.0 (CH=, cod), 68.3 (CH=, cod), 97.6 (CH=, cod), 105.7 (CH=, cod), 117.2 (C=), 117.7 (b, CH=, BAr_F), 119.1-131.2 (aromatic carbons), 135.0 (b, CH=, BAr_F), 136.1-150.2 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz), 172.6 (C=N). MS HR-ESI [found 871.2084, $C_{75}H_{51}BF_{24}IrN_2O_2PS$ (M-BAr_F)$^+$ requires 871.2090]. Elemental analysis calcd (%) for $C_{75}H_{51}BF_{24}IrN_2O_2PS$: C 51.94, H 2.96, N 1.62; found: C 54.90, H 2.94, N 1.60, S 1.83.

3.1.4.4. General procedure for the preparation of substrates S24, S29, S30, S32-S35

In a flame dried Schlenk, methyltriphenylphosphonium bromide (9.2 mmol) was stirred in dry THF (40 mL). The mixture solution was cooled to 0 ºC and ^{n}BuLi solution (1.6 M in hexane, 5.4 mL, 8.6 mmol) was slowly added. The reaction was left at 0 ºC for 30 min and then, aryl *tert*-butyl ketone[44] (6.2 mmol) in dry THF (6 mL) was added. The reaction mixture was warmed to room temperature. After 18 h, NH_4Cl (sat., 20 mL) was added, followed by extraction with diethyl ether (3 x 25 mL). The organic phases were dried over anhydrous $MgSO_4$. Removal of solvents gave a crude product, which was purified by flash column chromatography on silica gel (100% petroleum ether) to afford the corresponding 1,1'-disubstitued olefin as a colorless oil.

1-(3,3-Dimethylbut-1-en-2-yl)-4-methoxybenzene (S24): Yield: 695 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.10 (s, 9H), 3.81 (s, 3H), 4.74 (d, 1H, *J*= 1.6 Hz), 5.14 (d, 1H, *J*= 1.6 Hz), 6.81-7.26 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 29.7, 36.2, 55.1, 111.6, 112.7, 130.0, 135.9, 158.1, 159.4. MS HR-ESI [found 191.1390, $C_{13}H_{18}O$ $(M+H)^+$ requires 191.1391].

1-(3,3-Dimethylbut-1-en-2-yl)-4-(trifluoromethyl)benzene (S29): Yield: 862 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.18 (s, 9H), 4.80 (d, 1H, *J*= 1.6 Hz), 5.25 (d, 1H, *J*= 1.6 Hz), 7.23-7.61 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 29.6, 36.1, 112.3, 124.4, 124.8 (q, $^1J_{C\text{-}F}$= 6.0 Hz), 129.3, 130.2, 158.7. MS HR-ESI [found 229.1159, $C_{13}H_{15}F_3$ $(M+H)^+$ requires 229.1161].

1-(3,3-Dimethylbut-1-en-2-yl)-4-methylbenzene (S30): Yield: 755 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.17 (s, 9H), 2.40 (s, 3H), 4.80 (d, 1H, *J*= 1.6 Hz), 5.21 (d, 1H, *J*= 1.6 Hz), 7.08-7.15 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.1, 29.7, 36.2, 111.5, 128.0, 128.9, 135.7, 140.6, 159.8. MS HR-ESI [found 175.1440, $C_{13}H_{18}$ $(M+H)^+$ requires 175.1442].

1-(3,3-Dimethylbut-1-en-2-yl)-3-methylbenzene (S32): Yield: 486 mg (45 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.11 (s, 9H), 2.35 (s, 3H), 4.75 (d, 1H, *J*= 1.6 Hz), 5.15 (d, 1H, *J*= 1.6 Hz), 6.93-7.26 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.5, 29.7, 36.1, 111.3, 126.1, 126.9, 127.1, 129.7, 136.7, 143.4, 159.9. MS HR-ESI [found 175.1441, $C_{13}H_{18}$ $(M+H)^+$ requires 175.1442].

2-(3,3-Dimethylbut-1-en-2-yl)naphthalene (S33): Yield: 808 mg (62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.29 (s, 9H), 4.98 (d, 1H, *J*= 1.6 Hz), 5.38 (d, 1H, *J*= 1.6 Hz), 7.41-7.94 (m, 7H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 29.9, 36.5, 112.1, 125.6, 126.0, 126.7, 127.4, 127.7, 128.0, 128.1, 132.2, 133.0, 141.2, 159.9. MS HR-ESI [found 211.1443, $C_{16}H_{18}$ $(M+H)^+$ requires 211.1442].

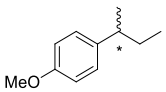
1-(3,3-Dimethylbut-1-en-2-yl)-2-methylbenzene (S34): Yield: 518 mg (48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.17 (s, 9H), 2.30 (s, 3H), 4.81 (d, 1H, *J*= 1.6 Hz), 5.34 (d, 1H, *J*= 1.6 Hz), 7.09-7.22 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 20.6, 29.9, 36.9, 112.3, 124.4, 126.4, 129.4, 129.9, 135.8, 142.6, 157.8. MS HR-ESI [found 175.1441, $C_{13}H_{18}$ $(M+H)^+$ requires 175.1442].

1-(3,3-Dimethylbut-1-en-2-yl)naphthalene (S35): Yield: 730 mg (56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.20 (s, 9H), 4.98 (d, 1H, *J*= 1.6 Hz), 5.57 (d, 1H, *J*= 1.6 Hz), 7.26-8.04 (m, 7H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 30.1, 37.0, 113.9, 124.6, 125.3, 125.4, 126.2, 126.8, 127.2, 128.0, 132.8, 133.6, 140.7, 156.6; MS HR-ESI [found 211.1441, $C_{16}H_{18}$ $(M+H)^+$ requires 211.1442].

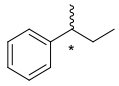
3.1.4.5. General procedure for the hydrogenation of olefins

The alkene (0.5 mmol) and Ir complex (2 mol%) were dissolved in CH_2Cl_2 (2 mL) in a high-pressure autoclave, which was purged four times with hydrogen. The apparatus was pressurized to the desired pressure and, after the required reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 mL) and filtered through a short Celite plug.

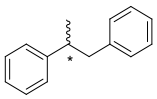
1-(sec-Butyl)-4-methoxybenzene.[9] Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 46.3 min (*S*); t_R 47.0 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.81 (t, 3H, *J*= 7.5 Hz), 1.21 (d, 3H, *J*= 6.6 Hz), 1.55 (m, 2H), 2.53 (m, 1H), 3.79 (s, 3H), 6.84 (m, 2H), 7.10 (m, 2H).



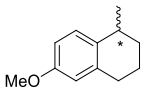
sec-Butylbenzene.[45] Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 50 °C for 30 min, 2 °C/min until 175 °C). t_R 20.4 min (*S*); t_R 20.8 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.80 (t, 3H, *J*= 7.6 Hz), 1.22 (d, 3H, *J*= 6.4 Hz), 1.61 (m, 2H), 2.60 (m, 1H), 7.18 (m, 3H), 7.33 (m, 2H).



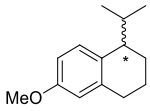
Propane-1,2-diyldibenzene.[9] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=99/1, 0.5 mL/min, 254 nm). t_R 13.2 min (*R*); t_R 18.7 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.24 (d, 3H, *J*= 6.8 Hz), 2.75 (m, 1H), 2.96 (m, 2H), 7.08 (m, 2H), 7.1-7.4 (m, 8H).



6-Methoxy-1-naphthyl-1,2,3,4-tetrahydronaphthalene.[9] Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 58.7 min (*R*); t_R 58.9 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.38 (d, 3H, *J*= 6.8 Hz), 1.59 (m, 1H), 1.78 (m, 1H), 1.94 (m, 2H), 2.81 (m, 2H), 2.97 (m, 1H), 3.87 (s, 3H), 6.77 (dd, 1H, *J*= 2.8 Hz, *J*= 8.4 Hz), 6.85 (d, 1H, *J*= 2.8 Hz), 7.06 (d, 1H, *J*= 8.4 Hz).

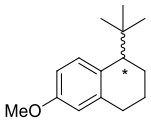


1-Isopropyl-6-methoxy-1,2,3,4-tetrahydronaphthalene.[46] Enantiomeric excess



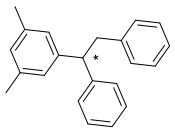
determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 63.6 min (*R*); t_R 63.8 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.76 (d, 3H, *J*= 7.2 Hz), 0.99 (d, 3H, *J*= 7.2 Hz), 1.62 (m, 2H), 1.78 (m, 1H), 1.91 (m, 1H), 2.21 (m, 1H), 2.70 (m, 3H), 3.77 (s, 3H), 6.67 (s, 1H), 6.67 (d, 1H, *J*= 8.0 Hz), 7.11 (d, 1H, *J*= 8.4 Hz).

1-(tert-Butyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene.[46] Enantiomeric excess



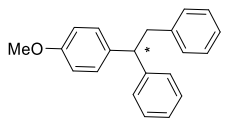
determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 65.2 min (*R*); t_R 65.5 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.87 (s, 9H), 1.41 (m, 1H), 1.81 (m, 2H), 1.90 (m, 1H), 2.60 (m, 3H), 3.75 (s, 3H), 6.59 (s, 1H), 6.62 (d, 1H, *J*= 8.0 Hz), 7.03 (d, 1H, *J*= 8.4 Hz).

(1-(3,5-Dimethylphenyl)ethane-1,2-diyl)dibenzene.[8f] Enantiomeric excess



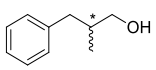
determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=98/2, 0.4 mL/min, 220 nm). t_R 21.0 min (-); t_R 24.8 min (+). ^{1}H NMR ($CDCl_3$), δ: 2.25 (s, 6H), 3.32 (m, 2H), 4.13 (m, 1H), 6.8-7.2 (m, 13H).

(1-(4-Methoxyphenyl)ethane-1,2-diyl)dibenzene.[8f] Enantiomeric excess



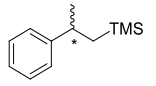
determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=80/20, 0.5 mL/min, 254 nm). t_R 20.1 min (-); t_R 22.6 min (+). ^{1}H NMR ($CDCl_3$), δ: 3.32 (d, 2H, *J*= 6.8 Hz), 3.72 (s, 3H), 4.19 (m, 1H), 6.8-7.3 (m, 14H).

2-Methyl-3-phenylpropan-1-ol. [9] Enantiomeric excess determined by HPLC using



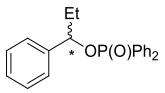
Chiracel IB column (hexane/2-propanol=98/2, 0.5 mL/min, 220 nm). t_R 19.2 min (*S*); t_R 22.1 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.92 (d, 3H, *J*= 6.8 Hz), 1.95 (m, 1H), 2.45 (dd, 1H, *J*= 13.2 Hz, *J*= 7.8 Hz), 2.75 (dd, 1H, *J*= 13.2 Hz, *J*= 6.4 Hz), 3.49 (m, 2H), 7.2-7.3 (m, 5H).

Trimethyl(2-phenylpropyl)silane.[13c] Enantiomeric excess determined by GC using



Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 48.2 min (*S*); t_R 48.7 min (*R*). ^{1}H NMR ($CDCl_3$), δ: -0.09 (s, 9H), 0.98 (dd, 1H, *J*= 5.2 Hz, *J*= 12.4 Hz), 1.13 (dd, 1H, *J*= 6.4 Hz, *J*= 12.4 Hz), 1.39 (d, 3H, *J*= 6.4 Hz), 3.01 (m, 1H), 7.2-7.4 (m, 5H).

1-Phenylpropyl diphenylphosphinate.[13b] Enantiomeric excess determined by HPLC



using Chiralcel AD (hexane/2-propanol=90/10, 0.5 mL/min, 220 nm). t_R = 28.9 min (*R*); t_R 41.7 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.87(dt, 3H, *J* = 7.2, 2.4 Hz), 1.98 (m, 1H), 2.12 (m, 1H), 5.30 (m, 1H), 7.2-7.3 (m, 7H), 7.4-7.7 (m, 6H), 7.8-7.9 (m, 2H).

Ethyl 3-((diphenylphosphoryl)oxy)-3-phenylpropanoate.[13b] Enantiomeric excess determined by HPLC using Chiralcel OD-H (hexane/2-propanol=90/10, 0.5 mL/min, 220 nm). t_R = 29.1 min (*R*); t_R 32.9 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.14 (t, 3H, *J* = 7.2 Hz), 2.92 (dd, 1H, *J* = 7.1 Hz, *J* = 15.2 Hz), 3.24 (dd, 1H, *J* = 7.1 Hz, *J* = 15.2 Hz), 4.01 (m, 2H), 5.82 (m, 1H), 7.32 (m, 7H), 7.48 (m, 4H), 7.61 (m, 2H), 7.82 (m, 2H).

2,2-dimethylpentan-3-yl diphenylphosphinate.[13b] Enantiomeric excess determined by HPLC using Chiralcel IA (hexane/2-propanol=95/5, 0.5 mL/min, 220 nm). t_R = 26.5 min (*R*); t_R 28.8 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.70 (t, 3H, *J*= 7.2 Hz), 0.90 (s, 3H), 1.14 (m, 2H), 1.01 (s, 9H), 1.55 (m, 2H), 4.26 (m, 1H), 7.3-7.8 (m, 10H)

Ethyl 3-((diphenylphosphoryl)oxy)-4-methylpentanoate.[13b] Enantiomeric excess determined by HPLC using Chiralcel AS-H (hexane/2-propanol=95/5, 0.5 mL/min, 220 nm). t_R = 17.0 min (*S*); t_R 25.2 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.92 (dd, 3H, *J*= 8.0 Hz, *J*= 6.8 Hz), 1.14 (t, 3H, *J*= 7.2 Hz), 2.07 (m, 1H), 2.56 (dd, 1H, *J*= 15.4 Hz, J= 5.2 Hz), 2.75 (dd, 1H, *J*= 15.2 Hz, *J*= 7.2 Hz), 3.93 (m, 2H), 4.73 (m, 1H), 7.4 - 7.7 (m, 10H).

Ethyl 3-((diphenylphosphoryl)oxy)-3-(4-(trifluoromethyl)phenyl)propanoate.[13b] Enantiomeric excess determined by HPLC using Chiralcel OD-H (hexane/2-propanol=90/10, 0.5 mL/min, 220 nm). t_R = 17.5 min (*R*); t_R 26.0 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.13 (t, 3H, *J* = 7.2 Hz), 2.89 (dd, 1H, *J* = 6.4 Hz, *J*= 15.6 Hz), 3.20 (dd, 1H, *J* = 6.4 Hz, *J*= 15.6 Hz), 4.00 (m, 2H), 5.82 (br, 1H), 7.3-7.8 (m, 14H)

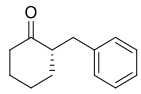
3-Methyl-4-phenylbutan-2-one.[47] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=97/3, 1 mL/min, 220 nm). t_R 10.2 min (*S*); t_R 10.4 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.09 (d, 3H, *J*= 6.8 Hz), 2.09 (s, 3H), 2.56 (m, 1H), 2.83 (m, 1H), 3.01 (m, 1H), 7.1-7.3 (m, 5H).

4-(4-Methoxyphenyl)-3-methylbutan-2-one.[48] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=95/5, 0.5 mL/min, 220 nm). t_R 25.5 min (*S*); t_R 27.8 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.07 (d, 3H, *J*= 6.8 Hz), 2.08 (s, 3H), 2.52 (dd, 1H, *J*= 7.4 Hz, *J*= 13.4 Hz), 2.78 (m, 1H), 2.93 (dd, 1H, *J*= 6.8 Hz, *J*= 13.4 Hz), 3.77 (s, 3H), 6.82 (m, 2H), 7.0-7.3 (m, 2H).

2-Methyl-1-phenylpentan-3-one.[48] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=99/1, 0.5 mL/min, 220 nm). t_R 15.2 min (*S*); t_R 16.2 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.96 (t, 3H,

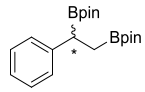
J= 7.2 Hz), 1.08 (d, 3H, *J*= 6.8 Hz), 2.21 (m, 1H), 2.43 (m, 1H), 2.57 (dd, 1H, *J*= 7.0 Hz, *J*= 13.4 Hz), 2.83 (m, 1H), 2.92 (dd, 1H, *J*= 6.8 Hz, *J*= 13.4 Hz), 7.1-7.3 (m, 5H).

2-Benzylcyclohexanone.[48] Enantiomeric excess determined by HPLC using Chiracel



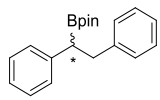
OJ-H column (hexane/2-propanol=97/3, 1 mL/min, 210 nm). t_R 8.4 min (*S*); t_R 9.1 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.35 (m, 1H), 1.63 (m, 2H), 1.83 (m, 1H), 2.04 (m, 2H), 2.44 (m, 4H), 3.24 (dd, 1H, *J* = 14.0 Hz, *J*= 4.6 Hz), 7.18 (m, 3H), 7.28 (m, 2H).

2,2'-(1-Phenylethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-



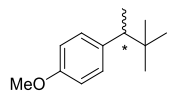
dioxaborolane).[13a] Enantiomeric excess were determined after oxidation of the pinacolborane derivative to the corresponding diol using NaOH (3N, 2.0 mL) and H_2O_2 (30%, 1.5 mL). Enantiomeric excess determined by HPLC using Chiracel OD-H column (hexane/2-propanol=95/5, 0.5 mL/min, 254 nm). t_R 18.3 min (*R*); t_R 19.6 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.10 (dd, 1H, *J*= 5.4 Hz, *J*= 16.0 Hz), 1.17 (s, 6H), 1.20 (s, 6H), 1.21 (s, 12H), 1.38 (dd, 1H, *J*= 11.2 Hz, *J*= 16.0 Hz), 2.53 (dd, 1H, *J*= 5.4 Hz, *J*= 11.2 Hz), 7.1-7.3 (m, 5H).

2-(1,2-Diphenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.[22] Enantiomeric



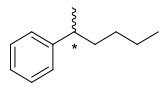
excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=99/1, 0.5 mL/min, 254 nm). t_R 9.5 min (-); t_R 12.9 min (+). ^{1}H NMR ($CDCl_3$), δ: 1.12 (s, 6H), 1.13 (s, 6H), 2.71 (dd, 1H, *J*= 6.8 Hz, *J*= 10.0 Hz), 2.98 (dd, 1H, *J*= 7.0 Hz, *J*= 13.6 Hz), 3.17 (dd, 1H, *J*= 9.6 Hz, *J*= 13.6 Hz), 7.1-7.4 (m, 10H).

1-(3,3-Dimethylbutan-2-yl)-4-methoxybenzene. Enantiomeric excess determined



by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 53.4 min (*S*); t_R 53.8 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.78 (s, 9H), 1.16 (d, 3H, *J*= 6.8 Hz), 2.42 (q, 1H, *J*= 6.8 Hz), 3.71 (s, 3H), 6.72 (d, 2H, *J*= 7.2 Hz), 6.94 (d, 2H, *J*= 7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.0, 27.8, 33.7, 49.0, 55.2, 112.8, 129.8, 137.6, 157.6. MS HR-ESI [found 193.1548, $C_{13}H_{20}O$ $(M+H)^+$ requires 193.1547].

Hexan-2-ylbenzene.[45] Enantiomeric excess determined by GC using Chiradex B-DM



column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 37.1 min (*S*); t_R 37.7 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.84 (t, 3H, *J* = 6.8 Hz), 1.17-1.35 (m, 3H), 1.24 (d, 3H, *J* = 7.2 Hz), 1.59 (m, 2H), 2.63 (m, 2H), 7.21 (m, 2H), 7.32 (m, 3H).

(4-Methylpentan-2-yl)benzene.[45] Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 27.9 min (*S*); t_R 29.5 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.84 (d, 3H, *J* = 6.8 Hz), 0.87 (d, 3H, *J* = 6.8 Hz), 1.21 (d, 3H, *J* = 7.2 Hz), 1.36 (m, 2H), 1.45 (m, 1H), 2.79 (m, 1H), 7.19 (m, 2H), 7.29 (m, 3H).

(4,4-Dimethylpentan-2-yl)benzene.[12e] Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 24.3 min (*S*); t_R 27.2 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.83 (s, 9H), 1.24 (d, 3H, *J*= 6.8 Hz), 1.42 (m, 1H), 1.73 (m), 2.80 (m, 1H), 7.17 (m, 2H), 7.29 (m, 3H).

(1-Cyclohexylethyl)benzene.[12e] Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 54.8 min (*S*); t_R 55.2 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.76 (m, 1H), 0.93 (m, 1H), 1.09 (m, 1H), 1.21 (d, 3H, *J*= 6.8 Hz), 1.23 (m, 1H), 1.39 (m, 2H), 1.59 (m, 2H), 1.71 (m, 1H), 1.83 (m, 1H), 2.40 (m, 2H), 7.1-7.3 (m, 5H).

1-(3,3-Dimethylbutan-2-yl)-4-(trifluoromethyl)benzene. Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 41.1 min (*S*); t_R 42.0 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.83 (s, 9H), 1.14 (d, 3H, *J*= 6.8 Hz), 2.44 (q, 1H, *J*= 6.8 Hz), 7.27 (d, 2H, *J*= 7.2 Hz), 7.53 (d, 2H, *J*= 7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 15.8, 27.7, 32.9, 49.8, 124.3, 129.2, 142.1, 160.4. MS HR-ESI [found 231.1316, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 231.1317].

1-(3,3-Dimethylbutan-2-yl)-4-methylbenzene. Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 39.3 min (*S*); t_R 39.7 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.82 (s, 9H), 1.23 (d, 3H, *J*= 6.8 Hz), 2.33 (s, 3H), 2.43 (q, 1H, *J*= 6.8 Hz), 7.06 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 15.9, 21.0, 27.8, 33.9, 49.5, 128.1, 128.9. 143.2, 163.0. MS HR-ESI [found 177.1599, $C_{13}H_{20}$ $(M+H)^+$ requires 177.1598].

(3,3-Dimethylbutan-2-yl)benzene.[9]**¡Error! Marcador no definido.** Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 47.2 min (*S*); t_R 47.8 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.83 (s, 9H), 1.24 (d, 3H, *J*= 6.8 Hz), 2.54 (q, 1H, *J*= 6.8 Hz), 7.1-7.3 (m, 5H).

1-(3,3-Dimethylbutan-2-yl)-3-methylbenzene. Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 41.7 min (*S*); t_R 42.5 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.79 (s, 9H), 1.18 (d, 3H, *J*= 6.8 Hz), 2.26 (s, 3H), 2.44 (q, 1H, *J*= 6.8 Hz), 6.92 (m, 3H), 7.06 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 15.9, 21.6, 27.9, 33.8, 49.8, 126.1, 126.5, 127.3, 129.9, 144.2, 162.3. MS HR-ESI [found 177.1599, $C_{13}H_{20}$ $(M+H)^+$ requires 177.1598].

2-(3,3-Dimethylbutan-2-yl)naphthalene. Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 63.5 min (*S*); t_R 63.7 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.93 (s, 9H), 1.36 (d, 3H, *J*= 6.8 Hz), 2.41 (q, 1H, *J*= 6.8 Hz), 6.8-7.0 (m, 2H), 7.2-7.8 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 15.9, 27.9, 34.0, 50.0, 125.0, 125.6, 126.6, 127.2, 127.5, 127.7, 128.1, 132.1, 133.1, 142.9. MS HR-ESI [found 213.1599, $C_{16}H_{20}$ $(M+H)^+$ requires 213.1597].

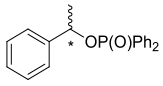
1-(3,3-Dimethylbutan-2-yl)-2-methylbenzene. Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 39.8 min (*S*); t_R 40.5 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.83 (s, 9H), 1.23 (d, 3H, *J*= 6.8 Hz), 2.37 (s, 3H), 2.93 (q, 1H, *J*= 6.8 Hz), 6.9-7.2 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.7, 20.9, 27.8, 34.8, 42.9, 125.3, 127.6, 130.8, 136.2, 144.2, 166.2. MS HR-ESI [found 177.1599, $C_{13}H_{20}$ $(M+H)^+$ requires 177.1598].

1-(3,3-Dimethylbutan-2-yl)naphthalene. Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 60.7 min (*S*); t_R 61.0 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.91 (s, 9H), 1.25 (d, 3H, *J*= 6.8 Hz), 2.81 (q, 1H, *J*= 6.8 Hz), 6.8-7.0 (m, 2H), 7.3-8.2 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 17.4, 28.6, 35.3, 41.7, 124.7, 125.3, 125.4, 125.5, 125.7, 126.7, 129.3, 133.5, 134.2, 142.6. MS HR-ESI [found 213.1598, $C_{16}H_{20}$ (M+H)+ requires 213.1597].

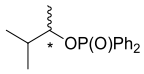
2-Phenylpropyl acetate.[9] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=99.5/0.5, 0.5 mL/min, 254 nm). t_R 28.4 min (*S*); t_R 35.8 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.34 (d, 3H, *J*= 6.4 Hz), 2.00 (s, 3H), 3.09 (m, 1H), 4.17 (m, 2H), 7.21 (m, 3H), 7.32 (m, 2H).

2-Phenylpropan-1-ol.[49] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=99/1, 0.5 mL/min, 254 nm). t_R 38.8 min (*S*); t_R 41.7 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.21 (d, 3H, *J*= 6.4 Hz), 2.83 (m, 1H), 3.62 (m, 2H), 7.18 (m, 3H), 7.26 (m, 2H).

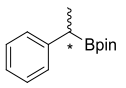
1-Phenylethyl diphenylphosphinate.[26a] Enantiomeric excess determined by HPLC using Chiralcel AD (hexane/2-propanol=90/10, 0.5 mL/min, 220 nm). t_R = 28.9 min (*R*); t_R 41.7 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.81 (dd, 3H, *J* = 7.2 Hz, *J* = 2.4 Hz). 5.60 (m, 1H), 7.18 (m, 3H), 7.31 (m, 2H), 7.42 (m, 4H), 7.52 (m, 2H), 7.82 (m, 4H).



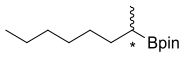
3-methylbutan-2-yl diphenylphosphinate.[13b] Enantiomeric excess determined by HPLC using Chiralcel S,S Whelk-01 (hexane/2-propanol=98/2, 0.5 mL/min, 220 nm). t_R = 93.7 min (*R*); t_R 102.0 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.92 (dd, 3H, *J*= 0.8 Hz, *J*= 6.8 Hz), 0.94 (dd, 3H, *J*= 0.8 Hz, *J*= 6.8 Hz), 1.22 (dd, 3H, *J*= 0.8 Hz, *J*= 6.4 Hz), 1.90 (m, 1H), 4.40 (m, 1H), 7.4 - 7.8 (m, 10H).



2-(1-Phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.[22] Enantiomeric excess were determined after oxidation of the pinacolborane derivative to the corresponding alcohol using sodium perborate monohydrate (75 mg, 0.75 mmol) in a THF/H_2O solution (1:1, 4 mL). Enantiomeric excess determined by GC using Chiralsil-Dex CB column (80 kPa H_2, 110 °C for 15 min, 10 °C/min, to 180 °C). t_R 14.9 min (*R*); t_R 16.0 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.12 (s, 6H), 1.14 (s, 6H), 1.26 (d, 3H, *J*= 7.2 Hz), 2.36 (q, 1H, *J*= 7.2 Hz), 7.05 (m, 1H), 7.16 (m, 4H).



2-(Octan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.[22] Enantiomeric excess were determined after oxidation/trifluoroacetylation of the pinacolborane derivative to the corresponding trifluoroacetylated compound using sodium perborate monohydrate (75 mg, 0.75 mmol) in a THF/H_2O solution (1:1, 4 mL). After 1 h, the reaction mixture was extracted with DCM (3×1 mL), dried with $MgSO_4$ and filtrated. To the filtrate trifluoroacetic anhydride (350 μL, 2.5 mmol) was added. After 30 min, the volatiles were carefully removed with a nitrogen stream. Enantiomeric excess determined by GC using Chiralsil-Dex CB column (54 kPa H_2, 50 °C for 30 min). t_R 15.6 min (*R*); t_R 16.0 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.88 (t, 3H, *J*= 6.8 Hz), 1.02 (m, 3H), 1.24 (m, 12H), 1.1-1.4 (b, 9H), 1.45 (m, 1H).



3.1.5. Acknowledgements

We thank the Spanish Government for providing grant CTQ2013-40568-P, the Catalan Government for grant 2014SGR670 and the ICREA Foundation for providing M. Diéguez and O. Pàmies with financial support through the ICREA Academia awards. We also thank the Swedish Research Council (VR), Stiftelsen Olle Engkvist Byggmästare, The Swedish Energy Agency and SYNFLOW (FP7) for supporting this work. We thank Mr. Xu Quan for his help in the analysis of the deuterium experiments.

3.1.6. References

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[23] Of all 22 substrates evaluated, only models **S1** and **S3** and extremely challenging dihydronaphthalenes and triaryl-substituted olefins are below the state of art, abeit with high enantioselectivities.

[24] Unlike the hydrogenation of trisubtituted olefins, the enantioselectivity in the reduction of terminal alkenes is highly pressure-dependent. Hydrogenation at an atmospheric pressure of H_2 therefore generally gave significantly higher ee values than at higher pressures. a) See Ref. 6a b) See Ref. 6g.

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[27] Only two catalytic systems have provided high enantioselectivities, see: a) See Ref. 22 (ee values up to 89%); b) See Ref. 11a (ee values up to 91%).

[28] Only one catalytic system has provided high enantioselectivity, see: a) See Ref. 6o (ee values up to 91% at rt and up to 96% at -20 ºC). Related *N*-phosphane-oxazoline/thiazole provided low enantioselectivity (ee values up to 18%, See Ref. 13a).

[29] Many of the hydrogenated products included in this paper can be prepared by other methods, for example 2-phenylpropanol analogues have been prepared by asymmetric Zr-catalyzed methylalumination of terminal olefins and the lipase-mediated kinetic resolution of racemic 2-phenyl propanol, see: a) Abate, A.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Giovenzana, T.; Malpezzi, L.; Serra, S. *J. Org. Chem.* **2005**, *70*, 1281; b) Thomas, S. P.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 1896; Other examples include conjugate addition using organometallic reagents for preparation of chiral ketones and the hydroboration of olefins for the preparation of chiral organoboranes, see for instance: c) Crudden, Cathleen M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695; d) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796; e) Wipf, P.; Ribe, S. *Org. Lett.* **2000**, *2*, 1713.

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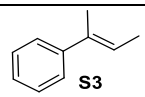
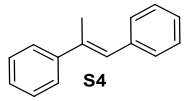
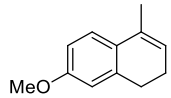
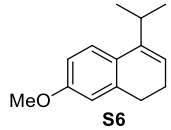
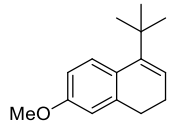
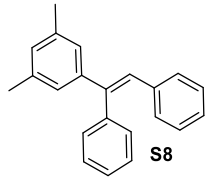
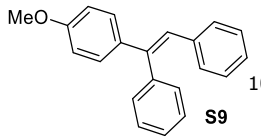
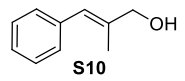
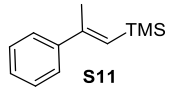
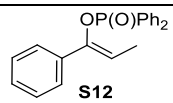
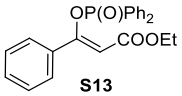
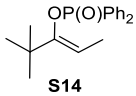
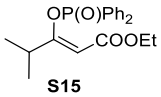
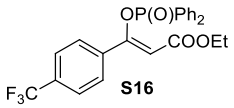
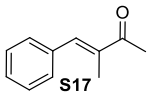
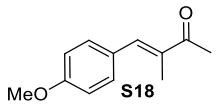
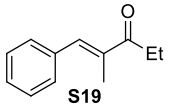
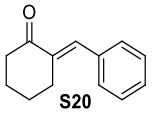
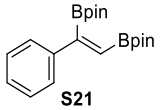
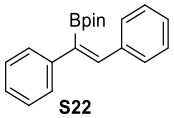
3.1.7. Supporting Information

3.1.7.1. Table SI.1. Full set of results for the asymmetric hydrogenation of trisubstituted olefins S3-S22[a]

Substrate	L1a % Conv[b] (% ee)[c]	L1b % Conv[b] (% ee)[c]	L2a % Conv[b] (% ee)[c]	L2b % Conv[b] (% ee)[c]
 **S3**	100 (93 (*R*))	100 (41 (*R*))	100 (95 (*R*))	100 (94 (*R*))
 **S4**	100 (92 (*R*))	100 (44 (*R*))	100 (98 (*R*))	100 (97 (*R*))
 **S5**	100 (70 (*S*))	100 (14 (*S*))	100 (41 (*S*))	100 (68 (*S*))
 **S6**	100 (68 (*S*))	100 (10 (*S*))	100 (33 (*S*))	100 (51 (*S*))
 **S7**	100 (69 (*S*))	100 (12 (*S*))	100 (28 (*S*))	100 (45 (*S*))
 **S8**	100 (82(-))	100 (14 (-))	100 (91 (-))	100 (74 (-))
 **S9**	100 (79(-))	100 (31 (-))	100 (89 (-))	100 (67 (-))
 **S10**	50 (62 (*R*))	100 (28 (*R*))	100 (98 (*R*))	100 (86 (*R*))
 **S11**	100 (20 (*R*))	100 (2 (*S*))	100 (98 (*R*))	100 (93 (*R*))

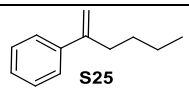
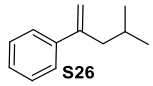
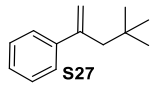
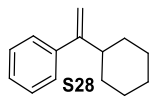
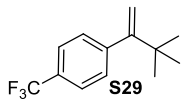
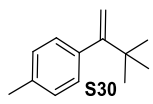
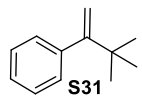
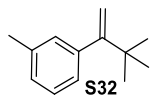
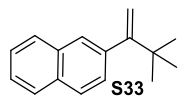
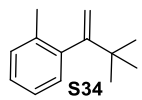
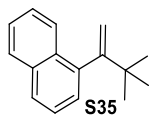
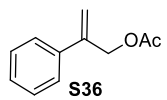
[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor at 50 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by GC or HPLC.

3.1.7.1. Table SI.1. Full set of results for the asymmetric hydrogenation of trisubstituted olefins S3-S22[a] (continuation)

Substrate	L1a % Conv[b] (% ee)[c]	L1b % Conv[b] (% ee)[c]	L2a % Conv[b] (% ee)[c]	L2b % Conv[b] (% ee)[c]
 **S12**	100 (90 (*R*))	100 (47 (*R*))	100 (63 (*R*))	100 (28 (*R*))
 **S13**	100 (>99 (*R*))	100 (67 (*R*))	100 (81 (*R*))	100 (14 (*R*))
 **S14**	100 (90 (*R*))	100 (59 (*R*))	100 (77 (*R*))	100 (22 (*R*))
 **S15**	100 (99 (*R*))	100 (64 (*R*))	100 (81 (*R*))	100 (30 (*R*))
 **S16**	100 (99 (*R*))	100 (70 (*R*))	100 (76 (*R*))	100 (19 (*R*))
 **S17**	99 (97 (*S*))	99 (96 (*S*))	100 (98 (*S*))	100 (97 (*S*))
 **S18**	100 (95 (*S*))	100 (96 (*S*))	100 (97 (*S*))	100 (97 (*S*))
 **S19**	100 (96 (*S*))	100 (95 (*S*))	100 (98 (*S*))	100 (96 (*S*))
 **S20**	100 (96 (*S*))	100 (>99 (*S*))	100 (94 (*S*))	100 (93 (*S*))
 **S21**	100 (80 (*R*))	100 (91 (*R*))	100 (85 (*R*))	100 (99 (*R*))
 **S22**	100 (74 (+))	100 (24 (+))	100 (>99 (+))	100 (93 (+))

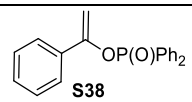
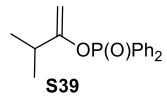
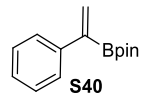
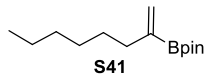
[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor at 50 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by GC or HPLC.

3.1.7.2. Table SI.2. Full set of results for the asymmetric hydrogenation of disubstituted olefins S25-S41[a]

Substrate	L1a % Conv[b] (% ee)[c]	L1b % Conv[b] (% ee)[c]	L2a % Conv[b] (% ee)[c]	L2b % Conv[b] (% ee)[c]
 **S25**	100 (17 (*R*))	100 (7 (*S*))	100 (63 (*S*))	100 (37 (*S*))
 **S26**	100 (11 (*R*))	100 (2 (*S*))	100 (64 (*S*))	100 (44 (*S*))
 **S27**	100 (21 (*R*))	100 (2 (*R*))	100 (68 (*S*))	100 (32 (*S*))
 **S28**	100 (9 (*R*))	100 (3 (*R*))	100 (69 (*S*))	100 (38 (*S*))
 **S29**	100 (97 (*S*))	100 (67 (*S*))	100 (77 (*S*))	100 (65 (*S*))
 **S30**	100 (91 (*S*))	100 (64 (*S*))	100 (71 (*S*))	100 (61 (*S*))
 **S31**	100 (92 (*S*))	100 (66 (*S*))	100 (71 (*S*))	100 (66 (*S*))
 **S32**	100 (92 (*S*))	100 (65 (*S*))	100 (73 (*S*))	100 (62 (*S*))
 **S33**	100 (95 (*S*))	100 (68 (*S*))	100 (72 (*S*))	100 (59 (*S*))
 **S34**	100 (98 (*S*))[d]	100 (62 (*S*))[d]	100 (74 (*S*))[d]	100 (61 (*S*))[d]
 **S35**	100 (97 (*S*))[d]	100 (63 (*S*))[d]	100 (77 (*S*))[d]	100 (60 (*S*))[d]
 **S36**	100 (64 (*R*))	100 (41 (*R*))	100 (89 (*R*))	100 (53 (*R*))

[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor at 50 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by GC or HPLC; [d] Reactions carried for 8 h; [e] Reaction carried out at 50 bar H_2 during 12 h.

3.1.7.2. Table SI.2. Full set of results for the asymmetric hydrogenation of disubstituted olefins S25-S41[a] (continuation)

Substrate	L1a % Conv[b] (% ee)[c]	L1b % Conv[b] (% ee)[c]	L2a % Conv[b] (% ee)[c]	L2b % Conv[b] (% ee)[c]
 S38	100 (98 (*R*))[e]	100 (71 (*R*))[e]	86 (62 (*R*))[e]	89 (37 (*R*))[e]
 S39	100 (92 (*R*))[e]	100 (70 (*R*))[e]	100 (64 (*R*))[e]	100 (28 (*R*))[e]
 S40	100 (88 (*R*))	100 (59 (*R*))	100 (46 (*R*))	100 (29 (*R*))
 S41	100 (87 (*R*))	100 (62 (*R*))	100 (44 (*R*))	100 (28 (*R*))

[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor at 50 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by GC or HPLC; [d] Reactions carried for 8 h; [e] Reaction carried out at 50 bar H_2 during 12 h.

3.1.7.3. Table SI.3. Comparison of ee values for Ir-based catalysts in the hydrogenation of trisubstituted substrates S1-S22

Substrate	New ligand	First generation	Ref	Best Ir-L	Ref
S1	95	99	Andersson et al. *Tetrahedron: Asymmetry* **2010**, *21*, 1328	>99	Pfaltz et al. *Science* **2006**, *311*, 642
S2	97	83	This work	98	Pfaltz et al. *Science* **2006**, *311*, 642
S3	95	94	This work	>99	Diéguez et al. *Chem. Commun.* **2008**, 3888
S4	98	99	Andersson et al. *Tetrahedron: Asymmetry* **2010**, *21*, 1328	>99	Pfaltz et al. *Science* **2006**, *311*, 642
S5	70	95	Andersson et al. *Chem. Eur. J.* **2006**, *12*, 2318	99	Pfaltz et al. *Chem. Sci.* **2010**, *1*, 72
S6	68	40	This work	98	Pfaltz et al. *Chem. Sci.* **2010**, *1*, 72
S7	69	12	This work	98	Diéguez et al. *Adv. Synth. Catal.* **2013**, *355*, 2569
S8	91	80	This work	>99	Andersson et al. *J. Am. Chem. Soc.* **2009**, *131*, 8855
S9	89	76	This work	99	Diéguez et al. *Adv. Synth. Catal.* **2013**, *355*, 143
S10	98	93	Andersson et al. *Tetrahedron: Asymmetry* **2010**, *21*, 1328	99	Andersson et al. *J. Am. Chem. Soc.* **2006**, *128*, 2995

3.1.7.3. Table SI.3. Comparison of ee values for Ir-based catalysts in the hydrogenation of trisubstituted substrates S1-S22 (continuation)

Substrate	New ligand	First generation	Ref	Best Ir-L	Ref
S11	98	98	Andersson et al. *Adv. Synth. Catal.* **2006**, *348*, 2575	98	Andersson et al. *Adv. Synth. Catal.* **2006**, *348*, 2575
S12	90	96	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595	96	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595
S13	>99	99	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595	99	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595
S14	90	91	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595	91	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595
S15	99	>99	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595	>99	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595
S16	99	99	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595	99	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595
S17	98	44	This work	98	Bolm et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 8920
S18	97	47	This work	98	Bolm et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 8920 and Hou et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 10133
S19	98	46	This work	99	Bolm et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 8920
S20	>99	49	This work	98	Hou et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 10133
S21	99	96	Andersson et al. *Chem. Commun.* **2009**, 5996	>99	Diéguez et al. *J. Am. Chem. Soc.* **2011**, *133*, 13634.
S22	>99	97	This work	>99	Pfaltz et al. *Chem. Eur. J.* **2012**, *18*, 6724

3.1.7.4. Table SI.4. Comparison of ee values for Ir-based catalysts in the hydrogenation of disubstituted substrates S23-S41

Substrate	New ligand	First generation	Ref	Best Ir-L	Ref
S23	65	43	This work	>99	Diéguez et al. *J. Am. Chem. Soc.* **2009**, *131*, 12344
S24	93	80	This work	-	
S25	63	25	This work	95	Diéguez et al. *Chem. Eur. J.* **2010**, *16*, 4567
S26	64	42	This work	94	Diéguez et al. *Chem. Eur. J.* **2010**, *16*, 4567
S27	68	61	This work	93	Diéguez et al. *J. Am. Chem. Soc.* **2011**, *133*, 13634
S28	69	38	This work	97	Diéguez et al. *J. Am. Chem. Soc.* **2009**, *131*, 12344
S29	97	65	This work	-	
S30	91	66	This work	-	
S31	92	86	Andersson et al. *Tetrahedron: Asymmetry* **2010**, *21*, 1328	>99	Diéguez et al. *J. Am. Chem. Soc.* **2009**, *131*, 12344
S32	92	79	This work	-	
S33	95	82	This work	-	
S34	98	92	This work	-	
S35	97	91	This work	-	
S36	89	32	This work	91	Diéguez et al. *J. Am. Chem. Soc.* **2009**, *131*, 12344
S37	87	34	This work	95	Diéguez et al. *J. Am. Chem. Soc.* **2009**, *131*, 12344
S38	98	95	Andersson et al. *Org. Lett*. **2007**, *9*, 1659	95	Andersson et al. *Org. Lett.* **2007**, *9*, 1659
S39	92	92	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595	92	Andersson et al. *J. Am. Chem. Soc.* **2008**, *130*, 5595
S40	88	89	Andersson et al. *Chem. Commun.* **2009**, 5996	91 at -20 ºC	Diéguez et al. *Chem. Eur. J.* **2014**, *20*, 12201
S41	87	18	Andersson et al. *Chem. Commun.* **2009**, 5996	>95 at -20 ºC	Pfaltz et al. *Chem. Eur. J.* **2012**, *18*, 6724

3.2. Alternatives to phosphinooxazoline (^{t}BuPHOX) ligands in the metal-catalyzed hydrogenation of minimally functionalized olefins and cyclic β-enamides

Biosca, M.; Magre, M.; Coll, M.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal*. **2017**, *359*, 2801.

Abstract: This study presents a new series of readily accessible iridium- and rhodium-phosphite/oxazoline catalytic systems that can efficiently hydrogenate, for the first time, both minimally functionalized olefins and functionalized olefins (62 examples in total) in high enantioselectivities (ee's up to >99%) and conversions. The phosphite-oxazoline ligands, which are readily available in only two synthetic steps, derive from previous privileged 4-alkyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline (PHOX) ligands by replacing the phosphine moiety by a biaryl phosphite group and/or the introduction of a methylene spacer between the oxazoline and the phenyl ring. The modular design of the ligands have given us the opportunity not only to overcome the limitations of the iridium-PHOX catalytic systems in the hydrogenation of minimally functionalized *Z*-olefins and 1,1'-disusbtituted olefins, but also to expand their use to unfunctionalized olefins containing other challenging scaffolds (i.e., exocyclic benzofused and triaryl substituted olefins) and also to olefins with poorly coordinative groups (i.e., α,β-unsaturated lactams, lactones, alkenylboronic esters, ...) with enantioselectivities typically >95% ee. Moreover, both enantiomers of the hydrogenation product could be obtained by simply changing the configuration of the biaryl phosphite moiety. Remarkably, the new catalytic systems also provided excellent enantioselectivities (up to 99% ee) in the asymmetric hydrogenation of another challenging class of olefins – the functionalized cyclic β-enamides. Again, both enantiomers of the reduced amides could be obtained by changing the metal from Ir to Rh. We also demonstrated that environmentally friendly propylene carbonate can be used with no loss of enantioselectivity. Another advantage of the new ligands over the PHOX ligands is that the best ligands are derived from the affordable (*S*)-phenylglycinol rather than from the expensive (*S*)-*tert*-leucinol.

3.2.1. Introduction

The demand for enantiomerically pure chemicals (i.e. drugs, agrochemicals, flavors...) has stimulated the search for efficient synthetic methodologies.[1] Among them, transition-metal based asymmetric catalysis is a reliable, selective, and atom-economic strategy to access optically pure compounds.[1] The catalyst's ability to transfer the chiral information to the product depends on key reaction parameters that must be optimized in order to achieve the desired activity and selectivity.[1] The ligand structure plays a

central role in the catalyst's performance, in which an electronically and sterically well-defined scaffold is the most important factor.[1-2] In this context, thousands of chiral ligands have been developed although only few of them - called privileged ligands - have a general scope.[2-3] Broad substrate and reaction scopes are desirable to reduce time consuming ligand design and synthesis. Phosphine-oxazoline PHOX ligands are considered privileged ligands. They have been successfully applied in asymmetric metal-catalyzed reactions such as hydrogenation, Heck coupling and allylic substitution reactions among others.[4] PHOX ligands have also the advantage that they are prepared from amino alcohols in just two steps. However, the catalyst that has provided the best enantiomeric excesses in most processes is the *tert*-leucinol-derived PHOX (^{t}BuPHOX (**1**)) ligand. One drawback of ^{t}BuPHOX (**1**) (and of other state-of-the-art oxazoline-based ligands) is that the high cost of the *tert*-leucinol as starting material makes them less appealing for industrial scale application. Another limitation is that the free PHOX ligands are prone to oxidation. Although related phosphine-oxazoline ligands have been developed to solve these limitations (such as SimplePHOX, ThrePHOX, NeoPHOX, etc)[5] they are limited in substrate and reaction scope and/or require more reaction steps.[5] The discovery of efficient ligands prepared in only a few steps from inexpensive raw materials, easy to handle (i.e., solid, robust and air stable) and that tolerate a broad range of substrates has therefore attracted the attention of many researchers. Our group has expertise in preparing easy to handle ligand families from readily available starting materials.[6] We and others have shown the benefits of having biaryl phosphite moieties in the ligands for several asymmetric catalytic transformations.[1,6b-f] Our group has contributed with an improved generation of phosphite-N ligand libraries.[6b] In this context, we found that replacing the phosphine moiety in phosphine-oxazoline PHOX ligands by a biaryl phosphite-moiety not only improved activity but also increased substantially the substrate scope in the Pd-allylic substitution[7] and the Ir-catalyzed hydroboration[8]. The reason for this exceptional performance is the flexiblility of the biaryl phosphite group that allows the chiral pocket of the catalyst to accommodate itself according to the steric demands of the substrate.[7b] Moreover, their easy preparation from alcohols and their higher stability towards air and other oxidizing agents than other commonly used phosphines make phosphite ligands very attractive.[2,6b-f] These features facilitate preparing large series of ligands in the quest to maximize catalytic performance for each particular reaction and substrate.

Because of its perfect atom economy, operational simplicity and effectiveness, the hydrogenation of prochiral olefins is one of the most reliable asymmetric catalytic methods for the synthesis of optically active compounds.[1,9] Nowadays, a remarkable range of ligands are being applied to transform a broad range of substrates. The best results are obtained when the substrate has a good coordinating group close to the C=X bond because its chelating ability facilitates transferring the chirality from the catalyst to the product. There are, however, functionalized substrates whose asymmetric

hydrogenation is still not solved. Among them cyclic β-enamides have recently attracted the attention because their reduction products are found in many pharmaceuticals and biologically active products.[10] In contrast to α-enamides, most of the catalysts for β-enamides give low enantiomeric excesses and are based on Rh- and Ru-catalysts modified with diphosphine ligands.[11] A breakthrough in this area came in 2016, when Verdaguer *et al*. showed that Ir-P,N catalysts, which had been mainly used to reduce unfunctionalized olefins, could also reduce cyclic β-enamides derived from 2-tetralones with better enantioselectivities than the Ru/Rh-catalysts described in the literature (up to 99% ee).[12] Just afterwards, our group showed that Ir catalysts modified with PHOX-based phosphite-oxazoline ligands **L3a**-**c**, **L5a**-**c** and **L6**-**L8b** (Figure 3.2.1) can also be successfully used to reduce cyclic β-enamides derived from both 2-tetralones and 3-chromanones.[13] More recently, our group also found that P,S-ligands can be also successfully applied in the hydrogenation of both, β-enamides derived from 2-aminotetralines and 3-aminochromanes with ee's up to 99%.[14] Despite these advances, the potential of P,X-ligands for the hydrogenation of functionalized olefins has been overlooked. The need for easy-to-synthesize, easy-to-handle and highly efficient P,X-ligands for the reduction of β-enamides derived from both, 2-tetralones and 3-chromanones continues.

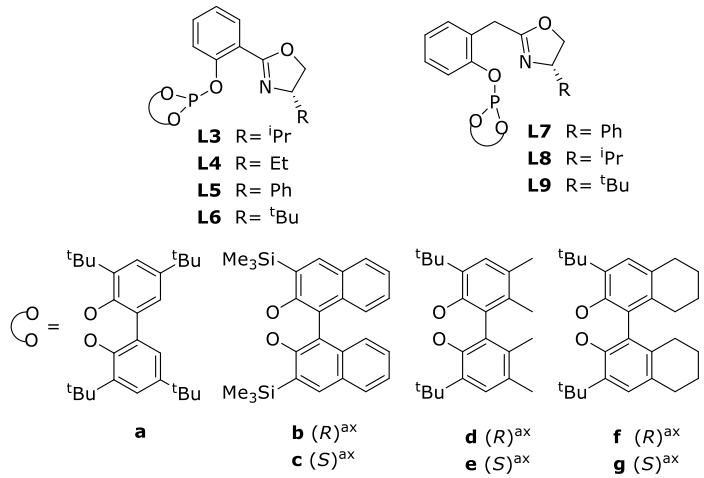


Figure 3.2.1. Phosphite-oxazoline ligands **L3**-**L9a**-**g**

Another important class of olefins are the so-called minimally functionalized olefins, that do not have an adjacent coordinative polar group.[15] The hydrogenation of minimally functionalized olefins has not reached the same level of development as the hydrogenation of functionalized olefins and its synthetic utility remains limited. Following the pioneering work of Pfaltz *et al*. using [Ir(cod)(PHOX)]BAr_F catalyst precursors,[16] research in this field has focussed in Ir-catalysts modified with chiral

heterodonor P,N-ligands.[17,18] However, most of the Ir-catalysts are still very sensitive to the olefin geometry as well as to the number and nature of substituents in the olefin. Many important substrates still provide suboptimal results with known catalysts. For example, Ir-phosphine-oxazoline PHOX catalysts have only been able to successfully hydrogenate a limited range of trisubstituted alkenes with *E*-geometry.[16,19] Our group has shown the benefits of using phosphite-oxazoline ligands for this process, which has become the state-of-art for the reduction of these challenging substrates.[20]

Combining Verdaguer *et al*.'s work and our biaryl phosphite-containing ligands, in this paper we report the family of phosphite-oxazoline ligands (**L3**-**L9a**-**g**, Figure 3.2.1) for the reduction of both, minimally functionalized olefins and cyclic β-enamides. Ligands **L3**-**L6** are based on privileged phosphine-oxazoline PHOX ligands in which the phosphine moiety was replaced with biaryl phosphite moieties.[21] Ligands **L7**-**L9** were designed to study the effect of the size of the chelate ring than has been found to influence the catalytic performance in the hydrogenation of several olefins. They differ from ligands **L3**-**L6** by a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone.[22]

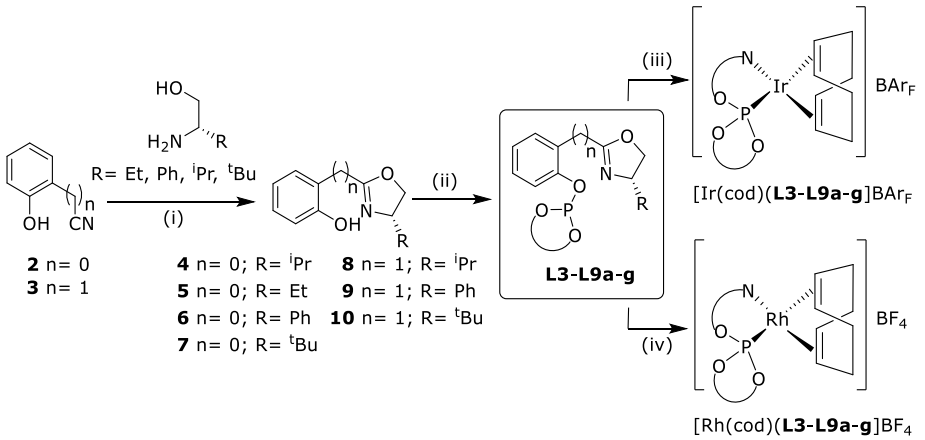
3.2.2. Results and Discussion

3.2.2.1. Synthesis of Ir(I)- and Rh(I)-catalyst precursors

The Ir- and Rh-catalyst precursors [Ir(cod)(**L3**-**L9a**-**g**)]BAr_F and [Rh(cod)(**L3**-**L9a**-**g**)]BF_4 have been synthesized in only three steps from readily available starting materials as shown in Scheme 3.2.1. First, the coupling of hydroxyl-cyanides **2** and **3** with the appropriate amino alcohol yielded the hydroxyl-oxazolines **3**-**9** with diverse oxazoline substituents (step i).[23] Then, condensation of the desired *in situ* formed phosphorochloridites ($ClP(OR)_2$; $(OR)_2$= **a**-**g**) with the corresponding hydroxyl-oxazoline yielded phosphite-oxazoline ligands with several biaryl phosphite groups **L3**-**L9a**-**g**′ in high yields as white solids (step ii). Advantageously, **L3**-**L9a**-**g** are stable in air, so manipulation and storage was performed in air. In the last step of the synthesis, complexation of the ligands to $[Ir(\mu\text{-}Cl)(cod)]_2$ followed by *in situ* Cl^-/BAr_F^- counterion exchange with $NaBAr_F$ gave access to the desired cationic Ir-catalyst precursors (step iii). These were isolated in pure form as air-stable red-orange solids in excellent yields after simple extraction. No further purification was required. For the Rh-catalyst precursors, in the last step of the synthesis $[Rh(cod)_2]BF_4$ reacted with one equivalent of the appropriate ligand and the complexes were isolated in pure form as yellow powders by adding cold hexane (step iv).

All ligands **L3**-**L9a**-**g** and complexes [M(cod)(**L3-L9a**-**g**)]X (M= Ir; X= BAr_F and M= Rh; X= BF_4) were characterized by $^{31}P\{^1H\}$, ^1H, and $^{13}C\{^1H\}$ NMR spectra and mass spectrometry. All data were in agreement with assigned structures. The spectra

assignments were supported by the information obtained from ^{1}H-^{1}H and ^{1}H-^{13}C correlation measurements. HRMS-ESI spectra showed the heaviest ions at m/z corresponding to the loss of the BAr_F anion from the molecular species for the Ir-complexes and the loss of BF_4 anion for Rh-complexes. The ^{1}H, ^{13}C, and ^{31}P NMR spectra showed the expected pattern for these C_1-complexes. The VT-NMR in CD_2Cl_2 (+35 to -85 °C) spectra showed only one isomer in solution. In all cases, one singlet in the ^{31}P-{^{1}H} NMR spectra was observed.



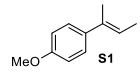
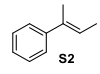
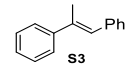
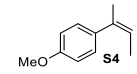
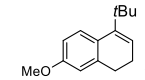
Scheme 3.2.1. Synthesis of phosphite-oxazoline ligands **L3**-**L9a**-**g** and the corresponding Ir- and Rh-catalyst precursors. (i) $ZnCl_2$, toluene or chlorobenzene, reflux, 18-72 h; (ii) $ClP(OR)_2$; $(OR)_2$= **a**-**g**, Py, toluene, rt, 18 h; (iii) $[Ir(\mu\text{-}Cl)(cod)]_2$, CH_2Cl_2, 40 ºC, 60 min then H_2O, $NaBAr_F$, rt, 30 min; (iv) $[Rh(cod)_2]BF_4$, CH_2Cl_2, rt, 60 min then precipitated with cold hexane.

3.2.2.2. Asymmetric hydrogenation of minimally functionalized olefins

Asymmetric hydrogenation of trisubstituted olefins

The efficiency of ligands **L3**-**L9** in the hydrogenation of trisubstituted olefins with different geometry was initially evaluated with *E*-substrates **S1** (model olefin), **S2** and **S3**; and the *Z*-substrates **S4** and **S5** (Table 3.2.1). *Z*-Trisubstituted olefins are usually hydrogenated less enantioselectively than the related *E*-trisubstituted olefins. By selecting the ligand parameters we could achieve high enantioselectivities in the reduction of *E*- and *Z*-olefins (ee's up to 97% and 90%, respectively) thus overcoming one of the limitations of the parent ^{t}BuPHOX phosphine-oxazoline ligand in the reduction of *Z*-olefins (ee values up to 42% for **S4**, entry 24)[16].

Table 3.2.1. Ir-catalyzed hydrogenation of *E*- and *Z*-subtrates **S1**-**S5** using ligands **L3**-**L9a-g**.[a]

		 **S1**	 **S2**	 **S3**	 **S4**	 **S5**
Entry	L	% ee[b]	% ee[b]	% ee[b]	% ee[b]	% ee[b]
1	**L3a**	72 (*R*)	72 (*R*)	78 (*R*)	86 (*S*)	51 (*S*)
2	**L3b**	78 (*R*)	68 (*R*)	74 (*R*)	30 (*S*)	7 (*R*)
3	**L3c**	61 (*R*)	58 (*R*)	63 (*R*)	85 (*S*)	81 (*S*)
4	**L3d**	25 (*R*)	21 (*R*)	24 (*R*)	15 (*S*)	14 (*R*)
5	**L3e**	55 (*R*)	59 (*R*)	56 (*R*)	72 (*S*)	83 (*S*)
6	**L3f**	29 (*R*)	31 (*R*)	34 (*R*)	0	4 (*R*)
7	**L3g**	58 (*R*)	54 (*R*)	61 (*R*)	90 (*S*)	87 (*S*)
8	**L4a**	9 (*R*)	11 (*R*)	7 (*R*)	47 (*S*)	41 (*S*)
9	**L5a**	0	6 (*R*)	4 (*R*)	60 (*S*)	64 (*S*)
10	**L5b**	40 (*R*)	35 (*R*)	43 (*R*)	78 (*S*)	81 (*R*)
11	**L5c**	15 (*S*)	22 (*S*)	19 (*S*)	91 (*S*)	89 (*S*)
12	**L6a**	72 (*R*)	73 (*R*)	74 (*R*)	88 (*S*)	71 (*S*)
13	**L6b**	19 (*R*)	17 (*R*)	21 (*R*)	17 (*S*)	3 (*R*)
14	**L6c**	44 (*R*)	46 (*R*)	45 (*R*)	84 (*S*)	75 (*S*)
15	**L7a**	15 (*R*)	11 (*R*)	14 (*R*)	5 (*S*)	6 (*R*)
16	**L7b**	94 (*R*)	94 (*R*)	96 (*R*)	17 (*R*)	48 (*R*)
17	**L7c**	95 (*S*)	96 (*S*)	97 (*S*)	3 (*S*)	51 (*R*)
18	**L8a**	81 (*R*)	78 (*R*)	84 (*R*)	56 (*S*)	31 (*R*)
19	**L8b**	92 (*R*)	91 (*R*)	93 (*R*)	3 (*R*)	40 (*S*)
20	**L8c**	65 (*S*)	69 (*S*)	68 (*S*)	45 (*S*)	31 (*R*)
21	**L9a**	76 (*R*)	71 (*R*)	72 (*R*)	56 (*S*)	87 (*S*)
22	**L9b**	23 (*R*)	24 (*R*)	28 (*R*)	24 (*S*)	69 (*S*)
23	**L9c**	0	4 (*S*)	8 (*S*)	51 (*S*)	28 (*R*)
24[c]	**1**	61 (*R*)	-[d]	97 (*R*)	42 (*S*)	-[d]
25[e]	**L5c**	14 (*S*)	21 (*S*)	19 (*S*)	91 (*S*)	88 (*S*)
26[e]	**L7b**	94 (*R*)	94 (*R*)	96 (*R*)	16 (*R*)	48 (*R*)
27[e]	**L7c**	95 (*S*)	96 (*S*)	97 (*S*)	3 (*S*)	51 (*R*)
28[f]	**L5c**	13 (*S*)	20 (*S*)	21 (*S*)	91 (*S*)	89 (*S*)
29[f]	**L7b**	93 (*R*)	94 (*R*)	96 (*R*)	14 (*R*)	46 (*R*)
30[f]	**L7c**	95 (*S*)	95 (*S*)	96 (*S*)	6 (*S*)	54 (*S*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (50 bar), CH_2Cl_2 (2 mL), rt. Unless otherwise noted, full conversions were achieved after 2 h; [b] Enantiomeric excesses measured by chiral GC or HPLC; [c] Data from Ref.[16]; [d] Data not reported; [e] Reactions carried out at 0.25 mol% of Ir-catalyst precursor for 6 h; [f] Reactions carried out using PC as solvent and 1 mol% of Ir-catalyst precursor at 100 bar of H_2 for 12 h.

In general, the enantioselectivities were found to be highly dependent on the ligand structure and the substrate type. While the best enantioselectivities for *E*-substrates were obtained with **L7b** and **L7c** that contain a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone (Table 3.2.1 entries 16 and 17), for *Z*-substrates the best enantioselectivities were obtained with the ligand without the methylene spacer **L5c** (Table 3.2.1, entry 11). Moreover, the oxazoline substituents and the substituent/configuration of the biaryl phosphite group also affected the enantioselectivity. Reactions conducted with ligands containing a Ph oxazoline group proceeded with the highest enantioselectivities for both substrate types (entries 11 and 17). This is economically advantageous because the (*S*)-phenylglycinol used in the preparation of **L7** is the cheapest of the amino alcohols employed (up to eight times cheaper than *tert*-leucinol that is used in **L6** and **L9** as well as in other state-of-art oxazoline-based ligands such as the ^{t}BuPHOX (**1**) phosphine-oxazoline ligand). Additionally, whereas for the more demanding *Z*-substrates the best enantioselectivity is obtained with **L5c**, which contains an (*S*)-binaphthyl group **c** (entry 11), for *E*-substrates the best enantioselectivities were obtained with either (*S*)- or (*R*)-binaphthyl groups (**b** and **c**; entries 16 and 17). From these latter results we can conclude that both enantiomers of the hydrogenated *E*-substrates can be obtained in high enantioselectivities by simply switching the configuration of the biaryl phosphite group in ligands **L7**.

We also studied these reactions at a low catalyst loading (0.25 mol%) with ligands **L5c** and **L7b**-**c**, which had provided the best results so far. The high enantioselectivities were retained (Table 3.2.1, entries 25-27). We also tested 1,2-propylene carbonate (PC) as a solvent. PC has emerged as an environmentally friendly alternative to standard organic solvents because of its high boiling point, low toxicity, and "green" synthesis.[24] Using PC we repeated the hydrogenation of substrates **S1**-**S5** with the ligands that provided the best enantioselectivities (Table 3.2.1, entries 28-30). We were pleased to see no loss of enantioselectivity.

Remarkably, we could also achieve high enantioselectivity in the hydrogenation of the challenging exocyclic benzofused five-membered olefin **S6** with Ir/**L3g** (Figure 3.2.2, entry 1). Chiral benzofused five-membered alkanes are key structural elements in several natural and bioactive molecules.[25] It should be noted that the hydrogenation of this type of olefins is not achieved using the parent phosphine-oxazoline ^{t}BuPHOX ligand (**1**) (conversions below 5%)[17y] and that only Ir/In-BiphPHOX has been recently reported to successfully reduce this type of substrate.[17y]

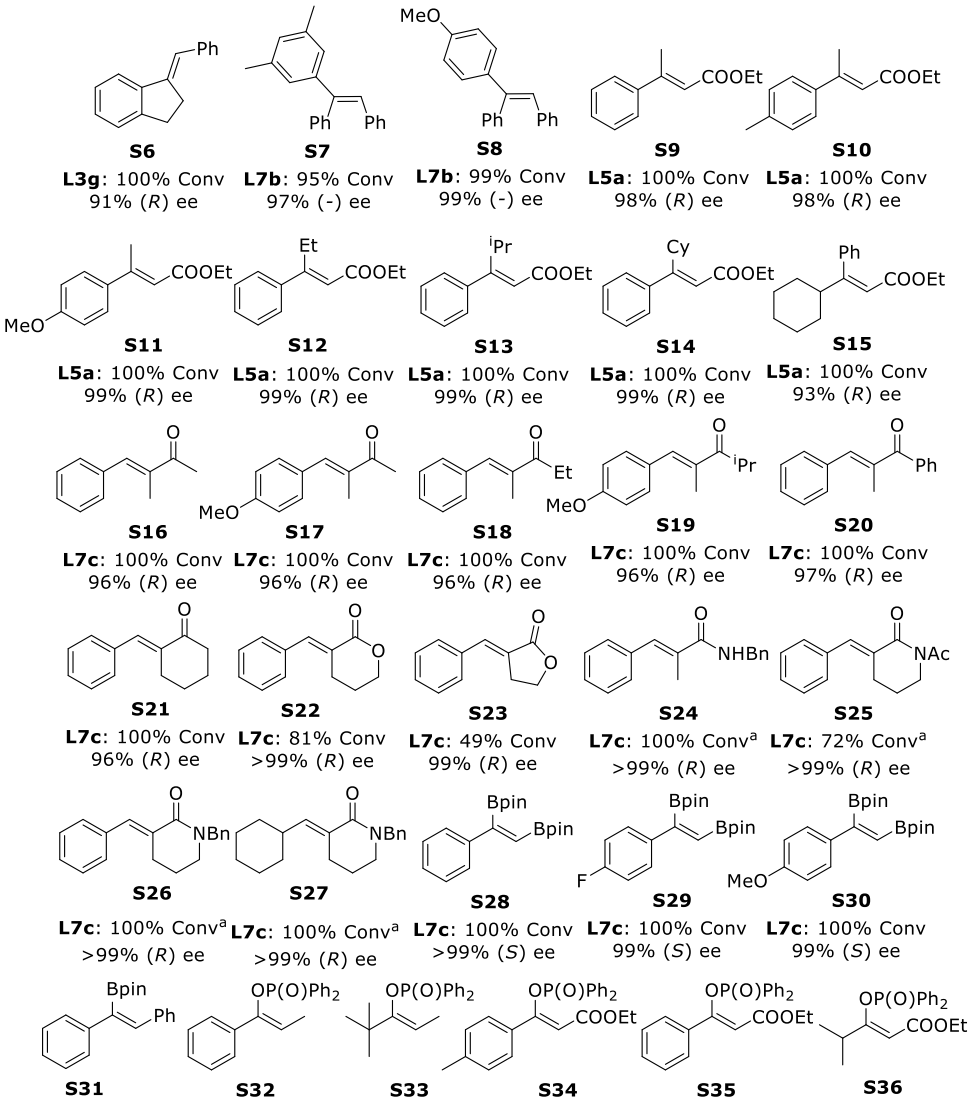


Figure 3.2.2. Selected results for the hydrogenation of trisubstituted olefins **S6**-**S36** using [Ir(cod)(**L3**-**L9a**-**g**)]BAr_F catalyst precursors. Reaction conditions: Catalyst precursor (2 mol%), CH_2Cl_2, H_2 (50 bar), 4 h. [a] Reactions carried out during 24 h.

High enantioselectivities (up to 97% ee, Figure 3.2.2) were also obtained in the reduction of substrates **S7**-**S8** with the Ir/**L7b** system. Triaryl-substituted substrates have been scarcely studied,[17p,18d,20e] although their hydrogenation is a sustainable and straightforward method to achieve diarylmethine chiral centers.[26]

We then moved towards the reduction of key trisubstituted substrates with poorly coordinative groups. Their hydrogenation is of interest because they can be further

functionalized and become key intermediates for more complex chiral molecules. The results are shown in Figure 3.2.2 (for a complete series of results, see Table SI-1 in the Supporting Information at the end of this chapter). We found that, again, the parameters of the ligands must be optimized for each substrate if enantioselectivities are to be high. We first hydrogenated a large series α,β-unsaturated esters **S9**-**S15** (Figure 3.2.2), with different electronic properties in the phenyl ring (**S9**-**S11**) and with different steric properties of the alkyl substituents (**S9**, **S12**-**S14**). The hydrogenation of these substrates provides a simple entry point to chiral carboxylic ester derivatives, which are found in relevant products.[27] For all of them enantioselectivities (ee's up to 99%) were excellent and comparable to the best reported to date. It should be highlighted the 93% ee obtained for the more demanding *Z*-isomer **S15**. The effect of the ligand parameters on enantioselectivity is different than for previous **S1**-**S8** substrates. The best enantioselectivities were obtained with ligand **L5a**, which maintains the economic benefits of a Ph oxazoline substituent but with the added advantage that an achiral inexpensive 3,3',5,5'-tetra-*tert*-butyl-[1,1'-biphenyl]-2,2'-diyl phosphite moiety (**a**) can be used. With the Ir/**L7c** catalytic system we were also able to hydrogenate α,β-unsaturated enones **S16**-**S21** with results (ee's up to 98%; Figure 3.2.2) comparable to the best enantioselectivities previously reported.[17t,19,28,29] Interestingly, Ir/**L7c** provided similar high enantioselectivities irrespective of the nature of the alkyl substituent and the electronic nature of the substrate phenyl ring. Being able to hydrogenate such a wide range of α,β-unsaturated enones is highly significant since the obtained ketones are found in many relevant products. Despite their importance, they have been less studied and less successfully hydrogenated than other trisubstituted olefins with poorly coordinative polar groups.[17t,19,28] Other difficult substrates such as α,β-unsaturated δ- and γ-lactones **S22**-**S23**, acyclic amide **S24** and δ-lactams **S25**-**S27** were also successfully reduced with the Ir/**L7c** system (ee's up to >99%). Chiral amides with stereogenic centres in the α-position and δ- and γ-lactones/lactams are common in a variety of natural products as well as useful building blocks in synthetic chemistry (i.e. amide group can be easily transformed into other useful compounds such as amines). Despite their relevance, very few successful examples of Ir-catalysts can be found in the literature and they have a limited substrate scope.[17x,27b,30]

Alkenylboronic esters and enol phosphinates are two other relevant sets of substrates that are receiving much attention. The asymmetric reduction of alkenylboronic esters will open up a new straightforward and sustainable route for preparing enantiomerically pure organoboron compounds. Chiral organoboron compounds are interesting because the boronate group can undergo stereospecific transformations to form C-N, C-O and C-C bonds. On the other hand, the effective hydrogenation of enol phosphinates opens up an appealing route for obtaining chiral organophosphinates, which can be easily transformed into high value compounds such as alcohols and phosphines. Despite the

importance of hydrogenating alkenylboronic esters and enol phosphinates, only a few reports have been published and show a limited success.[18d,31] In this context, it was noteworthy that by modifying the ligand parameters we could reach high enantioselectivities for alkenylboronic esters **S28**-**S31** and enol phosphinates **S32**-**S36** (Figure 3.2.2). In the reduction of alkenylboronic esters, the highest enantioselectivities (up to 99% ee) were achieved using [Ir(cod)(**L7c**)]BAr_F, while for enol phosphinates the best enantioselectivities (ee's up to 96%) were obtained with [Ir(cod)(**L7b**)]BAr_F.

In summary, the simple substitution of the phosphine by a phosphite group and/or the introduction of a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone in phosphine-oxazoline ^{t}BuPHOX ligand extended the range of trisubstituted olefins that could be successfully hydrogenated with enantioselectivities that were among the best reported so far.[15h] In addition, the ligands that provided the best enantioselectivities contained the Ph substituent in the oxazoline moiety instead of the pricy ^{t}Bu substituent.

Asymmetric hydrogenation of disubstituted olefins

To further study the potential of the **L3**-**L9a**-**g** ligands, we screened them in the Ir-catalyzed hydrogenation of 1,1'-disubstituted substrates. Enantioselectivity is more difficult to control in these substrates than in trisubstituted olefins. Most catalysts fail either to control the face-selective coordination of the less hindered disubstituted substrate or to suppress the isomerization of the olefin that leads to the formation of the more stable *E*-trisubstituted substrates, which in turn form the opposite enantiomer when hydrogenated.[15e]

As a model substrate we chose the 3,3-dimethyl-2-phenyl-1-butene **S37**. The results are summarized in Table SI-2 in the Supporting Information at the end of this chapter. The best enantioselectivity (ee's up to 98%), comparable to the best one reported in the literature, was obtained with **L5a** (Figure 3.2.3). This ligand has the economic benefits of both a Ph oxazoline substituent and an achiral biaryl phosphite moiety **a**. The introduction of a methylene spacer between the oxazoline and the phenyl ring of the ligand backbone did not improve the enantioselectivity.

We next studied the asymmetric hydrogenation of other terminal disubstituted olefins (Figure 3.2.3; for a complete series of results, see Table SI-3 in the Supporting Information at the end of this chapter). We noted that Ir/**L5a** easily tolerates variations in the electronic and steric properties of the substituents in the aryl moiety of the substrate. A broad range of terminal olefins (**S38**-**S44**) were reduced in high enantioselectivities comparable to **S37**. For **S43** and **S44** with *ortho*-substituents, longer reaction times were required to achieve full conversions.

Among the results, it is worth mentioning that the hydrogenation of α-alkylstyrenes bearing decreasingly sterically demanding alkyl substituents (**S45**-**S48**) proceeded with

somewhat lower enantioselectivities (from 83% to 91% ee). Nevertheless, we found that enantioselectivities for these substrates could be maximized by choosing the ligand parameters. A plausible explanation for the lower enantioselectivity can be either that hydrogenation competes with isomerization or that face selectivity problems occur. To clarify this aspect, we run deuterium labeling experiments (Scheme 3.2.2) in which we hydrogenated **S1** and **S48** with deuterium with Ir/**L3b** and Ir/**L8b** catalyst precursors.

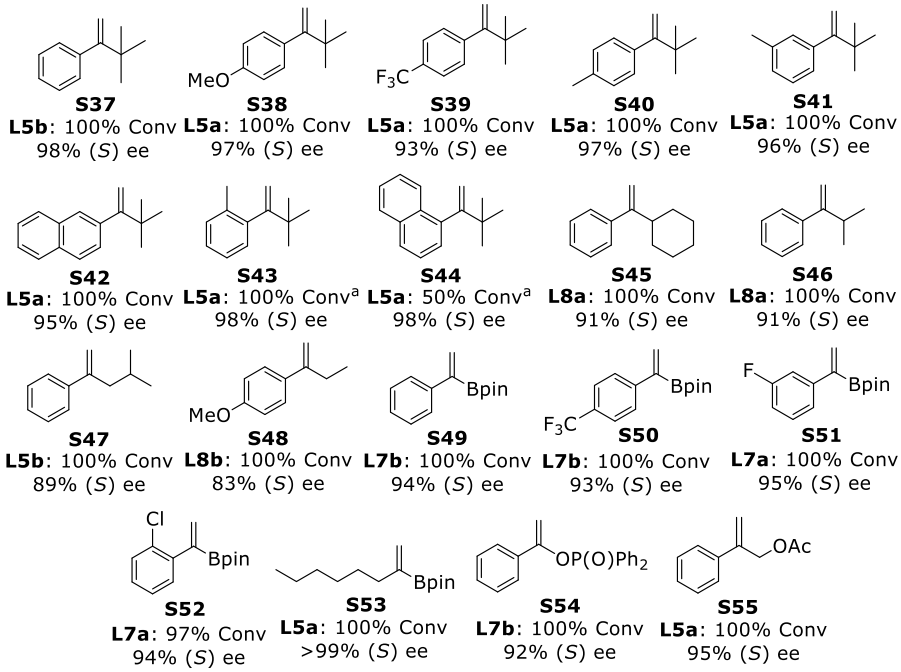
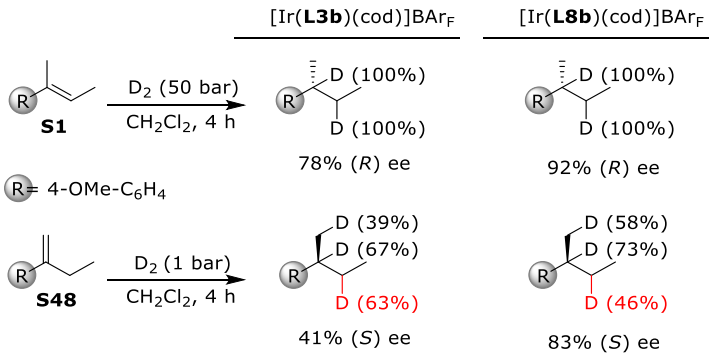


Figure 3.2.3. Selected results for the hydrogenation of disubstituted olefins **S37**-**S55** using [Ir(cod)(**L3**-**L9a**-**g**)]BAr_F catalyst precursors. Reaction conditions: Catalyst precursor (1 mol%), CH_2Cl_2, H_2 (1 bar), 4 h. [a] Reaction carried out for 12 h.

In contrast to **S1**, the reduction of **S48** led to the addition of deuterium not only at the double bond (as expected) but also at the allylic position. This agrees with the existence of a competing isomerization pathway.[32] This was supported by the mass spectra of the corresponding deuterated product from **S48** showing species with more than two deuterium atoms. In line with this, the Ir/**L8b** system shows less deuterium atoms incorporated at the allylic position than the Ir/**L3b**. This indicates that Ir/**L8b** controls better the isomerization than Ir/**L3b**, which agrees with the higher enantioselectivity observed with Ir/**L8b**. Although in olefins prone to isomerization (**S45**-**S48**) this competing reaction was not completely suppressed, the introduction of a biaryl phosphite group together with the combination of the right ligand parameters minimized this side reaction to achieve ee's comparable to the best ones reported. Besides, by introducing the biaryl phosphite moiety, the face coordination mode was

successfully controlled thus facilitating the reduction of a broad range of 1,1'-disubstituted substrates.



Scheme 3.2.2. Deuterium labeling experiments of substrates **S1** and **S48** using Ir/**L3b** and Ir/**L8b** catalyst precursors. The percentage of incorporation of deuterium atoms is shown in brackets. The results of the indirect addition of deuterium due to the isomerization process are shown in red.

Finally, due to the relevance of olefins with poorly coordinative groups, we wanted to see if the excellent catalytic performance in the reduction of the trisubstituted enol phosphinates and alkenylboronic esters was maintained for the even more challenging terminal analogues. We were able to obtain high-to-excellent enantioselectivities (ee's up to 99%) in the reduction of substrates **S49**-**S54** (Figure 3.2.3). The results are among the best in the literature for each substrate, even in the reduction of highly appealing substrates such as pinacolatoboron-containing substrates **S49**-**S53**[33] and enol phosphinate **S54**[34] for which only very few catalytic systems have provided high enantioselectivities. The successful reduction of aryl-substituted boronic esters **S49**-**S52** is a relevant finding that overcomes the results reported in the literature in the hydrogenation of this type of substrates and nicely complements the current state of the art. It is also noteworthy that although **S53** is prone to isomerization, it was hydrogenated with excellent enantioselectivity. Similarly, the hydrogenation of the allylic acetate **S55**[35] also proceeded with high activity and enantioselectivity with catalyst Ir/**L5a**. Derivatives of the hydrogenation product of **S55** are used as components of fragrance mixtures (i.e., Pamplefleur) and also as intermediates for the synthesis of natural products and drugs (i.e., modulators of dopamine D3 receptors).[36]

To summarize, the results for the asymmetric hydrogenation of disubstituted olefins are among the best reported for this type of challenging substrates and overcome one of the limitations of the parent phosphine-oxazoline ^{t}BuPHOX ligand, which was unable to reduce the 1,1'-disubstituted substrate class with high enantioselectivities.

Asymmetric hydrogenation of cyclic β-enamides

We finally turned our attention to the asymmetric reduction of challenging β-enamides. 2-Aminotetralines and 3-aminochromanes are key structural units in many therapeutic agents and biologically active natural products (Figure 3.2.4).[10]

The asymmetric hydrogenation of β-enamides will open up a direct, atom-efficient, path to synthesize these compounds. So far, only few successful examples can be found in the literature and they are limited in substrate scope. In contrast to the α-enamides, most of the catalysts for β-enamides provide low enantiomeric excesses and are based on Rh- and Ru-catalysts.[11] Among the most successful reports, Ratovelomanana *et al*. published the synthesis of 3-aminochromanes with enantioselectivities up to 96% ee using Ru-diphosphine catalysts.[11f] A more recent report showed similar high enantioselectivities in the reduction of enamides derived from 2-tetralones (ee's up to 96%) and enamides derived from 3-chromanones (ee's in the range 94-98%), using a Rh-diphosphine catalysts.[11k] They needed, however, to use WingPhos, a P-stereogenic diphosphine ligand synthesized in nine steps.

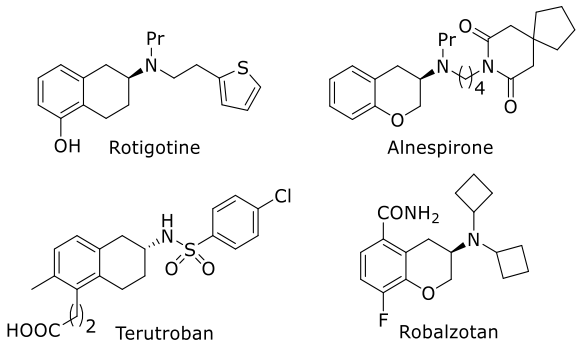


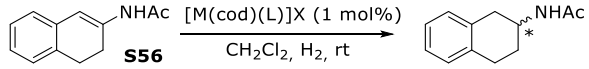
Figure 3.2.4. Examples of chiral 2-aminotetralines and 3-aminochromanes with pharmaceutical applications.

In 2016, two reports showed that Ir-P,N catalysts, that have been mainly used to reduce unfunctionalized olefins, are also able to reduce cyclic β-enamides.[12-13] In this respect, we identified that Ir-catalysts modified with the simple PHOX-based phosphite-oxazoline **L3a**-**c**, **L5a**-**c** and **L6**-**L8b** can be successfully used to reduce cyclic β-enamides derived from 2-tetralones and 3-chromanones.[13] Our preliminary results (at 50 bar of H_2 at room temperature using 1 mol% of the corresponding [Ir(cod)(L)]BAr_F catalyst precursors) showed that ligands with a methylene spacer between the oxazoline and the phenyl ring provided higher enantioselectivities than ligands without this methylene moiety. We also found that a chiral (*R*)-binaphthyl moiety **b** was needed for high enantioselectivities.[13]

Therefore, and in order to further improve enantioselectivities, in this work we expanded our previous study to other phosphite containing-PHOX based ligands with a

methylene spacer. Thus, we tested the new ligands containing a ^{t}Bu oxazoline moiety (ligand **L9**) and those incorporating other (*R*)-configured biaryl phosphite moieties (ligands **L7**-**L9c**,**d**,**f**). For comparison we also tested the new ligands **L3**-**L6d**,**f** that contain the (*R*)-biaryl phosphite moieties **d** and **f** but not the methylene spacer. See Table 3.2.2 for selected results (for a complete series of results, see Table SI-4 in the Supporting Information at the end of this chapter). Neither these new chiral biaryl phosphite groups nor the ^{t}Bu oxazoline moiety improved the previous enantioselectivities. Indeed the presence of the ^{t}Bu oxazoline group lowered both activity and enantioselectivity. The use of the new ligands with other (*R*)-biaryl phosphite moieties (**d**, **f**) provide the same enantioselectivities than the best ones obtained with ligands **L7**-**L8b**. Therefore, ligands **L7b** and **L8b**,**d**,**f** provided the reduced product in full conversion and 98% of ee (Table 3.2.2).

Table 3.2.2. Selected results for the reversal of enantioselectivity observed in the Ir- and Rh-catalyzed hydrogenation of **S56**.[a]



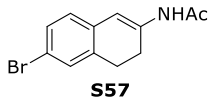
S56

		[Ir(cod)(L)]BAr$_F$		**[Rh(cod)$_2$]BF$_4$/L**	
Entry	L	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
11	**L7b**	100	98 (*S*)[d]	100	94 (*R*)
13	**L8b**	100	98 (*S*)[d]	100	94 (*R*)
14	**L8d**	100	98 (*S*)	100	93 (*R*)
15	**L8f**	100	98 (*S*)	100	94 (*R*)

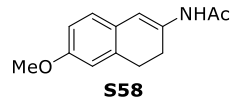
[a] Reactions conditions: Substrate (0.5 mmol), catalyst precursor (1 mol%), CH_2Cl_2 (2 mL), H_2 (50 bar), rt for Ir-catalysts or H_2 (30 bar), 5 °C for Rh-catalysts; [b] Conversion measured by ^{1}H-NMR after 20 h for Ir-catalysts and 36 h for Rh-catalysts; [c] Enantiomeric excess determined by HPLC; [d] Data from Ref.[13].

More recently, our group also found for the first time that with P-thioether ligands both enantiomers of the hydrogenated can been obtained by switching from Ir to Rh.[14] Therefore, in this paper we also extended the use of ligands **L3**-**L9** in the Rh-catalyzed hydrogenation of β-enamides. For comparison, we firstly evaluated ligands **L3**-**L9** in the Rh-catalyzed hydrogenation of the model *N*-(3,4-dihydronaphthalen-2-yl)acetamide **S56** substrate. The selected results are shown in Table 3.2.2 (for complete series of results see Table SI-4 in the Supporting Information at the end of this chapter). We used the same optimal reaction conditions found in our previous study with Rh-P,S catalytic systems in the reduction of cyclic β-enamides. The reactions were therefore performed in dichloromethane using 1 mol% of the catalyst loading under 30 bar of H_2. The catalysts were prepared *in situ* by adding the appropriate ligand to the [Rh(cod)$_2$]BF$_4$ catalyst precursor. Again, the methylene spacer between the oxazoline and the phenyl ring affected positively the enantioselectivity while the presence of a ^{t}Bu

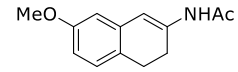
oxazoline group affected negatively. The effect of the methylene spacer is more significant in Rh-catalysts than in Ir-catalysts. As previously observed with Ir-catalysts, the results also indicated that the ligand backbone is not able to control the tropoisomerism of the biphenyl phosphite moiety (**a**). Therefore, the chiral (*R*)-biaryl phosphite moieties are needed to maximize enantioselectivities and activities. However, in contrast to Ir-catalysts, the presence of the corresponding chiral (*S*)-biaryl phosphite moiety also provided quite good enantioselectivities. In summary, the best enantioselectivities of up to 94% ee were therefore obtained with ligands **L7b** and **L8b**,**d**,**f**. Advantageously, we also found that both enantiomers of the hydrogenated products could be reached with the same ligand by simple exchanging Ir to Rh (Table 3.2.2).



S57

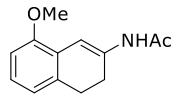


S58

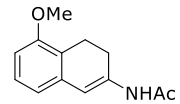


S59

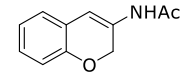
[Rh]	83% yield; 96% (*R*) ee	91% yield; 92% (*R*) ee	87% yield; 89% (*R*) ee
[Ir]	80% yield; 97% (*S*) ee	82% yield; 98% (*S*) ee	86% yield; 99% (*S*) ee



S60



S61
(Rotigotine precursor)



S62
(Alnespirone precursor)

[Rh]	88% yield; 88% (*R*) ee	89% yield; 93% (*R*) ee	81% yield; 91% (*S*) ee
[Ir]	87% yield; 99% (*S*) ee	89% yield; 97% (*S*) ee	58% yield; 98% (*R*) ee

Figure 3.2.5. Asymmetric Rh-catalyzed hydrogenation of cyclic β-enamides **S57**-**S62** using [Rh(cod)(**L8d**)]BF_4. Reactions conditions: Catalyst precursor (1 mol%), substrate (0.5 mmol), CH_2Cl_2 (2 mL), 10 bar H_2, 5 °C, 50 h. For comparative purposes the results achieved with related Ir/**L8d** catalytic system (1 mol%) using 50 bar of H_2 are also included.

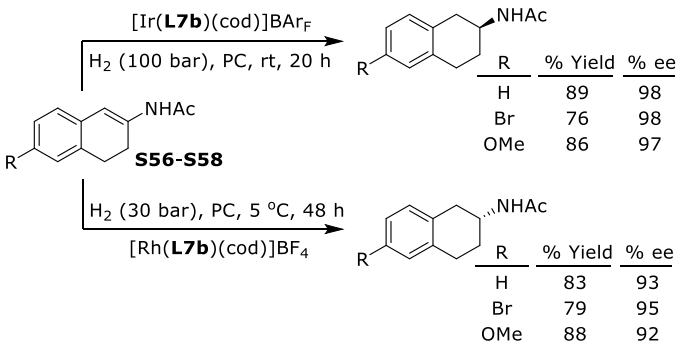
We then evaluated the effect of several reaction parameters on catalytic performance (see Table SI-5 in the Supporting Information at the end of this chapter). We were pleased to find that full conversions and high enantioselectivities can be maintained by lowering the pressure of H_2 to 10 bar. We also found that the catalytic performance is unaffected when using either the *in situ* formed or the preformed catalyst precursor [Rh(cod)(L)]BF_4. In the optimal reaction conditions we then evaluated the substrate scope with other cyclic β-enamides. Figure 3.2.5 shows the results using Rh/**L8d** catalyst as example (for a complete series of results, see Table SI-3 in the Supporting Information at the end of this chapter). For comparison, Figure 3.2.5 also collects the results with the corresponding Ir-catalyst.

A range of substituted cyclic enamides derived from β-tetralones (**S57**-**S61**), that contemplate all possible variations in the substitution pattern of the 3,4-dihydronaphthalene core were hydrogenated with high enantioselectivities comparable

to the best one reported (ee's up to 96%). Also, the replacement of the metal gave access again to both enantiomers of the reduced products with high enantioselectivities. Finally, we were pleased to find that we could also effectively hydrogenate the enamide derived from 3-chromanone, **S62**, in high enantioselectivities and yields (ee's up to 91%).

In summary, by simply choosing the metal center, we have been able to obtain both reduced enantiomers for a broad range of cyclic β-enamides in enantioselectivities comparable to the best one reported under mild reaction conditions. Again, the ligand that contains the phenyl substituent at the oxazoline instead of the pricy ^{t}Bu has provided excellent enantioselectivities.

Finally, we went one step further and evaluated this novel set of catalysts in the M-catalyzed (M= Rh and Ir) hydrogenation of cyclic β-enamides **S56**-**S58** using 1,2-propylene carbonate. The enantioselectivities in both enantiomers of the hydrogenated products remained as high as those achieved with dichloromethane (Scheme 3.2.3).



Scheme 3.2.3. Asymmetric hydrogenation of cyclic β-enamides **S56**-**S58** using 1,2-propylene carbonate (PC). Reactions conditions: Substrate (0.5 mmol), catalyst precursor (1 mol%), PC as solvent (2 mL).

3.2.3. Conclusions

We have identified readily accessible Ir- and Rh-phosphite-oxazoline PHOX-based catalytic systems that can hydrogenate, for the first time, both a broad range of minimally functionalized and functionalized olefins (62 examples in total) in high enantioselectivities (ee's up to >99%) and conversions. Starting from privileged PHOX ligands, the phosphine moiety was replaced by a biaryl phosphite group and, in some cases, a methylene spacer was introduced between the oxazoline and the phenyl ring. With these simple modifications, the phosphite-based ligands not only had a more modular design than the source phosphine-oxazoline PHOX, but also were air-stable solids with no increase in the number of synthetic steps. With a careful selection of the ligand components, the new ligands were superior to the privileged phosphine-oxazoline

PHOX ligands in the metal-catalyzed hydrogenation of challenging olefins, with enantioselectivities comparable to the best one reported. Therefore, these ligands improved the enantioselectivities achieved for challenging minimally functionalized *Z*-olefins and 1,1'-disubstituted olefins and expanded their use to olefins containing other challenging scaffolds (i.e., exocyclic benzofused and triaryl substituted olefins), olefins with poorly coordinative groups (i.e., α,β-unsaturated lactams, lactones, alkenylboronic esters, ...) and cyclic β-enamides that have a fully coordinative group. Interestingly, in the Ir-hydrogenation of minimally functionalized olefins, the sense of enantioselectivity was mainly controlled by the configuration of the biaryl phosphite moiety so both enantiomers of the hydrogenated product can be obtained with the same ligand scaffold. In the hydrogenation of cyclic β-enamides, both enantiomers of the corresponding 2-aminotetralines and 3-aminochromanes could also be obtained with the same ligand by simply changing the metal from Ir to Rh. Another advantage of the new ligands over the PHOX ligands is that the best ligands are derived from affordable (*S*)-phenylglycinol rather than from expensive (*S*)-*tert*-leucinol. This latter fact together with the small number of synthetic steps (only 2) to obtain the ligands, the modularity and air-stability, and the evidence that the new Ir- and Rh-catalyst precursors maintain their enantioselectivities with environmentally friendly propylene carbonate as solvent makes them very appealing for industrial applications.

3.2.4. Experimental Section

3.2.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. All reagents were used as received. ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and $^{13}C\{^{1}H\}$) as an internal standard or H_3PO_4 (^{31}P) as an external standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments. Phosphorochloridites were easily prepared in one step from the corresponding biaryl alcohols.[37] Substrates **S1**,[38] **S2**,[39] **S4**,[38] **S5**,[40] **S6**,[41] **S7**,[17p] **S8**,[42] **S9**-**S11**,[43] **S12**-**S15**,[27b] **S16**,[44] **S17**-**S20**,[19] **S21**,[45] **S22**-**S23**,[46] **S24**,[47] **S25**-**S27**,[46] **S29**-**S30**,[31b] **S32**-**S36**,[31a] **S37**-**S44**,[48] **S45**,[49] **S46**,[50] **S47**,[51] **S48**,[52] **S53**,[31b] **S54**,[31a] **S55**,[53] **S56**,[54] **S57**-**S58**,[11j] **S59**,[55] **S60**,[11j] **S61**,[11i] and **S62**[11a]were prepared following the reported procedures and **S3**, **S28**, **S31** and **S49**-**S52** were commercially available. Compounds **3**,[23a] **4**-**7**,[23b] **8**-**9**;[13] ligands **L3**-**L6a**,[7a] **L3b**-**L3c**,[13] **L3f**-**g**,[7b] and **L5**-**L7b**[13] and complexes [Ir(cod)(L)]BAr_F (L= **L3a**-**c**, **L5a**-**c** and **L6**-**L8b**)[13] were prepared as previously described.

3.2.4.2. General procedure for the preparation of hydroxyl-oxazoline 10

To a solution of $ZnCl_2$ (27.3 mg, 0.2 mmol) in dry chlorobenzene (1 mL), a solution of 2-(2-hydroxyphenyl)acetonitrile **3** (532.6 mg, 4 mmol) in dry chlorobenzene (7 mL) was added. Subsequently, chiral amino alcohol (4 mmol) was added to the reaction mixture, and it was left stirring at 90 ºC for 16 h. After that time, the solvent was evaporated and the crude was dissolved in the minimum amount of CH_2Cl_2 (2 mL). Then, Et_2O was slowly added and a solid precipitates. The precipitate solution is left at -18 ºC for 5 h and the corresponding pure hydroxyl-oxazoline was obtained as a green solid. Yield: 727.9 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.86 (s, 9H, CH_3, ^{t}Bu), 3.59 (d, 1H, CH_2, $^2J_{H-H}$= 16.1 Hz), 3.65 (d, 1H, CH_2, $^2J_{H-H}$= 16.1 Hz), 3.88 (m, 1H, CH-N), 4.17 (m, 1H, CH-O), 4.70 (m, 1H, CH-O), 6.83 (t, 1H, CH=, $^3J_{H-H}$= 8.2 Hz), 6.98 (dd, 1H, CH=, $^2J_{H-H}$= 8.2 Hz, $^3J_{H-H}$= 4.3 Hz), 7.05 (dd, 1H, CH=, $^2J_{H-H}$= 8 Hz, $^3J_{H-H}$= 4.3 Hz), 7.19 (t, 1H, CH=, $^3J_{H-H}$= 8.2 Hz). ^{13}C NMR (100.6 MH, $CDCl_3$): δ= 25.8 (CH_3, ^{t}Bu), 31.8 (CH_2), 33.7 (C, ^{t}Bu), 68.9 (CH_2-O), 74.9 (CH-N), 119.2 (CH=), 120.3 (CH=), 122.1 (C), 129.2 (CH=), 130.7 (CH=), 156.6 (C), 169.0 (C=N).

3.2.4.3. General procedure for the preparation of phosphite-oxazoline ligands L3-L9a-g

To a solution of *in situ* generated phosphorochloridite (1.1 mmol) in dry toluene (6 mL), pyridine (0.16 mL, 2.0 mmol) was added. Then, this solution was placed in a -78 ºC bath. After 2 min at that temperature, a solution of the alcohol-oxazoline (1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral alumina and dry toluene (1% NEt_3) as eluent system) to afford the corresponding phosphite-oxazoline as white solids.

L6c: Yield: 474.5 mg (70%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 138.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.48 (s, 9H, CH_3, $SiMe_3$), 0.71 (s, 9H, CH_3, $SiMe_3$), 1.04 (s, 9H, CH_3, ^{t}Bu), 4.06 (m, 3H, CH_2-O, CH-N), 6.74 (m, 1H, CH=), 6.91 (m, 2H, CH=), 7.01 (m, 1H, CH=), 7.13 (m, 3H, CH=), 7.35 (m, 2H, CH), 7.68 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.75 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.05 (m, 2H, CH=), 8.22 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= -0.4 (d, CH_3, $SiMe_3$, J_{C-P}= 5.0 Hz), 0.0 (CH_3, $SiMe_3$), 25.7 (CH_3, ^{t}Bu), 33.7 (C, ^{t}Bu), 67.7 (CH-N), 76.3 (CH_2-O), 121.4-152.9 (aromatic carbons), 160.8 (C=N). MS HR-ESI [found 700.2445, $C_{39}H_{44}NO_4PSi_2$ $(M+Na)^+$ requires 700.2439].

L7a: Yield: 449.7 mg (65%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.27 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3,

^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 3.61 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 3.80 (s, 2H, CH_2), 4.73 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.0 Hz), 4.89-4.91 (m, 1H, CH-N), 6.80-7.15 (m, 7H, CH=), 7.39 (m, 4H, CH=), 7.59 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 28.7 (CH_2), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 69.6 (CH-N), 74.1 (CH_2-O), 120.8-150.2 (aromatic carbons), 166.0 (C=N). MS HR-ESI [found 714.3679, $C_{44}H_{54}NO_4P$ $(M+Na)^+$ requires 714.3683].

L7c: Yield: 555.3 mg (78%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 143.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.00 (s, 9H, CH_3, $SiMe_3$), 0.20 (s, 9H, CH_3, $SiMe_3$), 3.10 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 3.20 (d, 1H, CH_2, $^2J_{H-H}$ = 16.0 Hz) 3.30 (d, 1H, CH_2, $^2J_{H-H}$ = 16.0 Hz), 3.50 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.0 Hz), 4.40 (m, 1H, CH-N), 6.54 (m, 4H, CH=), 6.69-6.82 (m, 8H, CH=), 7.04 (m, 4H, CH=), 7.38 (m, 5H, CH=), 7.75 (s, 1H, CH=), 7.86 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= -0.5 (d, CH_3, $SiMe_3$, J_{C-P}= 4.6 Hz), 0.0 (CH_3, $SiMe_3$), 28.3 (CH_2), 69.5 (CH-N), 73.9 (CH_2-O), 120.5-149.5 (aromatic carbons), 165.7 (C=N). MS HR-ESI [found 734.2279, $C_{42}H_{42}NO_4PSi_2$ $(M+Na)^+$ requires 734.2282].

L8a: Yield: 394.7 mg (60%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.71 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.8 Hz), 0.90 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ = 6.4 Hz), 1.28 (s, 18H, CH_3, ^{t}Bu), 1.50 (s, 18H, CH_3, ^{t}Bu), 1.55 (m, 1H, CH, ^{i}Pr), 3.55 (m, 1H, CH-O), 3.64 (m, 1H, CH-O), 3.77 (m, 3H, CH_2, CH-N), 6.8-6.9 (m, 2H, CH=), 7.0-7.15 (m, 2H, CH=), 7.38 (m, 2H, CH=), 7.59 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 19.0 (CH_3, ^{i}Pr), 19.4 (CH_3, ^{i}Pr), 28.7 (CH_2), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 33.6 (CH, ^{i}Pr), 35.0 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 70.5 (CH_2-O), 73.2 (CH-N), 121.5-150.8 (aromatic carbons), 165.1 (C=N). MS HR-ESI [found 680.3834, $C_{41}H_{56}NO_4P$ $(M+Na)^+$ requires 680.3839].

L8c: Yield: 508.4 mg (75%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 143.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.33 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 0.66 (d, 3H, CH^3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 0.85 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.41 (m, 1H, CH, ^{i}Pr), 3.37 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 3.50 (m, 2H), 3.60-3.71 (m, 2H), 6.82 (m, 2H, CH=), 6.90 (m, 2H, CH=), 7.00-7.15 (m, 3H, CH=), 7.34 (m, 3H, CH=), 7.68 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.72 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.07 (s, 1H, CH=), 8.19 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 0.21 (d, CH_3, $SiMe_3$, J_{C-P}= 3.8 Hz), 0.7 (CH_3, $SiMe_3$), 19.0 (CH_3, ^{i}Pr), 19.4 (CH_3, ^{i}Pr), 29.2 (CH_2), 33.5 (CH, ^{i}Pr), 70.4 (CH_2-O), 73.1 (CH-N), 121.4-153.1 (aromatic carbons), 164.9 (C=N). MS HR-ESI [found 700.2437, $C_{39}H_{44}NO_4PSi_2$ $(M+Na)^+$ requires 700.2439].

L8d: Yield: 409.2 mg (68%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 133.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.66 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 0.86 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.43 (m, 1H, CH, ^{i}Pr), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.69 (CH_3), 1.74 (CH_3), 2.01 (CH_3), 2.08 (CH_3), 3.48 (m, 1H, CH-O), 3.60 (m, 2H, CH-, CH-O), 3.70

(m, 2H, CH-, CH-N), 6.8-6.9 (m, 1H, CH=), 6.98 (m, 2H, CH=), 7.09 (m, 2H, CH=), 7.35 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.2 (CH_3), 16.5 (CH_3), 18.3 (CH_3, ^{i}Pr), 18.6 (CH_3, ^{i}Pr), 20.0 (CH_3), 20.1 (CH_3), 28.4 (CH_2), 31.6 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 4.6 Hz), 31.5 (CH_3, ^{t}Bu), 32.9 (CH, ^{i}Pr), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 69.8 (CH_2-O), 72.4 (CH-N), 120.7-150.0 (aromatic carbons), 164.4 (C=N).

L8f: Yield: 261.5 mg (40%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 134.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.75 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H\text{-}H}$= 6.4 Hz), 0.96 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H\text{-}H}$= 6.4 Hz), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.60 (m, 1H, CH, ^{i}Pr, 1.70 (s, 9H, CH_3, ^{t}Bu), 1.31-1.8 (m, 10H, CH_2), 2.27 (m, 2H, CH_2), 2.56 (m, 4H, CH_2), 2.78 (m, 2H, CH_2), 3.58 (m, 1H, CH-O), 3.75 (m, 3H, CH-O, CH_2), 3.81 (m, 1H, CH-N), 6.9 (m, 1H, CH=), 7.1 (m, 3H, CH=), 7.17 (m, 1H, CH=), 7.43 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 18.4 (CH_3, ^{i}Pr), 18.7 (CH_3, ^{i}Pr), 22.8 (CH_2), 23.0 (CH_2), 23.1 (CH_2), 23.2 (CH_2), 27.4 (CH_2), 27.7 (CH_2), 28.6 (CH_2), 28.6 (CH_2), 29.6 (CH_2), 30.0 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 4.7 Hz), 31.5 (CH_3, ^{t}Bu), 33.0 (CH, ^{i}Pr), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 69.9 (CH_2-O), 72.6 (CH-N), 120.9-150.1 (aromatic carbons), 164.5 (C=N).

L9a: Yield: 470.3 mg (70%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.79 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 18H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 3.63-3.75 (m, 5H, CH_2, CH_2-O, CH-N), 6.82-6.91 (m, 2H, CH=), 7.00-7.15 (m, 1H, CH=), 7.36 (m, 2H, CH=), 7.39 (m, 1H, CH=), 7.59 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 19.0 (CH_3, ^{i}Pr), 19.4 (CH_3, ^{i}Pr), 28.7 (CH_2), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 33.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 68.8 (CH_2-O), 76.6 (CH-N), 121.5-150.8 (aromatic carbons), 165.1 (C=N). MS HR-ESI [found 694.3992, $C_{42}H_{58}NO_4P$ $(M+Na)^+$ requires 694.3996].

L9b: Yield: 498.2 mg (72%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 144.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.33 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 0.73 (s, 9H, CH_3, ^{t}Bu), 3.45-3.65 (m, 5H, CH_2, CH_2-O, CH-N), 6.82 (m, 2H, CH=), 6.87 (m, 2H, CH=), 7.00-7.15 (m, 4H, CH=), 7.35 (m, 2H, CH=), 7.68 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.4 Hz), 7.73 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.4 Hz), 8.07 (s, 1H, CH=), 8.18 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 0.2 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$= 4.6 Hz), 0.7 (CH_3, $SiMe_3$), 26.3 (CH_3, ^{t}Bu), 29.1 (CH_2), 33.4 (C, ^{t}Bu), 68.6 (CH_2-O), 76.5 (CH-N), 121.1-153.1 (aromatic carbons), 164.9 (C=N). MS HR-ESI [found 714.2591, $C_{40}H_{46}NO_4PSi_2$ $(M+Na)^+$ requires 714.2595].

L9c: Yield: 512.0 mg (74%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 143.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.33 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$), 0.74 (CH_3, ^{t}Bu), 3.50-3.71 (m, 5H, CH_2, CH_2-O, CH-N), 6.81 (m, 2H, CH=), 6.89 (m, 2H, CH=), 7.00-7.16 (m, 3H, CH=), 7.34 (d, 2H, CH=, $^{4}J_{H\text{-}H}$= 2.2 Hz), 7.39 (m, 1H, CH=), 7.68 (d, 1H, CH=, $^{4}J_{H\text{-}H}$= 2.0 Hz), 7.72 (d, 1H, CH=, $^{4}J_{H\text{-}H}$= 2.1 Hz), 8.07 (s, 1H, CH=), 8.19 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= -0.5 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$= 4.6 Hz), 0.0 (CH_3, $SiMe_3$), 25.6 (CH_3, ^{t}Bu), 28.3 (CH_2), 33.1 (C, ^{t}Bu), 67.9 (CH_2-O), 75.7 (CH-N), 120.4-

152.3 (aromatic carbons), 164.1 (C=N). MS HR-ESI [found 714.2592, $C_{40}H_{46}NO_4PSi_2$ $(M+Na)^+$ requires 714.2595].

3.2.4.4. General procedure for the preparation of [Ir(cod)(L3-L9a-g)]BAr_F

The corresponding ligand (0.037 mmol) was dissolved in CH_2Cl_2 (2 mL) and [Ir(μ-Cl)(cod)]$_2$ (12.5 mg, 0.0185 mmol) was added. The reaction mixture was refluxed at 50 ºC for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol) and water (2 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the product as red-orange solids.

[Ir(cod)(L3d)]BAr_F: Yield: 59 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 114.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.82 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 0.98 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.08 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.97 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.4 (m, 1H, CH, ^{i}Pr), 1.72-2.52 (m, 8H, CH_2, cod), 3.87 (m, 1H, CH=, cod), 4.10 (m, 1H, CH=, cod), 4.25 (m, 1H, CH-N) 4.39 (pt, 1H, CH-O, J_{H-H}= 10.0 Hz), 4.54 (m, 1H, CH-O), 5.22 (m, 1H, CH=, cod), 5.35 (m, 1H, CH=, cod), 6.17 (d, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz), 7.87-7.27 (m, 3H, CH=), 7.53 (s, 4H, CH=), 7.71 (s, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 14.0 (CH_3, ^{i}Pr), 16.3 (CH_3), 16.8 (CH_3), 18.9 (CH_3, ^{i}Pr), 20.3 (CH_3), 20.5 (CH_3), 25.6 (CH_2, cod), 28.9 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 31.0 (CH_2, cod), 31.4 (CH_3, ^{t}Bu), 34.7 (CH, ^{i}Pr), 34.9 (C, ^{t}Bu), 35.4 (d, CH_2, cod, J_{C-P}= 6.1 Hz), 62.9 (CH=, cod), 67.9 (CH_2-O), 69.4 (CH=, cod), 73.6 (CH-N), 103.9 (d, CH=, cod, J_{C-P}= 20.6 Hz), 107.6 (d, CH=, cod, J_{C-P}= 15.3 Hz), 117.4-146.4 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 167.6 (C=N). MS HR-ESI [found 888.3737, $C_{44}H_{58}IrNO_4P$ $(M-BAr_F)^+$ requires 888.3733].

[Ir(cod)(L3e)]BAr_F: Yield: 60 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 106.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.97 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 1.02 (s, 9H, CH_3, ^{t}Bu), 1.03 (m, 3H, CH_3, ^{i}Pr), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.92-2.22 (m, 5H, CH_2, cod), 2.24 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.4 (m, 1H, CH, ^{i}Pr), 2.37-2.51 (m, 3H, CH_2, cod), 2.61 (m, 1H, CH=, cod), 4.05 (m, 1H, CH=, cod), 4.22 (m, 1H, CH-N) 4.41 (pt, 1H, CH-O, J_{H-H}= 10.0 Hz), 4.52 (m, 1H, CH-O), 5.24 (m, 1H, CH=, cod), 5.53 (m, 1H, CH=, cod), 6.88 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.06 (s, 1H, CH=), 7.28-7.36 (m, 2H, CH=), 7.53-7.58 (m, 5H, CH=), 7.71 (s, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 15.0 (CH_3, ^{i}Pr), 16.4 (CH_3), 16.6 (CH_3), 18.3 (CH_3, ^{i}Pr), 20.2 (CH_3), 20.6 (CH_3), 25.0 (CH_2, cod), 28.8 (CH_2, cod), 30.8 (CH_2, cod), 31.0 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 33.1 (CH, ^{i}Pr), 34.6 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 36.5 (CH_2, cod), 56.9 (CH=, cod), 68.4 (CH_2-O), 69.2 (CH=, cod), 72.4 (CH-N), 105.5 (d, CH=, cod, J_{C-P}= 15.3 Hz), 106.5 (d, CH=, cod, J_{C-P}= 18.3 Hz), 117.4-146.3 (aromatic carbons), 161.6

(q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 170.6 (C=N). MS HR-ESI [found 888.3736, $C_{44}H_{58}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 888.3733].

[Ir(cod)(L3f)]BAr_F: Yield: 63 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 114.9 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 0.84 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 0.97 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8Hz), 1.08 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.68-2.48 (m, 16H, CH_2), 2.41 (m, 1H, CH, ^{i}Pr), 2.01-2.48 (m, 4H, CH_2, cod), 2.75-2.91 (m, 4H, CH_2, cod), 3.88 (m, 1H, CH=, cod), 4.09 (m, 1H, CH=, cod), 4.25 (m, 1H, CH-N), 4.38 (pt, 1H, CH-O, J_{H-H}= 10.0 Hz), 4.53 (m, 1H, CH-O), 5.19 (m, 1H, CH=, cod), 5.30 (m, 1H, CH=, cod), 6.15 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.15 (m, 2H, CH=), 7.28 (m, 1H, CH=), 7.53 (s, 5H, CH=), 7.72 (s, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 14.1 (CH_3, ^{i}Pr), 18.4 (CH_3, ^{i}Pr), 22.5 (CH_2), 22.6 (CH_2), 22.7 (CH_2), 22.8 (CH_2), 25.6 (CH_2, cod), 27.0 (CH_2), 27.1 (CH_2), 28.9 (CH_2, cod), 29.5 (CH_2), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_2, cod), 31.0 (CH_2), 31.3 (CH_3, ^{t}Bu), 34.7 (CH, ^{i}Pr), 34.8 (C, ^{t}Bu), 35.5 (CH_2, cod), 62.9 (CH=, cod), 67.9 (CH_2-O), 69.2 (CH=, cod), 73.5 (CH-N), 103.8 (d, CH=, cod, J_{C-P}= 20.6 Hz), 106.7 (d, CH=, cod, J_{C-P}= 14.5 Hz), 117.4-146.3 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 50.5 Hz), 167.6 (C=N). MS HR-ESI [found 940.4051, $C_{48}H_{62}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 940.4046].

[Ir(cod)(L3g)]BAr_F: Yield: 64 mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 107.1 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 0.98 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.01 (s, 9H, CH_3, ^{t}Bu), 1.02 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.62-2.46 (m, 16H, CH_2), 2.55 (m, 1H, CH, ^{i}Pr), 2.06-2.51 (m, 4H, CH_2, cod), 2.74-2.90 (m, 4H, CH_2, cod), 2.71 (m, 1H, CH=, cod), 4.01 (m, 1H, CH=, cod), 4.20 (m, 1H, CH-N), 4.40 (pt, 1H, CH-O, J_{H-H}= 9.6 Hz), 4.50 (m, 1H, CH-O), 5.21 (m, 1H, CH=, cod), 5.50 (m, 1H, CH=, cod), 6.90 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 6.95 (s, 1H, CH=), 7.17 (s, 1H, CH=), 7.33 (m, 1H, CH=), 7.57 (m, 1H, CH=), 7.53 (s, 4H, CH=), 7.72 (s, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 15.1 (CH_3, ^{i}Pr), 18.4 (CH_3, ^{i}Pr), 22.6 (CH_2), 22.7 (CH_2), 22.8 (CH_2), 24.9 (CH_2, cod), 27.1 (CH_2), 27.2 (CH_2), 28.7 (CH_2, cod), 29.2 (CH_2), 29.6 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 33.1 (CH, ^{i}Pr), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.5 (d, CH_2, cod, J_{C-P}= 4.5 Hz), 57.1 (CH=, cod), 68.5 (CH_2-O), 69.0 (CH=, cod), 72.4 (CH-N), 105.3 (d, CH=, cod, J_{C-P}= 15.3 Hz), 106.0 (d, CH=, cod, J_{C-P}= 18.4 Hz), 117.4-146.3 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 170.4 (C=N). MS HR-ESI [found 940.4049, $C_{48}H_{62}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 940.4046].

[Ir(cod)(L4a)]BAr_F: Yield: 62 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 108.2 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 1.03 (d, 3H, CH_3, $^3J_{H-H}$= 7.6 Hz), 1.1 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.77 (b, 2H, CH_2, cod), 1.88-2.10 (b, 3H, CH_2, cod), 2.18 (m, 2H, CH_2), 2.36 (m, 2H, CH_2, cod), 2.56 (m, 1H, CH_2, cod), 3.6 (m, 1H, CH=, cod), 4.21 (m, 1H, CH=, cod), 4.28 (m, 1H, CH-N), 4.38 (dd, 1H, CH-O, $^2J_{H-H}$= 9.6 Hz, $^3J_{H-H}$= 6.4 Hz), 4.57 (pt, 1H, CH-O, J_{H-H}= 9.6 Hz), 5.27 (m, 1H, CH=, cod), 5.48 (m, 1H, CH=, cod), 6.10 (d, 1H, CH=, $^3J_{H-H}$= 8.4

Hz), 7.10 (d, 1H, CH=, $^{2}J_{H\text{-}H}$= 1.6 Hz) 7.26 (m, 1H, CH=), 7.39-7.75 (m, 7H, CH=), 7.63 (dd, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.0 Hz, $^{4}J_{H\text{-}H}$= 1.6 Hz), 7.70 (s, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 9.3 (CH_3, Et), 25.5 (CH_2, cod), 28.6 (CH_2, cod), 29.9 (CH_2, cod), 30.6 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_2, Et), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 36.1 (d, CH_2, cod, $J_{C\text{-}P}$= 6.1 Hz), 64.4 (CH=, cod), 66.5 (CH=, cod), 60.4 (CH-N), 72.4 (CH_2-O), 104.9 (d, CH=, cod, $J_{C\text{-}P}$= 19.9 Hz), 106.7 (d, CH=, cod, $J_{C\text{-}P}$= 15.3 Hz), 117.6-149.8 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$= 49.6 Hz), 169.5 (C=N). MS HR-ESI [found 930.4206, $C_{47}H_{64}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 930.4202].

[Ir(cod)(L6a)]BAr_F: Yield: 64 mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 107.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.02 (s, 9H, CH_3, ^{t}Bu), 1.15 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu,) 1.55 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 1H, CH_2, cod), 1.80 (m, 2H, CH_2, cod), 2.01 (m, 1H, CH_2, cod), 2.17 (m, 1H, CH_2, cod), 2.3 (m, 2H, CH_2, cod), 2.5 (m, 1H, CH_2, cod), 3.3 (m, 1H, CH=, cod), 4.12 (dd, 1H, CH-N, $^{2}J_{H\text{-}H}$= 9.2 Hz, $^{3}J_{H\text{-}H}$= 3.2 Hz), 4.18 (m, 1H, CH=, cod), 4.38 (pt, 1H, CH-O, $J_{H\text{-}H}$= 9.6 Hz), 4.6 (dd, 1H, CH-O, $^{2}J_{H\text{-}H}$= 10.0 Hz, $^{3}J_{H\text{-}H}$= 3.6 Hz), 5.25 (m, 1H, CH=, cod), 5.49 (m, 1H, CH=, cod), 6.23 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 7.2 Hz), 7.31 (t, 1H, CH=, $^{3}J_{H\text{-}H}$= 8 Hz), 7.39 (d, 3H, CH=, $^{3}J_{H\text{-}H}$= 6.4 Hz), 7.45 (t, 1H, CH=, $^{3}J_{H\text{-}H}$= 7.2 Hz), 7.52 (m, 5H, CH=), 7.71 (s, 9H, CH=) . ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 24.4 (CH_2, cod), 25.9 (CH_3, ^{t}Bu), 28.1 (CH_2, cod), 30.0 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.7 (d, CH_2, cod, $J_{C\text{-}P}$= 1.6 Hz), 34.3 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.7(C, ^{t}Bu), 36.4 (d, CH_2, cod, $J_{C\text{-}P}$= 6.0 Hz), 61.6 (CH=, cod), 66.0 (CH=, cod), 69.1 (CH_2-O), 77.5 (CH-N), 104.4 (d, CH=, cod, $J_{C\text{-}P}$= 19.9 Hz), 106.6 (d, CH=, cod, $J_{C\text{-}P}$= 13.6 Hz), 117.4-149.8 (aromatic carbons), 161.5 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$= 49.7 Hz), 168.9 (C=N). MS HR-ESI [found 958.4521, $C_{49}H_{68}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 958.4515].

[Ir(cod)(L6c)]BAr_F: Yield: 64 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 113.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.0 (s, 9H, CH_3, $SiMe_3$), 0.53 (s, 9H, CH_3, $SiMe_3$), 1.13 (s, 9H, CH_3, ^{t}Bu), 1.58 (m, 1H, CH_2, cod), 1.70 (m, 2H, CH_2, cod), 1.95 (m, 1H, CH_2, cod), 2.23 (m, 2H, CH_2, cod), 2.32 (m, 2H, CH_2, cod), 2.78 (m, 1H, CH=, cod), 3.89 (m, 1H, CH=, cod), 4.11 (m, 1H, CH-N), 4.40 (pt, 1H, CH-O, $^{3}J_{H\text{-}H}$= 9.2 Hz), 4.67 (dd, 1H, CH-O, $^{2}J_{H\text{-}H}$= 10.4 Hz, $^{3}J_{H\text{-}H}$= 2.0 Hz), 5.43 (m, 1H, CH=, cod), 5.58 (m, 1H, CH=, cod), 6.70 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.8 Hz), 6.87 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.0 Hz), 7.03 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.0 Hz), 7.19 (t, 1H, CH=, $^{3}J_{H\text{-}H}$= 7.6 Hz), 7.29 (m, 1H, CH=), 7.37 (t, 1H, CH=, $^{3}J_{H\text{-}H}$= 7.6 Hz), 7.47-7.59 (m, 7H, CH=), 7.71 (s, 8H, CH=), 7.87-7.98 (m, 4H, CH=), 8.17 (s, 1H, CH=).^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.0 (CH_3, $SiMe_3$), 0.1 (CH_3, $SiMe_3$), 24.5 (CH_2, cod), 25.9 (CH_3, ^{t}Bu), 28.8 (CH_2, cod), 29.7 (C, tBu), 30.9 (CH_2, cod), 36.7 (CH_2, cod), 56.3 (CH=, cod), 66.6 (CH=, cod), 69.1 (CH_2-O), 76.5 (CH-N), 106.9 (d, CH=, cod, $J_{C\text{-}P}$= 15.3 Hz), 108.4 (d, CH=, cod, $J_{C\text{-}P}$= 18.4 Hz), 117.4-

151.0 (aromatic carbons), 161.5 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 170.1 (C=N). MS HR-ESI [found 978.3119, $C_{47}H_{56}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 978.3115].

[Ir(cod)(L7a)]BAr_F: Yield: 65 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 100.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.28 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.80-2.05 (b, 4H, CH_2, cod), 2.17-2.50 (b, 4H, CH_2, cod), 3.20 (m, 1H, CH=, cod), 3.66 (d, 1H, CH_2, $^2J_{H-H}$= 12.1 Hz), 4.16 (m, 1H, CH-O), 4.45 (m, 1H, CH=, cod), 4.7 (d, 1H, CH2, $^2J_{H-H}$= 11.2 Hz), 4.84 (m, 1H, CH-O), 5.07 (b, 1H, CH=, cod), 5.27 (m, 1H, CH-N), 5.9 (m, 1H, CH=, cod), 6.98-7.55 (m, 17H, CH=), 7.72 (m, 8H, CH=).^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 22.6 (CH_2, cod), 25.5 (CH_2, cod), 29.3 (CH_2, cod) 29.7 (d, CH_2, cod, J_{C-P}= 6.1 Hz), 31.0 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.6 (CH_2), 34.8 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 58.3 (CH=, cod), 68.7 (CH=, cod), 71.7 (CH-N), 75.7 (CH_2-O), 105.6 (d, CH=, cod, J_{C-P}= 11.5 Hz), 105.7 (d, CH=, cod, J_{C-P}= 14.5 Hz), 117.6-149.5 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 172.4 (C=N). MS HR-ESI [found 992.4363, $C_{52}H_{66}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 992.4359].

[Ir(cod)(L7c)]BAr_F: Yield: 67 mg (96%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 102.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.48 (s, 9H, CH_3, $SiMe_3$), 0.62 (s, 9H, CH_3, $SiMe_3$), 1.48 (b, 2H, CH_2, cod), 1.65 (m, 2H, CH_2, cod), 1.85 (m, 2H, CH_2, cod), 2.08 (m, 1H, CH_2, cod), 2.4 (m, 1H, CH_2, cod), 2.6 (m, 1H, CH=, cod), 3.6 (d, 1H, CH_2, $^2J_{H-H}$= 14.8 Hz), 4.12 (m, 1H, CH=, cod), 4.15 (m, 1H, CH-O), 4.69 (d, 1H, CH_2, $^2J_{H-H}$= 14.4 Hz), 4.85 (pt, 1H, CH-O, J_{H-H}= 10.0 Hz), 5.2 (m, 1H, CH=, cod), 5.3 (m, 1H, CH-N), 5.7 (m, 1H, CH=, cod), 5.84 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 6.72 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 6.90 (t, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 6.98 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.04 (t, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.17 (t, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.40 (m, 4H, CH=), 7.45-7.82 (m, 9H, CH=), 7.71 (s, 8H, CH=), 7.91 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.00 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.08 (s, 1H, CH=), 8.29 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.6 (CH_3, $SiMe_3$), 0.8 (CH_3, $SiMe_3$), 25.2 (CH_2, cod), 29.7 (CH_2, cod), 30.3 (CH_2, cod), 34.1 (CH_2, cod), 35.4 (CH_2), 57.6 (CH=, cod), 69.5 (CH=, cod), 70.9 (CH-N), 77.2 (CH_2-O), 103.5 (d, CH=, cod, J_{C-P}= 19.8 Hz), 106.4 (d, CH=, cod, J_{C-P}= 15.3 Hz), 117.4-151.8 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 174.5 (C=N). MS HR-ESI [found 1012.2962, $C_{50}H_{54}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 1012.2958].

[Ir(cod)(L8a)]BAr_F: Yield: 63 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 101.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.79 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.0 Hz), 1.00 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 2.05-2.50 (b, 8H, CH_2, cod), 2.32 (m, 1H, CH, ^{i}Pr), 3.50 (m, 1H, CH=, cod), 3.60 (d, 1H, CH_2, $^2J_{H-H}$= 14.8Hz), 4.07 (m, 1H, CH-N), 4.31 (m, 2H, CH_2-O), 4.62 (d, 1H, CH_2, $^2J_{H-H}$= 14.4 Hz), 4.7 (m, 1H, CH=, cod), 5.12 (m, 1H, CH=, cod), 5.07 (b, 1H, CH=, cod), 5.42 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 5.7 (m, 1H, CH=, cod), 6.90 (t, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.00 (t, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.10 (d, 1H, CH=,

$^3J_{H-H}$= 8.4Hz), 7.16 (d, 1H, CH=, $^3J_{H-H}$= 6.8Hz), 7.4 (m, 1H, CH=), 7.53 (s, 5H, CH=), 7.64 (m, 1H, CH=), 7.72 (s, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 15.0 (CH_3, ^{i}Pr), 19.8 (CH_3, ^{i}Pr), 25.3 (CH_2, cod), 29.3 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_2, cod), 32.9 (CH, ^{i}Pr), 34.6 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.0 (CH_2), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 36.0 (CH_2, cod), 58.8 (CH=, cod), 69.5 (CH=, cod), 69.6 (CH_2-O), 71.2 (CH-N), 102.4 (d, CH=, cod, J_{C-P}= 19.9 Hz), 106.6 (d, CH=, cod, J_{C-P}= 14.5 Hz), 117.4-149.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 171.9 (C=N). MS HR-ESI [found 958.4522, $C_{49}H_{68}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 958.4515].

[Ir(cod)(L8c)]BAr$_F$: Yield: 63 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 103.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.46 (s, 9H, CH_3, $SiMe_3$), 0.58 (s, 9H, CH_3, $SiMe_3$), 0.80 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 0.97 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.52 (m, 1H, CH_2, cod), 1.67 (m, 1H, CH_2, cod), 1.95-2.07 (m, 2H, CH_2, cod), 2.27 (m, 2H, CH_2, cod), 2.34 (m, 1H, CH, ^{i}Pr), 2.49 (m, 2H, CH_2, cod), 3.09 (m, 1H, CH=, cod), 3.57 (d, 1H, CH_2, $^2J_{H-H}$= 14.4 Hz), 4.03 (m, 1H, CH-N), 4.30 (m, 2H, CH_2-O), 4.31 (m, 1H, CH=, cod), 4.57 (d, 1H, CH_2, $^2J_{H-H}$= 14.4 Hz), 5.33 (m, 1H, CH=, cod), 5.58 (m, 1H, CH=, cod), 5.59 (m, 1H, CH=), 6.73 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 6.78 (t, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 7.00 (m, 2H, CH=), 7.16 (m, 2H, CH=), 7.47 (m, 1H, CH=), 7.53 (s, 5H, CH=), 7.71 (s, 9H, CH=), 7.91 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 8.00 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 8.06 (s, 1H, CH=), 8.27 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.6 (CH_3, $SiMe_3$), 0.7 (CH_3, $SiMe_3$), 14.9 (CH_3, ^{i}Pr), 19.7 (CH_3, ^{i}Pr), 25.7 (CH_2, cod), 29.7 (CH_2, cod), 30.2 (CH, ^{i}Pr), 32.5 (CH_2, cod), 35.3 (CH_2), 35.6 (CH_2, cod), 59.3 (CH=, cod), 69.1 (CH=, cod), 69.5 (CH_2-O), 70.4 (CH-N), 105.8 (d, CH=, cod, J_{C-P}= 9.1 Hz), 106.0 (d, CH=, cod, J_{C-P}= 11.4 Hz), 117.4-151.2 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 48.9 Hz), 172.0 (C=N). MS HR-ESI [found 978.3122, $C_{47}H_{56}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 978.3115].

[Ir(cod)(L9a)]BAr$_F$: Yield: 62 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 100.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.09 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 2.05 (m, 2H, CH_2, cod), 2.06 (m, 2H, CH_2, cod), 2.27 (m, 2H, CH_2, cod), 2.39 (m, 2H, CH_2, cod), 3.46 (m, 1H, CH=, cod), 3.61 (d, 1H, CH_2, $^2J_{H-H}$= 14.8 Hz), 3.97 (m, 1H, CH-N), 4.31 (pt, 1H, CH-O, J_{H-H}= 10.4 Hz), 4.31 (m, 1H, CH-O), 4.72 (m, 1H, CH=, cod), 4.88 (d, 1H, CH_2, $^2J_{H-H}$= 14.4 Hz), 5.03 (m, 1H, CH=, cod), 5.57 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 5.70 (m, 1H, CH=, cod), 6.92-7.04 (m, 3H, CH=), 7.16 (m, 2H, CH=), 7.26 (m, 1H, CH=), 7.41 (m, 1H, CH=), 7.53 (s, 3H, CH=), 7.64 (m, 1H, CH=), 7.72 (s, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 24.8 (CH_2, cod), 26.0 (CH_3, ^{t}Bu), 29.5 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 32.5 (CH_2, cod), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.8 (CH_2), 36.0 (CH_2, cod), 57.8 (CH=, cod), 68.8 (CH=, cod), 71.1 (CH_2-O), 75.7 (CH-N), 99.3 (d, CH=, cod, J_{C-P}= 21.4 Hz), 106.7 (d, CH=, cod, J_{C-}

$_P$= 14.5 Hz), 117.5-151.3 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 171.8 (C=N). MS HR-ESI [found 972.4675, $C_{50}H_{70}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 972.4672].

[Ir(cod)(L9c)]BAr_F: Yield: 66 mg (96%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 101.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.47 (s, 9H, CH_3, $SiMe_3$), 0.58 (s, 9H, CH_3, $SiMe_3$), 1.05 (s, 9H, CH_3, ^{t}Bu), 1.44 (m, 1H, CH_2, cod), 1.58 (m, 1H, CH_2, cod), 1.92 (m, 1H, CH_2, cod), 2.06 (m, 1H, CH_2, cod), 2.17 (m, 1H, CH_2, cod), 2.31 (m, 1H, CH_2, cod), 2.38 (m, 1H, CH_2, cod), 2.48 (m, 1H, CH_2, cod), 2.89 (m, 1H, CH=, cod), 3.58 (d, 1H, CH_2, $^2J_{H-H}$= 14.4 Hz), 3.87 (m, 1H, CH-N), 4.29 (m, 1H, CH-O), 4.30 (m, 1H, CH=, cod), 4.63 (m, 1H, CH-O), 4.84 (d, 1H, CH_2, $^2J_{H-H}$= 14.4 Hz), 5.34 (m, 1H, CH=, cod), 5.58 (m, 1H, CH=, cod), 5.90 (d, 1H, CH=, $^3J_{H-H}$= 8.0Hz), 6.68 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 6.89-7.05 (m, 3H, CH=), 7.17 (m, 2H, CH=), 7.46 (m, 2H, CH=), 7.53 (s, 4H, CH=), 7.72 (s, 9H, CH=), 7.92 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.99 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.08 (s, 1H, CH=), 8.26 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 0.4 (CH_3, $SiMe_3$), 0.7 (CH_3, $SiMe_3$), 25.1 (CH_2, cod), 26.1 (CH_3, ^{t}Bu), 29.7 (CH_2, cod), 30.3 (d, CH_2, cod, J_{C-P}= 19.1 Hz), 34.6 (C, ^{t}Bu), 35.6 (d, CH_2, cod, J_{C-P}= 5.3 Hz), 36.1 (CH_2), 57.6 (CH=, cod), 68.1 (CH=, cod), 71.2 (CH_2-O), 74.9 (CH-N), 104.3 (d, CH=, cod, J_{C-P}= 18.0 Hz), 106.8 (d, CH=, cod, J_{C-P}= 15.3 Hz), 117.4-151.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 171.8 (C=N). MS HR-ESI [found 992.3274, $C_{48}H_{58}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 992.3271].

3.2.4.5. General procedure for the preparation of [Rh(cod)(L3-L9a-g)]BF_4

The corresponding ligand (0.05 mmol) was dissolved in CH_2Cl_2 (2 mL) and $[Rh(cod)_2]BF_4$ (20.3 mg, 0.05 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour. Then the solvent was partially evaporated and the desired complex was precipitated by adding cold hexane (3 mL). The precipitate was filtered off, washed twice with cold hexane (2 mL) and dried to afford the product as a yellow solid.

[Rh(cod)(L3a)]BF_4: Yield: 38 mg (90%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 124.3 (d, $^1J_{P-Rh}$= 284.0 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 1.04 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 1.31 (bs, 12H, CH_3, ^{t}Bu and CH_3, ^{i}Pr), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 9H, CH_3, ^{t}Bu,), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.99 (b, 2H, CH_2, cod), 2.09 (m, 1H, CH_2, cod), 2.18 (m, 1H, CH_2, cod), 2.34 (m, 1H, CH, ^{i}Pr), 2.55 (b, 4H, CH_2, cod), 3.81 (m, 1H, CH=, cod), 4.22 (m, 1H, CH-N), 4.49 (m, 2H, CH=, cod and CH_2-O), 4.67 (m, 1H, CH_2-O), 5.68 (m, 1H, CH=, cod), 5.84 (m, 1H, CH=, cod), 6.29 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.11 (s, 1H, CH=), 7.38-7.56 (m, 5H, CH=), 7.89 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 15.5 (CH_3, ^{i}Pr), 18.3 (CH_3, ^{i}Pr), 25.4 (CH_2, cod), 28.3 (CH_2, cod), 29.5 (CH_2, cod), 30.2 (CH_3, ^{t}Bu), 30.7 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 32.5 (CH, ^{i}Pr), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.1 (CH_2, cod), 35.3 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 68.5 (CH_2-O), 72.8 (CH-N), 77.1 (d, CH=, cod, J= 10.6 Hz), 80.8 (d, CH=, cod, J= 10.7 Hz), 114.4

(d, CH=, cod, *J*= 12.2 Hz), 116.3 (d, CH=, cod, *J*= 15.2 Hz), 118.3-149.6 (aromatic carbons), 167.4 (C=N). MS HR-ESI [found 854.3776, $C_{48}H_{66}NO_4PRh$ $(M\text{-}BF_4)^+$ requires 854.3779].

[Rh(cod)(L3b)]BF_4: Yield: 42.8 mg (89%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 136.9 (d, $^1J_{P\text{-}Rh}$= 278.0 Hz). ^1H NMR (400 MHz, CD_2Cl_2): δ= 0.11 (s, 9H, $SiMe_3$), 0.77 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 0.8 (s, 9H, $SiMe_3$), 1.05 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 2.04 (m, 1H, CH_2, cod), 2.07 (m, 2H, CH_2, cod), 2.21 (m, 1H, CH_2, cod), 2.37 (m, 1H, CH, ^{i}Pr), 2.49 (m, 1H, CH_2, cod), 2.57 (m, 2H, CH_2, cod), 2.74 (m, 1H, CH_2, cod), 4.07 (m, 1H, CH=, cod), 4.18 (m, 1H, CH-N), 4.52 (m, 1H, CH=, cod), 4.54 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$= 9.6 Hz, $^3J_{H\text{-}H}$= 4.0 Hz), 4.62 (m, 1H, CH_2-O), 5.69 (m, 1H, CH=, cod), 5.79 (m, 1H, CH=, cod), 6.32 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.1 Hz), 6.68 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.1 Hz), 7.10 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.8 Hz), 7.15 (m, 1H, CH=), 7.44-7.64 (m, 4H, CH=), 7.99 (m, 1H, CH=), 8.08 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.1 Hz), 8.24 (s, 2H, CH=).^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= -0.9 ($SiMe_3$), 0.7 ($SiMe_3$), 14.0 (CH_3, ^{i}Pr), 18.3 (CH_3, ^{i}Pr), 25.6 (CH_2, cod), 28.6 (CH_2, cod), 30.3 (CH_2, cod), 30.8 (CH, ^{i}Pr), 35.1 (d, CH_2, cod, *J*= 6.1 Hz), 67.8 (CH_2-O), 73.1 (CH-N), 76.5 (d, CH=, cod, *J*= 10.6 Hz), 84.3 (d, CH=, cod, *J*= 12.1 Hz), 115.7 (dd, CH=, cod, *J*= 16.0 Hz, *J*= 5.3 Hz), 116.3 (dd, CH=, cod, *J*= 12.2 Hz, *J*= 4.3 Hz), 118.0-151.5 (aromatic carbons), 166.4 (C=N). MS HR-ESI [found 874.2375, $C_{46}H_{54}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 874.2379].

[Rh(cod)(L3c)]BF_4: Yield: 44.2 mg (92%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 130.5 (d, $^1J_{P\text{-}Rh}$= 284.4 Hz). ^1H NMR (400 MHz, CD_2Cl_2): δ= 0.21 (s, 9H, $SiMe_3$), 0.58 (s, 9H, $SiMe_3$), 1.01 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 1,85 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 1.90 (m, 3H, CH_2, cod), 2.13 (m, 1H, CH_2, cod), 2.33 (m, 1H, CH, ^{i}Pr), 2.49 (m, 1H, CH_2, cod), 2.57 (m, 1H, CH_2, cod), 2.66 (m, 2H, CH_2, cod), 3.30 (m, 1H, CH=, cod), 4.12 (m, 1H, CH-N), 4.35 (m, 1H, CH=, cod), 4.54 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$= 9.6 Hz, $^3J_{H\text{-}H}$= 4.0 Hz), 4.64 (m, 1H, CH_2-O), 5.67 (m, 1H, CH=, cod), 5.95 (m, 1H, CH=, cod), 6.79 (m, 2H, CH=), 7.09 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.8 Hz), 7.19 (m, 1H, CH=), 7.28 (m, 1H, CH=), 7.41-7.55 (m, 4H, CH=), 7.91-8.01 (m, 3H, CH=), 8.07 (m, 1H, CH=), 8.23 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= -0.1.9 ($SiMe_3$), 0.0 ($SiMe_3$), 15.5 (CH_3, ^{i}Pr), 19.1 (CH_3, ^{i}Pr), 25.1 (CH_2, cod), 28.6 (CH_2, cod), 29.6 (CH_2, cod), 32.7 (CH, ^{i}Pr), 36.0 (b, CH_2, cod), 68.2 (CH_2-O), 71.7 (d, CH=, cod, *J*= 11.4 Hz), 72.5 (CH-N), 82.3 (d, CH=, cod, *J*= 11.4 Hz), 114.5 (dd, CH=, cod, *J*= 8.4 Hz, *J*= 2.1 Hz), 118.2 (dd, CH=, cod, *J*= 14.5 Hz, *J*= 6.1 Hz), 118.6-151.2 (aromatic carbons), 168.3 (C=N). MS HR-ESI [found 874.2374, $C_{46}H_{54}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 874.2379].

[Rh(cod)(L3d)]BF_4: Yield: 39.8 mg (90%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 129.4 (d, $^1J_{P\text{-}Rh}$= 277.5 Hz). ^1H NMR (400 MHz, CD_2Cl_2): δ= 0.79 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.4 Hz), 1.04 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 1.12 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 3H, CH_3), 1.75 (s, 9H, CH_3, ^{t}Bu), 1.96 (s, 3H, CH_3), 2.14 (m, 3H, CH_2, cod), 2.23 (m, 1H, CH_2, cod), 2.27 (s, 3H, CH_3), 2.38 (m, 4H, CH_3 and CH, ^{i}Pr), 2.48 (m, 4H, CH_2, cod), 4.17

(m, 1H, CH=, cod and CH-N), 4.52 (m, 1H, , CH_2-O), 4.60 (m, 2H, CH=, cod and CH_2-O), 5.62 (m, 1H, CH=, cod), 5.69 (m, 1H, CH=, cod), 6.22 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.29 (m, 2H, CH=), 7.43 (m, 1H, CH=), 7.57 (m, 1H, CH=), 7.91 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 13.9 (CH_3, ^{i}Pr), 16.1 (CH_3), 16.3 (CH_3), 18.3 (CH_3, ^{i}Pr), 19.9 (CH_3), 20.2 (CH_3), 25.8 (CH_2, cod), 28.9 (CH_2, cod), 29.9 (CH_2, cod), 30.7 (CH, ^{i}Pr), 30.8 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.4 (b, CH_2, cod), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 37.7 (CH_2-O), 73.0 (CH-N), 76.1 (d, CH=, cod, *J*= 10.7 Hz), 83.9 (d, CH=, cod, *J*= 12.1 Hz), 114.7 (dd, CH=, cod, *J*= 15.2 Hz, *J*= 5.4 Hz), 115.4 (dd, CH=, cod, *J*= 12.2 Hz, *J*= 4.6 Hz), 117.4-146.62 (aromatic carbons), 166.3 (C=N). MS HR-ESI [found 798.3149, $C_{44}H_{58}NO_4PRh$ $(M\text{-}BF_4)^+$ requires 798.3153].

[Rh(cod)(L3e)]BF_4: Yield: 39.4 mg (89%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 123.8 (d, $^1J_{P-Rh}$= 282.4 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 1.07 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.0 Hz), 1.12 (s, 9H, CH_3, ^{t}Bu), 1.15 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 1.54(s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.97 (m, 1H, CH_2, cod), 2.09 (m, 1H, CH_2, cod), 2.2-2.4 (m, 2H, CH_2, cod and CH, ^{i}Pr), 2.26 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.54 (m, 2H, CH_2, cod), 2.66 (m, 1H, CH_2, cod), 2.94 (m, 1H, CH=, cod), 4.13 (m, 1H, CH-N), 4.49 (m, 2H, CH_2, cod and CH_2-O), 4.57 (m, 1H, CH_2-O), 5.55 (m, 1H, CH=, cod), 5.84 (m, 1H, CH=, cod), 6.88 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.12 (s, 1H, CH=), 7.30 (s, 1H, CH=), 7.43 (m, 1H, CH=), 7.57 (m, 1H, CH=), 7.84 (d, 1H, CH=, $^3J_{H-H}$ = 8.0 Hz). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 15.5 (CH_3, ^{i}Pr), 16.1 (CH_3), 16.3 (CH_3), 18.5 (CH_3, ^{i}Pr), 19.9 (CH_3), 20.2 (CH_3), 25.0 (CH_2, cod), 28.4 (CH_2, cod), 29.8 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 33.0 (CH, ^{i}Pr), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 36.1 (b, CH_2, cod), 68.4 (CH_2-O), 70.7 (d, CH=, cod, *J*= 11.4 Hz), 72.6 (CH-N), 83.9 (d, CH=, cod, *J*= 11.4 Hz), 113.6 (dd, CH=, cod, *J*= 12.1 Hz, *J*= 4.5 Hz), 116.8 (dd, CH=, cod, *J*= 14.4 Hz, *J*= 6.1 Hz), 118.5-146.5 (aromatic carbons), 168.0 (C=N). MS HR-ESI [found 798.3150, $C_{44}H_{58}NO_4PRh$ $(M\text{-}BF_4)^+$ requires 798.3153].

[Rh(cod)(L3f)]BF_4: Yield: 41.2 mg (88%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 129.8 (d, $^1J_{P-Rh}$= 277.4 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.81 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.04 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.12 (s, 9H, CH_3, ^{t}Bu), 1.62-1.82 (m, 12H, CH_2), 1.73 (s, 9H, CH_3, ^{t}Bu), 2.11 (m, 4H, CH_2), 2.21 (m, 2H, CH_2), 2.33 (m, 1H, CH_2), 2.24-2.6 (b, 5H, CH_2 and CH, ^{i}Pr), 2.73 (m, 1H, CH_2), 2.82 (m, 1H, CH_2), 2.89 (m, 2H, CH_2), 4.16 (m, 2H, CH=, cod and CH-N), 4.50 (dd, 1H, CH_2-O, $^2J_{H-H}$= 9.6 Hz, $^3J_{H-H}$= 4 Hz), 4.57 (m, 2H, CH=, cod and CH_2-O), 5.61 (m, 1H, CH=, cod), 5.67 (m, 1H, CH=, cod), 6.22 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.18 (s, 1H, CH=), 7.22 (s, 1H, CH=), 7.41 (m, 1H, CH=), 7.56 (m, 1H, CH=), 7.89 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 14.0 (CH_3, ^{i}Pr), 18.4 (CH_3, ^{i}Pr), 22.6 (CH_2), 22.7 (CH_2), 22.8 (CH_2), 22.9 (CH_2), 25.9 (CH_2, cod), 26.9 (CH_2), 27.0 (CH_2), 28.9 (CH_2, cod), 29.4 (CH_2), 29.5 (CH_2), 29.9 (CH_2, cod), 30.7 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.5 (CH, ^{i}Pr), 34.4 (C, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (d, CH_2, cod, *J*= 6.1 Hz), 67.7 (CH_2-O), 72.9 (CH-N), 76.1 (d, CH=, cod, *J*=

10.7 Hz), 83.8 (d, CH=, cod, *J*= 12.2 Hz), 114.6 (dd, CH=, cod, *J*= 15.9 Hz, *J*= 6.1 Hz), 115.2 (dd, CH=, cod, *J*= 12.2 Hz, *J*= 4.2 Hz), 117.5-146.6 (aromatic carbons), 166.4 (C=N). MS HR-ESI [found 850.3462, $C_{48}H_{62}NO_4PRh$ $(M\text{-}BF_4)^+$ requires 850.3466].

[Rh(cod)(L3g)]BF_4: Yield: 43.1 mg (92%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 124.4 (d, $^1J_{P\text{-}Rh}$= 282.4 Hz). ^1H NMR (400 MHz, CD_2Cl_2): δ= 1.08 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 1.12 (s, 9H, CH_3, ^{t}Bu), 1.17 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 1.48-1.82 (m, 9H, CH_2), 1.95 (m, 1H, CH_2), 2.11 (m, 2H, CH_2), 2.2-2.41 (m, 4H, CH_2 and CH, ^{i}Pr), 2.52 (m, 2H, CH_2), 2.61-2.90 (m, 5H, CH_2 and CH=, cod), 4.12 (m, 1H, CH-N), 4.46 (m, 1H, CH=, cod), 4.49 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$= 9.2 Hz, $^3J_{H\text{-}H}$= 4.0 Hz), 4.55 (m, 1H, CH_2-O), 5.55 (m, 1H, CH=, cod), 5.82 (m, 1H, CH=, cod), 6.93 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 7.02 (s, 1H, CH=), 7.20 (s, 1H, CH=), 7.43 (m, 1H, CH=), 7.58 (m, 1H, CH=), 7.84 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 15.7 (CH_3, ^{i}Pr), 18.6 (CH_3, ^{i}Pr), 22.6 (CH_2), 22.7 (CH_2), 22.8 (CH_2), 22.9 (CH_2), 25.0 (CH_2, cod), 27.1 (CH_2), 28.3 (CH_2, cod), 29.2 (CH_2), 29.5 (CH_2), 29.9 (CH_2, cod), 30.6 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 33.0 (CH, ^{i}Pr), 34.4 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 36.1 (b, CH_2, cod), 68.5 (CH_2-O), 70.7 (d, CH=, cod, *J*= 12.2 Hz), 72.6 (CH-N), 83.8 (d, CH=, cod, *J*= 11.4 Hz), 113.4 (dd, CH=, cod, *J*= 13.0 Hz, *J*= 4.6 Hz), 116.3 (dd, CH=, cod, *J*= 14.5 Hz, *J*= 6.1 Hz), 118.6-146.5 (aromatic carbons), 167.9 (C=N MS HR-ESI [found 850.3463, $C_{48}H_{62}NO_4PRh$ $(M\text{-}BF_4)^+$ requires 850.3466].

[Rh(cod)(L4a)]BF_4: Yield: 42.2 mg (91%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 124.1 (d, $^1J_{P\text{-}Rh}$= 281.2 Hz). ^1H NMR (400 MHz, CD_2Cl_2): δ= 1.12 (t, 3H, CH_3, $^3J_{H\text{-}H}$= 7.6 Hz), 1.18 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.85 (m, 1H, CH_2), 2.04 (m, 2H, CH_2, cod), 2.10 (m, 1H, CH_2, cod), 2.19 (m, 2H, CH_2, cod), 2.28 (m, 1H, CH_2), 2.56 (m, 2H, CH_2, cod), 2.62 (m, 2H, CH_2, cod), 4.06 (m, 1H, CH=, cod), 4.26 (m, 1H, CH-N), 4.37 (m, 1H, CH_2-O), 4.57 (m, 1H, CH=, cod), 4.80 (m, 1H, CH_2-O), 5.65 (m, 1H, CH=, cod), 5.86 (m, 1H, CH=, cod), 6.18 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 7.11 (m, 1H, CH=), 7.40 (m, 2H, CH=), 7.50 (m, 3H, CH=), 7.84 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 9.23 (CH_3), 25.4 (CH_2, cod), 28.2 (CH_2, cod), 30.2 (CH_2, cod), 30.3 (CH_3, ^{t}Bu), 30.5 (CH_2, cod), 30.6 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.2 (b, CH_2, cod), 35.6 (C, ^{t}Bu), 72.2 (CH_2-O), 69.0 (CH-N), 78.4 (d, CH=, cod, *J*= 12.1 Hz), 80.5 (d, CH=, cod, *J*= 10.7 Hz), 114.6 (dd, CH=, cod, *J*= 12.1 Hz, *J*= 4.5 Hz), 115.0 (dd, CH=, cod, *J*= 15.2 Hz, *J*= 6.1 Hz), 118.5-149.5 (aromatic carbons), 167.4 (C=N). MS HR-ESI [found 840.3619, $C_{47}H_{64}NO_4PRh$ $(M\text{-}BF_4)^+$ requires 840.3623].

[Rh(cod)(L5a)]BF_4: Yield: 45.4 mg (93%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 124.9 (d, $^1J_{P\text{-}Rh}$ = 282.4 Hz). ^1H NMR (400 MHz, CD_2Cl_2): δ= 1.25 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.60-1.81 (m, 5H, CH_2, cod), 2.10 (m, 1H, CH_2, cod), 2.38 (m, 1H, CH_2, cod), 2.48 (m, 2H, CH_2, cod), 2.96 (m, 1H, CH=, cod), 4.35 (m, 1H, CH=, cod), 4.41 (m, 1H, CH_2-O), 5.13 (m, 1H, CH_2-O),

5.56 (m, 2H, CH=, cod and CH-N), 5.91 (m, 1H, CH=, cod), 6.92 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.12 (d, 1H, CH=, $^3J_{H-H}$= 4.8 Hz), 7.22 (d, 1H, CH=, $^3J_{H-H}$= 5.2 Hz), 7.51 (m, 4H, CH=), 7.58 (m, 5H, CH=), 7.62 (dd, 1H, CH=, $^3J_{H-H}$= 2.4 Hz, $^3J_{H-H}$= 7.6 Hz). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 25.2 (CH_2, cod), 29.0 (CH_2, cod), 29.8 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 34.3 (b, CH_2, cod), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 70.8 (d, CH=, cod, *J*= 11.4 Hz), 71.7 (CH-N), 75.5 (CH_2-O), 83.6 (d, CH=, cod, *J*= 11.4 Hz), 114.3 (dd, CH=, cod, *J*= 12.9 Hz, *J*= 5.3 Hz), 115.7 (dd, CH=, cod, *J*= 14.4 Hz, *J*= 5.3 Hz), 118.8-149.3 (aromatic carbons), 170.2 (C=N). MS HR-ESI [found 888.3618, $C_{51}H_{64}NO_4PRh$ $(M\text{-}BF_4)^+$ requires 888.3623].

[Rh(cod)(L5b)]BF_4: Yield: 44.3 mg (89%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 137.1 (d, $^1J_{P-Rh}$= 277.5 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.13 (s, 9H, $SiMe_3$), 0.28 (s, 9H, $SiMe_3$), 1.98 (m, 1H, CH_2, cod), 2.12 (m, 2H, CH_2, cod), 2.29 (m, 2H, CH_2, cod), 2.48 (m, 3H, CH_2, cod), 3.68 (m, 1H, CH=, cod), 4.42 (m, 2H, CH=, cod and CH_2-O), 5.00 (m, 1H, CH_2-O), 5.28 (m, 1H, CH-N), 5.77 (m, 1H, CH=, cod), 5.86 (m, 1H, CH=, cod), 6.62 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 6.75 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.06 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.19 (m, 2H, CH=), 7.31 (m, 1H, CH=), 7.43 (m, 4H, CH=), 7.56 (m, 2H, CH=), 7.72 (m, 1H, CH=), 7.94 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.07 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.15 (m, 2H, CH=), 8.23 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= -0.7 ($SiMe_3$), 0.0 ($SiMe_3$), 26.1 (CH_2, cod), 29.3 (CH_2, cod), 29.5 (CH_2, cod), 34.3 (b, CH_2, cod), 71.8 (CH-N), 74.4 (d, CH=, cod, *J*= 10.6 Hz), 76.4 (CH_2-O), 83.5 (d, CH=, cod, *J*= 12.2 Hz), 115.6 (dd, CH=, cod, *J*= 13.7 Hz, *J*= 4.5 Hz), 116.1 (dd, CH=, cod, *J*= 15.2 Hz, *J*= 5.3 Hz), 118.2-150.8 (aromatic carbons), 168.8 (C=N). MS HR-ESI [found 908.2221, $C_{49}H_{52}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 908.2222].

[Rh(cod)(L5c)]BF_4: Yield: 44.8 mg (90%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 130.5 (d, $^1J_{P-Rh}$= 283.5 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.32 (s, 9H, $SiMe_3$), 0.58 (s, 9H, $SiMe_3$), 1.67 (m, 5H, CH_2, cod), 1.96 (m, 1H, CH_2, cod), 2.36 (m, 1H, CH_2, cod), 2.54 (m, 1H, CH_2, cod), 2.74 (m, 1H, CH=, cod), 4.38 (m, 1H, CH=, cod), 4.43 (m, 1H, CH_2-O), 5.15 (m, 1H, CH_2-O), 5.56 (m, 2H, CH=, cod and CH-N), 6.00 (m, 1H, CH=, cod), 6.76 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 6.89 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.05 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.24 (m, 2H, CH=), 7.53 (m, 5H, CH=), 7.93 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.97 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.01 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.13 (s, 1H, CH=), 8.25 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= -0.1 ($SiMe_3$), 0.1 ($SiMe_3$), 24.9 (CH_2, cod), 29.1 (CH_2, cod), 29.9 (CH_2, cod), 34.4 (b, CH_2, cod), 69.3 (d, CH=, cod, *J*= 10.6 Hz), 72.0 (CH-N), 75.4 (CH_2-O), 83.9 (d, CH=, cod, *J*= 11.4 Hz), 115.2 (dd, CH=, cod, *J*= 12.2 Hz, *J*= 3.8 Hz), 116.1 (dd, CH=, cod, *J*= 13.7 Hz, *J*= 4.6 Hz), 118.9-150.1 (aromatic carbons), 170.6 (C=N). MS HR-ESI [found 908.2219, $C_{49}H_{52}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 908.2222].

[Rh(cod)(L6b)]BF_4: Yield: 44.4 mg (91%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 132.3 (d, $^1J_{P-Rh}$= 284.8 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.09 (s, 9H, $SiMe_3$), 0.69 (s,

9H, $SiMe_3$), 1.17 (s, 9H, CH_3, ^tBu), 2.11 (m, 3H, CH_2, cod), 2.27 (m, 1H, CH_2, cod), 2.60 (m, 3H, CH_2, cod), 2.86 (m, 1H, CH_2, cod), 3.95 (m, 1H, CH-N), 4.24 (m, 1H, CH=, cod), 4.62 (m, 2H, CH_2-O), 4.64 (m, 1H, CH=, cod), 5.31 (d, 1H, CH=, cod, $^3J_{H-H}$= 8.0 Hz), 5.82 (m, 1H, CH=, cod), 6.44 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.07 (m, 2H, CH=), 7.29 (m, 1H, CH=), 7.40 (m, 3H, CH=), 7.56 (m, 1H, CH=), 7.92 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.02 (dd, 1H, CH=, $^3J_{H-H}$= 7.2 Hz, $^3J_{H-H}$= 2.0 Hz), 8.09 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.14 (s, 1H, CH=), 8.19 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= -1.6 ($SiMe_3$), 0.4 ($SiMe_3$), 25.1 (CH_2, cod), 26.4 (CH_3, ^tBu), 28.7 (CH_2, cod), 30.2 (CH_2, cod), 34.2 (CH_2, cod), 35.3 (C, ^tBu), 68.7 (CH_2-O), 75.0 (d, CH=, cod, *J*= 10.7 Hz), 77.7 (CH-N), 83.3 (d, CH=, cod, *J*= 12.1 Hz), 115.9 (dd, CH=, cod, *J*= 12.1 Hz, *J*= 4.5 Hz), 116.6 (dd, CH=, cod, *J*= 16.8 Hz, *J*= 5.4 Hz), 118.2-152.8 (aromatic carbons), 166.9 (C=N). MS HR-ESI [found 888.2534, $C_{47}H_{56}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 888.2533].

[Rh(cod)(L6c)]BF_4: Yield: 43.9 mg (90%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 131.3 (d, $^1J_{P-Rh}$= 283.2 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.19 (s, 9H, $SiMe_3$), 0.59 (s, 9H, $SiMe_3$), 1.24 (s, 9H, CH_3, ^tBu), 1.6-1.9 (m, 3H, CH_2, cod), 2.10 (m, 1H, CH_2, cod), 2.39 (m, 1H, CH_2, cod), 2.49 (m, 1H, CH_2, cod), 2.62 (m, 2H, CH_2, cod), 3.10 (m, 1H, CH=, cod), 4.03 (m, 1H, CH-N), 4.36 (m, 1H, CH=, cod), 4.59 (m, 1H, CH_2-O), 4.67 (dd, 1H, CH_2-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 2.4 Hz), 5.82 (m, 1H, CH=, cod), 5.91 (m, 1H, CH=, cod), 6.74 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 6.83 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.06 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.38 (m, 1H, CH=), 7.54 (m, 1H, CH=), 7.52 (m, 4H, CH=), 7.93 (m, 3H, CH=), 8.01 (s, 1H, CH=), 8.23 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= -0.1 ($SiMe_3$), 0.0 ($SiMe_3$), 24.6 (CH_2, cod), 25.9 (CH_3, ^tBu), 28.5 (CH_2, cod), 29.8 (CH_2, cod), 34.9 (CH_2, cod), 36.2 (C, ^tBu), 68.8 (CH_2-O), 70.3 (d, CH=, cod, *J*= 11.4 Hz), 76.6 (CH-N), 81.5 (d, CH=, cod, *J*= 11.4 Hz), 114.8 (dd, CH=, cod, *J*= 12.2 Hz, *J*= 4.6 Hz), 118.6 (dd, CH=, cod, *J*= 14.4 Hz, *J*= 5.3 Hz), 118.4-151.5 (aromatic carbons), 168.2 (C=N). MS HR-ESI [found 888.2532, $C_{47}H_{56}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 888.2533].

[Rh(cod)(L7a)]BF_4: Yield: 45.5 mg (92%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 118.9 (d, $^1J_{P-Rh}$= 282.2 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 1.31 (s, 9H, CH_3, ^tBu), 1.41 (s, 9H, CH_3, ^tBu), 1.61 (s, 9H, CH_3, ^tBu), 1.69 (s, 9H, CH_3, ^tBu), 1.6-1.9 (m, 4H, CH_2, cod), 2.04 (m, 1H, CH_2, cod), 2.18 (m, 1H, CH_2, cod), 2.45 (m, 1H, CH_2, cod), 2.64 (m, 1H, CH_2, cod), 3.60 (m, 1H, CH=, cod), 3.85 (m, 1H, CH_2), 4.10 (m, 1H, CH=, cod), 4.64 (m, 1H, CH_2), 4.76 (m, 1H, CH=, cod), 5.01 (m, 1H, CH-N), 5.37 (m, 3H, CH=, cod and CH_2-O), 5.63 (m, 1H, CH=), 6.25 (m, 1H, CH=), 6.97 (m, 2H, CH=), 7.07 (m, 2H, CH=), 7.23 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 7.45 (m, 1H, CH=), 7.57 (m, 4H, CH=), 7.71 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 24.6 (CH_2, cod), 25.2 (CH_2, cod), 30.9 (CH_3, ^tBu), 31.1 (CH_3, ^tBu), 31.8 (CH_2, cod), 34.5 (CH_2, cod), 34.7 (C, ^tBu), 35.2 (CH_2), 35.6 (C, ^tBu), 70.2 (b, CH=, cod), 70.6 (CH_2-O), 76.8 (CH-N), 84.0 (b, CH=), 111.5 (b,

CH=), 114.7 (b, CH=), 120.5-149.2 (aromatic carbons), 172.2 (C=N). MS HR-ESI [found 902.3778, $C_{52}H_{66}NO_4PRh$ $(M\text{-}BF_4)^+$ requires 902.3779].

[Rh(cod)(L7b)]BF_4: Yield: 44.4 mg (88%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 121.3 (d, $^1J_{P\text{-}Rh}$= 276.9 Hz). ^1H NMR (400 MHz, CD_2Cl_2): δ= 0.4 (s, 9H, $SiMe_3$), 0.70 (s, 9H, $SiMe_3$), 1.60-1.82 (m, 3H, CH_2, cod), 2.03 (m, 1H, CH_2, cod), 2.31 (m, 1H, CH_2, cod), 2.55 (m, 1H, CH_2, cod), 2.63 (m, 2H, CH_2, cod), 3.69 (m, 1H, CH=, cod), 4.16 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 15.6 Hz), 4.46 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$= 8.8 Hz, $^3J_{H\text{-}H}$= 4.4 Hz), 4.74 (m, 4H, CH=, cod, CH_2 and CH_2-O), 5.21 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 5.30 (m, 1H, CH-N), 5.64 (m, 1H, CH=), 6.69 (m, 1H, CH=), 6.77 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 7.04 (m, 2H, CH=), 7.24 (m, 2H, CH=), 7.35 (m, 3H, CH=), 7.49 (m, 5H, CH=), 7.93 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.06 (s, 1H, CH=), 8.07 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.33 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= -0.1 ($SiMe_3$), 0.0 ($SiMe_3$), 25.6 (CH_2, cod), 29.1 (CH_2, cod), 30.4 (CH_2, cod), 34.8 (CH_2, cod), 35.4 (CH_2), 70.7 (CH-N), 73.8 (d, CH=, cod, *J*= 10.6 Hz), 78.3 (CH_2-O), 84.3 (d, CH=, cod, *J*= 10.6 Hz), 112.6 (dd, CH=, cod, *J*= 8.3 Hz, *J*= 4.6 Hz), 113.7 (dd, CH=, cod, *J*= 8.4 Hz, *J*= 4.2 Hz), 119.5-151.1 (aromatic carbons), 175.3 (d, C=N, *J*= 6.1 Hz). MS HR-ESI [found 922.2376, $C_{50}H_{54}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 922.2379].

[Rh(cod)(L7c)]BF_4: Yield: 45 mg (89%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 120.3 (d, $^1J_{P\text{-}Rh}$= 282.4 Hz). ^1H NMR (400 MHz, CD_2Cl_2): δ= 0.64 (s, 9H, $SiMe_3$), 0.69 (s, 9H, $SiMe_3$), 1.54 (m, 1H, CH_2, cod), 1.74 (m, 3H, CH_2, cod), 1.91 (m, 1H, CH_2, cod), 1.99 (m, 1H, CH_2, cod), 2.29 (m, 1H, CH_2, cod), 2.70 (m, 1H, CH_2, cod), 3.04 (m, 1H, CH=, cod), 3.86 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 14.8 Hz), 4.54 (m, 1H, CH=, cod), 4.65 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 14.8 Hz), 5.05 (m, 1H, CH_2-O), 5.40 (m, 1H, CH-N), 5.54 (m, 1H, CH=, cod), 5.89 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 6.17 (m, 1H, CH=, cod), 6.74 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 6.88 (m, 1H, CH=), 6.98 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 7.05 (m, 1H, CH=), 7.17 (m, 1H, CH=), 7.22 (m, 1H, CH=), 7.34 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.6 Hz), 7.51 (m, 7H, CH=), 7.96 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.04 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.17 (s, 1H, CH=), 8.36 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 0.4 ($SiMe_3$), 0.7 ($SiMe_3$), 25.2 (CH_2, cod), 29.3 (CH_2, cod), 30.4 (CH_2, cod), 33.5 (CH_2, cod), 35.5 (CH_2), 70.4 (CH-N), 71.2 (d, CH=, cod, *J*= 11.4 Hz), 76.9 (CH_2-O), 83.7 (d, CH=, cod, *J*= 11.4 Hz), 113.3 (dd, CH=, cod, *J*= 15.2 Hz, *J*= 5.3 Hz), 114.7 (dd, CH=, cod, *J*= 13.0 Hz, *J*= 4.6 Hz), 120.1-152.2 (aromatic carbons), 172.6 (d, C=N, *J*= 5.8 Hz). MS HR-ESI [found 922.2378, $C_{50}H_{54}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 922.2379].

[Rh(cod)(L8a)]BF_4: Yield: 45.8 mg (93%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 118.9 (d, $^1J_{P\text{-}Rh}$= 282.2 Hz). ^1H NMR (400 MHz, CD_2Cl_2): δ= 0.88 (d. 3H, CH_3, ^iPr, $^3J_{H\text{-}H}$= 7.2 Hz), 1.16 (d. 3H, CH_3, ^iPr, $^3J_{H\text{-}H}$= 7.2 Hz), 1.30 (s, 9H, CH_3, ^tBu), 1.41 (s, 9H, CH_3, ^tBu), 1.54 (s, 9H, CH_3, ^tBu), 1.63 (s, 9H, CH_3, ^tBu), 2.07 (m, 2H, CH_2, cod), 2.19 (m, 2H, CH_2, cod), 2.40 (m, 1H, CH, ^iPr), 2.6-2.8 (m, 4H, CH_2, cod), 3.79 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 14.8 Hz), 3.93 (m, 1H, CH=, cod), 4.05 (m, 1H, CH-N), 4.32 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$= 9.2

Hz, $^3J_{H-H}$= 5.6 Hz), 4.54 (m, 1H, CH_2-O), 4.59 (d, 1H, CH_2, $^2J_{H-H}$= 14.8 Hz), 5.05 (m, 1H, CH=, cod), 5.45 (m, 1H, CH=, cod), 5.48 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 6.12 (m, 1H, CH=, cod), 6.93 (m, 1H, CH=), 7.04 (m, 1H, CH=), 7.07 (m, 2H, CH=), 7.25 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.43 (d, 1H, CH=, $^3J_{H-H}$= 2.0 Hz), 7.66 (d, 1H, CH=, $^3J_{H-H}$= 2.0 Hz). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 15.5 (CH_3, ^{i}Pr), 19.9 (CH_3, ^{i}Pr), 25.4 (CH_2, cod), 29.0 (CH_2, cod), 30.7 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 32.6 (C, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.2 (CH_2), 35.5 (CH_2, cod), 69.8 (CH_2-O), 70.9 (CH-N), 72.4 (d, CH=, cod, *J*= 11.4 Hz), 84.2 (d, CH=, cod, *J*= 11.4 Hz), 112.6 (dd, CH=, cod, *J*= 15.9 Hz, *J*= 5.3 Hz), 114.7 (dd, CH=, cod, *J*= 11.4 Hz, *J*= 4.6 Hz), 120.5-151.9 (aromatic carbons), 170.1 (d, C=N, *J*= 6.0 Hz). MS HR-ESI [found 868.3931, $C_{49}H_{68}NO_4PRh$ $(M\text{-}BF_4)^+$ requires 868.3936].

[Rh(cod)(L8b)]BF_4: Yield: 43.4 mg (89%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 121.5 (d, $^1J_{P-Rh}$= 276.0 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.42 (s, 9H, $SiMe_3$), 0.64 (s, 9H, $SiMe_3$), 0.88 (d. 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.02 (d. 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.81 (m, 1H, CH, ^{i}Pr), 1.94 (m, 1H, CH_2, cod), 2.02 (m, 1H, CH_2, cod), 2.16 (m, 1H, CH_2, cod), 2.24 (m, 1H, CH_2, cod), 2.54 (m, 2H, CH_2, cod), 2.71 (m, 1H, CH_2, cod), 2.85 (m, 1H, CH_2, cod), 3.83 (m, 1H, CH=, cod), 3.91 (d, 1H, CH_2, $^2J_{H-H}$= 16.0 Hz), 4.16 (m, 1H, CH-N), 4.29 (m, 1H, CH_2-O), 4.53 (m, 2H, CH_2-O and CH_2), 4.78 (m, 1H, CH=, cod), 5.09 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 5.73 (m, 1H, CH=, cod), 6.01 (m, 1H, CH=, cod), 6.64 (m, 1H, CH=), 6.76 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 6.99 (m, 1H, CH=), 7.04 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.24 (m, 3H, CH=), 7.48 (m, 1H, CH=), 7.53 (m, 1H, CH=), 7.94 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 8.06 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz), 8.07 (s, 1H, CH=), 8.31 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= -0.1 ($SiMe_3$), 0.0 ($SiMe_3$), 13.8 (CH_3, ^{i}Pr), 18.7 (CH_3, ^{i}Pr), 26.1 (CH_2, cod), 29.3 (CH_2, cod), 30.5 (CH_2, cod), 34.9 (CH_2, cod), 35.3 (CH_2), 70.8 (CH_2-O), 71.8 (CH-N), 74.5 (d, CH=, cod, *J*= 11.4 Hz), 83.5 (d, CH=, cod, *J*= 11.4 Hz), 110.5 (dd, CH=, cod, *J*= 9.2 Hz, *J*= 3.5 Hz), 114.6 (dd, CH=, cod, *J*= 14.4 Hz, *J*= 6.2 Hz), 119.5-151.8 (aromatic carbons), 176.0 (d, C=N, *J*= 7.6 Hz). MS HR-ESI [found 888.2531, $C_{47}H_{56}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 888.2535].

[Rh(cod)(L8c)]BF_4: Yield: 43 mg (88%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 121.2 (d, $^1J_{P-Rh}$ = 283.5 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.59 (s, 9H, $SiMe_3$), 0.66 (s, 9H, $SiMe_3$), 0.84 (d. 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.10 (d. 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.93 (m, 2H, CH_2, cod), 2.12 (m, 1H, CH_2, cod), 2.19 (m, 1H, CH_2, cod), 2.43 (m, 3H, CH_2, cod and CH, ^{i}Pr), 2.74 (m, 1H, CH_2, cod), 2.83 (m, 1H, CH_2, cod), 3.52 (m, 1H, CH=, cod), 3.77 (d, 1H, CH_2, $^2J_{H-H}$= 14.8 Hz), 3.99 (m, 1H, CH-N), 4.34 (dd, 1H, CH_2-O, $^2J_{H-H}$= 9.6 Hz, $^3J_{H-H}$= 5.2 Hz), 4.57 (m, 2H, CH_2-O and CH_2), 4.75 (m, 1H, CH=, cod), 5.61 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 5.66 (m, 1H, CH=, cod), 6.03 (m, 1H, CH=, cod), 6.73 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 6.78 (m, 1H, CH=), 7.01 (m, 2H, CH=), 7.17 (m, 1H, CH=), 7.24 (m, 2H, CH=), 7.48 (m, 2H, CH=), 7.95 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.03 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.13 (s, 1H, CH=), 8.33 (s, 1H, CH=). ^{13}C NMR (100.6 MHz,

CD_2Cl_2): δ= 0.4 ($SiMe_3$), 0.5 ($SiMe_3$), 15.3 (CH_3, ^{i}Pr), 19.8 (CH_3, ^{i}Pr), 25.7 (CH_2, cod), 29.4 (CH_2, cod), 29.9 (CH_2, cod), 32.3 (CH, ^{i}Pr), 35.1 (CH_2, cod), 35.4 (CH_2), 69.5 (CH-N), 70.4 (CH_2-O), 73.1 (d, CH=, cod, *J*= 11.4 Hz), 83.7 (d, CH=, cod, *J*= 10.6 Hz), 114.3 (dd, CH=, cod, *J*= 13.7 Hz, *J*= 4.6 Hz), 115.3 (dd, CH=, cod, *J*= 14.4 Hz, *J*= 6.1 Hz), 120.1-151.8 (aromatic carbons), 170.2 (d, C=N, *J*= 5.3 Hz). MS HR-ESI [found 888.2533, $C_{47}H_{56}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 888.2535].

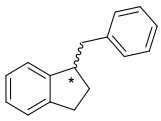
[Rh(cod)(L9a)]BF_4: Yield: 43.6 mg (90%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 117.6 (d, $^1J_{P\text{-}Rh}$ = 281.2 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 1.21 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.00 (m, 2H, CH_2, cod), 2.17 (m, 2H, CH_2, cod), 2.54 (m, 2H, CH_2, cod), 2.73 (m, 2H, CH_2, cod), 3.83 (m, 2H, CH_2, and CH=, cod), 3.95 (m, 1H, CH-N), 4.42 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$= 9.6 Hz, $^3J_{H\text{-}H}$= 4.4 Hz), 4.54 (m, 1H, CH_2-O), 4.82 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 10.4 Hz), 5.01 (m, 1H, CH=, cod), 5.46 (m, 1H, CH=, cod), 5.63 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 6.12 (m, 1H, CH=, cod), 6.95 (m, 1H, CH=), 7.05 (m, 3H, CH=), 7.26 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.6 Hz), 7.43 (s, 1H, CH=), 7.65 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 25.0 (CH_2, cod), 25.9 (CH_3, ^{t}Bu), 29.3 (CH_2, cod), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_2, cod), 31.7 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.5 (CH_2, cod), 36.2 (CH_2), 70.9 (CH-N), 71.5 (d, CH=, cod, *J*= 11.4 Hz), 75.1 (CH_2-O), 83.2 (d, CH=, cod, *J*= 12.1 Hz), 111.0 (dd, CH=, cod, *J*= 17.5 Hz, *J*= 6.1 Hz), 115.3 (dd, CH=, cod, *J*= 11.4 Hz, *J*= 5.4 Hz), 120.5-151.9 (aromatic carbons), 170.1 (C=N). MS HR-ESI [found 882.4090, $C_{50}H_{70}NO_4PRh$ $(M\text{-}BF_4)^+$ requires 882.4092].

[Rh(cod)(L9c)]BF_4: Yield: 45 mg (90%). ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 119.6 (d, $^1J_{P\text{-}Rh}$ = 282.4 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.59 (s, 9H, $SiMe_3$), 0.65 (s, 9H, $SiMe_3$), 1.16 (s, 9H, CH_3, ^{t}Bu), 1.84 (m, 1H, CH_2, cod), 1.94 (m, 1H, CH_2, cod), 2.07 (m, 1H, CH_2, cod), 2.18 (m, 1H, CH_2, cod), 2.38 (m, 2H, CH_2, cod), 2.68 (m, 1H, CH_2, cod), 2.87 (m, 1H, CH_2, cod), 3.32 (m, 1H, CH=, cod), 3.84 (m, 2H, CH-N and CH_2), 4.47 (dd, 1H, CH_2-O, $^2J_{H\text{-}H}$= 10.0 Hz, $^3J_{H\text{-}H}$= 4.0 Hz), 4.55 (m, 1H, CH_2-O), 4.69 (m, 1H, CH=, cod), 4.79 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 14.8 Hz), 5.71 (m, 1H, CH=, cod), 5.92 (d, 1H, CH=, $^3J_{H\text{-}H}$ = 8.4 Hz), 5.96 (m, 1H, CH=, cod), 6.68 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 6.89 (m, 1H, CH=), 6.95 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 7.04 (m, 1H, CH=), 7.15 (m, 1H, CH=), 7.24 (m, 1H, CH=), 6.95 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.2 Hz), 7.48 (m, 2H, CH=), 7.96 (d, 1H, CH=, $^3J_{H\text{-}H}$ = 8.0 Hz), 8.01 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.16 (s, 1H, CH=), 8.31 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ= 0.2 ($SiMe_3$), 0.5 ($SiMe_3$), 25.2 (CH_2, cod), 26.0 (CH_3, ^{t}Bu), 29.5 (CH_2, cod), 30.1 (CH_2, cod), 34.8 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 35.2 (CH_2, cod), 36.3 (CH_2), 71.1 (CH_2-O), 71.5 (d, CH=, cod, *J*= 11.4 Hz), 74.4 (CH-N), 82.7 (d, CH=, cod, *J*= 11.4 Hz), 114.6 (dd, CH=, cod, *J*= 15.2 Hz, *J*= 6.1 Hz), 115.2 (dd, CH=, cod, *J*= 12.2 Hz, *J*= 4.6 Hz), 120.1-151.7 (aromatic carbons), 170.1 (d, C=N, *J*= 5.4 Hz). MS HR-ESI [found 902.2686, $C_{48}H_{58}NO_4PRhSi_2$ $(M\text{-}BF_4)^+$ requires 902.2692].

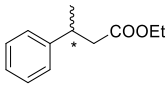
3.2.4.6. General procedure for the hydrogenation of minimally functionalized olefins S1-S55

The alkene (0.5 mmol) and Ir complex (0.25-2 mol %) were dissolved in the corresponding solvent CH_2Cl_2 or PC (2 mL) and placed in a high-pressure autoclave. The autoclave was purged 4 times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short plug of celite. The enantiomeric excess was determined by chiral GC or chiral HPLC and conversions were determined by ^1H NMR (for the hydrogenation products from substrates **S1**-**S5**, **S7**-**S8**, **S16**-**S18**, **S21**, **S31**-**S33**, **S35**-**S45**, **S47**-**S49** and **S53**-**S55** see previous Section 3.1.4.5).

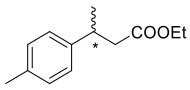
1-Benzyl-2,3-dihydro-1H-indene.[17z] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=95/5, 0.5 mL/min, 210 nm). t_R 12.0 min (*S*); t_R 13.1 min (*R*). ^1H NMR ($CDCl_3$), δ: 1.80 (m, 1H), 2.20 (m, 1H), 2.74 (dd, 1H, *J*= 13.6 Hz, *J*= 9.2 Hz), 2.87 (m, 2H), 3.20 (dd, 1H, *J*= 13.6 Hz, *J*= 5.6 Hz), 3.51 (m, 1H), 7.1-7.4 (m, 9H).



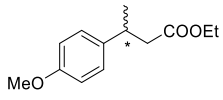
Ethyl 3-phenylbutanoate.[17i] Enantiomeric excess determined by HPLC using Chiracel IB column (hexane/2-propanol=99.5/0.5, 1 mL/min, 254 nm). t_R 9.5 min (*R*); t_R 18.2 min (*S*). ^1H NMR ($CDCl_3$), δ: 1.16 (t, 3H, *J*= 7.2 Hz), 1.30 (d, 3H, *J*= 6.8 Hz), 2.54 (m, 2H), 3.28 (m, 1H), 4.08 (q, 2H, *J*= 7.2 Hz), 7.2-7.4 (m, 5H).



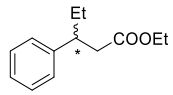
Ethyl 3-(p-tolyl)butanoate.[17q] Enantiomeric excess determined by HPLC using Chiracel IB column (hexane/2-propanol=99.5/0.5, 0.5 mL/min, 254 nm). t_R 12.3 min (*R*); t_R 13.0 min (*S*). ^1H NMR ($CDCl_3$), δ: 1.18 (t, 3H, *J*= 7.2 Hz), 1.28 (d, 3H, *J*= 6.0 Hz), 2.31 (s, 3H), 2.56 (m, 2H), 3.25 (m, 1H), 4.08 (q, 2H, *J*= 7.2 Hz), 7.12 (m, 4H).



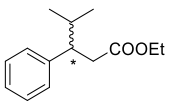
Ethyl 3-(4-methoxyphenyl)butanoate.[17q] Enantiomeric excess determined by HPLC using Chiracel IB column (hexane/2-propanol=99.5/0.5, 0.5 mL/min, 254 nm). t_R 18.5 min (*R*); t_R 19.5 min (*S*). ^1H NMR ($CDCl_3$), δ: 1.19 (t, 3H, *J*= 7.2 Hz), 1.26 (d, 3H, *J*= 6.4 Hz), 2.54 (m, 2H), 3.24 (m, 1H), 3.29 (s, 3H), 4.07 (q, 2H, *J*= 7.2 Hz), 6.83 (m, 2H), 7.15 (m, 2H).



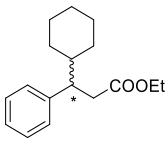
Ethyl 3-phenylpentanoate.[17q] Enantiomeric excess determined by HPLC using Chiracel IC column (hexane/2-propanol=99.5/0.5, 0.5 mL/min, 254 nm). t_R 11.6 min (*R*); t_R 12.1 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.79 (t, 3H, *J*= 7.2 Hz), 1.13 (t, 3H, *J*= 7.2 Hz), 1.53 (d, 3H, *J*= 6.0 Hz), 1.62 (m, 2H), 2.60 (m, 2H), 2.99 (m, 1H), 4.03 (q, 2H, *J*= 7.2 Hz), 7.21 (m, 2H), 7.34 (m, 3H).



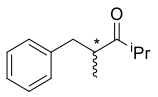
Ethyl 4-methyl-3-phenylpentanoate.[56] Enantiomeric excess determined by HPLC using Chiracel OD-H column (hexane/2-propanol=99/1, 0.5 mL/min, 254 nm). t_R 11.0 min (*R*); t_R 18.8 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.77 (d, 3H, *J*= 6.0 Hz), 0.97 (d, 3H, *J*= 6.0 Hz), 1.06 (t, 3H, *J*= 6.8 Hz), 1.86 (m, 1H), 2.60 (m, 1H), 2.80 (m, 1H), 2.88 (m, 1H), 3.96 (q, 2H, *J*= 6.8 Hz), 7.1-7.3 (m, 5H).



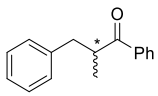
Ethyl 3-cyclohexyl-3-phenylpropanoate.[57] Enantiomeric excess determined by HPLC using Chiracel OD-H column (hexane/2-propanol=99/1, 0.5 mL/min, 254 nm). t_R 10.3 min (*R*); t_R 17.0 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.90 (m, 1H), 0.93 (m, 1H), 1.06 (t, 3H, *J*= 7.2 Hz), 1.12 (m, 1H), 1.24 (m, 2H), 1.42 (m, 2H), 1.60 (m, 2H), 1.72 (m, 1H), 1.80 (m, 1H), 2.54 (m, 1H), 2.78 (m, 1H), 2.89 (m, 1H), 3.92 (q, 2H, *J*= 7.2 Hz), 7.1-7.3 (m, 5H).



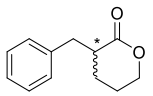
2,4-Dimethyl-1-phenylpentan-3-one.[19] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=99/1, 0.5 mL/min, 220 nm). t_R 25.1 (*S*); t_R 27.0 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.87 (d, 3H, *J*= 6.8 Hz), 1.01 (d, 3H, *J*= 6.8 Hz), 1.08 (d, 1H, *J*= 6.8 Hz), 2.51 (m, 2H), 2.97 (m, 2H), 7.1-7.5 (m, 5H).



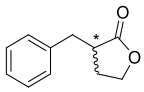
2-Methyl-1,3-diphenylpropan-1-one.[19] Enantiomeric excess determined by HPLC using Chiracel OB column (hexane/2-propanol=98.2, 0.5 mL/min, 220 nm). t_R 16.4 min (*S*); t_R 17.1 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.21 (d, 3H, *J*= 6.8 Hz), 2.69 (dd, 1H, *J*= 13.2 Hz, *J*= 7.2 Hz), 3.18 (dd, 1H, *J*= 13.2 Hz, *J*= 6.4 Hz), 3.74 (m, 1H), 7.1-8.0 (m, 10H).



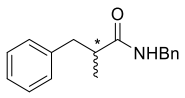
3-Benzyltetrahydro-2H-pyran-2-one.[17y] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=90/10, 1 mL/min, 210 nm). t_R 39.4 min (*R*); t_R 43.9 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.51 (m, 1H), 1.83 (m, 3H), 2.71 (m, 2H), 3.35 (m, 1H), 4.26 (m, 2H), 7.1-7.3 (m, 5H).



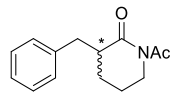
3-Benzyldihydrofuran-2(3H)-one.[17y] Enantiomeric excess determined by HPLC using Chiracel OD-H column (hexane/2-propanol=90/10, 1 mL/min, 254 nm). t_R 17.3 min (*S*); t_R 18.8 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.98 (m, 1H), 2.12 (m, 1H), 2.64 (m, 1H), 2.84 (m, 1H), 3.12 (m, 1H), 4.16 (m, 1H), 4.22 (m, 1H), 7.2-7.4 (m, 5H).



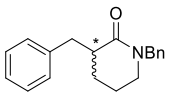
N-Benzyl-2-methyl-3-phenylpropanamide.[30c,58] Enantiomeric excess determined by HPLC using Chiracel OD-H column (hexane/2-propanol=95/5, 1 mL/min, 210 nm). t_R 26.5 min (*S*); t_R 29.9 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.23 (d, 3H, *J*= 6.8 Hz), 2.47 (m, 1H), 2.70 (dd, 1H, *J*= 6.4 Hz, *J*= 13.4 Hz), 2.98 (dd, 1H, *J*= 8.8 Hz, *J*= 13.4 Hz), 4.32 (m, 2H), 5.66 (b, 1H), 7.0-7.3 (m, 10H).



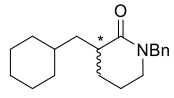
1-Acetyl-3-benzylpiperidin-2-one.[17y] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=80/20, 0.5 mL/min, 210 nm). t_R 21.5 min (*S*); t_R 23.6 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.47 (m, 1H), 1.71 (m, 1H), 1.82 (m, 2H), 2.54 (s, 3H), 2.72 (m, 2H), 3.38 (m, 1H), 3.62 (m, 1H), 3.84 (m, 1H), 7.1-7.3 (m, 5H). ^{13}C NMR ($CDCl_3$), δ: 21.2, 25.1, 27.7, 37.4, 43.2, 45.5, 126.5, 128.5, 129.2, 139.3, 173.8, 175.7.



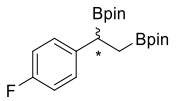
1,3-dibenzylpiperidin-2-one. Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=80/20, 0.5 mL/min, 220 nm). t_R 14.4 min (-); t_R 22.3 min (+). ^{1}H NMR ($CDCl_3$), δ: 1.51 (m, 1H), 1.69 (m, 3H), 2.64 (m, 1H), 2.75 (dd, 1H, *J*= 13.2 Hz, *J*= 10 Hz), 3.17 (m, 2H), 3.45 (dd, 1H, *J*= 13.2 Hz, *J*= 3.6 Hz), 4.61 (s, 2H), 7.2-7.4 (m, 10H).

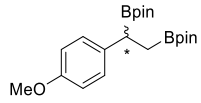


1-benzyl-3-(cyclohexylmethyl)piperidin-2-one. Enantiomeric excess determined by HPLC using Chiracel IA column (hexane/2-propanol=90/10, 0.5 mL/min, 210 nm). t_R 16.3 min (*S*); t_R 19.1 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.85 (m, 1H), 0.92 (m, 1H), 1.0-1.4 (m, 5H), 1.43 (m, 1H), 1.64 (m, 5H), 1.81 (m, 1H), 1.92 (m, 2H), 2.41 (m, 1H), 3.18 (m, 1H), 4.42 (m, 2H), 7.2-7.3 (m, 5H). ^{13}C NMR ($CDCl_3$), δ: 26.1, 26.4, 26.7, 31.9, 34.4, 34.7, 38.4, 39.6, 47.5, 50.6, 127.4, 127.9, 128.6, 134.8, 137.1, 174.2.

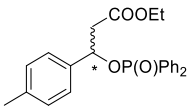


2,2'-(1-(4-Fluorophenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane).[59] Enantiomeric excess were determined after oxidation of the pinacolborane derivative to the corresponding diol using NaOH (3N, 2.0 mL) and H_2O_2 (30%, 1.5 mL). Enantiomeric excess determined by HPLC using Chiracel OD-H column (hexane/2-propanol=95/5, 0.5 mL/min, 254 nm). t_R 21.0 min (*R*); t_R 24.1 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.07 (dd, 1H, *J*= 16.0 Hz, *J*= 5.8 Hz), 1.17 (s, 6H), 1.19 (s, 6H), 1.21 (s, 12H), 1.33 (dd, 1H, *J*= 16.0 Hz, *J*= 10.8 Hz), 2.46 (dd, 1H, *J*= 10.8 Hz, *J*= 5.8 Hz), 3.78 (s, 3H), 6.8-7.4 (m, 4H).

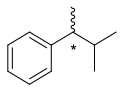


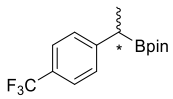
2,2'-(1-(4-Methoxyphenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane).[59] 

Enantiomeric excess were determined after oxidation of the pinacolborane derivative to the corresponding diol using NaOH (3N, 2.0 mL) and H_2O_2 (30%, 1.5 mL). Enantiomeric excess determined by HPLC using Chiracel OD-H column (hexane/2-propanol=90/10, 0.5 mL/min, 254 nm). t_R 26.0 min (*R*); t_R 31.4 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.07 (dd, 1H, *J*= 16.0 Hz, *J*= 5.8 Hz), 1.17 (s, 6H), 1.19 (s, 6H), 1.21 (s, 12H), 1.33 (dd, 1H, *J*= 16.0 Hz, *J*= 10.8 Hz), 2.46 (dd, 1H, *J*= 10.8 Hz, *J*= 5.8 Hz), 3.78 (s, 3H), 6.8-7.4 (m, 4H).

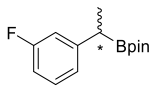
Ethyl 3-((diphenylphosphoryl)oxy)-3-(p-tolyl)propanoate.[31a] 

Enantiomeric excess determined by HPLC using Chiralcel AD (hexane/2-propanol=90/10, 0.5 mL/min, 220 nm). t_R = 24.1 min (*R*); t_R 32.3 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.85 (t, 3H, *J* = 7.2 Hz), 1.85 (m, 1H), 2.08 (m, 1H),3.95 (m, 2H), 5.34 (m, 1H), 7.2-7.9 (m, 14H).

(3-Methylbutan-2-yl)benzene.[17i] 
Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 20.9 min (*S*); t_R 22.4 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.76 (d, 3H, *J*= 7.6 Hz), 0.92 (d, 3H, *J*= 7.6 Hz), 1.23 (d, 3H, *J*= 6.8 Hz), 1.79 (m, 1H), 2.42 (m, 1H), 7.1-7.3 (m, 5H).

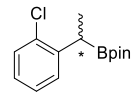
4,4,5,5-Tetramethyl-2-(1-(4-(trifluoromethyl)phenyl)ethyl)-1,3,2-dioxaborolane. 

Enantiomeric excess were determined after oxidation of the pinacolborane derivative to the corresponding alcohol using sodium perborate monohydrate (75 mg, 0.75 mmol) in a THF/H_2O solution (1:1, 4 mL).[60] Enantiomeric excess determined by GC using Chiralsil-Dex CB column (100 kPa H_2, 130 °C for 15 min, 10 °C/min, to 180 °C). t_R 3.1 min (*R*); t_R 3.4 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.21 (s, 6H), 1.23 (s, 6H), 1.35 (d, 3H, *J*= 7.2 Hz), 2.51 (q, 1H, *J*= 7.2 Hz), 7.29 (d, 1H, *J*= 6.8 Hz), 7.51 (d, 1H, *J*= 6.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 16.7, 24.5, 24.6, 83.5, 125.1 (d, *J*= 7.6 Hz), 127.9, 149.2.

2-(1-(3-Fluorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. 

Enantiomeric excess were determined after oxidation of the pinacolborane derivative to the corresponding alcohol using sodium perborate monohydrate (75 mg, 0.75 mmol) in a THF/H_2O solution (1:1, 4 mL).[61] Enantiomeric excess determined by GC using Chiralsil-Dex CB column (100 kPa H_2, 110 °C for 15 min, 10 °C/min, to 180 °C). t_R 5.5 min (*R*); t_R 5.9min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.21 (s, 6H), 1.23 (s, 6H), 1.34 (d, 3H, *J*= 7.2 Hz), 2.42 (q, 1H, *J*= 7.2 Hz), 6.82 (m, 1H), 6.93 (m, 1H), 6.97 (m, 1H), 7.19 (m, 1H). ^{13}C NMR ($CDCl_3$), δ: 15.3, 24.6, 24.8, 83.4, 126.4, 126.8, 128.8, 129.1, 133.8, 142.8.

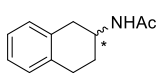
2-(1-(2-Chlorophenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Enantiomeric excess were determined after oxidation of the pinacolborane derivative to the corresponding alcohol using sodium perborate monohydrate (75 mg, 0.75 mmol) in a THF/H_2O solution (1:1, 4 mL).[62] Enantiomeric excess determined by GC using Chiralsil-Dex CB column (100 kPa H_2, 130 °C for 15 min, 10 °C/min, to 180 °C). t_R 5.6 min (*R*); t_R 6.5 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.23 (s, 12H), 1.37 (d, 3H, *J*= 7.2 Hz), 2.74 (q, 1H, *J*= 7.2 Hz), 7.09 (m, 1H), 7.19 (m, 1H), 7.06 (m, 1H), 7.12 (m, 1H).



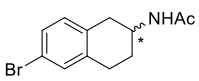
3.2.4.7. General procedure for the hydrogenation of cyclic β-enamides S56-S62

The enamide (0.25 mmol) and the corresponding catalyst precursor [M(cod)(**L**)]X (M= Rh, X= BF_4 or M= Ir, X= BAr_F; 1 mol%) were dissolved in in the corresponding solvent CH_2Cl_2 or PC (1 mL) and placed in a high-pressure autoclave, which was purged four times with hydrogen. It was then pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short celite plug. Conversions were determined by ^{1}H NMR and enantiomeric excesses by HPLC.

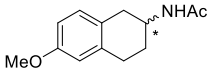
N-(1,2,3,4-Tetrahydronaphthalen-2-yl)acetamide.[11j] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (80% hexane/2-propanol, flow 1 mL/min). t_R 5.7 min (*R*); t_R 6.6 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.70-1.85 (m, 1H, CH_2), 1.98 (s, 3H, CH_3, NAc), 2.0-2.1 (m, 1H, CH_2), 2.64 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 2.83-2.91 (m, 2H, CH_2), 3.11 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 4.28 (m, 1H, CH-N), 5.62 (bs, 1H, NH), 7.04-7.14 (m, 4H, CH=).



N-(6-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide.[11j] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (80% hexane/2-propanol, flow 1 mL/min). t_R 5.8 min (*R*); t_R 6.6 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.75 (m, 1H, CH_2), 1.98 (s, 3H, CH_3, NAc), 2.02 (m, 1H, CH_2), 2.56 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 2.86 (m, 2H, CH_2), 3.07 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 4.26 (m, 1H, CH-N), 5.52 (bs, 1H, NH), 6.92 (d, 1H, CH=, *J*= 8.0 Hz), 6.73 (m, 2H, CH=).

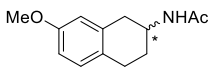


N-(6-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide.[11j] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (80% hexane/2-propanol, flow 1 mL/min). t_R 8.4 min (*R*); t_R 11.2 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.79 (m, 1H, CH_2), 1.98 (s, 3H, CH_3, NAc), 2.03 (m, 1H, CH_2), 2.57 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 2.85 (m, 2H, CH_2), 3.05

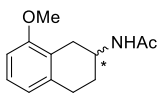


(dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 3.78 (s, 3H, CH_3, OMe), 4.28 (m, 1H, CH-N), 5.51 (bs, 1H, NH), 6.64 (d, 1H, CH=, *J*= 8.0 Hz), 6.77 (dd, 1H, CH=, *J*= 8.0 Hz, *J*= 2.6 Hz), 6.97 (d, 1H, CH=, *J*= 8.0 Hz).

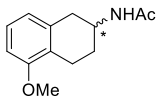
N-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide.[55] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (80% hexane/2-propanol, flow 1 mL/min). t_R 7.7 min (*R*); t_R 10.9 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.80 (m, 1H, CH_2), 1.98 (s, 3H, CH_3, NAc), 2.00 (m, 1H, CH_2), 2.63 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 2.80 (m, 2H, CH_2), 3.10 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 3.78 (s, 3H, CH_3, OMe), 4.29 (m, 1H, CH-N), 5.58 (bs, 1H, NH), 6.59 (d, 1H, CH=, *J*= 2.6 Hz), 6.72 (dd, 1H, CH=, *J*= 8.0 Hz, *J*= 2.6 Hz), 7.01 (d, 1H, CH=, *J*= 8.0 Hz).



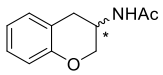
N-(8-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide.[11j] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (80% hexane/2-propanol, flow 1 mL/min). t_R 6.7 min (*S*); t_R 7.6 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.78 (m, 1H, CH_2), 1.99 (s, 3H, CH_3, NAc), 2.01 (m, 1H, CH_2), 2.43 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 2.84 (m, 2H, CH_2), 3.07 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 3.80 (s, 3H, CH_3, OMe), 4.26 (m, 1H, CH-N), 5.51 (bs, 1H, NH), 6.67 (d, 1H, CH=, *J*= 8.0 Hz), 6.72 (d, 1H, CH=, *J*= 8.0 Hz), 7.12 (t, 1H, CH=, *J*= 8.0 Hz).



N-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide.[11i] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (80% hexane/2-propanol, flow 1 mL/min). t_R 6.9 min (*R*); t_R 7.8 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.79 (m, 1H, CH_2), 1.98 (s, 3H, CH_3, NAc), 2.01 (m, 1H, CH_2), 2.65 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 2.77 (m, 2H, CH_2), 3.09 (dd, 1H, CH_2, *J*= 16.0 Hz, *J*= 8.0 Hz), 3.82 (s, 3H, CH_3, OMe), 4.28 (m, 1H, CH-N), 5.54 (bs, 1H, NH), 6.67 (d, 2H, CH=, *J*= 8.0 Hz), 7.11 (t, 1H, CH=, *J*= 8.0 Hz).



N-(Chroman-3-yl)acetamide.[11f] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (95% hexane/2-propanol, flow 1 mL/min). t_R 37.4 min (*R*); t_R 40.1 min (*S*). Mp: 76.5-78.9 °C. $[\alpha]_D^{20}$= -41.2 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.96 (s, 3H, CH_3, NAc), 2.75 (m, 1H, CH-O), 3.12 (m, 1H, CH-O), 4.08 (m, 1H, CH_2), 4.18 (m, 1H, CH_2), 4.49 (m, 1H, CH-N), 5.89 (bs, 1H, NH), 6.85 (d, 1H, CH=, *J*= 8.0 Hz), 6.91 (t, 1H, CH=, *J*= 8.0 Hz), 7.05 (d, 1H, CH=, *J*= 8.0 Hz), 7.14 (t, 1H, CH=, *J*= 8.0 Hz).



3.2.5. Acknowledgements

Financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P) and European Regional Development Fund (A EI/FEDER, UE), the

Catalan Government (2014SGR670) and the ICREA Foundation (ICREA Academia award to M.D.) is gratefully acknowledged.

3.2.6. References

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[22] Ligands **L7**-**L9b** have been tested in the Ir-hydrogenation of β-enamides (See Ref. 13). The new ligands **L7**-**L8a**, **c**-**g** and **L9a**-**g** are variations of them that include a bulky ^{t}Bu group in the oxazoline and new biaryl phosphite groups with different substituents and configurations. .

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[29] The hydrogenation of **S16**-**S21** yields products with opposite configuration than those achieved with the other *E*-trisubstituted olefins studied (i.e., **S1**-**S3**). This behavior has been observed previously and is attributed to the strong polaritzation of the double bond. See ref. 15h. .

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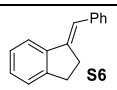
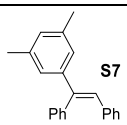
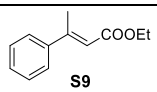
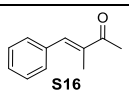
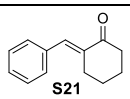
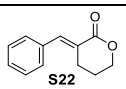
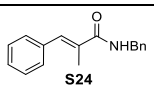
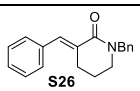
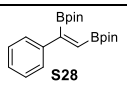
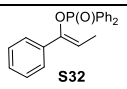
3.2.7. Supporting Information

3.2.7.1. Table SI.1. Complete series of results for the asymmetric hydrogenation of trisubstituted olefins using [Ir(cod)(L)]BAr$_F$[a]

		 S6	 S7	 S9	 S16	 S21
Entry	L	% ee[b]	% ee[b]	% ee[b]	% ee[b]	% ee[b]
1	**L3a**	81 (*R*)	45 (-)	97 (*R*)	18 (*S*)	21 (*S*)
2	**L3b**	40 (*S*)	66 (-)	10 (*S*)	20 (*R*)	21 (*R*)
3	**L3c**	77 (*R*)	10 (-)	98 (*R*)	17 (*S*)	18 (*S*)
4	**L3d**	48 (*S*)	63 (-)	11 (*S*)	18 (*R*)	15 (*R*)
5	**L3e**	87 (*R*)	9 (-)	97 (*R*)	16 (*S*)	19 (*S*)
6	**L3f**	43 (*S*)	67 (-)	9 (*S*)	21 (*R*)	19 (*R*)
7	**L3g**	91 (*R*)	10 (-)	97 (*R*)	20 (*S*)	18 (*S*)
8	**L4a**	31 (*R*)	14 (-)	69 (*R*)	10 (*S*)	19 (*S*)
9	**L5a**	40 (*R*)	44 (-)	98 (*R*)	4 (*S*)	14 (*S*)
10	**L5b**	51 (*S*)	71 (-)	21 (*S*)	22 (*R*)	16 (*R*)
11	**L5c**	80 (*R*)	15 (-)	96 (*R*)	19 (*S*)	26 (*S*)
12	**L6a**	11 (*S*)	21 (-)	80 (*R*)	35 (*S*)	28 (*S*)
13	**L6b**	20 (*R*)	65 (-)	34 (*S*)	16 (*R*)	11 (*R*)
14	**L6c**	18 (*S*)	5 (-)	28 (*R*)	11 (*S*)	9 (*S*)
15	**L7a**	20 (*R*)	78 (-)	33 (*R*)	87 (*R*)	89 (*R*)
16	**L7b**	71 (*R*)	97 (-)	74 (*R*)	94 (*R*)	91 (*R*)
17	**L7c**	61 (*S*)	11 (-)	50 (*S*)	96 (*R*)	96 (*R*)
18	**L8a**	31 (*R*)	54 (-)	66 (*R*)	57 (*R*)	60 (*R*)
19	**L8b**	44 (*R*)	85 (-)	81 (*R*)	18 (*R*)	21 (*R*)
20	**L8c**	39 (*S*)	6 (-)	48 (*S*)	84 (*R*)	87 (*R*)
21	**L9a**	27 (*R*)	21 (-)	20(*S*)	29 (*R*)	30 (*R*)
22	**L9b**	21 (*S*)	34 (-)	78 (*R*)	11 (*R*)	16 (*R*)
23	**L9c**	19 (*R*)	4 (-)	48 (*S*)	6 (*R*)	20 (*R*)

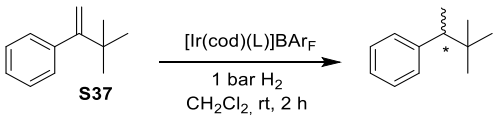
[a] Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 50 bar H_2, 4 h or 24 h. [b] Enantiomeric excesses measured by chiral GC or HPLC.

3.2.7.1. Table SI.1. Complete series of results for the asymmetric hydrogenation of trisubstituted olefins using [Ir(cod)(L)]BAr_F (continuation)[a]

		 S22	 S24	 S26	 S28	 S32
Entry	L	% ee[b]	% ee[b]	% ee[b]	% ee[b]	% ee[b]
1	**L3a**	28 (*S*)	8 (*S*)	13 (*S*)	44 (*R*)	42 (*S*)
2	**L3b**	13 (*R*)	26 (*S*)	24 (*S*)	75 (*R*)	29 (*S*)
3	**L3c**	11 (*S*)	13 (*S*)	9 (*S*)	82 (*R*)	4 (*R*)
4	**L3d**	19 (*R*)	29 (*S*)	31 (*S*)	71 (*R*)	31 (*S*)
5	**L3e**	22 (*S*)	14 (*S*)	12 (*S*)	85 (*R*)	10 (*R*)
6	**L3f**	21 (*R*)	30 (*S*)	28 (*S*)	70 (*R*)	33 (*S*)
7	**L3g**	19 (*S*)	11 (*S*)	13 (*S*)	84 (*R*)	3 (*R*)
8	**L4a**	21 (*S*)	14 (*S*)	18 (*S*)	18 (*R*)	19 (*S*)
9	**L5a**	26 (*S*)	21 (*S*)	25 (*S*)	38 (*R*)	20 (*S*)
10	**L5b**	32 (*R*)	41 (*S*)	44 (*S*)	61 (*R*)	23 (*S*)
11	**L5c**	41 (*S*)	32 (*S*)	35 (*S*)	69 (*R*)	1 (*S*)
12	**L6a**	22 (*S*)	12 (*S*)	15 (*S*)	17 (*S*)	12 (*R*)
13	**L6b**	35 (*R*)	10 (*S*)	11 (*S*)	21 (*R*)	4 (*R*)
14	**L6c**	7 (*S*)	30 (*S*)	38 (*S*)	19 (*S*)	2 (*S*)
15	**L7a**	87 (*R*)	81 (*R*)	84 (*R*)	36 (*S*)	73 (*R*)
16	**L7b**	93 (*R*)	26 (*S*)	32 (*S*)	64 (*S*)	95 (*R*)
17	**L7c**	>99 (*R*)	>99 (*R*)	>99 (*R*)	>99 (*S*)	6 (*S*)
18	**L8a**	71 (*R*)	32 (*R*)	37 (*R*)	82 (*R*)	40 (*R*)
19	**L8b**	33 (*R*)	50 (*S*)	56 (*S*)	75 (*S*)	89 (*R*)
20	**L8c**	94 (*R*)	97 (*R*)	98 (*R*)	36 (*R*)	4 (*R*)
21	**L9a**	21 (*R*)	14 (*S*)	21 (*S*)	14 (*S*)	20 (*S*)
22	**L9b**	19 (*R*)	37 (*R*)	33 (*R*)	33 (*R*)	19 (*S*)
23	**L9c**	14 (*R*)	21 (*S*)	17 (*S*)	21 (*S*)	4 (*R*)

[a] Reaction conditions: 2 mol % catalyst precursor, CH_2Cl_2 as solvent, 50 bar H_2, 4 h or 24 h. [b] Enantiomeric excesses measured by chiral GC or HPLC.

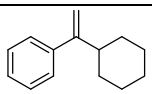
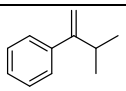
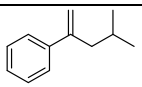
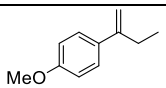
3.2.7.2. Table SI.2. Complete series of results for the asymmetric hydrogenation of model disubstituted olefin S37 using [Ir(cod)(L)]BAr_F



Entry	Ligand	% Conv[b]	% ee[c]
1	**L3a**	100	88 (*S*)
2	**L3b**	100	61 (*S*)
3	**L3c**	100	90 (*S*)
4	**L3d**	100	65 (*S*)
5	**L3e**	100	84 (*S*)
6	**L3f**	100	66 (*S*)
7	**L3g**	100	82 (*S*)
8	**L4a**	100	84 (*S*)
9	**L5a**	100	98 (*S*)
10	**L5b**	100	97 (*S*)
11	**L5c**	100	97 (*S*)
12	**L6a**	100	84 (*S*)
13	**L6b**	100	66 (*S*)
14	**L6c**	100	93 (*S*)
15	**L7a**	100	78 (*S*)
16	**L7b**	100	84 (*S*)
17	**L7c**	100	54 (*R*)
18	**L8a**	100	96 (*S*)
19	**L8b**	100	93 (*S*)
20	**L8c**	100	57 (*S*)
21	**L9a**	100	90 (*S*)
22	**L9b**	87	66 (*S*)
23	**L9c**	42	15 (*S*)

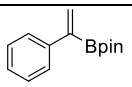
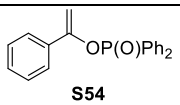
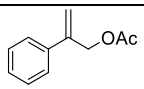
[a] Reactions carried out at room temperature by using 0.5 mmol of substrate and 0.5 mol% of Ir-catalyst precursor at 1 bar of H_2 using dichloromethane (2 mL) as solvent. [b] Conversion measured by ^{1}H-NMR after 2 h. [c] Enantiomeric excess determined by GC.

3.2.7.3. Table SI.3. Complete series of results for the asymmetric hydrogenation of disubstituted olefins using [Ir(cod)(L)]BAr$_F$[a]

		 S45	 S46	 S47	 S48
Entry	L	% ee[b]	% ee[b]	% ee[b]	% ee[b]
1	**L3a**	61 (*S*)	54 (*S*)	59 (*S*)	41 (*S*)
2	**L3b**	81 (*S*)	78 (*S*)	73 (*S*)	76 (*S*)
3	**L3c**	35 (*S*)	42 (*S*)	25 (*S*)	3 (*R*)
4	**L3d**	79 (*S*)	77 (*S*)	78 (*S*)	77 (*S*)
5	**L3e**	33 (*S*)	40 (*S*)	41 (*S*)	2 (*R*)
6	**L3f**	72 (*S*)	79 (*S*)	77 (*S*)	79 (*S*)
7	**L3g**	34 (*S*)	38 (*S*)	39 (*S*)	3 (*R*)
8	**L4a**	42 (*S*)	43 (*S*)	46 (*S*)	53 (*S*)
9	**L5a**	84 (*S*)	83 (*S*)	84 (*S*)	73 (*S*)
10	**L5b**	83 (*S*)	89 (*S*)	89 (*S*)	80 (*S*)
11	**L5c**	84 (*S*)	81 (*S*)	81 (*S*)	33 (*S*)
12	**L6a**	39 (*S*)	64 (*S*)	41 (*S*)	43 (*S*)
13	**L6b**	41 (*S*)	59 (*S*)	60 (*S*)	35 (*S*)
14	**L6c**	14 (*S*)	45 (*S*)	14 (*S*)	41 (*S*)
15	**L7a**	61 (*S*)	74 (*S*)	71 (*S*)	28 (*S*)
16	**L7b**	64 (*S*)	79 (*S*)	77 (*S*)	55 (*S*)
17	**L7c**	21 (*R*)	42 (*R*)	43 (*R*)	60 (*R*)
18	**L8a**	91 (*S*)	91 (*S*)	78 (*S*)	79 (*S*)
19	**L8b**	81 (*S*)	79 (*S*)	80 (*S*)	83 (*S*)
20	**L8c**	33 (*S*)	41 (*S*)	40 (*S*)	50 (*S*)
21	**L9a**	80 (*S*)	61 (*S*)	70 (*S*)	41 (*S*)
22	**L9b**	61 (*S*)	59 (*S*)	66 (*S*)	42 (*S*)
23	**L9c**	40 (*S*)	28 (*S*)	38 (*S*)	38 (*S*)

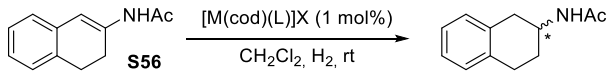
[a] Reaction conditions: 1 mol % catalyst precursor, CH_2Cl_2 as solvent, 1 bar H_2, 4 h. [b] Enantiomeric excesses measured by chiral GC or HPLC.

3.2.7.3. Table SI.3. Complete series of results for the asymmetric hydrogenation of disubstituted olefins using [Ir(cod)(L)]BAr_F (continuation)[a]

		 **S49**	 **S54**	 **S55**
Entry	L	% ee[b]	% ee[b]	% ee[b]
1	**L3a**	61 (*S*)	74 (*S*)	78 (*S*)
2	**L3b**	23 (*S*)	90 (*S*)	61 (*S*)
3	**L3c**	24 (*S*)	4 (*S*)	79 (*S*)
4	**L3d**	33 (*S*)	89 (*S*)	63 (*S*)
5	**L3e**	31 (*S*)	4 (*S*)	80 (*S*)
6	**L3f**	28 (*S*)	89 (*S*)	62 (*S*)
7	**L3g**	27 (*S*)	6 (*S*)	80 (*S*)
8	**L4a**	16 (*S*)	41 (*S*)	-
9	**L5a**	76 (*S*)	18 (*R*)	95 (*S*)
10	**L5b**	60 (*S*)	67 (*S*)	84 (*S*)
11	**L5c**	25 (*R*)	42 (*R*)	94 (*S*)
12	**L6a**	90 (*S*)	13 (*S*)	56 (*S*)
13	**L6b**	78 (*S*)	23 (*S*)	43 (*S*)
14	**L6c**	86 (*S*)	18 (*S*)	74 (*S*)
15	**L7a**	41 (*S*)	1 (*S*)	81 (*S*)
16	**L7b**	94 (*S*)	92 (*S*)	82 (*S*)
17	**L7c**	66 (*S*)	81 (*R*)	45 (*R*)
18	**L8a**	71 (*S*)	32 (*S*)	86 (*S*)
19	**L8b**	80 (*S*)	82 (*S*)	87 (*S*)
20	**L8c**	66 (*S*)	20 (*R*)	67 (*S*)
21	**L9a**	45 (*S*)	16 (*S*)	57 (*S*)
22	**L9b**	20 (*S*)	43 (*S*)	54 (*S*)
23	**L9c**	30 (*S*)	22 (*R*)	19 (*S*)

[a] Reaction conditions: 1 mol % catalyst precursor, CH_2Cl_2 as solvent, 1 bar H_2, 4 h. [b] Enantiomeric excesses measured by chiral GC or HPLC.

3.2.7.4. Table SI.4. Results for the Ir- and Rh-catalyzed hydrogenation of cyclic β-enamide S56[a]



		[Ir(cod)(L)]BAr$_F$		[Rh(cod)$_2$]BF$_4$/L	
Entry	**L**	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L3a**	75	30 (*S*)[d]	100	< 2
2	**L3b**	80	92 (*S*)[d]	100	27 (*R*)
3	**L3c**	56	50 (*R*)[d]	100	21 (*S*)
4	**L3d**	74	90 (*S*)	100	19 (*R*)
5	**L3f**	82	91 (*S*)	100	26 (*R*)
6	**L5a**	80	34 (*S*)[d]	100	5 (*S*)
7	**L5b**	95	96 (*S*)[d]	100	36 (*R*)
8	**L5c**	65	54 (*R*)[d]	100	34 (*S*)
9	**L6b**	30	30 (*S*)[d]	100	18 (*R*)
10	**L7a**	84	29 (*S*)	100	41 (*R*)
11	**L7b**	100	98 (*S*)[d]	100	94 (*R*)
12	**L7c**	59	61 (*R*)	100	86 (*S*)
13	**L8b**	100	98 (*S*)[d]	100	94 (*R*)
14	**L8d**	100	98 (*S*)	100	93 (*R*)
15	**L8f**	100	98 (*S*)	100	94 (*R*)
16	**L9a**	48	3 (*S*)	100	11 (*R*)
17	**L9b**	50	6 (*S*)	100	35 (*R*)
18	**L9c**	37	21 (*R*)	100	29 (*S*)

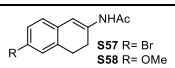
[a] Reactions carried out using 0.5 mmol of substrate, 1 mol% of catalyst precursor using dichloromethane (2 mL) as solvent and at room temperature and 50 bar of H_2 for Ir-catalysts or at 5 °C and 30 bar of H_2 for Rh-catalysts. [b] Conversion measured by ^{1}H-NMR after 20 h for Ir-catalysts and 36 h for Rh-catalysts. [c] Enantiomeric excess determined by HPLC. [d] Data from reference [Magre, M.; Pàmies, O.; Diéguez, M. *ACS Catal.* **2016**, *6*, 5186].

3.2.7.5. Table SI.5. Asymmetric Rh-catalyzed hydrogenation of S56 using ligand L7b. Optimization studies[a]

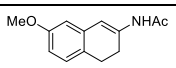
Entry	Catalyst precursor	P_{H2}[b]	T[c]	% Conv (h)[d]	% ee[e]
1	$[Rh(cod)_2]BF_4$	30	5	100 (36)	94 (*R*)
2	$[Rh(cod)_2]BF_4$	10	5	100 (48)	94 (*R*)
3	$[Rh(cod)_2]BF_4$	30	-5	87 (48)	92 (*R*)
4	$[Rh(cod)_2]BF_4$	30	25	100 (12)	88 (*R*)
5	$[Rh(cod)_2]BF_4$	30	40	100 (6)	82 (*R*)
6	[Rh(cod)(**L7b**)]BF_4	30	5	100 (36)	94 (*R*)

[a] Reactions conditions: Catalyst precursor (1 mol%), ligand (1 mol%), **S56** (0.5 mmol), CH_2Cl_2 (2 mL). [b] Hydrogen pressure in bars. [c] Reaction temperature in °C. [d] Conversion determined by ^1H NMR. [e] Enantiomeric excesses determined by chiral HPLC.

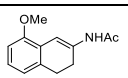
3.2.7.6. Table SI.6. Complete series of results for the asymmetric hydrogenation of cyclic β-enamides using [Rh(cod)(L)]BF_4



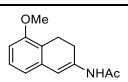
S57 **S58**



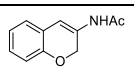
S59



S60



S61



S62

Entry	L	% ee	% ee	% ee[b]	% ee[b]	% ee[b]	% ee[b]
1	**L3a**	< 2	< 2	4 (*S*)	3 (*S*)	4 (*S*)	< 2
2	**L3b**	32 (*R*)	34 (*R*)	32 (*R*)	29 (*R*)	32 (*R*)	29 (*S*)
3	**L3c**	29 (*S*)	30 (*S*)	31 (*S*)	27 (*S*)	30 (*S*)	27 (*R*)
4	**L3d**	20 (*R*)	22 (*R*)	24 (*R*)	26 (*R*)	24 (*R*)	24 (*S*)
5	**L3f**	29 (*R*)	23 (*R*)	21 (*R*)	22 (*R*)	19 (*R*)	24 (*S*)
6	**L4a**	5 (*S*)	3 (*S*)	3 (*S*)	4 (*S*)	3 (*S*)	3 (*R*)
7	**L5a**	4 (*S*)	< 2	3 (*R*)	3 (*R*)	< 2	3 (*S*)
8	**L5b**	40 (*R*)	43 (*R*)	39 (*R*)	42 (*R*)	41 (*R*)	42 (*S*)
9	**L5c**	38 (*S*)	41 (*S*)	38 (*S*)	40 (*S*)	36 (*S*)	39 (*R*)
10	**L6b**	21 (*R*)	23 (*R*)	22 (*R*)	26 (*R*)	22 (*R*)	26 (*S*)
11	**L7a**	39 (*R*)	37 (*R*)	35 (*R*)	41 (*R*)	38 (*R*)	41 (*S*)
12	**L7b**	96 (*R*)	92 (*R*)	89 (*R*)	88 (*R*)	93 (*R*)	91 (*S*)
13	**L7c**	87 (*S*)	84 (*S*)	86 (*S*)	83 (*S*)	88 (*S*)	87 (*R*)
14	**L8b**	96 (*R*)	92 (*R*)	89 (*R*)	88 (*R*)	93 (*R*)	91 (*S*)
15	**L8d**	96 (*R*)	92 (*R*)	88 (*R*)	88 (*R*)	92 (*R*)	91 (*S*)
16	**L8f**	95 (*R*)	92 (*R*)	87 (*R*)	88 (*R*)	93 (*R*)	91 (*S*)
17	**L9b**	29 (*R*)	27 (*R*)	24 (*R*)	21 (*R*)	31 (*R*)	24 (*S*)

[a] Reaction conditions: Reactions conditions: catalyst precursor (1 mol%), substrate (0.5 mmol), CH_2Cl_2 (2 mL), 10 bar H_2, 5 °C, 50 h. [b] enantiomeric excess measured by chiral HPLC.

UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull

3.3. Asymmetric hydrogenation of di-, tri- and tetrasubstituted minimally functionalized olefins and cyclic β-enamides with easily accessible Ir-P,oxazoline catalysts

Biosca, M.; Magre, M.; Pàmies, O.; Diéguez, M. *Manuscript submitted to ACS Catal.*

Abstract: We have developed a family of Ir-P,oxazoline catalysts for asymmetric hydrogenation. The new catalysts, with a simple modular architecture, have shown an unprecedented high tolerance to the olefin geometry and substitution pattern, and to the presence of several neighboring polar groups. Thus, they were able to successfully hydrogenate di-, tri- and tetrasubstituted minimally functionalized olefins (ee's up to 99%). The excellent catalytic performance was also extended to the hydrogenation of cyclic β-enamides.

3.3.1. Introduction

Asymmetric hydrogenation of olefins is a well-known approach to introduce chirality into target molecules. It has perfect atom economy, uses low catalyst loading and it is operationally simple.[1] The asymmetric hydrogenation of functionalized olefins has been thoroughly studied for decades and can now be considered a mature field.[2] Rh- and Ru-catalysts, mostly based on diphosphine ligands have performed the best. Their performance is critically influenced by the substrate coordinative groups that guide the chiral transfer to the product. When those coordinative groups are absent (minimally functionalized olefins), the introduction of chirality becomes a much greater challenge and, in this field, Ir-catalysts have performed the best.[3] The best catalysts have two characteristics in common: (i) they contain P,N-ligands and (ii) their optimal structure is highly dependent on the geometry and substitution pattern of the olefin.[3] The consequence is that for each particular olefin type a different ligand family needs to be developed. Figure 3.3.1 shows a selection of the most efficient chiral ligands and illustrates how different the ligand motifs need to be to achieve high enantioselectivity for each particular olefin substitution pattern. It is also important to notice that catalysis has been developed in different grades for each olefin substitution pattern.[3] The most successful cases have been reported for trisubstituted olefins[3] and, to a less extend, for disubstituted[4]. The asymmetric hydrogenation of tetrasubstituted unfunctionalized substrates is still underdeveloped. Only four publications have reported high catalytic performance for certain substrates,[5] being the Pfaltz catalysts the ones that work under milder conditions and are applicable to more substrates. The discovery of a family of catalysts with a wide substrate scope remains a central task in asymmetric hydrogenation of unfunctionalized olefins. A desired additional condition is that the

catalyst family should be synthesized from available starting materials and be easy to handle.

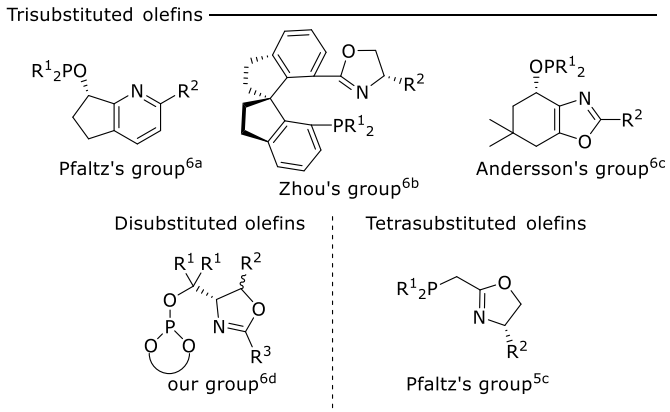


Figure 3.3.1. Representative ligands developed for the Ir-catalyzed asymmetric hydrogenation of di-, tri- and tetrasubstituted minimally functionalized olefins.[5c,6]

Here we report the first P,N-ligand family (**L10**-**L16a**-**h**, Figure 3.3.2) that performs well for the Ir-catalyzed asymmetric hydrogenation of different types of unfunctionalized olefins. From a common skeleton, the right choice of either a phosphite group or phosphinite group results in ligands that are suitable for di-, tri- and tetrasubstituted unfunctionalized olefins. The "ligand family" concept helps to reduce the time dedicated to ligand design and preparation and facilitates the discovery of the optimal ligand for a wide range of substrates. This family has also been successfully applied to the asymmetric hydrogenation of challenging functionalized cyclic β-enamides.[7]

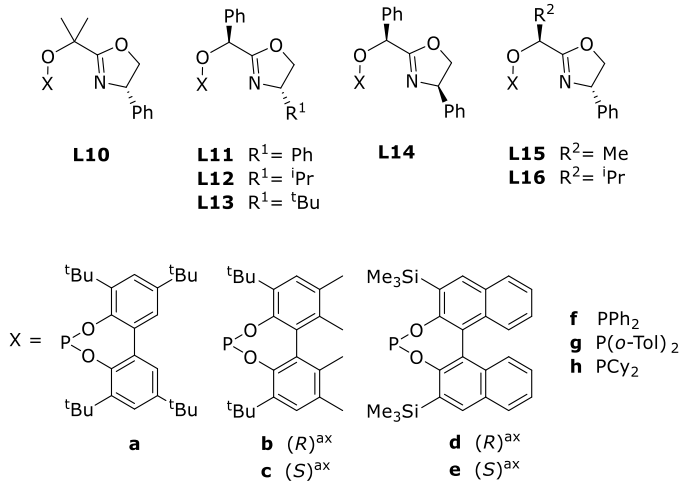
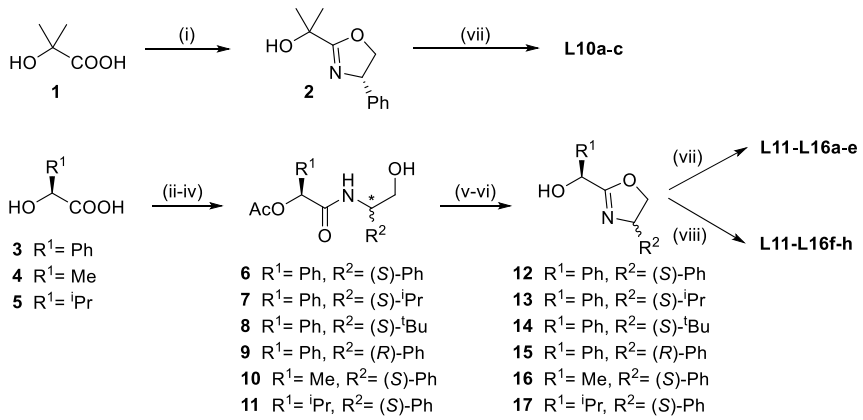


Figure 3.3.2. Phosphite/phosphinite-oxazoline ligands **L10**-**L16a**-**h**.

3.3.2. Results and Discussion

3.3.2.1. Synthesis of ligands

The synthesis of phosphite/phosphinite-oxazoline ligands **L10**-**L16a**-**h** is shown in Scheme 3.3.1.[8] Phosphite-oxazoline ligands **L10**-**L16a**-**h** are easily accessible by coupling hydroxyl-oxazoline intermediates **2** and **12**-**17** with the desired phosphorochloridites ($ClP(OR)_2$; $(OR)_2$= **a**-**e**; step vii). Similarly, phosphinite-oxazoline ligands **L11**-**L16f**-**h** were synthetized by treating the corresponding hydroxyl-oxazoline **12**-**13** and **15** with one equivalent of the corresponding chlorophosphine ($ClPR_2$, R= **f**-**h**; step viii). Hydroxyl-oxazolines are straightforwardly made in multigram scale from cheap α-hydroxy acids **1**, **3**-**5**, these α-hydroxy acids have been chosen because they incorporate the desired diversity in the substituents and configuration at the alkyl backbone chain.



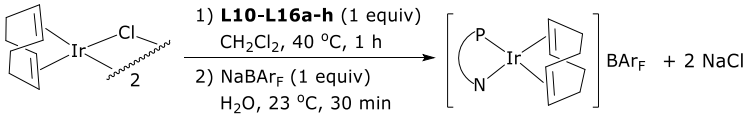
Scheme 3.3.1. Synthesis of new phosphite/phosphinite-oxazoline ligans **L10**-**L16a**-**h**. (i) (*S*)-phenylglycinol, toluene, reflux (ii) acetylchloride, rt, 2 h; (iii) $SOCl_2$, DCM, rt, 2 h;; (iv) amino alcohol, NEt_3, CH_2Cl_2, rt, 5 h; (v) DAST, K_2CO_3, CH_2Cl_2, -78 ºC to rt, 3 h; (vi) NaOH (aq), EtOH, 0 ºC, 2 h; (vii) $ClP(OR)_2$; $(OR)_2$= **a**-**f**, Py, toluene, 16 h; (viii) $ClPR_2$; R=**g**-**i**, NEt_3, DMAP cat., toluene, rt, 20 min.

α-Hydroxyisobutyric acid **1** was condensed with (*S*)-phenylglycinol to provide hydroxyl-oxazoline **2**.[9] For the synthesis of hydroxyl-oxazoline **12**-**17**, the alcohol group in the α-hydroxy acids **3**-**5** was protected using acetylchloride (step ii) and then these acids were transformed to the corresponding acid chlorides (step iii).[10] The synthesis continues with the coupling of these acid chlorides with the desired chiral amino alcohol to afford the corresponding amides **6**-**11** (step iv).[10a] At this stage the desired diversity in the substituents and configuration of the oxazoline moiety is introduced. In the next step, compounds **6**-**11** were converted to the corresponding oxazoline esters in the presence of diethylaminosulfur trifluoride (DAST; step v).[10a,11] Finally, standard

deprotection of the oxazoline esters afforded the corresponding hydroxyl-oxazolines **12**-**17** (step vi).[10a,11] All ligands were stable during purification on neutral alumina under an atmosphere of argon and they were isolated as white solids or colorless oils. HRMS-ESI spectra were in agreement with the assigned structures. The ^{1}H and ^{13}C NMR spectra were as expected for these C_1 ligands. Only singlet for each compound was observed in the ^{31}P NMR spectrum.

3.3.2.2. Synthesis of Ir-catalyst precursors

The catalyst precursors were prepared by treating 0.5 equivalent of $[Ir(\mu\text{-}Cl)(cod)]_2$ with an equimolar amount of the appropriate phosphite/phosphinite-oxazoline ligand (**L10**-**L16a**-**h**) in dichloromethane at 40 ºC for 1 h. The Cl^-/BAr_F^- counterion exchange was then performed by reaction with sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate ($NaBAr_F$) (1 equiv) in water (Scheme 3.3.2). The catalyst precursors were obtained in pure form as air-stable orange solids, so they were further manipulated and stored in air.



Scheme 3.3.2. Synthesis of catalyst precursors [Ir(cod)(**L10**-**L16a**-**h**)]BAr_F.

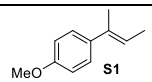
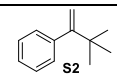
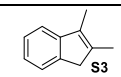
The HRMS-ESI spectra show the heaviest ions at m/z which correspond to the loss of the BAr_F anion from the molecular species. The complexes were also characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The spectral assignments, made using ^{1}H–^{1}H and ^{13}C–^{1}H correlation measurements, were as expected for these C_1-symmetric iridium complexes.

3.3.2.3. Asymmetric hydrogenation of minimally functionalized olefins

[Ir(cod)(**L10**-**L16a**-**h**)]BAr_F complexes were first evaluated in the hydrogenation of model di-, tri- and tetrasubstituted minimally functionalized alkenes (**S1**-**S3**; Table 3.3.1). For comparison, catalyst precursors were tested in the optimal reaction conditions reported in previous studies with other P,N-ligands.[3] High enantioselectivities, comparable to the best ones reported,[3] were obtained for all substrates, regardless the olefin substitution pattern. The results also reveal several trends in the obtained enantioselectivities: (i) the highest enantioselectivity in the reduction of di- and trisubstituted olefins (ee's up to 98%,) were obtained with phosphite-based ligands (e.g. **L14a** and **L15d**) while phosphinite-based ligands were required for tetrasubstituted olefins (e.g. **L12f** vs. **L12a**, ee's up to 97%), (ii) oxazolines derived from expensive *tert*-leucinol (e.g. ligands **L13**) were not needed to achieve high

ees, which is an important advantage over the most widely used P-oxazoline ligands (e.g. PHOX-derived ligands);[3] (iii) finally, for substrates **S1** and **S2**, both enantiomers of the hydrogenated products were accessible in high enantioselectivities by using diastereoisomeric ligands (e.g. 98% (*R*) for **S1** with **L14a** vs 96% (*S*) with **L11a**; or 93% (*S*) for **S2** with **L14a** vs 98 (*R*) with **L15d**).

Table 3.3.1. Ir-catalyzed asymmetric hydrogenation of model tri-, di- and tetrasubstituted minimally functionalized olefins **S1**–**S3**.[a]

	 **S1**		 **S2**		 **S3**	
P,N	Conv [%][b]	ee [%][c]	Conv [%][b]	ee [%][c]	Conv [%][b]	ee [%][c]
L10a	100	91 (*R*)	100	98 (*S*)	15[d]	29 (*S,S*)
L10d	100	24 (*R*)	100	74 (*S*)	10[d]	33 (*S,S*)
L10e	100	93 (*R*)	100	95 (*S*)	10[d]	30 (*S,S*)
L11a	100	58 (*R*)	100	96 (*S*)	39[d]	37 (*S,S*)
L11b	100	75 (*R*)	100	88 (*S*)	14[d]	29 (*S,S*)
L11c	100	67 (*S*)	100	40 (*S*)	25[d]	16 (*S,S*)
L11d	100	92 (*R*)	100	93 (*S*)	22[d]	23 (*S,S*)
L11e	100	68 (*S*)	100	42 (*S*)	36[d]	18 (*S,S*)
L11f	100	60 (*R*)	100	81 (*S*)	100	84 (*S,S*)
L11g	100	70 (*R*)	100	82 (*S*)	100	80 (*S,S*)
L12a	100	30 (*R*)	100	95 (*S*)	25[d]	82 (*S,S*)
L12b	100	64 (*R*)	100	89 (*S*)	10[d]	50 (*S,S*)
L12f	100	38 (*R*)	100	80 (*S*)	100[e]	97 (*S,S*)
L12g	100	44 (*R*)	100	84 (*S*)	100	87 (*S,S*)
L12h	100	15 (*R*)	100	54 (*S*)	100	75 (*S,S*)
L13a	100	9 (*R*)	100	97 (*S*)	5[d]	34 (*R,R*)
L13b	100	88 (*R*)	100	77 (*S*)	<5	nd[f]
L14a	100	76 (*S*)	100	98 (*R*)	50[d]	64 (*S,S*)
L14d	100	0	100	74 (*R*)	5[d]	4 (*S,S*)
L14e	100	93 (*S*)	100	92 (*R*)	24	47 (*R,R*)
L14f	100	71 (*S*)	100	85 (*R*)	100	75 (*R,R*)
L14g	100	66 (*S*)	100	83 (*R*)	100	70 (*R,R*)
L14h	100	80 (*S*)	100	85 (*R*)	100	20 (*R,R*)
L15a	100	78 (*R*)	100	92 (*S*)	15[d]	42 (*S,S*)
L15d	100	98 (*R*)	100	92 (*S*)	10[d]	25 (*S,S*)
L15e	100	40 (*S*)	100	10 (*S*)	15[d]	21 (*S,S*)
L16a	100	81 (*R*)	100	96 (*S*)	20[d]	53 (*S,S*)
L16d	100	94 (*R*)	100	91 (*S*)	13[d]	12 (*S,S*)
L16e	100	30 (*R*)	100	60 (*S*)	25[d]	30 (*S,S*)

[a] Reaction conditions: Ir-catalyst precursor (1 mol%), substrate (0.5 mmol), DCM, rt for 4 h, P_{H2}= 50 bar (for **S1** and **S3**), 1 bar (for **S2**); [b] Conversions determined by GC; [c] Enantiomeric excesses determined by chiral GC; [d] Reactions carried out for 20 h; [e] Reaction performed at 25 bar H_2; [f] Not determined.

We then performed a broad unfunctionalized substrate screening that included di-, tri- and tetrasubstituted olefins, different geometries (*E* and *Z*), and different

neighbouring polar groups. A summary of the asymmetric hydrogenation results of 53 olefins is shown in Figures 3.3.3-3.3.5 (see Supporting Information at the end of this chapter for a complete series of results). As seen previously, the best results for di- and trisubstituted olefins were achieved with phosphite-based ligands and for tetrasubstituted with phosphinite-based ligands. The other ligand parameters had a different influence depending on the substrate and had to be specifically selected to obtain high enantioselectivities.

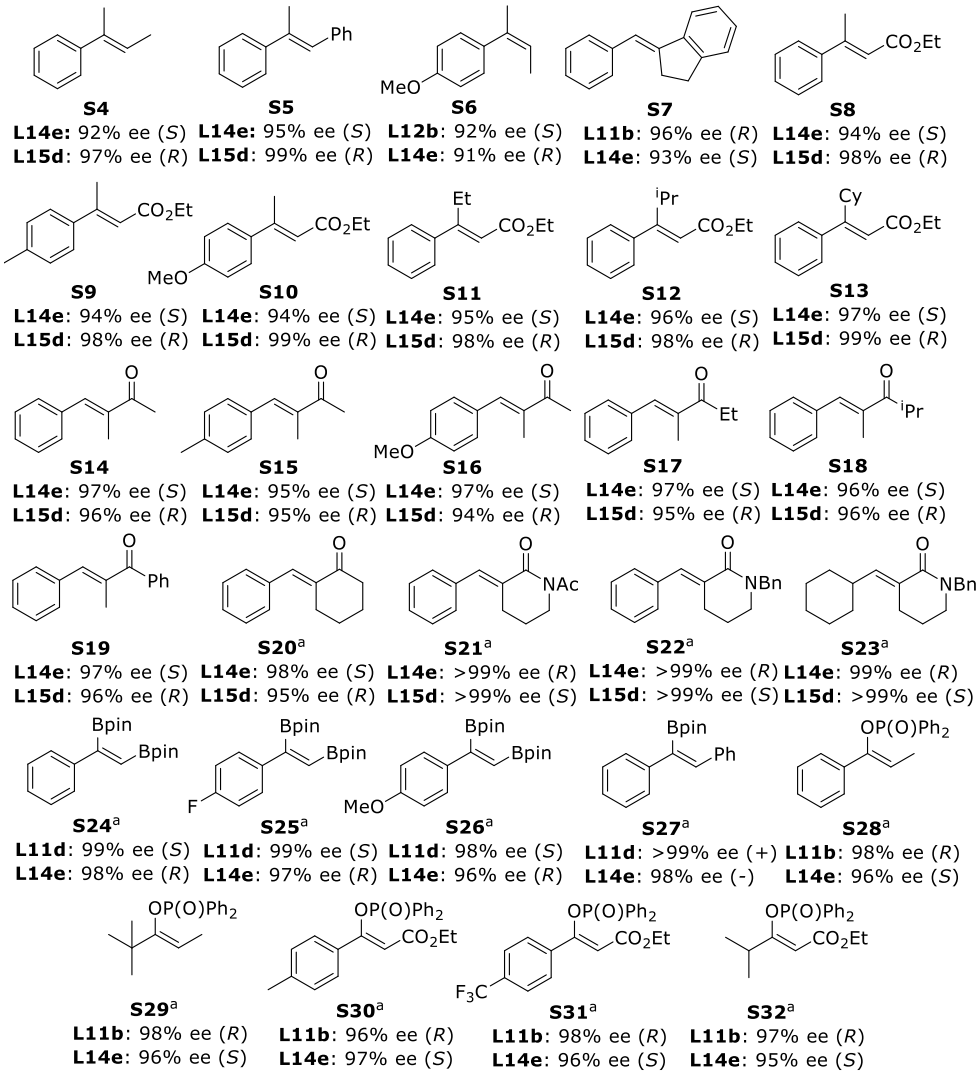


Figure 3.3.3. Selected results for asymmetric hydrogenation of a range of trisubstituted minimally functionalized olefins. Typical reaction conditions: 1 mol% of [Ir(cod)(P,N)]BAr_F, 50 bar H_2, DCM, rt for 4 h. Full conversions were achieved in all cases. [a] Reactions carried out at 50 bar H_2 for 24 h.

For the reduction of minimally unfunctionalized trisubstituted olefins, the new catalyst precursors were found to be well suited for those with *E*-geometry (**S4**-**S5**) and for those with the challenging *Z*-geometry (**S6**) and the exocyclic olefin (**S7**), obtaining in all cases both enantiomers of the reduced products. They also worked well for olefins with a variety of relevant neighbouring polar groups such as α,β-unsaturated esters, ketones and lactams, vinyl boronates and enol phosphinates (**S8**-**S32**). All the substrates were hydrogenated with excellent enantiocontrol (ee's up to >99%), comparable to the best ones reported.[3] In addition, for each type of neighbouring group, the enantioselectivities were quite independent on the electronic and steric nature of the substituents decorating such motifs. The effective hydrogenation of such a range of olefins is of great importance since their reduced products are key structural chiral units found in many high value chemicals (e.g. α- and β-chiral ketones and carboxylic acid derivatives are ubiquitous in natural products, fragrances, agrochemicals, and drugs).[12]

Our catalyst precursors also proved to be highly competent in the hydrogenation of a broad range of disubstituted olefins (**S33**-**S45**; Figure 3.3.4). Excellent enantio-selectivities were achieved (up to >99% ee) in the asymmetric hydrogenation of a series of 1,1'-disubstituted (hetero)aryl/alkyl olefins and also aryl- and alkyl-enol phosphinates. The reduction α-alkylstyrenes with less sterically demanding alkyl substituents proceeded with somewhat lower enantioselectivities, like in previous successful reports.[4,13]

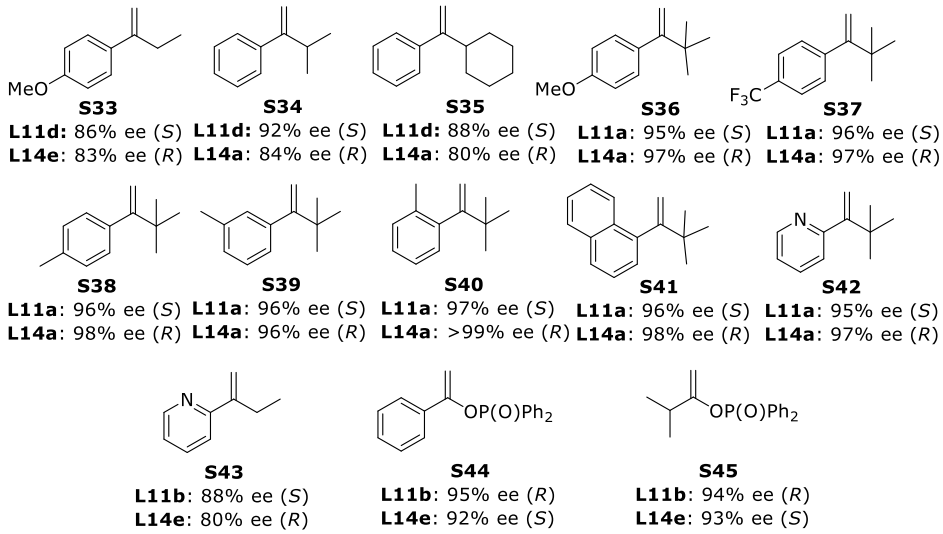
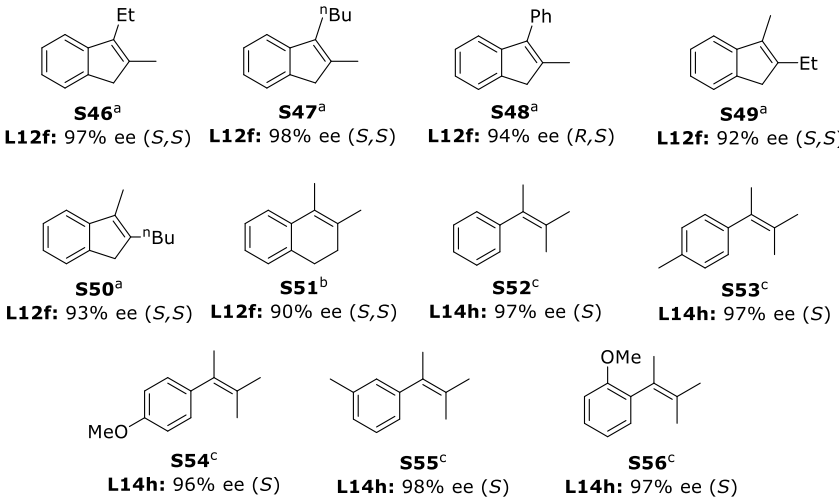


Figure 3.3.4. Selected results for asymmetric hydrogenation of a range of disubstituted minimally functionalized olefins. Typical reaction conditions: 1 mol% of [Ir(cod)(P,N)]BAr_F, 1 bar H_2, DCM, rt for 4 h. Full conversions were achieved in all cases.

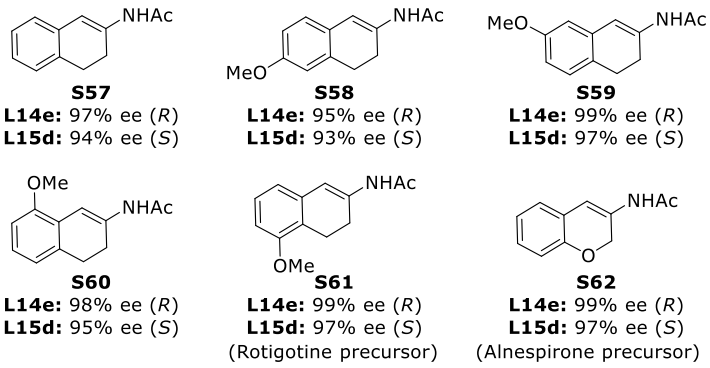
Finally, for tetrasubstituted olefins our catalyst precursors proved to be highly efficient in the reduction of several indenes (**S46**-**S50**) with different substituents at both the benzylic and vinylic position as well as substituents in the aryl ring (ee's up to 98%), under the comparable mild reactions conditions developed by Pfaltz[5c] (Figure 3.3.5). This improved previously reported results. The high enantiocontrol for the more challenging 3,4-dimehtyl-1,2-dihydronaphthalene and the acyclic tetrasubstituted olefins (**S51**-**S56**; ee's up to 98%), is even more remarkable, surpassing the best results reported so far. For acyclic substrates, only the Pfaltz's catalysts have been successful but enantioselectivity was high (97% ee) in the asymmetric hydrogenation of one substrate only. Interestingly the hydrogenation of the latter substrates can be achieved at only 1 bar of H_2.



S46[a] **L12f:** 97% ee (*S,S*)
S47[a] **L12f:** 98% ee (*S,S*)
S48[a] **L12f:** 94% ee (*R,S*)
S49[a] **L12f:** 92% ee (*S,S*)
S50[a] **L12f:** 93% ee (*S,S*)
S51[b] **L12f:** 90% ee (*S,S*)
S52[c] **L14h:** 97% ee (*S*)
S53[c] **L14h:** 97% ee (*S*)
S54[c] **L14h:** 96% ee (*S*)
S55[c] **L14h:** 98% ee (*S*)
S56[c] **L14h:** 97% ee (*S*)

Figure 3.3.5. Selected results for asymmetric hydrogenation of a range of tetrasubstituted minimally functionalized olefins. Typical reaction conditions: 1 mol% of [Ir(cod)(P,N)]BAr_F, DCM, rt. Full conversions were achieved in all cases [a] Reactions carried out at 25 bar H_2 for 24 h; [b] Reaction carried out at 75 bar H_2 for 24 h; [c] Reactions carried out at 1 bar H_2 for 24 h.

Encouraged by these remarkable results, we decided to study the asymmetric hydrogenation of cyclic β-enamides (Figure 3.3.6) which are a challenging type of functionalized olefins.[7] While the reduction of α-enamides can be carried out with good success,[2] the asymmetric hydrogenation of β-enamides remains one of the puzzling transformations, albeit the corresponding products are key units in many drugs and biologically active natural products such as Rotigotine,[14] Alnespirone[15] and Robalzotan[16]. We found that catalyst precursors with ligands **L14e** and **L15d** provided both enantiomers of the hydrogenated products in high enantioselectivities (ee's up to 99%) for a range of cyclic β-enamides, including the less studied enamides derived from 3-chromanones. These results are comparable to the best one reported in the literature.[7]



S57
L14e: 97% ee (*R*)
L15d: 94% ee (*S*)

S58
L14e: 95% ee (*R*)
L15d: 93% ee (*S*)

S59
L14e: 99% ee (*R*)
L15d: 97% ee (*S*)

S60
L14e: 98% ee (*R*)
L15d: 95% ee (*S*)

S61
L14e: 99% ee (*R*)
L15d: 97% ee (*S*)
(Rotigotine precursor)

S62
L14e: 99% ee (*R*)
L15d: 97% ee (*S*)
(Alnespirone precursor)

Figure 3.3.6. Selected hydrogenation results for the asymmetric hydrogenation of cyclic β-enamides. Typical reaction conditions: 1 mol% of [Ir(cod)(P,N)]BAr_F, 50 bar H_2, DCM, rt for 24 h. Full conversions were achieved in all cases.

3.3.3. Conclusions

We have presented the first Ir/P-oxazoline catalytic family, with a simple modular architecture, that is able to successfully hydrogenate di-, tri- and tetrasubstituted minimally functionalized olefins (ee's up to 99%). This family of catalysts has been synthesized in a few steps from inexpensive starting materials and are solid and stable in air. From a common skeleton, the right choice of either a phosphite group or phosphinite group gives ligands that are suitable for di-, tri- and also tetrasubstituted olefins (62 examples). Improving previous results reported, these catalysts are able to efficiently reduce a range of indenes and the challenging 1,2-dihydro-naphthalene (ee's up to 98%) and also a range of the most elusive acyclic olefins with unprecedented enantioselectivities (ee's up to 98%) under mild reaction conditions. The catalysts not only exhibited an unprecedented high tolerance to the geometry and steric constrains of the olefin, but they also could tolerate different functional groups very well. Thus, a broad range of olefins containing both minimally coordinative groups (e.g. α,β-unsaturated carboxylic esters, enones, lactames, vinyl boronates and enol phosphinates) and coordinative groups (the challenging β-enamides) could be hydrogenated with high levels of enantioselectivity.

3.3.4. Experimental Section

3.3.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[17] ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer. Chemical

shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H, ^{13}C, and ^{31}P assignments were made on the basis of ^1H-^1H gCOSY, ^1H-^{13}C gHSQC and ^1H-^{31}P gHMBC experiments. Substrates **S1**,[18] **S2**,[13d] **S3**,[5a] **S4**,[19] **S6**,[18] **S7**,[20] **S8**-**S10**,[21] **S11**-**S13**,[22] **S14**,[23] **S15**-**S19**,[24] **S20**,[25] **S21**-**S23**,[25] **S25**-**S27**,[26] **S28**-**S32**,[27] **S33**,[28] **S34**,[29] **S35**,[30] **S36**-**S41**,[13d] **S42**-**S43**,[6d] **S44**-**S45**,[27] **S46**-**S54**,[5a] **S56**,[5a] **S57**,[31] **S58**,[32] **S59**,[33] **S60**,[32] **S61**[34] and **S62**[35] were prepared following the reported procedures and **S5** and **S24** were commercially available. Acetyl acid chlorides[10], acetoxyoxazoline **8**-**9**[10a], hydroxyl-oxazolines **2**[9] and **13**-**15**[10a,11] and **L10a**[36] were prepared as previously described.

3.3.4.2. General procedure for the preparation of acetyl hydroxyl-amides 6-7 and 10-11

In a flame-dried, round-bottom Schlenk flask under an inert atmosphere of argon, the appropriate amino alcohol (50 mmol, 1.0 equiv) and NEt_3 (10.12 g, 100 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (80 mL). The mixture was cooled to 0 °C, and a solution of the corresponding acetyl acid chloride (10.63 g, 50 mmol, 1.0 equiv) in dry CH_2Cl_2 (70 mL) was added dropwise over 10 min. The resulting reaction mixture was allowed to warm to rt, stirred for 5 h and then washed with aq HCl (1 M; 2 × 100 mL). The combined aq phases were extracted with CH_2Cl_2 (100 mL), and the combined organic layers washed with sat. aq NaCl (2 × 100 mL). Drying over $MgSO_4$ followed by removal of the solvent *in vacuo* afforded **6**-**7** and **10**-**11** as crude product. Pure **6**-**7** and **10**-**11** were obtained by recrystallization.

(*S*)-2-(((*S*)-2-hydroxy-1-phenylethyl)amino)-2-oxo-1-phenylethyl acetate (6): Yield: 2.66 g (85%). ^1H NMR (400 MHz, $CDCl_3$): δ= 2.11 (s, 3H, CH_3, OAc), 3.98 (m, 2H, CH_2-O), 5.17 (m, 1H, CH-N), 6.20 (s, 1H, CH), 6.90 (bs, 1H, NH), 7.30-7.51 (m, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.2 (CH_3, OAc), 55.6 (CH-N), 66.2 (CH_2-O), 75.8 (CH), 126.7 (CH=), 127.5 (CH=), 127.7 (CH=), 127.8 (CH=), 128.1 (CH=), 128.9 (C=), 129.0 (CH=), 129.1 (C), 129.2 (CH=), 129.3 (CH=), 129.4 (CH=), 138.6 (C), 168.8 (C=O), 169.7 (C=O).

(*S*)-2-(((*S*)-1-hydroxy-3-methylbutan-2-yl)amino)-2-oxo-1-phenylethyl acetate (7): Yield: 2.48 g (89%). ^1H NMR (400 MHz, $CDCl_3$): δ= 0.90 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 8.0 Hz), 0.96 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 8.0 Hz), 1.95 (m, 1H, CH, ^{i}Pr), 2.19 (s, 3H, CH_3, OAc), 3.72 (m, 3H, CH_2-O, CH-N), 6.08 (s, 1H, CH), 6.35 (bs, 1H, NH), 7.29-7.56 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 19.0 (CH_3, ^{i}Pr), 19.7 (CH_3, ^{i}Pr), 21.2 (CH_3, OAc), 29.2 (CH, ^{i}Pr), 57.1 (CH-N), 63.6 (CH_2-O), 75.9 (CH), 127.5 (CH=), 129.0 (CH=), 129.2 (CH=), 135.0 (C), 168.7 (C=O), 169.8 (C=O).

(*S*)-1-(((*S*)-2-hydroxy-1-phenylethyl)amino)-1-oxopropan-2-yl acetate (10): Yield: 2.0 g (90%). ^1H NMR (400 MHz, $CDCl_3$): δ= 1.38 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8

Hz), 2.03 (s, 3H, CH_3, OAc), 2.64 (bs, 1H, OH), 3.69 (m, 2H, CH_2-O), 4.94 (m, 1H, CH-N), 5.10 (q, 1H, CH, $^3J_{H-H}$= 6.8 Hz), 6.87 (bs, 1H, NH), 7.16-7.30 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 17.7 (CH_3), 20.9 (CH_3, OAc), 55.0 (CH-N), 65.3 (CH_2-O), 70.5 (CH-O), 126.5 (CH=), 127.6 (CH=), 128.6 (CH=), 138.9 (C), 169.9 (C=O), 171.0 (C=O).

(*S*)-1-(((*S*)-2-hydroxy-1-phenylethyl)amino)-3-methyl-1-oxobutan-2-yl acetate (11): Yield: 2.51 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.88 (m, 6H, CH_3, ^{i}Pr), 2.07 (s, 3H, CH_3, OAc), 2.19 (m, 1H, CH, ^{i}Pr), 3.23 (bs, 1H, OH), 3.66 (m, 2H, CH_2-O), 4.95 (m, 2H, CH-O, CH-N), 6.93 (bs, 1H, NH), 7.07 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 7.21-7.29 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 17.1 (CH_3, ^{i}Pr), 18.6 (CH_3, ^{i}Pr), 20.7 (CH_3, OAc), 30.6 (CH, ^{i}Pr), 55.0 (CH-N), 65.3 (CH_2-O), 78.2 (CH-O), 126.6 (CH=), 127.5 (CH=), 128.6 (CH=), 139.1 (C), 169.8 (C=O), 170.4 (C=O).

3.3.4.3. General procedure for the preparation of hydroxyl-oxazolines 12 and 16-17

In a flame-dried, round-bottomed Schlenk flask under an inert atmosphere of argon, the appropriate acetyl hydroxyl-amide **6** or **10**-**11** (10.0 mmol) was dissolved in dry CH_2Cl_2 (100 mL). The solution was cooled to −78 °C and diethylaminosulfur trifluoride (DAST) was added dropwise (1.44 mL, 11.0 mmol, 1.1 equiv) over 5 min. After the addition, the reaction mixture was stirred at −78 °C for 1 h. Then, K_2CO_3 (2.07 g, 15 mmol, 1.5 equiv) was added in one portion and the reaction was allowed to warm to rt. Subsequently, the reaction mixture was poured into sat. aq $NaHCO_3$ (200 mL) and the organic layer was collected. The aqueous layer was extracted once more with CH_2Cl_2 (200 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded the corresponding crude acetoxyoxazoline as a brown or yellow oil. Purification by flash column chromatography (EtOAc–PE, 1:2) afforded the desired pure acetoxyoxazoline.

Next, in a round-bottomed flask, the appropriate acetoxyoxazoline (5.0 mmol) was dissolved in MeOH (30 mL). The solution was cooled to 0 °C and aq NaOH solution (1 M; 15 mL, 3.0 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h and allowed to warm to rt. The mixture was then extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with sat. aq NaCl (2 × 50 mL). After drying over $MgSO_4$ and evaporation of the solvent crude of the corresponding hydroxy-oxazoline was obtained as a yellow solid or oil. Recrystallization with ethyl acetate afforded the desired pure product **12** or **16**-**17**.

(*S*)-phenyl((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)methanol (12): Yield: 1.87 g (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.18 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 4.62 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.4 Hz), 5.14 (t, 1H, CH-N, $^3J_{H-H}$= 9.2 Hz), 5.33 (s, 1H,

CH-O), 7.18-7.45 (m, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 68.8 (CH-N), 69.7 (CH-O), 76.3 (CH-O), 126.7 (CH=), 126.8 (CH=), 126.9 (CH=), 127.9 (CH=), 128.0 (CH=), 128.6 (CH=), 128.8 (CH=), 129.0 (CH=), 139.3 (C), 141.7 (C), 170.0 (C=N).

(*S*)-1-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)ethan-1-ol (16): Yield: 1.16 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.47 (d, 3H, CH3, $^3J_{H-H}$= 6.8 Hz), 3.45 (bs, 1H, OH), 4.21 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 4.45 (m, 1H, CH-O), 4.72 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.4 Hz), 5.21 (t, 1H, CH-N, $^3J_{H-H}$= 9.2 Hz), 7.23-7.38 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.0 (CH_3), 63.7 (CH-O), 69.1 (CH-N), 76.1 (CH-O), 126.7 (CH=), 128.0 (CH=), 129.0 (CH=), 141.8 (C), 171.5 (C=N).

(*S*)-2-methyl-1-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)propan-1-ol (17): Yield: 1.64 g (98%). ^{1}H NMR (400 MHz, CDCl3): δ= 0.96 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 1.06 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 2.08 (m, 1H, CH, ^{i}Pr), 2.94 (bs, 1H, OH), 4.22 (m, 2H, CH-O, CH-O), 4.73 (t, 1H, CH-N, $^3J_{H-H}$= 8.4 Hz), 5.21 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 7.24-7.38 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.5 (CH_3, ^{i}Pr), 18.8 (CH_3, ^{i}Pr), 32.5 (CH, ^{i}Pr), 68.9 (CH_2-O), 72.2 (CH-N), 76.1 (CH-O), 126.7 (CH=), 127.9 (CH=), 129.0 (CH=), 141.7 (C), 171.0 (C=N).

3.3.4.4. General procedure for the preparation of phosphite-oxazoline ligands L10-L16a-e

To a solution of *in situ* generated phosphochloridite (1.1 mmol) in dry toluene (6 mL), pyridine (0.16 mL, 2.0 mmol) was added. Then, this solution was placed in a -78 ºC bath. After 2 min at that temperature, a solution of the corresponding hydroxyl-oxazoline (1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral alumina and dry toluene as eluent system (1% NEt_3)) to afford the corresponding phosphite-oxazoline **L10**-**L16a**-**e** as white solids.

L10d: Yield: 398.3 mg (60%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 153.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.52 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.57 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 3.76 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 4.07 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.4 Hz), 4.92 (dd, 1H, CH-N, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.4 Hz), 6.82 (m, 2H, CH=), 6.96-7.13 (m, 7H, CH=), 7.26 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.27 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.66 (m, 2H, CH=), 8.09 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = -0.3 (d, CH_3, $SiMe_3$, J_{C-P}= 4.5 Hz), 0.4 (CH_3, $SiMe_3$), 28.2 (d, CH_3, $^3J_{C-P}$= 3.8 Hz), 28.7 (d, CH_3, $^3J_{C-P}$= 7.7 Hz), 69.8 (CH-N), 74.9 (CH_2-O), 76.2 (d, C,

CMe_2, $^3J_{C\text{-}P}$= 5.3 Hz), 122.6-152.4 (aromatic carbons), 169.1 (C=N). MS HR-ESI [found 686,2285, $C_{38}H_{42}NNaO_4PSi_2$ $(M+Na)^+$ requires 686,2282].

L10e: Yield: 331.9 mg (50%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 153.6 (s). ^1H NMR (400 MHz, C_6D_6): δ = 0.53 (s, 9H, CH_3, $SiMe_3$), 0.58 (s, 9H, CH_3, $SiMe_3$), 1.62 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 3.65 (pt, 1H, CH-O, $J_{H\text{-}H}$= 8.0 Hz), 4.06 (dd, 1H, CH-O, $^2J_{H\text{-}H}$= 10.8 Hz, $^3J_{H\text{-}H}$= 8.8 Hz), 4.92 (dd, 1H, CH-N, $^2J_{H\text{-}H}$= 10.0 Hz, $^3J_{H\text{-}H}$= 8.0 Hz), 6.81 (m, 2H, CH=), 6.95-7.11 (m, 7H, CH=), 7.26 (m, 2H, CH=), 7.67 (m, 2H, CH=), 8.11 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = -0.3 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$= 4.6 Hz), 0.4 (CH_3, $SiMe_3$), 28.0 (d, CH_3, $^3J_{C\text{-}P}$= 3.9 Hz), 28.7 (d, CH_3, $^3J_{C\text{-}P}$= 6.9 Hz), 69.5 (CH-N), 74.8 (CH_2-O), 75,9 (d, C, CMe_2, $^3J_{C\text{-}P}$= 5.3 Hz), 122.5-152.4 (aromatic carbons), 169.0 (C=N). MS HR-ESI [found 686,2280 $C_{38}H_{42}NNaO_4PSi_2$ $(M+Na)^+$ requires 686,2282].

L11a: Yield: 339.0 mg (49%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.2 (s). ^1H NMR (400 MHz, C_6D_6): δ= 1.20 (s, 18H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 3.64 (pt, 1H, CH-O, $J_{H\text{-}H}$= 8.8 Hz), 4.07 (pt, 1H, CH-O, $J_{H\text{-}H}$= 8.4 Hz), 4.90 (pt, 1H, CH-N, $J_{H\text{-}H}$= 8.8 Hz), 6.08 (d, 1H, CH-OP, $^3J_{H\text{-}P}$= 10.0 Hz), 6.89-7.11 (m, 8H, CH=), 7.27 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.0 Hz), 7.29 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.8 Hz), 7.39 (d, 2H, CH=, $^3J_{H\text{-}H}$= 7.2 Hz), 7.49 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.4 Hz), 7.57 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.8 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 30.7 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 69.3 (CH-N), 73.1 (CH-OP), 74.6 (CH_2-O), 124.0-146.6 (aromatic carbons), 166.1 (C=N). MS HR-ESI [found 714,3682 $C_{44}H_{54}NNaO_4P$ $(M+Na)^+$ requires 714,3683].

L11b: Yield: 508 mg (74%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 133.0 (s). ^1H NMR (400 MHz, C_6D_6): δ= 1.23-1.63 (m, 9H, CH_2), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 2.43-2.73 (m, 7H, CH_2), 3.62 (pt, 1H, CH-O, $J_{H\text{-}H}$= 8.0 Hz), 4.19 (pt, 1H, CH-O, $J_{H\text{-}H}$= 8.4 Hz), 4.96 (pt, 1H, CH-N, $J_{H\text{-}H}$= 9.6 Hz), 5.55 (d, 1H, CH-OP, $^3J_{H\text{-}P}$= 9.2 Hz), 6.88 (d, 2H, CH=, $^3J_{H\text{-}H}$= 3.6 Hz), 6.95-7.17 (m, 8H, CH=), 7.50 (d, 2H, CH=, $^3J_{H\text{-}H}$= 7.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 23.4 (CH_2), 23.6 (CH_2), 23.8 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 30.3 (CH_2), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 70.1 (CH-N), 73.9 (CH-OP), 75.3 (CH_2-O), 126.0-146.0 (aromatic carbons), 167.1 (C=N). MS HR-ESI [found 710.3372 $C_{44}H_{50}NO_4P$ $(M+Na)^+$ requires 710.3370].

L11c: Yield: 394 mg (62%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 133.0 (s). ^1H NMR (400 MHz, C_6D_6): δ= 1.4 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.66 (pt, 1H, CH-O, $J_{H\text{-}H}$= 8.4 Hz), 4.17 (dd, 1H, CH-O, $^2J_{H\text{-}H}$= 10.0 Hz, $^3J_{H\text{-}H}$= 8.4 Hz), 4.95 (dd, 1H, CH-N, $^3J_{H\text{-}H}$= 10.0 Hz, $^3J_{H\text{-}H}$= 8.4 Hz), 5.74 (d, 1H, CH-OP, $^3J_{H\text{-}P}$= 9.2 Hz), 6.9 (m, 2H, CH=), 6.96-7.15 (m, 4H, CH=), 7.19 (s, 1H, CH=), 7.23 (s, 1H, CH=), 7.47-7.50 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.8 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.7 (CH_3, ^{t}Bu), 31.8

(d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 2.3 Hz), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 70.1 (CH-N), 73.9 (d, CH-OP, $J_{C\text{-}P}$= 2.3 Hz), 75.3 (CH_2-O), 126.0-146.5 (aromatic carbons), 167.0 (C=N). MS HR-ESI [found 658.3061 $C_{40}H_{46}NO_4P$ $(M+Na)^+$ requires 658.3057].

L11d: Yield: 398.7 mg (56%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.8 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.33 (s, 9H, CH_3, $SiMe_3$), 0.48 (s, 9H, CH_3, $SiMe_3$), 3.68 (pt, 1H, CHO, $J_{H\text{-}H}$= 8.0 Hz), 4.07 (dd, 1H, CH-O, $^2J_{H\text{-}H}$= 10.0 Hz, $^3J_{H\text{-}H}$= 8.0 Hz), 4.92 (dd, 1H, CH-N, $^3J_{H\text{-}H}$= 10.0 Hz, $^3J_{H\text{-}H}$= 8.8 Hz), 5.95 (d, 1H, CH-OP, $^3J_{H\text{-}P}$= 9.6 Hz), 6.83 (m, 3H, CH=), 6.92-7.06 (m, 6H, CH=), 7.09-7.18 (m, 3H, CH=), 7.24 (m, 2H, CH=), 7.33 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 7.69 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 7.73 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.04 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ= -0.3 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), 69.3 (CH-N), 72.9 (CH-OP), 74.6 (CH_2-O), 122.1-152.2 (aromatic carbons), 165.8 (C=N). MS HR-ESI [found 734,2278 $C_{42}H_{42}NNaO_4PSi_2$ $(M+Na)^+$ requires 734,2282].

L11e: Yield: 484.1 mg (68%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 140.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.32 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$), 3.59 (pt, 1H, CHO, $J_{H\text{-}H}$= 8.4 Hz), 4.05 (dd, 1H, CH-O, $^2J_{H\text{-}H}$= 10.0 Hz, $^3J_{H\text{-}H}$= 8.8 Hz), 4.83 (dd, 1H, CH-N, $^2J_{H\text{-}H}$= 9.6 Hz, $^3J_{H\text{-}H}$= 7.6 Hz), 5.93 (d, 1H, CH-OP, $^3J_{H\text{-}P}$= 9.6 Hz), 6.80-7.05 (m, 7H, CH=), 7.09 (m, 4H, CH=), 7.26 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.8 Hz), 7.35 (m, 3H, CH=), 7.66 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.6 Hz), 7.71 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.0 Hz), 8.06 (s, 1H, CH=), 8.22 (s, 1H, CH=). ^{13}C NMR (C_6D_6): δ= -0.4 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 69.2 (CH-N), 73.6 (CH-OP), 74.5 (CH_2-O), 122.6-152.3 (aromatic carbons), 165.3 (C=N). MS HR-ESI [found 734,2281 $C_{42}H_{42}NNaO_4PSi_2$ $(M+Na)^+$ requires 734,2282].

L12a: Yield: 395.5 mg (52%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.55 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.4 Hz), 0.76 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.4 Hz), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.35 (m, 1H, CH, ^{i}Pr), 1.54 (s, 9H, CH_3, ^{t}Bu), 3.64 (pt, 1H, CH-O, $J_{H\text{-}H}$= 8.4 Hz), 3.62 (m, 1H, CH-N), 3.85 (dd, 1H, CH-O, $^2J_{H\text{-}H}$= 9.2 Hz, $^3J_{H\text{-}H}$= 8.0 Hz), 6.04 (d, 1H, CH-OP, $^3J_{H\text{-}P}$= 10.0 Hz), 6.99-7.15 (m, 3H, CH=), 7.27 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.8 Hz), 7.29 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.4 Hz), 7.38 (m, 2H, CH=), 7.51 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.8 Hz), 7.59 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 18.8 (CH_3, ^{i}Pr), 19.2 (CH_3, ^{i}Pr), 31.4 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 33.4 (CH, ^{i}Pr), 35.0 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 71.1 (CH_2-O), 72.9 (CH-N), 73.9 (CH-OP), 124.7-147.2 (aromatic carbons), 165.2 (C=N). MS HR-ESI [found 680,3839 $C_{41}H_{56}NNaO_4P$ $(M+Na)^+$ requires 680,3839].

L12b: Yield: 409 mg (68%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 133.6 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.53 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 0.74 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 1.35 (m, 1H, CH, ^{i}Pr), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.50 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.51 (pt, 1H, CH-O, $J_{H\text{-}H}$=

8.0 Hz), 3.63 (m, 1H, CH-N), 3.85 (pt, 1H, CH-O, J_{H-H}= 8.8 Hz), 6.65 (d, 1H, CH-OP, $^3J_{H-P}$= 9.2 Hz), 6.99-7.14 (m, 3H, CH=), 7.17 (s, 1H, CH=), 7.20 (s, 1H, CH=), 7.39 (s, 1H, CH=), 7.41 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.8 (CH_3), 17.1 (CH_3), 18.8 (CH_3, ^{i}Pr), 19.2 (CH_3, ^{i}Pr), 20.7 (CH_3), 20.8 (CH_3), 31.8 (d, CH_3, ^{t}Bu, J_{C-P}= 4.6 Hz), 32.0 (CH_3, ^{t}Bu), 33.4 (CH, ^{i}Pr), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 71.0 (CH_2-O), 72.8 (CH-N), 74.0 (CH-OP), 126.0-146.4 (aromatic carbons), 165.4 (C=N). MS HR-ESI [found 624.3216$C_{37}H_{48}NO_4P$ $(M+Na)^+$ requires 624.3213].

L13a: Yield: 436.0 mg (67%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.61 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 3.69 (m, 2H, CH-O, CH-N), 3.88 (dd, 1H, CH-O, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 7.6 Hz), 6.07 (d, 1H, CH-OP, $^3J_{H-P}$= 9.6 Hz), 6.99-7.15 (m, 3H, CH=), 7.27 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.31 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.41 (m, 2H, CH=), 7.52 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.60 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 26.0 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.8 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 69.2 (CH_2-O), 74.0 (CH-OP), 76.1 (CH-N), 124.7-147.3 (aromatic carbons), 165.2 (C=N). MS HR-ESI [found 694,3995 $C_{42}H_{58}NNaO_4P$ $(M+Na)^+$ requires 694,3996].

L13b: Yield: 412 mg (67%). ^{31}P NMR (161.9 MHz, C6D6): δ= 134.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.61 (s, 9H, CH_3, ^{t}Bu), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.69 (m, 2H, CH-O, CH-N), 3.91 (m, 1H, CH-O), 5.70 (d, 1H, CH-OP, $^3J_{H-P}$= 9.6 Hz), 6.99-7.15 (m, 3H, CH=), 7.18 (s, 1H, CH=), 7.20 (s, 1H, CH=), 7.41 (s, 1H, CH=), 7.44 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.8 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 26.1 (CH_3, ^{t}Bu), 31.7 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.9 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 69.2 (CH_2-O), 74.0 (d, CH-OP, J_{C-P}= 4.6 Hz), 76.2 (CH-N), 126.0-146.4 (aromatic carbons), 165.4 (C=N). MS HR-ESI [found 638.3372 $C_{38}H_{50}NO_4P$ $(M+Na)^+$ requires 638.3370].

L14a: Yield: 420.3 mg (60%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.29 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 3.62 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 3.99 (dd, 1H, CH-O, $^2J_{H-H}$= 10.4 Hz, $^3J_{H-H}$= 8.4 Hz), 4.92 (pt, 1H, CH-N, J_{H-H}= 10.0 Hz), 6.01 (d, 1H, CH-OP, $^3J_{H-P}$= 9.6 Hz), 6.99-7.14 (m, 8H, CH=), 7.32 (m, 2H, CH=), 7.39 (m, 2H, CH=), 7.53 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.60 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 70.0 (CH-N), 73.8 (CH-OP), 75.3 (CH_2-O), 124.7-147.3 (aromatic carbons), 167.0 (C=N). MS HR-ESI [found 714,3681 $C_{44}H_{54}NNaO_4P$ $(M+Na)^+$ requires 714,3683].

L14d: Yield: 440.1 mg (65%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 137.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.30 (s, 9H, CH_3, $SiMe_3$), 0.50 (s, 9H, CH_3, $SiMe_3$), 3.61 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 3.92 (dd, 1H, CH-O, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.0 Hz), 4.92 (m, 1H, CH-N), 5.70 (d, 1H, CH-OP, $^{3}J_{H-P}$= 9.2 Hz), 6.86 (m, 2H, CH=), 6.98-7.06 (m, 6H, CH=), 7.10-7.24 (m, 6H, CH=), 7.26 (d, 1H, CH=, $^{3}J_{H-H}$= 8.8 Hz), 7.42 (d, 1H, CH=, $^{3}J_{H-H}$= 8.8 Hz), 7.70 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.77 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.04 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 0.3 (d, CH_3, $SiMe_3$, J_{C-P}= 3.1 Hz), 0.4 (CH_3, $SiMe_3$), 69.7 (CH-N), 73.5 (d, CH-OP, J_{C-P}= 5.3 Hz), 75.4 (CH_2-O), 123.3-153.0 (aromatic carbons), 166.8 (C=N). MS HR-ESI [found 734,2280 $C_{42}H_{42}NNaO_4PSi_2$ $(M+Na)^+$ requires 734,2282].

L14e: Yield: 498.6 mg (71%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 143.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.33 (s, 9H, CH_3, $SiMe_3$), 0.50 (s, 9H, CH_3, $SiMe_3$), 3.52 (dd, 1H, CH-O, $^{2}J_{H-H}$= 9.2 Hz, $^{3}J_{H-H}$= 8.4 Hz), 3.91 (dd, 1H, CH-O, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.4 Hz), 4.74 (pt, 1H, CH-N, J_{H-H}= 10.0 Hz), 5.87 (d, 1H, CH-OP, $^{3}J_{H-P}$= 8.8 Hz), 6.83-7.17 (m, 12H, CH=), 7.27 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.36 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.41 (m, 2H, CH=), 7.67 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 7.77 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.06 (s, 1H, CH=), 8.19 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 0.7 (d, CH_3, $SiMe_3$, J_{C-P}= 4.5 Hz), 1.0 (CH_3, $SiMe_3$), 70.4 (CH-N), 74.5 (CH-OP), 75.3 (CH_2-O), 125.9-153.4 (aromatic carbons), 166.6 (C=N). MS HR-ESI [found 734,2281 $C_{42}H_{42}NNaO_4PSi_2$ $(M+Na)^+$ requires 734,2282].

L15a: Yield: 445.3 mg (65%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 144.6 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.25 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.45 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.4 Hz), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 3.77 (pt, 1H, CH-O, J_{H-H}= 8.8 Hz), 4.14 (dd, 1H, CH-O, $^{2}J_{H-H}$= 10.4 Hz, $^{3}J_{H-H}$= 8.4 Hz), 4.92 (pt, 1H, CH-N, J_{H-H}= 10.0 Hz), 5.18 (m, 1H, CH-OP), 6.99-7.14 (m, 5H, CH=), 7.33 (m, 2H, CH=), 7.60 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 20.7 (d, CH_3, $^{3}J_{C-P}$= 3.0 Hz), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 36.1 (C, ^{t}Bu), 67.9 (d, CH-OP, $^{2}J_{C-P}$= 9.9 Hz), 70.2 (CH-N), 75.3 (CH_2-O), 124.7-147.2 (aromatic carbons), 167.6 (C=N). MS HR-ESI [found 652,3525 $C_{39}H_{52}NNaO_4P$ $(M+Na)^+$ requires 652,3526].

L15d: Yield: 398.0 mg (58%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 142.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.54 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 1.27 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.8 Hz), 3.76 (pt, 1H, CH-O, J_{H-H}= 8.8 Hz), 4.15 (dd, 1H, CH-O, $^{2}J_{H-H}$= 10.0 Hz, $^{3}J_{H-H}$= 8.8 Hz), 4.91 (pt, 1H, CH-N, J_{H-H}= 9.2 Hz), 5.13 (m, 1H, CH-OP), 6.86 (m, 2H, CH=), 6.99-7.15 (m, 7H, CH=), 7.27 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.36 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 7.70 (d, 2H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 8.13 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 0.4 (d, CH_3, $SiMe_3$, J_{C-P}= 5.3 Hz), 0.8 (CH_3, $SiMe_3$), 20.4 (d, CH_3, $^{3}J_{C-P}$= 1.0 Hz), 67.3 (CH-OP), 70.2 (CH-N), 75.2 (CH_2-O), 123.3-152.9

(aromatic carbons), 167.3 (C=N). MS HR-ESI [found 672,2124 $C_{37}H_{40}NNaO_4PSi$ $(M+Na)^+$ requires 672,2126].

L15e: Yield: 405.0 mg (59%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 144.7 (s). ^1H NMR (400 MHz, C_6D_6): δ= 0.55 (s, 9H, CH_3, $SiMe_3$), 0.56 (s, 9H, CH_3, $SiMe_3$), 1.51 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 3.67 (pt, 1H, CH-O, J_{H-H}= 8.4 Hz), 4.01 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.4 Hz), 4.85 (dd, 1H, CH-N, $^3J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.4 Hz), 5.05 (m, 1H, CH-OP), 6.86 (m, 2H, CH=), 6.86 (m, 2H, CH=), 6.99-7.15 (m, 7H, CH=), 7.27 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.34 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.70 (pt, 2H, CH=, J_{H-H}= 7.6 Hz), 8.12 (s, 1H, CH=), 8.16 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 0.5 (d, CH_3, $SiMe_3$, J_{C-P}= 4.5 Hz), 0.8 (CH_3, $SiMe_3$), 21.5 (d, CH_3, $^3J_{C-P}$= 3.0 Hz), 68.7 (d, CH-OP, $^2J_{C-P}$= 6.1 Hz), 70.0 (CH-N), 75.2 (CH_2-O), 122.6-153.0 (aromatic carbons), 166.9 (C=N). MS HR-ESI [found 672,2125 $C_{37}H_{40}NNaO_4PSi_2$ $(M+Na)^+$ requires 672,2126].

L16a: Yield: 429.0 mg (60%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 146.2 (s). ^1H NMR (400 MHz, C_6D_6): δ= 0.95 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.00 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.2 Hz), 1.26 (s, 18H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.26 (m, 1H, CH, ^{i}Pr), 3.77 (pt, 1H, CH-O, J_{H-H}= 8.8 Hz), 4.15 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.0 Hz), 4.97 (m, 2H, CH-N, CH-OP), 6.98-7.14 (m, 5H, CH=), 7.32 (m, 2H, CH=), 7.58 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 18.6 (CH_3, ^{i}Pr), 18.7 (CH_3, ^{i}Pr), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.7 (d, CH, ^{i}Pr, ^{3} J_{C-P}= 2.3 Hz), 35.0 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 36.1 (C, ^{t}Bu), 70.2 (CH-N), 75.0 (CH_2-O), 76.3 (d, CH-OP, $^2J_{C-P}$= 8.3 Hz), 124.6-147.2 (aromatic carbons), 166.1 (C=N). MS HR-ESI [found 680,3842 $C_{41}H_{56}NNaO_4P$ $(M+Na)^+$ requires 680,3839].

L16d: Yield: 480.3 mg (68%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 149.0 (s). ^1H NMR (400 MHz, C_6D_6): δ= 0.56 (s, 9H, CH_3, $SiMe_3$), 0.60 (s, 9H, CH_3, $SiMe_3$), 0.72 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 0.82 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 2.20 (m, 1H, CH, ^{i}Pr), 3.80 (pt, 1H, CH-O, J_{H-H}= 8.8 Hz), 4.22 (dd, 1H, CH-O, $^2J_{H-H}$= 10.4 Hz, $^3J_{H-H}$= 8.8 Hz), 4.77 (dd, 1H, CH-OP, $^3J_{H-P}$= 9.6 Hz, $^3J_{H-H}$= 6.8 Hz), 5.03 (pt, 1H, CH-N, J_{H-H}= 10.4 Hz), 6.86 (m, 2H, CH=), 6.99-7.15 (m, 7H, CH=), 7.28 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.33 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.71 (t, 2H, CH=, $^3J_{H-H}$= 7.2 Hz), 8.12 (s, 1H, CH=), 8.18 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 0.5 (d, CH_3, $SiMe_3$, J_{C-P}= 3.8 Hz), 0.8 (CH_3, $SiMe_3$), 18.4 (CH_3, ^{i}Pr), 18.6 (CH_3, ^{i}Pr), 32.6 (CH, ^{i}Pr), 70.3 (CH-N), 75.2 (CH_2-O), 75.8 (CH-OP), 123.3-153.0 (aromatic carbons), 165.9 (C=N). MS HR-ESI [found 700,2441 $C_{39}H_{44}NNaO_4PSi_2$ $(M+Na)^+$ requires 700,2439].

L16e: Yield: 481.0 mg (69%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 147.3 (s). ^1H NMR (400 MHz, C_6D_6): δ= 0.56 (s, 9H, CH_3, $SiMe_3$), 0.60 (s, 9H, CH_3, $SiMe_3$), 0.93 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.06 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 2.33 (m, 1H, CH, ^{i}Pr), 3.52 (pt, 1H, CH-O, J_{H-H}= 8.8 Hz), 3.81 (dd, 1H, CH-O, $^2J_{H-H}$= 10.4 Hz, $^3J_{H-H}$= 8.4 Hz), 4.05 (pt, 1H, CH-N, J_{H-H}= 9.2 Hz), 4.96 (pt, 1H, CH-OP, J_{H-H}= 7.6 Hz), 6.83 (m, 2H, CH=),

6.96-7.15 (m, 7H, CH=), 7.24 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.30 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.69 (t, 2H, CH=, $^3J_{H-H}$= 8.8 Hz), 8.18 (s, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 0.5 (d, CH_3, $SiMe_3$, J_{C-P}= 4.6 Hz), 0.8 (CH_3, $SiMe_3$), 18.7 (CH_3, ^{i}Pr), 19.5 (CH_3, ^{i}Pr), 32.7 (d, CH, ^{i}Pr, $^3J_{C-P}$= 4.6 Hz), 69.7 (CH-N), 74.7 (CH_2-O), 77.0 (CH-OP), 123.2-153.1 (aromatic carbons), 165.2 (C=N). MS HR-ESI [found 700,2438 $C_{39}H_{44}NNaO_4PSi_2$ $(M+Na)^+$ requires 700,2439].

3.3.4.5. General procedure for the preparation of phosphinite-oxazoline ligands L10-L16f-h

The corresponding hydroxyl-oxazoline compound (0.5 mmol) and DMAP (6.7 mg, 0.055 mmol) were dissolved in toluene (1 ml), and triethylamine was added (0.09 ml, 0.65 mmol) at rt, followed by the addition of the corresponding chlorophosphine (0.55 mmol) via syringe. The reaction was stirred for 20 min at rt. The solvent was removed *in vacuo* and the product was purified by flash chromatography on alumina (toluene/NEt_3= 100/1) to afford the corresponding phosphinite-oxazoline **L10**-**L16f-h**.

L11f: Yield: 425 mg (67%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 116.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ = 3.64 (pt, 1H, CH-O, J_{H-H}= 7.6 Hz), 3.87 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.0 Hz), 4.82 (dd, 1H, CH-N, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 8.0 Hz), 5.86 (d, 1H, CH-OP, $^3J_{H-P}$= 8.4 Hz), 6.95-7.11 (m, 14H, CH=), 7.56 (dt, 2H, CH=, $^3J_{H-H}$= 8.0 Hz, $^4J_{H-H}$= 2.0 Hz), 7.62 (d, 2H, CH=, $^3J_{H-H}$= 7.2 Hz), 7.39 (t, 2H, CH=, $^3J_{H-H}$= 7.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 69.4 (CH-N), 74.6 (CH_2-O), 77.2 (CH-OP), 125.3-142.6 (aromatic carbons), 166.6 (C=N). MS HR-ESI [found 460.1439, $C_{40}H_{46}NO_4P$ $(M-Na)^+$ requires 460.1437].

L11g: Yield: 121 mg (58%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 105.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ = 2.31 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.59 (m, 1H, CH-O), 3.87 (m, 1H, CH-O), 4.82 (m, 1H, CH-N), 5.92 (d, 1H, CH-OP, $^3J_{H-P}$= 8.4 Hz), 6.88 (m, 1H, CH=), 6.95-7.15 (m, 14H, CH=), 7.63 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.72 (m, 1H, CH=), 8.09 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 20.2 (d, CH_3, J_{C-P}= 9.1 Hz), 20.4 (d, CH_3, J_{C-P}= 9.1 Hz) 69.3 (CH-N), 74.4 (CH_2-O), 77.6 (d, CH-OP, J_{C-P}= 24.4 Hz), 125.9-142.6 (aromatic carbons), 166.8 (C=N). MS HR-ESI [found 488.1754 $C_{26}H_{28}NO_2P$ $(M+Na)^+$ requires 488.1750].

L12f: Yield: 116 mg (58%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 116.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.63 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 0.77 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.37 (m, 1H, CH, ^{i}Pr), 3.49 (pt, 1H, CH-O, J_{H-H}= 6.6 Hz), 3.54-.65 (m, 2H, CH-O, CH-N), 5.80 (d, 1H, CH-OP, $^3J_{H-P}$= 8.6 Hz), 6.99-7.18 (m, 9H, CH=), 7.55-7.63 (m, 3H, CH=), 7.79-7.84 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 18.3 (CH3, ^{i}Pr), 32.7 (CH, ^{i}Pr), 70.1 (CH-N), 71.9 (CH_2-O), 77.3 (d, CH-OP, $^3J_{C-P}$= 23.1 Hz), 125.4-142.3

(aromatic carbons), 165.0 (C=N). MS HR-ESI [found 426.1597 $C_{25}H_{26}NO_2P$ $(M+Na)^+$ requires 426.1593].

L12g: Yield: 121 mg (56%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 104.9 (s). ^1H NMR (400 MHz, C_6D_6): δ= 0.60 (d, 1H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.7 Hz), 0.75 (d, 1H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.7 Hz), 2.25 (s, 3H, CH_3), 1.31-1.39 (m, 1H, CH, ^{i}Pr), 2.39 (s, 3H, CH_3), 3.44 (pt, 1H, CH-O, $^3J_{H-H}$= 7.5 Hz), 3.48-3.63 (m, 2H, CH-O, CH-N), 5.78 (d, 1H, CH-OP, $^3J_{H-P}$= 8.6 Hz), 6.82-7.12 (m, 9H, CH=), 7.55 (d, 2H, CH=, $^3J_{H-H}$= 7.8 Hz), 7.58-7.65 (m, 1H, CH=), 7.97-8.07 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 18.5 (CH_3, ^{i}Pr), 20.5 (CH_3), 20.7 (CH_3), 32.7 (CH, ^{i}Pr), 70.1 (CH-N), 72.1 (CH_2-O), 77.9 (d, CH-OP, $^2J_{C-P}$= 24.2 Hz), 126.1-141.3 (aromatic carbons), 165.1 (C=N). MS HR-ESI [found 454.1911 $C_{27}H_{30}NO_2P$ $(M+Na)^+$ requires 454.1906].

L12h: Yield: 170 mg (82%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 154.06 (s). ^1H NMR (400 MHz, C_6D_6): δ= 0.66 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.7 Hz), 0.81 (d, 3H, CH_3, iPr, $^3J_{H-H}$= 6.7 Hz), 0.93-1.11 (m, 4H, CH_2, Cy), 1.17-1.33 (m, 4H, CH_2, Cy), 1.35-1.50 (m, 3H, CH_2, Cy, CH, ^{i}Pr), 1.48-1.68 (m, 6H, CH_2, Cy), 1.72-1.76 (m, 4H, CH_2, CH, Cy), 2.11-2.15 (m, 1H, CH_2, Cy), 3.52 (pt, 1H, CH-O, J_{H-H}= 7.7 Hz), 3.61-3.70 (m, 1H, CH-O), 3.72-3.79 (m, 1H, CH-N), 5.53 (d, 1H, CH-OP, $^3J_{C-P}$= 8.8 Hz), 6.98-7.05 (m, 1H, CH=), 7.07-7.14 (m, 2H, CH=), 7.56-7.61 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 18.2 (CH_3, ^{i}Pr), 18.3 (CH_3, ^{i}Pr), 26.3-27.2 (CH_2, Cy), 27.9 (CH_2, Cy), 28.1 (CH_2, Cy), 28.2 (CH_2, Cy), 32.7 (CH, ^{i}Pr), 37.9 (d, CH, Cy, $^1J_{C-P}$= 2.5 Hz), 38.1 (d, CH, Cy, $^1J_{C-P}$= 4.5 Hz), 69.9 (CH-N), 72.0 (CH_2-O), 79.5 (d, CH-OP, $^2J_{C-P}$= 23.6 Hz), 127.2-139.3 (aromatic carbons), 165.4 (C=N). MS HR-ESI [found 438.2535 $C_{25}H_{38}NO_2P$ $(M+Na)^+$ requires 438.2532].

L14f: Yield: 118 mg (54%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 116.6 (s). ^1H NMR (400 MHz, C_6D_6): δ= 3.59 (t, 1H, CH-O, J_{H-H}= 8.6 Hz), 3.90-3.98 (m, 1H, CH-O), 4.83 (pt, 1H, CH-N, J_{H-H}= 9.6 Hz), 5.98 (d, 1H, CH-OP, $^3J_{H-P}$= 8.7 Hz), 6.96-7.19 (m, 14H, CH=), 7.56-7.64 (m, 2H, C=H), 7.65-7.72 (m, 2H, C=H), 7.76-7.84 (m, 2H, C=H). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 69.5 (CH-N), 74.6 (CH_2-O), 77.4 (d, CH-OP, $^2J_{C-P}$= 23.1 Hz), 125.3-142.4 (aromatic carbons), 166.5 (C=N). MS HR-ESI [found 460.1439 $C_{28}H_{24}NO_2P$ $(M+Na)^+$ requires 460.1437].

L14g: Yield: 155 mg (67%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 105.2 (s). ^1H NMR (400 MHz, C_6D_6): δ= 2.33 (s, 3H, CH_3, *o*-Tol), 2.41 (s, 3H, CH_3, *o*-Tol), 3.57 (pt, 1H, CH-O, J_{H-H}= 8.6 Hz), 3.90-3.95 (m, 1H, CH-O), 4.80 (pt, 1H, CH-N, J_{H-H}= 9.6 Hz), 5.97 (d, 1H, CH-OP, $^3J_{H-P}$= 8.8 Hz), 6.75-7.25 (m, 15H, C=H), 7.51-7.74 (m, 2H, CH=), 8.02-8.07 (m, 1H, C=H). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 20.2 (CH_3, *o*-Tol), 20.5 (CH_3, *o*-Tol), 69.5 (CH-N), 74.5 (CH_2-O), 77.8 (d, CH-OP, $^2J_{C-P}$= 24.6 Hz), 125.3-142.4 (aromatic carbons), 166.4 (C=N). MS HR-ESI [found 488.1749 $C_{30}H_{28}NO_2P$ $(M+Na)^+$ requires 488.1750].

L14h: Yield: 120 mg (54%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 154.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.00-1.14 (m, 4H, CH_2, Cy), 1.17-1.28 (m, 4H, CH_2, Cy), 1.31-1.40 (m, 2H, CH_2, Cy), 1.45-1.52 (m, 2H, CH_2, Cy), 1.59-1.66 (m, 4H, CH_2, Cy), 1.69-1.72 (m, 2H, CH_2, Cy), 1.77-1.84 (m, 3H, CH_2, CH, Cy), 2.17-2.21 (m, 1H, CH_2, Cy), 3.74 (pt, 1H, CH-O, J_{H-H}= 8.6 Hz), 4.00 (dd, 1H, CH-O, $^{2}J_{H-H}$= 10.1 Hz, $^{3}J_{H-H}$= 8.4 Hz), 4.86 (pt, 1H, CH-N, J_{H-H}= 9.6 Hz), 5.79 (d, 1H, CH-OP, $^{3}J_{H-P}$= 8.6 Hz), 7.02-7.10 (m, 3H, C=H), 7.11-7.21 (m, 2H, CH=), 7.21-7.24 (m, 3H, CH=), 7.71 (dd, 2H, CH=, $^{3}J_{H-H}$= 7.9 Hz, $^{4}J_{H-H}$= 0.9 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 26.3-27.0 (CH_2, Cy), 27.9 (CH_2, Cy), 28.1 (CH_2, Cy), 28.2 (CH_2, Cy), 28.3 (CH_2, Cy), 38.0 (d, CH, $^{1}J_{C-P}$= 11.3 Hz), 38.2 (d, CH, $^{1}J_{C-P}$=13.2 Hz), 69.4 (CH-N), 74.5 (CH_2-O), 79.6 (d, CH-OP, $^{2}J_{C-P}$= 23.4 Hz), 126.7-142.6 (aromatic carbons), 167.0 (C=N). MS HR-ESI [found 472.2378 $C_{28}H_{36}NO_2P$ $(M+Na)^+$ requires 472.2376].

3.3.4.6. General procedure for preparation of [Ir(cod)(L10-L16a-h)]BAr_F

The corresponding ligand (0.074 mmol) was dissolved in CH_2Cl_2 (5 mL) and [Ir(μ-Cl)(cod)]$_2$ (25.0 mg, 0.037 mmol) was added. The reaction mixture was heated to reflux at 40 °C for 1 h. After 5 min at rt, $NaBAr_F$ (77.2 mg, 0.080 mmol) and water (5 mL) were added and the reaction mixture was stirred vigorously for 30 min at rt. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ filtered through a plug of Celite and the solvent was evaporated to give the product as an orange solid.

[Ir(cod)(L10a)]BAr_F: Yield: 63 mg (94%). ^{31}P NMR (161.9 MHz, CDCl3): δ = 97.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.83 (s, 6H, CH_3), 1.75-2.20 (m, 8H, CH_2, cod), 3.21 (m, 1H, CH=, cod), 3.64 (m, 1H, CH=, cod), 4.54 (dd, 1H, CH-O, $^{2}J_{H-H}$= 9.6 Hz, $^{3}J_{H-H}$= 3.6 Hz), 4.74 (m, 1H, CH=, cod), 4.81 (pt, 1H, CH-O, J_{H-H}= 9.6 Hz), 5.21 (m, 1H, CH-N), 5.24 (m, 1H, CH=, cod), 7.12 (m, 3H, CH=), 7.19 (d, 1H, CH=, $^{4}J_{H-H}$= 2.0 Hz), 7.42 (m, 3H, CH=), 7.52 (m, 6H, CH=), 7.71 (s, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.8 (CH_2, cod), 28.6 (CH_3), 28.9 (CH_3), 30.2 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 31.7 (CH_2, cod), 32.2 (CH_2, cod), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 62.2 (CH=, cod), 65.8 (CH=, cod), 71.5 (CH-N), 78.7 (CH_2-O), 79.5 (d, CH-OP, $^{2}J_{C-P}$= 1.5 Hz), 102.4 (d, CH=, cod, J_{C-P}= 16.0 Hz), 104.2 (d, CH=, cod, J_{C-P}= 16.1 Hz), 117.4-149.1 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^{1}J_{C-B}$= 50.4 Hz), 176.3 (d, C=N, $^{3}J_{C-P}$= 6.1 Hz). MS HR-ESI [found 944.4362, $C_{48}H_{66}IrNO_4P$ $(M-BAr_F)^+$ requires 944.4359].

[Ir(cod)(L10d)]BAr_F: Yield: 63 mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 103.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.53 (s, 9H, CH_3, $SiMe_3$), 0.61 (s, 9H, CH_3, $SiMe_3$), 1.83 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.58-2.0 (m, 7H, CH_2, cod), 2.17 (m, 1H, CH_2,

cod), 2.93 (m, 1H, CH=, cod), 3.96 (m, 1H, CH=, cod), 4.54 (dd, 1H, CH-O, $^{2}J_{H-H}$= 8.8 Hz, $^{3}J_{H-H}$= 2.8 Hz), 4.81 (m, 2H, CH=, cod and CH-O), 5.35 (m, 2H, CH-N and CH=, cod), 6.63 (d, 1H, CH=, $^{3}J_{H-H}$= 8.8 Hz), 7.02 (d, 1H, CH=, $^{3}J_{H-H}$= 8.8 Hz), 7.16 (m, 2H, CH=), 7.24 (m, 3H, CH=), 7.42-7.51 (m, 8H, CH=), 7.71 (s, 8H, CH=), 7.96 (d, 2H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 8.16 (d, 2H, CH=, $^{3}J_{H-H}$= 8.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.6 (CH_3, $SiMe_3$), 1.3 (CH_3, $SiMe_3$), 28.2 (CH_2, cod), 28.9 (CH_3), 29.4 (CH_2, cod), 29.9 (CH_3), 31.5 (CH_2, cod), 33.1 (d, CH_2, cod, J_{C-P}= 4.6 Hz), 59.3 (CH=, cod), 68.3 (CH=, cod), 71.5 (CH-N), 78.7 (CH_2-O), 79.7 (d, CH-OP, $^{2}J_{C-P}$= 2.9 Hz), 105.5 (d, CH=, cod, J_{C-P}= 15.4 Hz), 106.0 (d, CH=, cod, J_{C-P}= 16.7 Hz), 117.6-150.6 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^{1}J_{C-B}$= 50.0 Hz), 176.8 (d, C=N, $^{3}J_{C-P}$= 6.4 Hz). MS HR-ESI [found 964.2859, $C_{46}H_{54}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 964.2858].

[Ir(cod)(L10e)]BAr$_F$: Yield: 60 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 104.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.43 (s, 9H, CH_3, $SiMe_3$), 0.50 (s, 9H, CH_3, $SiMe_3$), 1.56 (s, 3H, CH_3), 1.62 (m, 2H, CH_2, cod), 1.68 (s, 3H, CH_3), 1.78 (m, 1H, CH_2, cod), 1.96-2.07 (m, 3H, CH_2, cod), 2.30 (m, 1H, CH_2, cod), 3.30 (m, 1H, CH=, cod), 4.03 (m, 1H, CH=, cod), 4.47 (dd, 1H, CH-O, $^{2}J_{H-H}$= 9.2 Hz, $^{3}J_{H-H}$= 4.0 Hz), 4.79 (pt, 1H, CH-O, J_{H-H}= 9.2 Hz), 4.97 (m, 1H, CH=, cod), 5.30 (m, 1H, CH-N), 5.71 (m, 1H, CH=, cod), 6.95 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.00 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.10 (m, 2H, CH=), 7.24 (m, 3H, CH=), 7.44-7.51 (m, 8H, CH=), 7.70 (s, 8H, CH=), 7.90 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 7.96 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 8.07 (s, 1H, CH=), 8.11 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.4 (CH_3, $SiMe_3$), 0.9 (CH_3, $SiMe_3$), 26.1 (CH_2, cod), 29.0 (d, CH_2, cod, J_{C-P}= 6.9 Hz), 29.5 (CH_3), 29.7 (CH_3), 31.4 (CH_2, cod), 34.7 (d, CH_2, cod, J_{C-P}= 6.0 Hz), 61.4 (CH=, cod), 68.8 (CH=, cod), 70.7 (CH-N), 78.0 (CH_2-O), 79.3 (d, CH-OP, $^{2}J_{C-P}$= 3.8 Hz), 100.8 (d, CH=, cod, J_{C-P}= 18.3 Hz), 106.4 (d, CH=, cod, J_{C-P}= 14.4 Hz), 117.4-150.9 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{1}J_{C-B}$= 49.7 Hz), 175.3 (d, C=N, $^{3}J_{C-P}$= 5.3 Hz). MS HR-ESI [found 964.2862, $C_{46}H_{54}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 964.2858].

[Ir(cod)(L11a)]BAr$_F$: Yield: 63 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 102.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.80-2.00 (m, 7H, CH_2, cod), 2.12 (m, 1H, CH_2, cod), 3.30 (m, 1H, CH=, cod), 3.60 (m, 1H, CH=, cod), 4.55 (dd, 1H, CH-O, $^{2}J_{H-H}$= 12.0 Hz, $^{3}J_{H-H}$= 4.0 Hz), 4.80 (pt, 1H, CH-O, J_{H-H}= 8.0 Hz), 4.90 (m, 1H, CH=, cod), 5.19 (dd, 1H, CH-N, $^{2}J_{H-H}$= 12.0 Hz, $^{3}J_{H-H}$= 4.0 Hz), 5.33 (m, 1H, CH=, cod), 6.33 (d, 1H, CH-OP, $^{3}J_{H-P}$= 16.0 Hz), 7.13 (d, 1H, CH=, $^{4}J_{H-H}$= 2.6 Hz), 7.18 (m, 3H, CH=), 7.42-7.52 (m, 12H, CH=), 7.61 (m, 2H, CH=), 7.72 (m, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.7 (CH_2, cod), 28.9 (CH_2, cod), 31.2 (CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_2, cod), 31.7 (CH_3, ^{t}Bu), 32.0 (CH_2, cod), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 62.9 (CH=, cod), 65.8 (CH=, cod), 71.2 (CH-N), 74.8 (CH-OP), 79.4 (CH_2-O), 103.5 (d, CH=, cod, J_{C-P}= 18.0 Hz), 104.4 (d, CH=, cod, J_{C-P}= 16.0 Hz), 117.4-

149.2 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 50.3 Hz), 173.6 (C=N). MS HR-ESI [found 992.4362, $C_{52}H_{66}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 992.4359].

[Ir(cod)(L11b)]BAr_F: Yield: 64 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 100.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (s, 9H, CH_3, ^{t}Bu), 1.19 (s, 9H, CH_3, ^{t}Bu), 1.21-2.77 (m, 16H, CH_2), 1.21-2.77 (m, 8H, CH_2, cod), 1.70 (m, 1H, CH=, cod), 3.98 (m, 1H, CH=, cod), 4.54 (m, 1H, CH-O), 4.64 (pt, 1H, CH-O, J_{H-H}= 9.2 Hz), 5.19 (m, 1H, CH-N), 5.20 (m, 1H, CH=, cod), 5.58 (m, 1H, CH=, cod), 6.00 (d, 1H, CH-OP, $^3J_{H-P}$= 16.4 Hz), 6.97 (m, 1H, CH=), 7.08 (m, 1H, CH=), 7.20 (m, 2H, CH=), 7.26 (m, 1H, CH=), 7.46-7.52 (m, 9H, CH=), 7.71 (s, 8H, CH=), 7.83 (d, 2H, CH=, $^3J_{H-H}$= 6.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.6 (CH_2), 26.5 (CH_2), 26.0 (d, CH_2, cod, J_{C-P}= 11.4 Hz), 29.3 (CH_2), 30.1 (CH_2, cod), 31.1 (CH_2, cod), 31.1 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (d, CH_2, cod, J_{C-P}= 4.6 Hz), 34.6 (C, ^{t}Bu), 61.1 (CH=, cod), 66.6 (CH=, cod), 70.4 (CH-N), 76.2 (CH-OP), 78.7 (CH_2-O), 100.4 (d, CH=, cod, J_{C-P}= 18.3 Hz), 103.6 (d, CH=, cod, J_{C-P}= 15.3 Hz), 117.4-143.1 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 46.5 Hz), 170.8 (d, C=N, $^3J_{C-P}$= 7.6 Hz). MS HR-ESI [found 988.4048, $C_{52}H_{62}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 988.4046].

[Ir(cod)(L11c)]BAr_F: Yield: 61 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 100.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.74 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.89 (m, 3H, CH_2, cod), 2.10 (m, 1H, CH_2, cod), 2.18 (s, 3H, CH_3), 2.19 (m, 1H, CH_2, cod), 2.26 (s, 3H, CH_3), 2.30-2.47 (m, 3H, CH_2, cod), 2.85 (m, 1H, CH=, cod), 4.03 (m, 1H, CH=, cod), 4.55 (m, 1H, CH-O), 4.67 (pt, 1H, CH-O, J_{H-H}= 9.6 Hz), 4.95 (m, 2H, CH-N and CH=, cod), 5.66 (m, 1H, CH=, cod), 6.01 (d, 1H, CH-OP, $^3J_{H-P}$= 14.8 Hz), 7.09-7.28 (m, 4H, CH=), 7.47-7.54 (m, 10H, CH=), 7.77 (m, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.4 (CH_3), 16.5 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 26.3 (CH_2, cod), 29.9 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_2, cod), 32.2 (CH_3, ^{t}Bu), 35.1 (C, ^{t}Bu), 34.6 (d, CH_2, cod, J_{C-P}= 5.3 Hz), 34.8 (C, ^{t}Bu), 61.5 (CH=, cod), 66.7 (CH=, cod), 70.5 (CH-N), 76.0 (CH-OP), 78.7 (CH_2-O), 100.1 (d, CH=, cod, J_{C-P}= 18.3 Hz), 103.6 (d, CH=, cod, J_{C-P}= 13.8 Hz), 117.4-143.5 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 170.8 (d, C=N, $^3J_{C-P}$= 7.6 Hz). MS HR-ESI [found 936.3735, $C_{48}H_{58}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 936.3733].

[Ir(cod)(L11d)]BAr_F: Yield: 64 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 107.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.37 (s, 9H, CH_3, $SiMe_3$), 0.49 (s, 9H, CH_3, $SiMe_3$), 1.53 (m, 2H, CH_2, cod), 1.63 (m, 1H, CH_2, cod), 1.76 (m, 1H, CH_2, cod), 1.94 (m, 1H, CH_2, cod), 2.09 (m, 1H, CH_2, cod), 2.15 (m, 1H, CH_2, cod), 2.37 (m, 1H, CH_2, cod), 3.11 (m, 1H, CH=, cod), 4.07 (m, 1H, CH=, cod), 4.42 (m, 1H, CH-O), 4.76 (m, 1H, CH-O), 5.43 (m, 1H, CH-N), 5.82 (m, 1H, CH=, cod), 6.00 (m, 1H, CH-OP), 6.95 (m, 2H, CH=), 7.22 (m, 5H, CH=), 7.33-7.52 (m, 10H, CH=), 7.71 (m, 8H, CH=), 7.93 (m, 5H, CH=), 8.13 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.2 (CH_3, $SiMe_3$), 1.4 (CH_3, $SiMe_3$), 26.4 (CH_2, cod), 29.4 (CH_2, cod), 31.4 (CH_2, cod), 34.7 (CH_2, cod), 61.4 (CH=, cod),

67.0 (CH=, cod), 71.5 (CH-N), 74.4 (CH-OP), 80.3 (CH_2-O), 102.3 (d, CH=, cod, J_{C-P}= 15.9 Hz), 106.5 (d, CH=, cod, J_{C-P}= 16.2 Hz), 117.4-150.1 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 172.8 (C=N). MS HR-ESI [found 1012.2961, $C_{50}H_{54}IrNO_4PSi_2$ (M-BAr_F)$^+$ requires 1012.2958].

[Ir(cod)(L11e)]BAr_F: Yield: 65 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 108.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.35 (s, 9H, CH_3, $SiMe_3$), 0.62 (s, 9H, CH_3, $SiMe_3$), 1.55 (m, 1H, CH_2, cod), 1.62 (m, 1H, CH_2, cod), 1.75 (m, 1H, CH_2, cod), 1.89 (m, 2H, CH_2, cod), 1.99 (m, 3H, CH_2, cod), 2.99 (m, 1H, CH=, cod), 3.99 (m, 1H, CH=, cod), 4.50 (dd, 1H, CH-O, $^2J_{H-H}$= 12.0 Hz, $^3J_{H-H}$= 4.0 Hz), 4.89 (m, 2H, CH-O and CH=, cod), 5.19 (m, 1H, CH=, cod), 5.32 (m, 1H, CH-N), 6.48 (d, 1H, CH-OP, $^3J_{H-H}$= 12.0 Hz), 6.99 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.03 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.25 (m, 3H, CH=), 7.37-7.53 (m, 14H, CH=), 7.73 (m, 9H, CH=), 6.92 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.99 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.04 (s, 1H, CH=), 8.21 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.0 (CH_3, $SiMe_3$), 1.2 (CH_3, $SiMe_3$), 27.3 (CH_2, cod), 30.2 (CH_2, cod), 30.5 (CH_2, cod), 33.4 (CH_2, cod), 61.8 (CH=, cod), 69.8 (CH=, cod), 71.8 (CH-N), 74.6 (d, CH-OP, $^2J_{C-P}$= 6.0 Hz), 79.6 (CH_2-O), 104.4 (d, CH=, cod, J_{C-P}= 17.1 Hz), 106.0 (d, CH=, cod, J_{C-P}= 14.0 Hz), 117.4-150.2 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.3 Hz), 174.3 (d, C=N, $^3J_{C-P}$= 5.0 Hz). MS HR-ESI [found 1012.2960, $C_{50}H_{54}IrNO_4PSi_2$ (M-BAr_F)$^+$ requires 1012.2958].

[Ir(cod)(L11f)]BAr_F: This compound was further purified by flash chromatography using neutral silica and dichloromethane as eluent. Yield: 50 mg (42%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 111.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56-1.73 (m, 2H, CH_2, cod), 1.77-1.86 (m, 1H, CH_2, cod), 1.92-2.01 (m, 1H, CH_2, cod), 2.10-2.15 (m, 2H, CH_2, cod), 2.25-2.36 (m, 2H, CH_2, cod), 2.48 (m, 1H, CH=, cod), 3.21 (m, 1H, CH=, cod), 4.33 (dd, 1H, CH-O, $^2J_{H-H}$= 9.4 Hz, $^3J_{H-H}$= 6.3 Hz), 4.70 (t, 1H, CH-O, J_{H-H}= 9.9 Hz), 5.10 (m, 1H, CH=, cod), 5.24 (dd, 1H, CH-N, $^3J_{H-H}$= 10.3 Hz, $^3J_{H-H}$= 6.3 Hz), 5.32 (m, 1H, CH=, cod), 6.00 (d, 1H, CH-OP, $^3J_{H-H}$= 21.3 Hz), 6.51 (dd, 2H, CH=, $^3J_{H-H}$= 11.7 Hz, $^3J_{H-H}$= 7.4 Hz), 6.74 (d, 2H, CH=, $^3J_{H-H}$= 7.3 Hz), 7.10-7.14 (m, 4H, CH=), 7.24-7.32 (m, 2H, CH=), 7.36-7.48 (m, 6H, CH=), 7.49-7.69 (m, 14H, CH=), 7.97 (d, 2H, CH=, $^3J_{H-H}$= 6.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.4 (CH_2, cod), 30.3 (CH_2, cod), 30.9 (CH_2, cod), 34.0 (CH_2, cod), 61.2 (CH=, cod), 65.5 (CH=, cod), 69.3 (CH-N), 76.8 (CH-OP), 77.8 (CH_2-O), 97.4 (d, CH=, cod, J_{C-P}= 12.9 Hz), 98.7 (d, CH=, cod, J_{C-P}= 11.6 Hz), 117.5-137.6 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz), 170.4 (d, C=N, $^3J_{C-P}$= 9.7 Hz) . MS HR-ESI [found 738.2109, $C_{36}H_{36}IrNO_2P$ (M-BAr_F)$^+$ requires 738.2107].

[Ir(cod)(L11g)]BAr_F: This compound was further purified by flash chromatography using neutral silica and dichloromethane as eluent. Yield: 56 mg (46%). Major isomer (55%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 115.8 (b). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55-2.60 (m, 8H, CH_2, cod), 2.23 (s, 3H, CH_3, *o*-Tol), 2.31 (m, 1H, CH=, cod), 2.60 (s, 3H,

CH_3, *o*-Tol), 3.15 (m, 1H, CH=, cod), 4.29 (m,1H, CH-O), 4.62 (m, 1H, CH-O), 4.91 (m, 1H, CH=, cod), 5.34 (m, 1H, CH-N), 5.58 (m, 2H, CH=, cod and CH-OP), 6.93-8.14 (m, 32H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): $\delta =$ 21.4-22.7 (CH_3, *o*-Tol), 26.4-35.0 (CH_2, cod), 62.9 (CH=, cod), 65.9 (CH=, cod), 70.2 (CH-N), 75.3 (CH-OP), 77.7 (CH_2-O), 117.4-142.6 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C-B}$= 49.9 Hz), 170.0 (C=N). Minor isomer (45%): ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta =$ 115.8 (b). ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 1.55-2.60 (m, 15H, CH_2, cod, CH_3, *o*-Tol and CH=, cod), 2.87 (m, 1H, CH=, cod), 4.36 (m, 1H, CH-O), 4.72 (m, 1H, CH-O), 4.95 (m, 1H, CH=, cod), 5.34 (m, 1H, CH-N), 5.58 (m, 1H, CH=, cod), 5.86 (m, 1H, CH-OP), 6.93-8.14 (m, 32H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): $\delta =$ 21.4-22.7 (CH_3, *o*-Tol), 26.4-35.0 (CH_2, cod), 62.9 (CH=, cod), 65.9 (CH=, cod), 69.6 (CH-N), 75.3 (CH-OP), 78.3 (CH_2-O), 117.4-142.6 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C-B}$= 49.9 Hz), 174.0 (C=N). MS HR-ESI [found 766.2423, $C_{38}H_{40}IrNO_2P$ $(M\text{-}BAr_F)^+$ requires 766.2420].

[Ir(cod)(L12a)]BAr_F: Yield: 63 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta =$ 101.7 (s). ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.90 (m, 6H, CH_3, ^{i}Pr), 1.04 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.71 (m, 2H, CH_2, cod), 2.05 (m, 1H, CH, ^{i}Pr), 2.06 (m, 3H, CH_2, cod), 2.26 (m, 1H, CH_2, cod), 2.39 (m, 2H, CH_2, cod), 3.29 (m, 1H, CH=, cod), 3.85 (m, 1H, CH=, cod), 4.07 (m, 1H, CH-N), 4.21 (pt, 1H, CH-O, J_{H-H}= 9.6 Hz), 4.58 (dd, 1H, CH-O, $^2J_{H-H}$= 10.4 Hz, $^3J_{H-H}$= 3.2 Hz), 5.03 (m, 1H, CH=, cod), 5.59 (m, 1H, CH=, cod), 5.93 (d, 1H, CH-OP, $^3J_{H-P}$= 17.6 Hz), 7.08 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.15 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz), 7.38 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.51 (m, 7H, CH=), 7.56 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz), 7.70 (m, 10H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta =$ 14.5 (CH_3, ^{i}Pr), 18.8 (CH_3, ^{i}Pr), 26.0 (CH_2, cod), 29.7 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.0 (CH, ^{i}Pr), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.8 (CH_2, cod), 32.2 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.2 (d, CH_2, cod, J_{C-P}= 7.08 Hz), 35.6 (C, ^{t}Bu), 64.2 (CH=, cod), 66.5 (CH=, cod), 70.7 (CH-N), 70.8 (CH_2-O), 76.2 (CH-OP), 98.7 (d, CH=, cod, J_{C-P}= 19.1 Hz), 104.7 (d, CH=, cod, J_{C-P}= 13.8 Hz), 117.4-149.1 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz), 169.7 (C=N). MS HR-ESI [found 958.4517, $C_{49}H_{68}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 958.4515].

[Ir(cod)(L12b)]BAr_F: Yield: 59 mg (90%). ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta =$ 101.0 (s). ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.91 (m, 6H, CH_3, ^{i}Pr), 0.98 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.73 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.75 (m, 2H, CH_2, cod), 2.09 (m, 1H, CH, ^{i}Pr), 2.09-2.16 (m, 4H, CH_2, cod), 2.17 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.43 (m, 2H, CH_2, cod), 3.24 (m, 1H, CH=, cod), 4.05 (m, 1H, CH=, cod), 4.06 (m, 1H, CH-N), 4.16 (pt, 1H, CH-O, J_{H-H}= 9.2 Hz), 4.55 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 2.8 Hz), 4.87 (m, 1H, CH=, cod), 5.59 (m, 1H, CH=, cod), 5.83 (d, 1H, CH-OP, $^3J_{H-P}$= 12.8 Hz), 7.06 (s, 1H, CH=), 7.26 (s, 2H, CH=), 7.46 (m, 2H, CH=), 7.52 (s, 4H, CH=), 7.63 (m, 2H, CH=), 7.71 (s, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta =$ 14.6 (CH_3, ^{i}Pr), 16.4 (CH_3), 16.5 (CH_3), 18.8 (CH_3, ^{i}Pr), 20.2 (CH_3), 20.3 (CH_3), 25.4 (CH_2, cod), 29.1

(CH_2, cod), 31.0 (CH, ^{i}Pr), 31.3 (CH_3, ^{t}Bu), 32.4 (CH_3, ^{t}Bu), 32.6 (CH_2, cod), 34.4 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.9 (d, CH_2, cod, J_{C-P}= 5.4 Hz), 63.3 (CH=, cod), 67.4 (CH=, cod), 70.4 (CH-N), 70.7 (CH_2-O), 76.0 (CH-OP), 97.1 (d, CH=, cod, J_{C-P}= 19.9 Hz), 104.3 (d, CH=, cod, J_{C-P}= 13.8 Hz), 117.4-143.9 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^{1}J_{C-B}$= 49.7 Hz), 169.0 (d, C=N, $^{3}J_{C-P}$= 8.3 Hz). MS HR-ESI [found 902.3892, $C_{45}H_{60}IrNO_4P$ (M-BAr_F)$^+$ requires 902.3889].

[Ir(cod)(L12f)]BAr_F: This compound was further purified by flash chromatography using neutral silica and dichloromethane as eluent. Yield: 64 mg (55%). Major isomer (74%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 110.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.6 Hz), 0.83 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 7.0 Hz), 1.22-1.74 (m, 2H, CH_2, cod), 1.81-1.96 (m, 1H, CH_2, cod), 1.95-2.10 (m, 2H, CH_2, cod, CH, ^{i}Pr), 2.15-2.28 (m, 2H, CH_2, cod), 2.41-2.52 (m, 2H, CH_2, cod), 2.61 (m, CH=, cod), 3.50 (m, CH=, cod), 4.11 (m, 1H, CH-N), 4.29 (pt, 1H, CH-O, J_{H-H}= 9.7 Hz), 4.50 (m, 1H, CH-O), 5.08 (m, 1H, CH=, cod), 5.33 (m, 1H, CH=, cod), 5.91 (d, 1H, CH-OP, $^{3}J_{H-P}$= 21.0 Hz), 6.61-6.66 (m, 2H, CH=), 7.22-7.25 (m, 2H, CH=), 7.31-7.38 (m, 2H, CH=), 7.52 (s, 4H, CH=), 7.55-7.63 (m, 5H, CH=), 7.71 (s, 8H, CH=), 7.89-7.93 (m, 2H, CH=), 8.00 (d, 2H, CH=, $^{3}J_{H-H}$= 6.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.1 (CH_3, ^{i}Pr), 18.3 (CH_3, ^{i}Pr), 26.8 (CH_2, cod), 29.6 (CH_2, cod), 31.5 (CH_2, cod), 32.3 (CH, ^{i}Pr), 35.3 (CH_2, cod), 61.8 (CH=, cod), 65.3 (CH=, cod), 70.1 (CH-N), 70.4 (CH_2-O), 76.5 (d, CH-OP, $^{2}J_{C-P}$= 4.6 Hz), 97.8 (d, CH=, cod, J_{C-P}= 12.0 Hz), 98.0 (d, CH=, cod, J_{C-P}= 12.5 Hz), 117.5-134.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^{2}J_{C-B}$= 49.9 Hz), 168.9 (d, C=N, J_{C-P}= 10.2 Hz). Minor isomer (26%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 109.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.38 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.8 Hz), 0.84 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.9 Hz), 1.24-1.72 (m, 2H, CH_2, cod), 1.80-1.95 (m, 1H, CH_2, cod), 1.97-2.11 (m, 2H, CH_2, cod, CH, ^{i}Pr), 2.16-2.29 (m, 2H, CH_2, cod), 2.41-2.52 (m, 2H, CH_2, cod), 2.86 (m, CH=, cod), 3.67 (m, CH=, cod), 4.07 (m, 1H, CH=, cod), 4.11 (m, 1H, CH-N), 4.29 (m, 1H, CH-O), 4.45 (m, 1H, CH-O), 5.01 (m, 1H, CH=, cod), 6.04 (d, 1H, CH-OP, $^{3}J_{H-P}$= 8.7 Hz), 6.61-6.66 (m, 2H, CH=), 7.22-7.25 (m, 2H, CH=), 7.31-7.38 (m, 2H, CH=), 7.52 (s, 4H, CH=), 7.55-7.63 (m, 5H, CH=), 7.71 (s, 8H, CH=), 7.89-8.03 (m, 4H, CH=). MS HR-ESI [found 704.2272, $C_{33}H_{38}IrNO_2P$ (M-BAr_F)$^+$ requires 704.2269].

[Ir(cod)(L12g)]BAr_F: This compound was further purified by flash chromatography using neutral silica and dichloromethane as eluent. Yield: 45 mg (38%). Major isomer (63%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 233 K): δ = 117.3 (s). ^{1}H NMR (400 MHz, CD_2Cl_2, 233 K): δ = 0.35 (b, 3H, CH_3, ^{i}Pr), 0.89 (b, 3H, CH_3, ^{i}Pr), 1.28-2.60 (m, 8H, CH_2, cod and CH, ^{i}Pr), 2.24 (m, 1H, CH=, cod), 2.57 (s, 3H, CH_3, *o*-Tol), 2.73 (s, 3H. CH_3, *o*-Tol), 3.36 (m, 1H, CH=, cod), 4.14 (m, 1H, CH-O), 4.40 (b, 1H, CH-O), 4.46 (b, 1H, CH-N), 4.83 (m, 1H, CH=, cod), 5.60 (m, 1H, CH=, cod), 5.30 (b, 1H, CH-OP), 6.64-8.65 (m, 25H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, rt): δ = 18.2 (CH_3, ^{i}Pr), 18.6 (CH_3, ^{i}Pr), 22.4 (CH_3, *o*-Tol), 25.6-36.5 (CH_2, cod and CH, ^{i}Pr), 63.3 (CH=, cod), 65.4 (CH=, cod), 70.3

(CH_2-O), 71.3 (CH-N), 75.1 (CH-OP), 95.7 (b, CH=, cod), 99.3 (b, CH=, cod), 117.4-142.7 (aromatic carbons), 171.9 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz), 167.8 (C=N). Minor isomer (37%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 233 K): δ = 119.2 (s). ^{1}H NMR (400 MHz, CD_2Cl_2, 233 K): δ = 0.23 (b, 3H, CH_3, ^{i}Pr), 0.82 (b, 3H, CH_3, ^{i}Pr), 1.28-2.60 (m, 8H, CH_2, cod and CH, ^{i}Pr), 2.07 (s, 3H, CH_3, *o*-Tol), 2.12 (s, 3H. CH_3, *o*-Tol), 2.31 (m, 1H, CH=, cod), 3.22 (m, 1H, CH=, cod), 4.14 (m, 1H, CH-O), 4.34 (b, 1H, CH-O), 4.46 (b, 1H, CH-N), 5.02 (m, 1H, CH=, cod), 5.36 (m, 1H, CH=, cod), 6.01 (b, 1H, CH-OP), 6.56-8.61 (m, 25H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, rt): δ = 13.0 (CH_3, ^{i}Pr), 13.8 (CH_3, ^{i}Pr), 22.0 (CH_3, *o*-Tol), 22.7 (CH_3, *o*-Tol), 25.6-36.5 (CH_2, cod and CH, ^{i}Pr), 63.3 (CH=, cod), 65.4 (CH=, cod), 70.7 (CH_2-O), 70.9 (CH-N), 75.1 (CH-OP), 95.7 (b, CH=, cod), 99.7 (b, CH=, cod), 117.4-142.7 (aromatic carbons), 171.9 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz), 171.9 (C=N). MS HR-ESI [found 732.2585, $C_{35}H_{42}IrNO_2P$ $(M\text{-}BAr_F)^+$ requires 732.2582].

[Ir(cod)(L12h)]BAr_F: This compound was further purified by flash chromatography using neutral silica and dichloromethane as eluent. Yield: 65 mg (55%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 131.0 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.25 (m, 1H, CH_2, Cy), 0.71-0.95 (m, 3H, CH_2, Cy), 0.75 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.6 Hz), 0.89 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 7.0 Hz), 0.96-1.36 (m, 10H, CH_2, Cy), 1.42-1.76 (m, 7H, CH_2, Cy, cod), 1.82-2.04 (m, 5H, CH_2, Cy, cod), 2.05-2.13 (m, 1H, CH, iPr), 2.20-2.38 (m, 4H, CH_2, CH, cod, Cy), 3.28 (m, CH=, cod), 3.78 (m, CH=, cod), 3.98 (m, CH-N), 4.19 (pt, CH-O, J_{H-H}= 9.6 Hz), 4.51 (dd, 1H, CH-O, $^2J_{H-H}$= 9.6 Hz, $^3J_{H-H}$= 3.2 Hz), 4.68 (m, CH=, cod), 5.07 (m, 1H, CH=, cod), 5.68 (d, 1H, CH-OP, $^3J_{H-P}$= 24.0 Hz), 7.34-7.40 (m, 4H, CH=), 7.41-7.43 (s, 2H, CH=), 7.56-7.68 (s, 11H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.4 (CH_3, ^{i}Pr), 19.3 (CH_3, ^{i}Pr), 25.5-31.9 (CH_2, cod, Cy), 35.6 (CH, ^{i}Pr), 39.0 (d, CH, Cy, $^1J_{C-P}$= 30.3 Hz), 41.8 (d, CH, Cy, $^1J_{C-P}$= 34.4 Hz), 61.1 (CH=, cod), 61.5 (CH=, cod), 69.5 (CH-N), 70.5 (CH_2-O), 76.3 (d, $^2J_{C-P}$= 5.9 Hz), 93.2 (d, CH=, cod, J_{C-P}= 11.7 Hz), 95.2 (d, CH=, cod, J_{C-P}= 11.2 Hz), 117.4-134.8 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49.9 Hz), 169.8 (C=N). MS HR-ESI [found 716.3206, $C_{33}H_{50}IrNO_2P$ $(M\text{-}BAr_F)^+$ requires 716.3203].

[Ir(cod)(L13a)]BAr_F: Yield: 64 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 103.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 9H, CH_3, ^{t}Bu), 1.12 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 2H, CH_2, cod), 2.02 (m, 2H, CH_2, cod), 2.33 (m, 2H, CH_2, cod), 2.43 (m, 1H, CH_2, cod), 2.59 (m, 1H, CH_2, cod), 3.81 (m, 1H, CH=, cod), 4.04 (m, 1H, CH-N), 4.35 (pt, 1H, CH-O, J_{H-H}= 8.8 Hz), 4.72 (dd, 1H, CH-O, $^2J_{H-H}$= 10.0 Hz, $^3J_{H-H}$= 2.4 Hz), 5.00 (m, 1H, CH=, cod), 5.71 (m, 1H, CH=, cod), 5.83 (d, 1H, CH-OP, $^3J_{H-P}$= 20.8 Hz), 7.04 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.17 (d, 2H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.22 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz), 7.29 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz), 7.41 (t, 2H, CH=, $^3J_{H-H}$= 7.6 Hz), 7.47-7.52 (m, 4H, CH=), 7.71 (s, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.9 (CH_2, cod), 25.6 (CH_3, ^{t}Bu), 27.9

(CH_2, cod), 29.7 (CH_2, cod), 30.1 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 33.6 (CH_2, cod), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 36.9 (d, CH_2, cod, $J_{C\text{-}P}$= 6.8 Hz), 63.3 (CH=, cod), 67.4 (CH=, cod), 72.1 (CH_2-O), 74.5 (CH-N), 75.0 (CH-OP), 97.5 (d, CH=, cod, $J_{C\text{-}P}$= 22.2 Hz), 104.8 (d, CH=, cod, $J_{C\text{-}P}$= 12.1 Hz), 117.4-148.7 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.7 Hz), 169.6 (d, C=N, $^3J_{C\text{-}P}$= 7.6 Hz). MS HR-ESI [found 972.4675, $C_{50}H_{70}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 972.4672].

[Ir(cod)(L13b)]BAr_F: Yield: 60 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 102.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 9H, CH_3, ^{t}Bu), 1.11 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.65 (m, 1H, CH_2, cod), 1.73 (m, 1H, CH_2, cod), 1.80 (s, 3H, CH_3), 1.99 (m, 1H, CH_2, cod), 2.15 (m, 1H, CH_2, cod), 2.23 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.26 (m, 1H, CH_2, cod), 2.43 (m, 2H, CH_2, cod), 2.54 (m, 1H, CH_2, cod), 3.98 (m, 1H, CH-N), 4.07 (m, 1H, CH=, cod), 4.16 (m, 1H, CH=, cod), 4.25 (pt, 1H, CH-O, $J_{H\text{-}H}$= 9.6 Hz), 4.64 (dd, 1H, CH-O, $^2J_{H\text{-}H}$= 10.0 Hz, $^3J_{H\text{-}H}$= 2.4 Hz), 4.92 (m, 1H, CH=, cod), 5.63 (m, 1H, CH=, cod), 5.74 (d, 1H, CH-OP, $^3J_{H\text{-}P}$= 12.4 Hz), 6.99 (s, 1H, CH=), 7.21 (s, 1H, CH=), 7.32 (m, 2H, CH=), 7.40-7.49 (m, 1H, CH=), 7.52 (s, 6H, CH=), 7.71 (s, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.5 (CH_3), 16.6 (CH_3), 20.1 (CH_3), 20.3 (CH_3), 23.8 (CH_2, cod), 26.0 (CH_3, ^{t}Bu), 28.0 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 33.9 (CH_2, cod), 34.3 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 37.0 (d, CH_2, cod, $J_{C\text{-}P}$= 7.6 Hz), 65.5 (CH=, cod), 66.9 (CH=, cod), 71.9 (CH_2-O), 74.7 (CH-N), 75.2 (d, CH-OP, $J_{C\text{-}P}$= 4.6 Hz), 95.5 (d, CH=, cod, $J_{C\text{-}P}$= 22.1 Hz), 103.5 (d, CH=, cod, $J_{C\text{-}P}$= 12.3 Hz), 117.4-145.1 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.7 Hz), 169.8 (d, C=N, $^3J_{C\text{-}P}$= 7.64 Hz). MS HR-ESI [found 916.4049, $C_{46}H_{62}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 916.4046].

[Ir(cod)(L14a)]BAr_F: Yield: 61 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 101.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.75-2.1 (m, 8H, CH_2, cod), 3.28 (m, 1H, CH=, cod), 3.61 (m, 1H, CH=, cod), 4.50 (dd, 1H, CH-O, $^2J_{H\text{-}H}$= 9.2 Hz, $^3J_{H\text{-}H}$= 3.6 Hz), 4.77 (pt, 1H, CH-O, $J_{H\text{-}H}$= 10.0 Hz), 5.13 (m, 1H, CH=, cod), 5.18 (m, 1H, CH-N), 5.26 (m, 1H, CH=, cod), 6.22 (d, 1H, CH-OP, $^3J_{H\text{-}P}$= 8.4 Hz), 6.97 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.6 Hz), 7.13 (m, 3H, CH=), 7.36-7.52 (m, 10H, CH=), 7.60 (d, 1H, CH=, $^3J_{H\text{-}H}$= 6.4 Hz), 7.72 (m, 9H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.3 (CH_2, cod), 29.1 (CH_2, cod), 29.7 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.7 (CH_2, cod), 34.7 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 63.5 (CH=, cod), 66.2 (CH=, cod), 70.8 (CH-N), 74.6 (CH-OP), 79.5 (CH_2-O), 103.4 (d, CH=, cod, $J_{C\text{-}P}$= 15.3 Hz), 104.9 (d, CH=, cod, $J_{C\text{-}P}$= 12.2 Hz), 117.4-149.0 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 50.5 Hz), 172.5 (C=N). MS HR-ESI [found 992.4361, $C_{52}H_{66}IrNO_4P$ $(M\text{-}BAr_F)^+$ requires 992.4359].

[Ir(cod)(L14d)]BAr_F: Yield: 62 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 107.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.30 (s, 9H, CH_3, $SiMe_3$), 0.66 (s, 9H, CH_3, $SiMe_3$), 1.56 (m, 1H, CH_2, cod), 1.69 (m, 1H, CH_2, cod), 1.96-2.17 (m, 6H, CH_2, cod), 3.08 (m,

1H, CH=, cod), 3.85 (m, 1H, CH=, cod), 4.41 (dd, 1H, CH-O, $^{2}J_{H-H}$= 8.8 Hz, $^{3}J_{H-H}$= 3.2 Hz), 4.80 (pt, 1H, CH-O, J_{H-H}= 9.2 Hz), 4.93 (m, 1H, CH=, cod), 5.10 (m, 1H, CH=, cod), 5.33 (m, 1H, CH-N), 5.97 (d, 1H, CH-OP, $^{3}J_{H-P}$= 4.4 Hz), 6.91 (d, 2H, CH=, $^{3}J_{H-H}$= 7.6 Hz), 6.96 (d, 1H, CH=, $^{3}J_{H-H}$= 8.8 Hz), 7.07 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 7.22-7.56 (m, 14H, CH=), 7.62 (d, 1H, CH=, $^{3}J_{H-H}$= 6.0 Hz), 7.71 (s, 8H, CH=), 7.89 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.00 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.03 (s, 1H, CH=), 8.22(s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.1 (CH_3, $SiMe_3$), 1.2 (CH_3, $SiMe_3$), 26.1 (CH_2, cod), 28.9 (CH_2, cod), 32.1 (CH_2, cod), 35.0 (CH_2, cod), 61.4 (CH=, cod), 66.8 (CH=, cod), 72.5 (CH-N), 74.6 (CH-OP), 78.6 (CH_2-O), 103.3 (d, CH=, cod, J_{C-P}= 18.3 Hz), 104.9 (d, CH=, cod, J_{C-P}= 13.7 Hz), 117.4-150.2 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^{1}J_{C-B}$= 49.7 Hz), 172.0 (d, C=N, $^{3}J_{C-P}$= 7.6 Hz). MS HR-ESI [found 1012.2960, $C_{50}H_{54}IrNO_4PSi2$ $(M\text{-}BAr_F)^+$ requires 1012.2958].

[Ir(cod)(L14e)]BAr$_F$: Yield: 64 mg (96%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 105.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.48 (s, 9H, CH_3, $SiMe_3$), 0.71 (s, 9H, CH_3, $SiMe_3$), 1.91 (m, 1H, CH_2, cod), 2.04 (m, 1H, CH_2, cod), 2.37 (m, 4H, CH_2, cod), 2.49 (m, 1H, CH_2, cod), 2.51 (m, 1H, CH_2, cod), 3.11 (m, 1H, CH=, cod), 4.27 (m, 1H, CH=, cod), 4.75 (m, 1H, CH-O), 5.00 (pt, 1H, CH-O, J_{H-H}= 10.0 Hz), 5.40 (m, 1H, CH-N), 5.75 (m, 1H, CH=, cod), 5.81 (m, 1H, CH=, cod), 6.66 (d, 1H, CH-OP, $^{3}J_{H-P}$= 6.8 Hz), 7.19 (t, 2H, CH=, $^{3}J_{H-H}$= 9.6 Hz), 7.32 (d, 2H, CH=, $^{3}J_{H-H}$= 6.8 Hz), 7.48 (m, 3H, CH=), 7.62-7.79 (m, 13H, CH=), 7.98 (s, 8H, CH=), 8.11 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.18 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.25 (s, 1H, CH=), 8.34 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.5 (CH_3, $SiMe_3$), 0.6 (CH_3, $SiMe_3$), 26.4 (CH_2, cod), 30.1 (CH_2, cod), 30.6 (CH_2, cod), 34.3 (d, CH_2, cod, J_{C-P}= 7.4 Hz), 61.3 (CH=, cod), 68.6 (CH=, cod), 69.8 (CH-N), 74.6 (CH-OP), 78.8 (CH_2-O), 102.5 (d, CH=, cod, J_{C-P}= 18.3 Hz), 107.5 (d, CH=, cod, J_{C-P}= 14.4 Hz), 117.5-149.9 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^{1}J_{C-B}$= 49.7 Hz), 172.4 (C=N). MS HR-ESI [found 1012.2962, $C_{50}H_{54}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 1012.2958].

[Ir(cod)(L14f)]BAr$_F$: This compound was further purified by flash chromatography using neutral silica and dichloromethane as eluent. Yield: 48 mg (40%). Major isomer (78%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 111.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67-1.90 (m, 2H, CH_2, cod), 2.04-2.12 (m, 4H, CH_2, cod), 2.27-2.36 (m, 2H, CH_2, cod), 2.95 (m, 1H, CH=, cod), 3.36 (m, CH=, cod), 4.38 (m, 1H, CH-O), 4.78 (m, 1H, CH-O), 5.01 (m, 1H, CH=, cod), 5.27 (m, 1H, CH-N), 5.34 (m, 1H, CH=, cod), 6.10 (d, 1H, CH-OP, $^{3}J_{C-P}$= 9.0 Hz), 6.91 (d, 2H, CH=, $^{3}J_{H-H}$= 7.5 Hz), 7.19-7.27 (m, CH=, 3H), 7.30-7.40 (m, 4H, CH=), 7.43-7.50 (m, 7H, CH=), 7.53 (s, 4H, CH=), 7.59-7.64 (m, 4H, CH=), 7.73 (s, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.5 (CH_2, cod), 29.7 (CH_2, cod), 30.5 (CH_2, cod), 33.6 (CH_2, cod), 62.6 (CH=, cod), 65.5 (CH=, cod), 69.1 (CH-N), 77.2 (CH-OP), 78.6 (CH_2-O), 99.0 (d, CH=, cod, J_{C-P}= 11.9 Hz), 100.3 (d, CH=, cod, J_{C-P}= 12.0 Hz), 117.4-137.8 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^{1}J_{C-B}$= 49.6 Hz), 173.5 (C=N). Minor isomer (22%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 111.2 (s). ^{1}H NMR (400

MHz, $CDCl_3$): $\delta =$ 1.66-1.92 (m, 4H, CH_2, cod), 2.04-2.12 (m, 2H, CH_2, cod), 2.27-2.36 (m, 2H, CH_2, cod), 2.61 (m, 1H, CH=, cod), 3.31 (m, CH=, cod), 4.43 (m, 1H, CH-O), 4.78 (m, 1H, CH-O), 5.20 (m, 1H, CH=, cod), 5.27 (m, 1H, CH-N), 5.40 (m, 1H, CH=, cod), 6.10 (m, 1H, CH-OP), 6.57-6.62 (m, 2H, CH=), 6.83 (d, 2H, CH=, $^3J_{H-H}$= 7.3 Hz), 7.19-7.27 (m, CH=, 2H), 7.30-7.40 (m, 3H, CH=), 7.43-7.50 (m, 6H, CH=), 7.53 (s, 4H, CH=), 7.59-7.64 (m, 4H, CH=), 7.73 (s, 8H, CH=), 8.07 (d, 1H, CH=, $^3J_{H-H}$= 7.0 Hz). MS HR-ESI [found 738.2111, $C_{36}H_{36}IrNO_2P$ $(M\text{-}BAr_F)^+$ requires 738.2107].

[Ir(cod)(L14g)]BAr_F: This compound was further purified by flash chromatography using neutral silica and dichloromethane as eluent. Yield: 52 mg (43%). Major isomer (57%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): $\delta =$ 116.4 (b). ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta =$ 1.58-2.63 (m, 8H, CH_2, cod), 2.28 (s, 3H, CH_3, *o*-Tol), 2.42 (m, 1H, CH=, cod), 2.64 (s, 3H, CH_3, *o*-Tol), 3.21 (m, 1H, CH=, cod), 4.39 (m,1H, CH-O), 4.67 (m, 1H, CH-O), 4.95 (m, 1H, CH=, cod), 5.38 (m, 1H, CH-N), 5.66 (m, 2H, CH=, cod and CH-OP), 6.75-8.12 (m, 32H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): $\delta =$ 21.3-22.6 (CH_3, *o*-Tol), 25.9-35.2 (CH_2, cod), 63.0 (CH=, cod), 64.7 (CH=, cod), 70.2 (CH-N), 75.1 (CH-OP), 77.9 (CH_2-O), 117.5-142.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.9 Hz), 170.6 (C=N). Minor isomer (43%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): $\delta =$ 116.4 (b). ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta =$ 1.58-2.63 (m, 15H, CH_2, cod, CH_3, *o*-Tol and CH=, cod), 2.96 (m, 1H, CH=, cod), 4.42 (m, 1H, CH-O), 4.79 (m, 1H, CH-O), 5.01 (m, 1H, CH=, cod), 5.38 (m, 1H, CH-N), 5.48 (m, 1H, CH=, cod), 5.93 (m, 1H, CH-OP), 6.75-8.12 (m, 32H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): $\delta =$ 21.3-22.6 (CH_3, *o*-Tol), 25.9-35.2 (CH_2, cod), 63.0 (CH=, cod), 64.7 (CH=, cod), 69.6 (CH-N), 75.1 (CH-OP), 78.7 (CH_2-O), 117.5-142.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.9 Hz), 173.3 (C=N). MS HR-ESI [found 766.2423, $C_{38}H_{40}IrNO_2P$ $(M\text{-}BAr_F)^+$ requires 766.2420].

[Ir(cod)(L14h)]BAr_F: This compound was further purified by flash chromatography using neutral silica and dichloromethane as eluent. Yield: 66 mg (55%). ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta =$ 132.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.83-0.94 (m, 2H, CH_2, Cy), 1.06-1.52 (m, 12H, CH_2, cod, Cy), 1.65-1.94 (m, 10H, CH_2, cod, Cy), 2.10-2.41 (m, 6H, CH_2, CH, cod, Cy), 3.53 (m, 1H, CH=, cod), 3.67 (m, 1H, CH=, cod), 4.61 (dd, 1H, CH-O, $^2J_{H-H}$= 9.7 Hz, $^3J_{H-H}$= 4.9 Hz), 4.76 (pt, 1H, CH-O, J_{H-H}= 9.7 Hz), 5.04-5.16 (m, 2H, CH=, cod), 5.19 (dd, 1H, CH-N, $^3J_{H-H}$= 9.7 Hz, $^3J_{H-H}$= 4.9 Hz), 5.80 (d, 1H, CH-OP, $^3J_{C-P}$= 9.3 Hz), 7.17-7.20 (m, 1H, CH=), 7.40-7.45 (m, 2H, CH=), 7.46-7.50 (m, 2H, CH=), 7.55 (s, 3H, CH=), 7.75 (s, 6H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta =$ 25.6-26.9 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 29.7 (CH_2), 30.1 (CH_2), 30.8 (CH_2), 34.2 (CH_2), 40.71 (d, CH, Cy, J_{C-P}= 36.3 Hz), 39.2 (d, CH, Cy, J_{C-P}= 27.0 Hz), 60.6 (CH=, cod), 62.6 (CH=, cod), 68.6 (CH-N), 77.1 (d, CH-OP, $^2J_{C-P}$= 3.1 Hz), 78.2 (CH_2-O), 95.8 (d, CH=, cod, J_{C-P}= 12.0 Hz), 96.9 (d, CH=, cod, J_{C-P}= 11.2 Hz), 117.4-137.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz), 173.7 (C=N). MS HR-ESI [found 750.3049, $C_{36}H_{48}IrNO_2P$ $(M\text{-}BAr_F)^+$ requires 750.3046].

[Ir(cod)(L15a)]BAr$_F$: Yield: 64 mg (96%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 103.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.74 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.75-2.06 (m, 8H, CH_2, cod), 3.17 (m, 1H, CH=, cod), 3.76 (m, 1H, CH=, cod), 4.58 (dd, 1H, CH-O, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 4.0 Hz), 4.71 (m, 1H, CH=, cod), 4.90 (pt, 1H, CH-O, J_{H-H}= 9.2 Hz), 5.17 (m, 1H, CH-N), 5.18 (m, 1H, CH=, cod), 5.55 (m, 1H, CH-OP), 7.17 (m, 4H, CH=), 7.40 (m, 3H, CH=), 7.53 (m, 6H, CH=), 7.32 (s, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.1 (d, CH_3, $^3J_{C-P}$= 9.9 Hz), 28.2 (CH_2, cod), 29.4 (CH_2, cod), 31.2 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.5 (CH_2, cod), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 62.0 (CH=, cod), 67.5 (CH=, cod), 69.2 (CH-OP), 71.4 (CH-N), 79.4 (CH_2-O), 103.9 (CH=, cod) 117.4-149.3 (aromatic carbons), 161.6 (q, C-B, BAr$_F$, $^1J_{C-B}$= 49.7 Hz), 174.4 (C=N). MS HR-ESI [found 930.4205, $C_{47}H_{64}IrNO_4P$ (M-BAr$_F$)$^+$ requires 930.4202].

[Ir(cod)(L15d)]BAr$_F$: Yield: 63 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 107.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.48 (s, 9H, CH_3, $SiMe_3$), 0.51 (s, 9H, CH_3, $SiMe_3$), 1.62 (d, 3H, CH_3, $^3J_{H-H}$= 6.4 Hz), 1.63 (m, 2H, CH_2, cod), 1.72 (m, 1H, CH_2, cod), 1.92 (m, 2H, CH_2, cod), 2.05 (m, 1H, CH_2, cod), 2.17 (m, 1H, CH_2, cod), 2.34 (m, 1H, CH_2, cod), 3.14 (m, 1H, CH=, cod), 4.03 (m, 1H, CH=, cod), 4.44 (dd, 1H, CH-O, $^2J_{H-H}$= 9.6 Hz, $^3J_{H-H}$= 4.8 Hz), 4.84 (m, 2H, CH-O, CH=, cod), 5.20 (m, 1H, CH-OP), 5.38 (m, 1H, CH-N), 5.75 (m, 1H, CH=, cod), 6.98 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.04 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.11 (d, 2H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.26 (t, 3H, CH=, $^3J_{H-H}$= 6.4 Hz), 7.44-7.52 (m, 8H, CH=), 7.71 (s, 8H, CH=), 7.93 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.96 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.10 (s, 1H, CH=), 8.13 (s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ = 0.2 (CH_3, $SiMe_3$), 1.3 (CH_3, $SiMe_3$), 19.3 (d, CH_3, $^3J_{C-P}$= 6.8 Hz), 26.3 (CH_2, cod), 29.4 (CH_2, cod), 31.4 (CH_2, cod), 34.7 (CH_2, cod), 60.9 (CH=, cod), 66.4 (CH=, cod), 68.2 (CH-OP), 71.2 (CH-N), 78.4 (CH_2-O), 101.8 (d, CH=, cod, J_{C-P}= 18.3 Hz), 106.7 (d, CH=, cod, J_{C-P}= 15.3 Hz), 117.4-150.3 (aromatic carbons), 161.6 (q, C-B, BAr$_F$, $^1J_{C-B}$= 50.5 Hz), 173.4 (d, C=N, $^3J_{C-P}$= 7.6 Hz). MS HR-ESI [found 950.2804, $C_{45}H_{52}IrNO_4PSi_2$ (M-BAr$_F$)$^+$ requires 950.2802].

[Ir(cod)(L15e)]BAr$_F$: Yield: 61 mg (92%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 109.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.50 (s, 9H, CH_3, $SiMe_3$), 0.64 (s, 9H, CH_3, $SiMe_3$), 1.66 (m, 1H, CH_2, cod), 1.73 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.81 (m, 1H, CH_2, cod), 1.92 (m, 5H, CH_2, cod), 2.06 (m, 1H, CH_2, cod), 3.05 (m, 1H, CH=, cod), 3.97 (m, 1H, CH=, cod), 4.60 (dd, 1H, CH-O, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 4.0 Hz), 4.91 (m, 2H, CH-O, CH=, cod), 5.18 (m, 1H, CH=, cod), 5.28 (m, 1H, CH-N), 5.47 (m, 1H, CH-OP), 6.96 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.03 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.18 (m, 2H, CH=), 7.25 (m, 2H, CH=), 7.46-7.52 (m, 6H, CH=), 7.72 (s, 9H, CH=), 7.95 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.97 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.13 (s, 1H, CH=), 8.18 (s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ = 0.0 (CH_3, $SiMe_3$), 1.2 (CH_3, $SiMe_3$), 18.2 (d, CH_3, $^3J_{C-P}$= 7.6 Hz), 27.5

(CH_2, cod), 29.7 (CH_2, cod), 29.8 (CH_2, cod), 33.2 (CH_2, cod), 60.7 (CH=, cod), 69.2 (CH=, cod), 69.8 (CH-OP), 71.3 (CH-N), 79.2 (CH_2-O), 104.6 (d, CH=, cod, $J_{C\text{-}P}$= 17.5 Hz), 105.7 (d, CH=, cod, $J_{C\text{-}P}$= 14.4 Hz), 117.4-150.6 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.7 Hz), 174.2 (C=N). MS HR-ESI [found 950.2805, $C_{45}H_{52}IrNO_4PSi_2$ (M-BAr_F)$^+$ requires 950.2802].

[Ir(cod)(L16a)]BAr_F: Yield: 65 mg (96%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 104.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.57 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 0.89 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 1.35 (s, 18H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 3H, CH_2, cod) 1.89 (m, 1H, CH_2, cod), 2.17 (m, 3H, CH_2, cod), 2.30 (m, 1H, CH_2, cod), 2.40 (m, 1H, CH, ^{i}Pr), 3.97 (m, 2H, CH=, cod), 4.48 (dd, 1H, CH-O, $^2J_{H\text{-}H}$= 8.8 Hz, $^3J_{H\text{-}H}$= 4.4 Hz), 4.63 (m, 1H, CH=, cod), 4.84 (pt, 1H, CH-O, $J_{H\text{-}H}$= 9.6 Hz), 4.90 (m, 1H, CH-OP), 5.34 (dd, 1H, CH-N, $^2J_{H\text{-}H}$= 9.6 Hz, $^3J_{H\text{-}H}$= 4.4 Hz), 5.65 (m, 1H, CH=, cod), 7.14-7.25 (m, 3H, CH=), 7.405-7.52 (m, 9H, CH=), 7.71 (s, 8H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ = 15.8 (CH_3, ^{i}Pr), 17.6 (CH_3, ^{i}Pr), 26.1 (CH_2, cod), 29.4 (CH_2, cod), 31.1 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.5 (CH_2, cod), 34.6 (CH, ^{i}Pr), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 63.9 (CH=, cod), 64.0 (CH=, cod), 70.4 (CH-N), 75.9 (CH-OP), 78.9 (CH_2-O), 101.4 (d, CH=, cod, $J_{C\text{-}P}$= 18.3 Hz), 105.4 (d, CH=, cod, $J_{C\text{-}P}$= 14.4 Hz), 117.4-149.1 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 50.5 Hz), 173.0 (C=N). MS HR-ESI [found 958.4518, $C_{49}H_{68}IrNO_4P$ (M-BAr_F)$^+$ requires 958.4515].

[Ir(cod)(L16d)]BAr_F: Yield: 64 mg (95%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 108.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.28 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 0.55 (s, 18H, CH_3, $SiMe_3$), 0.84 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 7.2 Hz), 1.64 (m, 4H, CH_2, cod), 2.08 (m, 2H, CH_2, cod), 2.20 (m, 1H, CH_2, cod), 2.35 (m, 1H, CH_2, cod), 2.40 (m, 1H, CH, ^{i}Pr), 3.52 (m, 1H, CH=, cod), 4.08 (m, 1H, CH=, cod), 4.47 (dd, 1H, CH-O, $^2J_{H\text{-}H}$= 9.2 Hz, $^3J_{H\text{-}H}$= 4.4 Hz), 4.75 (m, 1H, CH=, cod), 4.87 (m, 2H, CH-O, CH-OP), 5.38 (m, 1H, CH-N), 5.85 (m, 1H, CH=, cod), 6.98 (t, 2H, CH=, $^3J_{H\text{-}H}$= 9.2 Hz), 7.11 (m, 2H, CH=), 7.25 (m, 3H, CH=), 7.45-7.52 (m, 8H, CH=), 7.71 (s, 8H, CH=), 7.94 (m, 2H, CH=), 8.11 (s, 1H, CH=), 8.14 (s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ = 0.1 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 15.8 (CH_3, ^{i}Pr), 17.8 (CH_3, iPr), 25.9 (CH_2, cod), 29.2 (CH_2, cod), 30.6 (d, CH, ^{i}Pr, $^3J_{C\text{-}P}$= 6.8 Hz), 31.7 (CH_2, cod), 35.0 (CH_2, cod), 61.2 (CH=, cod), 65.5 (CH=, cod), 70.5 (CH-N), 75.2 (CH-OP), 78.4 (CH_2-O), 101.7 (d, CH=, cod, $J_{C\text{-}P}$= 19.1 Hz), 106.7 (d, CH=, cod, $J_{C\text{-}P}$= 13.6 Hz), 117.4-151.1 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 50.4 Hz), 173.4 (C=N). MS HR-ESI [found 978.3119, $C_{47}H_{56}IrNO_4PSi_2$ (M-BAr_F)$^+$ requires 978.3115].

[Ir(cod)(L16e)]BAr_F: Yield: 63 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 108.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.51 (s, 9H, CH_3, $SiMe_3$), 0.64 (s, 9H, CH_3, $SiMe_3$), 0.95 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.4 Hz), 1.00 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.4 Hz), 1.85 (m, 5H, CH_2, cod), 2.00 (m, 2H, CH_2, cod), 2.14 (m, 1H, CH_2, cod), 2.45 (m, 1H, CH, ^{i}Pr), 3.33

(m, 1H, CH=, cod), 4.02 (m, 1H, CH=, cod), 4.62 (dd, 1H, CH-O, $^{2}J_{H-H}$= 9.2 Hz, $^{3}J_{H-H}$= 4.4 Hz), 4.92 (m, 3H, CH=, cod, CH-O, CH-OP), 5.29 (m, 2H, CH-N, CH=, cod), 6.99 (m, 2H, CH=), 7.26 (m, 4H, CH=), 7.42-7.53 (m, 9H, CH=), 7.73 (s, 8H, CH=), 7.96 (m, 2H, CH=), 8.13 (s, 1H, CH=), 8.16 (s, 1H, CH=). ^{13}C (100.6 MHz, $CDCl_3$): δ = 0.1 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 18.3 (CH_3, ^{i}Pr), 18.3 (CH_3, ^{i}Pr), 28.1 (CH_2, cod), 29.3 (CH_2, cod), 31.4 (CH_2, cod), 32.2 (d, CH, ^{i}Pr, $^{3}J_{C-P}$= 6.1 Hz), 32.6 (CH_2, cod), 60.6 (CH=, cod), 69.1 (CH=, cod), 71.0 (CH-N), 78.2 (CH_2-O), 78.6 (CH-OP), 104.6 (d, CH=, cod, J_{C-P}= 16.9 Hz), 105.4 (d, CH=, cod, J_{C-P}= 14.6 Hz), 117.4-150.2 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^{1}J_{C-B}$= 49.7 Hz), 173.6 (d, C=N, $^{3}J_{C-P}$= 6.1 Hz). MS HR-ESI [found 978.3118, $C_{47}H_{56}IrNO_4PSi_2$ $(M\text{-}BAr_F)^+$ requires 978.3115].

3.3.4.7. Procedure for the preparation of substrate S55

A flame-dried Schkenk flask was charged with potassium *tert*-butoxide (4 mmol, 0.43 g) and stir bar. Dry DMSO (4 mL) was added, followed by isopropyltriphenyl-phosphonium iodide (4 mmol, 0.43 g). This mixture was added dropwise with a syringe to a solution of the corresponding ketone (1 mmol) in toluene (3.5 mL). The reaction was heated to reflux overnight. It was allowed to cool to room temperature, and petroleum ether and water were added. The organic phase was separated and washed with water (x2) and brine, died over $MgSO_4$, filtered, and concentrated *in vacuo*. All products were purified by flash column chromatography (petroleum ether) affording the corresponding product as colorless oil (222 mg, 84%). $_{1}$H NMR (400 MHz, $CDCl_3$): δ= 1.61 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 2.36 (s, 3H, CH_3, PhMe), 6.93-7.03 (m, 3H, CH=, Ar), 7.20 (td, 1H, CH=, Ar, J= 7.5 Hz, J=1.1 Hz). $_{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 20.7 (CH_3), 21.0 (CH_3), 21.6 (CH_3), 22.2 (CH_3), 125.6 (CH=), 126.6 (CH=), 127.1 (C), 127.9 (CH=), 129.2 (CH=), 130.2 (C), 137.7 (C), 145.4 (C).

3.3.4.8. General procedure for the hydrogenation of minimally functionalized olefins

The alkene (0.5 mmol) and Ir complex (2 mol%) were dissolved in the corresponding solvent CH_2Cl_2 (2 mL) and placed in a high-pressure autoclave. The autoclave was purged 4 times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short plug of Celite. Conversions were determined by ^{1}H NMR and enantiomeric excesses were determined by chiral GC or chiral HPLC (for hydrogenation products **S1**-**S2**, **S4**-**S6**, **S14**, **S16**-**S17**, **S20**, **S23**, **S27**-**S29**, **S31**-**S33**, **S35**-**S41** and **S44**-**S45** see previous Section 3.1.4.5 and for hydrogenation products from **S7**-**S13**, **S18**-**S19**, **S21**-**S23**, **S25**-**S26**, **S30**, **S34** and **S52** see previous Section 3.2.4.6).

1,2-Dimethyl-2,3-dihydro-1H-indene.[5a] Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, Isotherm at 90 ºC). t_R 11.7 (*R,R*); t_R 12.6 (*S,S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.96 (d, 3H, CH_3, *J*= 6.8 Hz), 1.12 (d, 3H, CH_3, J= 7.1 Hz), 2.51-2.61 (m, 2H, CH_2), 2.94-2.98 (m, 1H, CH), 3.12-3.16 (m, 1H, CH), 7.10-7.19 (m, 4H, CH=).

3-Methyl-4-(p-tolyl)butan-2-one.[24] Enantiomeric excess determined by HPLC using Chiracel OJ-H column (hexane/2-propanol=97/3, 1 mL/min, 220 nm). t_R 10.2 min (*S*); t_R 10.4 min (*R*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (d, 3H, *J*= 6.9 Hz), 2.31 (s, 3H), 2.09 (s, 3H), 2.52 (dd, 1H, *J*= 13.5 Hz, *J*= 7.7 Hz), 2.78-2.85 (m, 1H), 2.96 (dd, 1H, *J*= 13.6 Hz, *J*= 6.7 Hz), 7.03-7.10 (m, 4H).

2-(3,3-Dimethylbutan-2-yl)pyridine.[6c] Enantiomeric excess determined by GC using Chiral β-Dex column (120 kPa H_2, 60 °C for 60 min, 3 °C/min until 150 °C). t_R 63.5 min (-); t_R 65.4 min (+). ^{1}H NMR ($CDCl_3$), δ: 0.93 (s, 9H), 1.12 (d, 3H, *J*= 7.2 Hz), 2.79 (q, 1H, *J*= 7.2 Hz), 7.02 (m, 1H), 7.40 (m, 1H), 7.58 (m, 1H), 8.43 (m, 1H).

2-(sec-Butyl)pyridine.[6d] Enantiomeric excess determined by GC using Chiral β-Dex column (120 kPa H_2, 50 °C for 60 min, 3 °C/min until 150 °C). t_R 75.1 min (-); t_R 75.4 min (+). ^{1}H NMR ($CDCl_3$), δ: 0.84 (t, 3H *J*= 7.0 Hz), 1.28 (d, 3H, *J*= 6.8 Hz), 1.63 (m, 1H), 1.76 (m, 1H), 2.78 (m, 1H), 7.04 (m, 2H), 7.59 (m, 1H), 8.54 (d, 1H, *J*= 4.0 Hz).

1-Ethyl-2-methyl-2,3-dihydro-1H-indene.[5a] Enantiomeric excess determined by GC using Hydrodex β-3P (100 kPa H_2, Isotherm at 90 ºC). t_R 18.0 (*R,R*); t_R 18.9 (*S,S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.94 (d, 3H, CH_3, *J*= 6.9 Hz), 1.01 (t, 3H, CH_3, Et, *J*= 7.4 Hz), 1.49-1.68 (m, 2H, CH_2, Et), 2.51-2.66 (m, 2H, CH_2), 2.87-2.96 (m, 2H, CH), 7.10-7.20 (m, 4H, CH=).

1-Butyl-2-methyl-2,3-dihydro-1H-indene.[5c] Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, Isotherm at 120 ºC). t_R 12.8 (*R,R*); t_R 13.3 (*S,S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.91 – 0.95 (m, 6H, CH_3), 1.36-1.40 (m, 4H, CH_2, ^{n}Bu), 1.53-1.57 (m, 2H, CH_2, ^{n}Bu), 2.51-2.65 (m, 2H, CH_2), 2.90-3.00 (m, 2H, CH), 7.11-7.20 (m, 4H, CH=).

2-Methyl-1-phenyl-2,3-dihydro-1H-indene.[5a] Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, Isotherm at 150 ºC). t_R 13.6 (S,*R*); t_R 14.6 (*R,S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.70 (d, 3H, CH_3, *J*= 7.0 Hz), 2.68 (dd, 1H, CH_2, *J*= 15.4 Hz, *J*= 7.4 Hz), 2.83 (m, 1H, CH), 3.05 (dd, 1H, CH_2, *J*= 15.4 Hz, *J*= 7.4 Hz), 4.37 (d, 1H, CH-Ph, *J*= 7.9 Hz), 6.98 (m, 2H, CH=), 7.14-7.33 (m, 7H, CH=).

2-Ethyl-1-methyl-2,3-dihydro-1H-indene.[37] Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, Isotherm at 90 ºC). t_R 18.9 (*R,R*); t_R 19.9 (*S,S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.95 (t, 3H, CH_3, Et, *J*= 8.0 Hz), 1.04 (d, 3H, CH_3, *J*= 7.5 Hz), 1.42 (m, 1H, CH_2, Et), 1.53 (m, 1H, CH_2, Et), 2.30 (m, 1H, CH_2), 2.60 (dd, 1H, CH_2, *J*= 9.4 Hz, *J*= 15.4 Hz), 2.90 (dd, 1H, CH, *J*= 7.5 Hz, *J*= 15.4 Hz), 3.16 (m, 1H, CH), 7.08-7.18 (m, 4H, CH=).

2-Butyl-1-methyl-2,3-dihydro-1H-indene.[5a] Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, 90 ºC, 45 min – 5 ºC/min – 175 ºC). t_R 53.2 (*R,R*); t_R 53.8 (*S,S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.93 (m, 3H, CH_3, ^{n}Bu), 1.03 (d, 3H, CH_3, *J*= 7.0 Hz), 1.30-1.45 (m, 5H, CH_2, ^{n}Bu), 1.69-1.74 (1H, m, CH_2, ^{n}Bu), 1.85-1.95 (m, 1H, CH_2), 2.51 (dd, 1H, CH_2, *J*= 9.2 Hz, *J*= 15.7 Hz), 2.76 (qd, 1H, CH, *J*= 6.6 Hz, *J*= 7.0 Hz), 3.05 (dd, 1H, CH, *J*= 7.7 Hz, *J*= 15.6 Hz), 7.11-7.19 (m, 4H, CH=).

1,2-Dimethyl-1,2,3,4-tetrahydronaphthalene.[5a] Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, Isotherm at 90 ºC). t_R 28.1 (*R,R*); t_R 33.7 (*S,S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.99 (d, 3H, CH_3, *J*= 6.9 Hz), 1.11 (d, 3H, CH_3, *J*= 7.2 Hz), 1.64 (dq, 2H, CH_2, *J*= 6.4 Hz, *J*= 2.0 Hz), 1.98 (m, 1H, CH), 2.82 (m, 3H, CH, CH_2), 7.08-7.16 (m, 4H, CH=).

1-Methyl-4-(3-methylbutan-2-yl)benzene.[38] Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, 60 ºC, 30 min – 3 ºC/min – 175 ºC). t_R 38.7 (*S*); t_R 40.0 (*R*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.78 (d, 3H, CH_3, *J*= 6.7 Hz), 0.92 (d, 3H, CH_3, *J*= 6.7 Hz), 1.21 (d, 3H, CH_3, *J*= 7.1 Hz), 1.68 (m, 1H, CH), 2.32 (s, 3H, CH_3), 2.39 (q, 1H, CH, *J*= 7.2 Hz), 7.05 (d, 2H, CH=, *J*= 7.9 Hz), 7.09 (d, 2H, CH=, *J*= 7.9 Hz).

1-Methoxy-4-(3-methylbutan-2-yl)benzene.[5c] Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, 60 ºC, 30 min – 3 ºC/min – 175 ºC). t_R 50.7 (*S*); t_R 51.3 (*R*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.74 (d, 3H, CH_3, *J*= 6.7 Hz), 0.91 (d, 3H, CH_3, *J*= 6.7 Hz), 1.20 (d, 3H, CH_3, *J*= 7.1 Hz), 1,71 (m, 1H, CH), 2.38 (m, 1H, CH), 3.78 (s, 3H, CH_3-O), 7.02-7.09 (m, 4H, CH=).

1-Methyl-3-(3-methylbutan-2-yl)benzene. Enantiomeric excess determined by GC using Hydrodex β-3P (100 kPa H_2, 50 ºC, 30 min – 3 ºC/min – 170 ºC). t_R 43.2 (*S*); t_R 43.5 (*R*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.76 (d, 3H, CH_3, *J*= 6.7 Hz), 0.92 (d, 3H, CH_3, *J*= 6.7 Hz), 1.23 (d, 3H, CH_3, *J*= 7.0 Hz), 1.78 (m, 1H, CH), 2.33 (s, 3H, CH_3), 2.39 (m, 1H, CH), 6.98 (m, 3H, CH=), 7.17 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 18.9 (CH_3), 20.3 (CH_3), 21.4 (CH_3), 21.7 (CH_3), 34.5 (CH), 47.0 (CH), 124.8 (CH=), 126.5 (CH=), 128.0 (CH=), 128.6 (CH=), 137.5 (C), 147.3 (C).

1-Methoxy-2-(3-methylbutan-2-yl)benzene. Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, 60 ºC, 30 min – 3 ºC/min – 175 ºC). t_R 48.7 (*S*); t_R 49.1 (*R*). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.77 (d, 3H, CH_3, *J*= 6.7 Hz), 0.92 (d, 3H, CH_3, *J*= 6.7 Hz), 1.21 (d, 3H, CH_3, *J*= 7.0 Hz), 1.76 (m, 1H, CH), 2.39 (m, 1H, CH), 3.8 (s, 3H, CH_3-O), 6.72 (m, 3H, CH=), 7.18 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 18.6 (CH_3), 20.2 (CH_3), 21.1 (CH_3), 34.4 (CH), 46.9 (CH), 55.1 (CH_3-O), 110.6 (CH=), 113.7 (CH=), 120.2 (CH=), 129.0 (CH=), 148.9 (C), 159.4 (C).

3.3.4.9. General procedure for the hydrogenation of cyclic β-enamides

The enamide (0.25 mmol) and the corresponding catalyst precursor [Ir(cod)(L)]BAr_F (1 mol%) were dissolved in in the corresponding solvent CH_2Cl_2 (1 mL) and placed in a high-pressure autoclave, which was purged four times with hydrogen. It was then pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short celite plug. Conversions were determined by ^{1}H NMR and enantiomeric excesses by HPLC (for hydrogenation products from **S57**-**S62** see previous Section 3.2.4.7).

3.3.5. Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P), European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D.).

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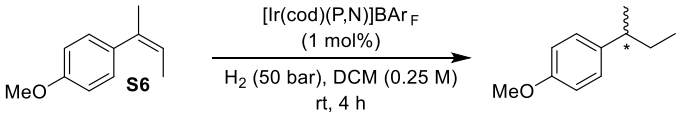
3.3.7. Supporting Information

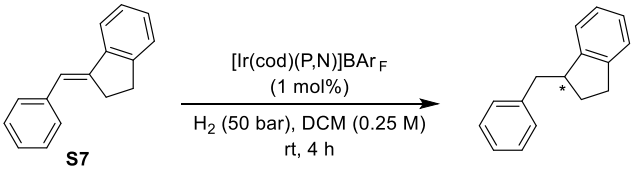
3.3.7.1. Complete series of results for the asymmetric hydrogenation of unfunctionalized olefins S4-S57 and cyclic β-enamide S58 sing [Ir(cod)(L10-L16a-h)]BAr$_F$

Table SI-1. Asymmetric hydrogenation of S6 using [Ir(cod)(L10-L16a-h)]BAr$_F$



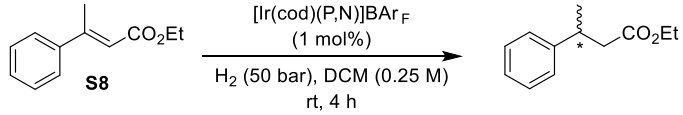
Entry	L	% Conv	% ee	Entry	L	% Conv	% ee
1	**L10a**	100	40 (*S*)	16	**L13a**	60	37 (*S*)
2	**L10d**	100	40 (*S*)	17	**L13b**	60	25 (*S*)
3	**L10e**	100	53 (*S*)	18	**L14a**	100	71 (*R*)
4	**L11a**	100	21 (*S*)	19	**L14d**	100	33 (*R*)
5	**L11b**	100	91 (*S*)	20	**L14e**	100	91 (*R*)
6	**L11c**	100	44 (*R*)	21	**L14f**	100	71 (*S*)
7	**L11d**	100	86 (*S*)	22	**L14g**	100	66 (*S*)
8	**L11e**	100	41 (*R*)	23	**L14h**	100	80 (*S*)
9	**L11f**	100	53 (*S*)	24	**L15a**	100	5 (*S*)
10	**L11g**	100	50 (*S*)	25	**L15d**	100	80 (*S*)
11	**L12a**	100	33 (*S*)	26	**L15e**	100	45 (*R*)
12	**L12b**	100	92 (*S*)	27	**L16a**	100	70 (*S*)
13	**L12f**	100	71 (*S*)	28	**L16d**	100	78 (*S*)
14	**L12g**	100	82 (*S*)	29	**L16e**	100	8 (*S*)
15	**L12h**	100	10 (*R*)				

Table SI-2. Asymmetric hydrogenation of trisubstituted exocyclic olefin S7 [Ir(cod)(L10-L16a-h)]BAr$_F$



Entry	L	% Conv	% ee
1	**L11a**	100	54 (*R*)
2	**L11b**	100	96 (*R*)
3	**L11e**	100	2 (*R*)
4	**L11f**	100	21 (*R*)
5	**L11g**	100	29 (*R*)
6	**L12a**	100	51 (*R*)
7	**L12b**	100	91 (*R*)
8	**L12f**	100	43 (*R*)
9	**L12g**	100	64 (*R*)
10	**L12h**	100	61(*R*)
11	**L13b**	100	46 (*R*)
12	**L14a**	100	50 (*S*)
13	**L14c**	100	93 (*S*)
14	**L14d**	100	14 (*S*)
15	**L14f**	100	31 (*S*)
16	**L14g**	100	49 (*S*)
17	**L14h**	100	53 (*S*)
18	**L15d**	100	89 (*R*)
19	**L15e**	100	1 (*S*)
20	**L16d**	100	86 (*R*)

Table SI-3. Asymmetric hydrogenation of α,β-unsaturated ester S8 using [Ir(cod)(L10-L16a-h)]BAr$_F$

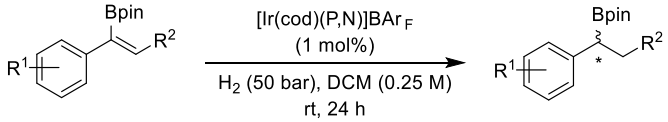


Entry	L	% Conv	% ee	Entry	L	% Conv	% ee
1	**L11a**	100	92 (*R*)	14	**L13b**	100	21 (*R*)
2	**L11b**	100	87 (*R*)	15	**L14a**	100	81 (*S*)
3	**L11c**	100	74 (*R*)	16	**L14d**	100	75 (*S*)
4	**L11d**	100	79 (*R*)	17	**L14e**	100	94 (*S*)
5	**L11e**	100	68 (*R*)	18	**L14f**	100	35 (*S*)
6	**L11f**	100	78 (*R*)	19	**L14g**	100	72 (*S*)
7	**L11g**	100	90 (*R*)	20	**L14h**	100	75 (*S*)
8	**L12a**	100	90 (*R*)	21	**L15a**	100	93 (*R*)
9	**L12b**	100	87 (*R*)	22	**L15d**	100	98 (*R*)
10	**L12f**	100	73 (R)	23	**L15e**	100	65 (*R*)
11	**L12g**	100	87 (R)	24	**L16a**	100	79 (*R*)
12	**L12h**	100	61 (R)	25	**L16d**	100	81 (*R*)
13	**L13a**	100	19 (*R*)	26	**L16e**	100	65 (*R*)

Table SI-4. Asymmetric hydrogenation of α,β-unsaturated enone S14 using [Ir(cod)(L10-L16a-h)]BAr$_F$

Entry	L	% Conv	% ee	Entry	L	% Conv	% ee
1	**L11a**	100	61 (*S*)	14	**L13b**	100	49 (*R*)
2	**L11b**	100	88 (*R*)	15	**L14a**	100	24 (*S*)
3	**L11c**	100	93 (*S*)	16	**L14d**	100	40 (*S*)
4	**L11d**	100	40 (*R*)	17	**L14e**	100	97 (*S*)
5	**L11e**	100	85 (*S*)	18	**L14f**	100	40 (*S*)
6	**L11f**	100	8 (*R*)	19	**L14g**	100	9 (*S*)
7	**L11g**	100	10 (*R*)	20	**L14h**	100	44 (*S*)
8	**L12a**	100	52 (*S*)	21	**L15a**	100	71 (*S*)
9	**L12b**	100	90 (*R*)	22	**L15d**	100	96 (*R*)
10	**L12f**	100	41 (*S*)	23	**L15e**	100	84 (*S*)
11	**L12g**	100	68 (*R*)	24	**L16a**	100	59 (*S*)
12	**L12h**	100	25 (*S*)	25	**L16d**	100	89 (*R*)
13	**L13a**	100	18 (*S*)	26	**L16e**	100	86 (*S*)

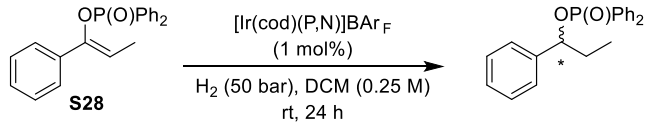
Table SI-5. Asymmetric hydrogenation of vinyl boronates S24-S27 using [Ir(cod)(L10-L16a-h)]BAr$_F$



S24 R^1= H; R^2= Bpin
S25 R^1= 4-F-C_6H_3; R^2= Bpin
S26 R^1= 4-OMe-C_6H_3; R^2= Bpin
S27 R^1= H; R^2= Ph

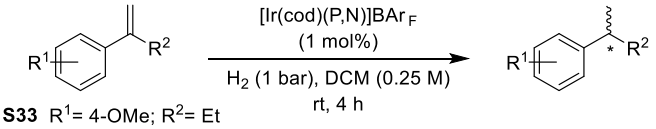
		S24		**S25**		**S26**		**S27**	
Entry	L	%Conv	% ee	%Conv	% ee	%Conv	% ee	%Conv	% ee
1	**L11a**	100	92 (*S*)	100	91 (*S*)	100	92 (*S*)	99	93 (+)
2	**L11d**	100	99 (*S*)	100	99 (*S*)	100	98 (*S*)	100	>99 (+)
3	**L11e**	100	32 (*S*)	100	29 (*S*)	100	31 (*S*)	98	32 (+)
4	**L11f**	100	84 (*S*)	100	85 (*S*)	100	86 (*S*)	42	83 (+)
5	**L11g**	100	90 (*S*)	100	90 (*S*)	100	91 (*S*)	46	92 (+)
6	**L12a**	100	87 (*S*)	100	85 (*S*)	100	87 (*S*)	100	87 (+)
7	**L12b**	100	92 (*S*)	100	91 (*S*)	100	89 (*S*)	100	90 (+)
8	**L12f**	100	81 (*S*)	100	72 (*S*)	100	83 (*S*)	49	86 (+)
9	**L12g**	100	92 (*S*)	100	91 (*S*)	100	92 (*S*)	68	94 (+)
10	**L12h**	100	30 (*S*)	100	28 (*S*)	100	31 (*S*)	36	36 (+)
11	**L13b**	100	81 (*S*)	100	81 (*S*)	100	80 (*S*)	49	84 (+)
12	**L14a**	100	90 (*R*)	100	92 (*R*)	100	90 (*R*)	100	89 (-)
13	**L14d**	100	62 (*R*)	100	59 (*R*)	100	61 (*R*)	100	63 (-)
14	**L14e**	100	98 (*R*)	100	97 (*R*)	100	98 (*R*)	100	98 (-)
15	**L14f**	100	96 (*R*)	100	94 (*R*)	100	94 (*R*)	84	94 (-)
16	**L14g**	100	86 (*R*)	100	83 (*R*)	100	87 (*R*)	81	83 (-)
17	**L14h**	100	90 (*R*)	100	92 (*R*)	100	89 (*R*)	46	91 (-)
18	**L15d**	100	97 (*S*)	100	95 (*S*)	100	96 (*S*)	100	93 (+)
19	**L15e**	100	23 (*S*)	100	22 (*S*)	100	25 (*S*)	100	43 (+)
20	**L16d**	100	91 (*S*)	100	89 (*S*)	100	90 (*S*)	68	88 (+)

Table SI-6. Asymmetric hydrogenation of enol phosphonate S28 using [Ir(cod)(L10-L16a-h)]BAr$_F$



Entry	L	% Conv	% ee	Entry	L	% Conv	% ee
1	**L11a**	100	95 (*R*)	14	**L13b**	68	87 (*R*)
2	**L11b**	100	98 (*R*)	15	**L14a**	100	83 (*S*)
3	**L11c**	100	18 (*S*)	16	**L14d**	100	8 (*R*)
4	**L11d**	100	95 (*R*)	17	**L14e**	100	96 (*S*)
5	**L11e**	100	26 (*S*)	18	**L14f**	62	95 (*S*)
6	**L11f**	74	93 (*R*)	19	**L14g**	45	96 (*S*)
7	**L11g**	68	98 (*R*)	20	**L14h**	55	65 (*S*)
8	**L12a**	100	92 (*R*)	21	**L15a**	100	83 (*R*)
9	**L12b**	100	93 (*R*)	22	**L15d**	100	81 (*R*)
10	**L12f**	73	67 (*R*)	23	**L15e**	100	60 (*R*)
11	**L12g**	56	92 (*R*)	24	**L16a**	100	89 (*R*)
12	**L12h**	35	17 (*S*)	25	**L16d**	100	92 (*R*)
13	**L13a**	77	88 (*R*)	26	**L16e**	100	15 (*R*)

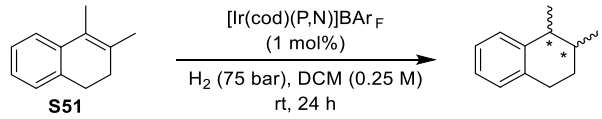
Table SI-7. Asymmetric hydrogenation of disubstituted olefins S33-S35 using [Ir(cod)(L10-L16a-h)]BAr$_F$



S33 R^1= 4-OMe; R^2= Et
S34 R^1= H; R^2= ^{i}Pr
S35 R^1= H; R^2= Cy

		S33		**S34**		**S35**	
Entry	L	%Conv	% ee	%Conv	% ee	%Conv	% ee
1	**L11a**	100	48 (*S*)	100	62 (*S*)	100	39 (*S*)
2	**L11d**	100	86 (*S*)	100	92 (*S*)	100	88 (*S*)
3	**L11e**	100	21 (*R*)	100	3 (*R*)	100	3 (*R*)
4	**L11f**	100	41 (*S*)	100	50 (*S*)	100	51 (*S*)
5	**L11g**	100	55 (*S*)	100	47 (*S*)	100	60 (*S*)
6	**L12a**	100	43 (*S*)	100	51 (*S*)	100	48 (*S*)
7	**L12b**	100	78 (*S*)	100	86 (*S*)	100	83 (*S*)
8	**L12f**	100	50 (*S*)	100	52 (*S*)	100	43 (*S*)
9	**L12g**	100	28 (*S*)	100	33 (*S*)	100	26 (*S*)
10	**L12h**	100	11 (*S*)	100	9 (*S*)	100	10(*S*)
11	**L13b**	100	19 (*S*)	100	26 (*S*)	100	26 (*S*)
12	**L14a**	100	54 (*R*)	100	84 (*R*)	100	80 (*R*)
13	**L14d**	100	22 (*R*)	100	36 (*R*)	100	51 (*R*)
14	**L14e**	100	83 (*R*)	100	70 (*R*)	100	66 (*R*)
15	**L14f**	100	50 (*R*)	100	48 (*R*)	100	49 (*R*)
16	**L14g**	100	53 (*R*)	100	53 (*R*)	100	50 (*R*)
17	**L14h**	100	55 (*R*)	100	58 (*R*)	100	48 (*R*)
18	**L15d**	100	76 (*S*)	100	77 (*S*)	100	82 (*S*)
19	**L15e**	100	32 (*R*)	100	28 (*R*)	100	11 (*R*)
20	**L16d**	100	84 (*S*)	100	81 (*S*)	100	83 (*S*)

Table SI-8. Asymmetric hydrogenation of dihydronapthalene S51 using [Ir(cod)(L10-L16a-h)]BAr$_F$



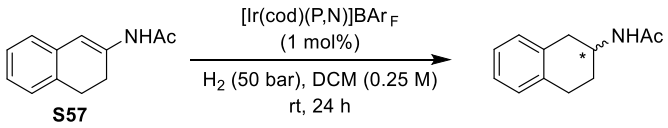
Entry	L	% Conv	% ee
1	**L12f**	100	81 (*S,S*)
2	**L12g**	100	90 (*S,S*)
3	**L12h**	100	71 (*S,S*)
4	**L14f**	100	77 (*R,R*)
5	**L14g**	100	75 (*R,R*)
6	**L14h**	100	66 (*R,R*)

Table SI-9. Asymmetric hydrogenation of acyclic tetrasubstituted substrate S52 using [Ir(cod)(L10-L16a-h)]BAr$_F$

Entry	L	% Conv	% ee	Entry	L	% Conv	% ee
1	**L10a**	65	33 (*S*)	16	**L13b**	5	8 (*R*)
2	**L10d**	50	32 (*S*)	17	**L14a**	50	41 (*R*)
3	**L10e**	70	30 (*S*)	18	**L14d**	40	13 (*R*)
3	**L11a**	80	28 (*S*)	19	**L14e**	35	36 (*R*)
4	**L11b**	20	2 (*S*)	20	**L14f**	65	12 (*S*)
5	**L11c**	65	1 (*S*)	21	**L14g**	100	26 (*S*)
6	**L11d**	25	2 (*S*)	22	**L14h**	100	91 (*S*)
7	**L11e**	70	4 (*R*)	23	**L15a**	70	36 (*S*)
8	**L11f**	85	1 (*R*)	24	**L15d**	40	28 (*S*)
9	**L11g**	75	2 (*R*)	25	**L15e**	40	11 (*S*)
10	**L12a**	75	15 (*S*)	26	**L16a**	80	37 (*S*)
11	**L12b**	25	3 (*R*)	27	**L16d**	40	30 (*S*)
12	**L12f**	100	25 (*R*)	28	**L16e**	50	13 (*S*)
13	**L12g**	95	8 (*R*)	29[a]	**L14h**	100	97 (*S*)
14	**L12h**	98	38 (*R*)	30[b]	**L14h**	100	97 (*S*)
15	**L13a**	5	4 (*R*)				

[a] Reaction carried out at 25 bar H_2. [b] Reaction carried out at 1 bar H_2

Table SI-10. Asymmetric hydrogenation of cyclic β-enamide S57 using [Ir(cod)(L10-L16a-h)]BAr$_F$



S57

Entry	L	% Conv	% ee	Entry	L	% Conv	% ee
1	**L11a**	100	20 (*R*)	14	**L13b**	100	40 (*S*)
2	**L11b**	100	85 (*S*)	15	**L14a**	100	18 (S)
3	**L11c**	100	51 (*R*)	16	**L14d**	100	66 (S)
4	**L11d**	100	85 (*S*)	17	**L14e**	100	97 (*R*)
5	**L11e**	100	53 (*R*)	18	**L14f**	100	13 (*R*)
6	**L11f**	100	19 (*S*)	19	**L14g**	100	41 (*R*)
7	**L11g**	100	37 (*S*)	20	**L14h**	100	55 (*R*)
8	**L12a**	100	32 (*R*)	21	**L15a**	100	36 (*R*)
9	**L12b**	100	91 (*S*)	22	**L15d**	100	94 (*S*)
10	**L12f**	100	47 (*S*)	23	**L15e**	100	58 (*R*)
11	**L12g**	100	64 (*S*)	24	**L16a**	100	34 (*R*)
12	**L12h**	100	65 (*S*)	25	**L16d**	100	92 (*S*)
13	**L13a**	100	16 (*R*)	26	**L16e**	100	60 (*R*)

UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull

3.4. Inclusion of an Ir-catalyst containing a phosphite-oxazoline ligand in a supramolecular metallocage

Biosca, M.; Fuertes, C.; Ribas, X.; Pàmies, O.; Diéguez, M. *Preliminary results.*

In collaboration with the group of Dr. X. Ribas (University of Girona).

Abstract: A new phosphite-oxazoline ligand and its corresponding [Ir(acac)(P,N)] complex have been successfully synthetized and entrapped in a supramolecular metallocage. The ligand shows a high binding constant with the supramolecular cage, which suggests that the *meta*-pyridine groups of the biaryl phosphite moiety interact with the Zn-porphyrins fragments in a ditopic fashion inside the supramolecular cage. The entrapped Ir-complex is designed for its specific application in the asymmetric hydrogenation of minimally functionalized olefins.

3.4.1. Introduction

Asymmetric catalysis is one of the most applied approach in the preparation of enantiopure compounds due to it exhibits very high activity and selectivity and is environmentally friendly.[1] In this field, a wide variety of catalysts and transformations has been developed. Towards the different catalytic systems, enzymes catalysts are typically praised for exhibit high reaction rates and excellent selectivities.[2] These excellent results are attributed to the well-defined cavities around the active site of enzymes that allows the perfectly embedding of reagents and substrates. This cavity is the so-called second coordination sphere. However, many enzymes evolved to target a single substrate or functionality. In contrast, transition metal catalysts make possible thousands of different transformations with a typically broad substrate scope. However, despite the successfully application of some transition metal catalysts in several asymmetric transformations, generally they still do not provide the activities and enantioselectivities obtained with enzymatic catalysts. In transition metal complexes, catalyst optimizations in order to improve the levels of reactivity and selectivity achieved are mainly based on modifications of the ligand, which is related with the primary coordination sphere.[1] With the aim of mimicking the second coordination sphere of enzymes, it has been reported some examples of transition metal catalysts entrapped in restricted environments.[3] In some cases, these pioneering works demonstrated that the activity and selectivity can be improved with the presence of this second coordination sphere, however the number of successful transformations carried out using this methodology is limited.[4] In this context, Ribas *et al*. have developed a metal nanocage **1**·$(BArF)_8$ (Figure 3.4.1) prepared by metal-directed self-assembly.[5] The **1**·$(BArF)_8$ nanocage is constituted for two opposed Zn-porphyrin building blocks, linked

by four bridging macrocyclic walls which assembles the cage structure through Pd-carboxylate coordination bonds. Due to the ability of Zn-porphyrins to interact with pyridine moieties, this nanocage was used for the inclusion of a Rh-phosphoroamidite catalyst containing a biaryl with *ortho*-pyridine groups and it was further applied in the enantioselective Rh-catalyzed hydroformylation of styrenes. The results showed that supramolecular catalyst converts styrene derivatives into aldehyde products with much higher asymmetric induction than the non-encapsulated Rh-catalyst.[6]

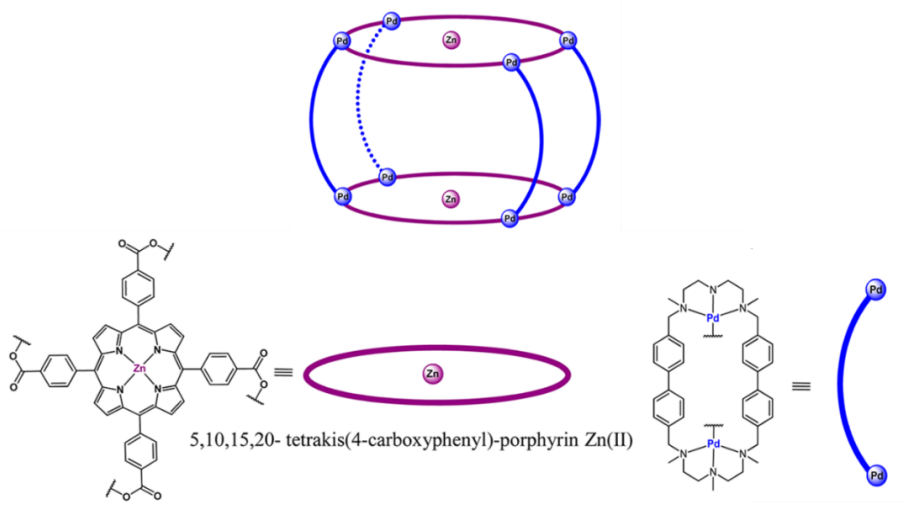


Figure 3.4.1. Schematic representation of the fragments used in the synthesis of the metallocage **1**·$(BAr_F)_8$.

We envisage that the asymmetric hydrogenation of unfunctionalized olefins may benefit from the confinement of the metal catalysts in the metal nanocage. The spatial constraints inside the nanocage may limit the number of possible coordination modes of the substrate to the Ir-catalyst and should also avoid the formation of inactive trimeric species $[Ir_3(\eta^3\text{-}H)(H)_6(L)_3](BArF)_2$.[7] In this context, we took one of the most successful ligands developed for this transformation[8] and modified the design to facilitate its inclusion in the nanocage. For this purpose, we took advantage of the high affinity of the Zn-porphyrin units towards pyridine units and we therefore decided to introduce pyridine groups in the *ortho*-positions of the biaryl phosphite moiety, resulting in ligand **L17** (Figure 3.4.2). In this section, we discuss the synthesis of ligand **L17**, its inclusion in the nanocage as well as the preparation of Ir-catalyst precursor ([Ir(**L17**)(acac)]) in the tetragonal prismatic nanocage **1**·$(BArF)_8$ (Figure 3.4.2).

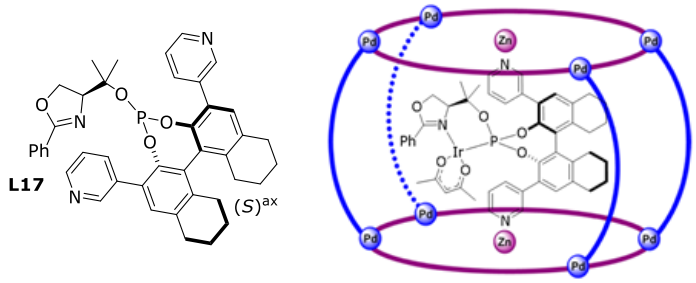
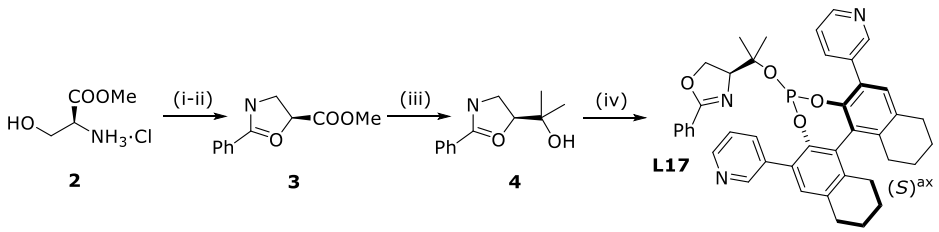


Figure 3.4.2. [Ir(**L17**)(acac)] encapsulated in the supramolecular metallocage **1**·$(BArF)_8$.

3.4.2. Results and Discussions

3.4.2.1. Synthesis of phosphite-oxazoline ligand

The straightforward synthesis of phosphite-oxazoline ligand **L17** is illustrated in Scheme 3.4.1. Ligand **L17** was synthesized very efficiently from the commercially available (*S*)-serine methyl ester **2**.[9] In the first step of the ligand synthesis, compound **2** was coupled with benzoyl chloride in the presence of triethylamine to produce the desired amide (step i).[9] Then, it was converted to the oxazoline ester **3** in the presence of diethylaminosulfur trifluoride (DAST; step ii).[9] Next, the reduction with a Grignard reagent (CH_3MgCl) of the oxazoline ester afforded the hydroxyl-oxazoline intermediate **4** (step iv).[9] In the last step, treatment of hydroxyl-oxazoline **4** with one equivalent of the *in situ* formed phosphorochloridite[10] in the presence of pyridine and catalytic amounts of DMAP provided easy access to the desired phosphite–oxazoline ligand **L17**. Phosphite-oxazoline ligand **L17** was stable during purification on neutral silica under an atmosphere of argon and it was isolated as white solid. The ^1H and ^{13}C NMR spectra were as expected for this C_1-ligand.



Scheme 3.4.1. Synthesis of phosphite-oxazoline ligand **L17**: (i) PhCOCl, NEt_3, CH_2Cl_2, 3 h, rt; (ii) DAST, CH_2Cl_2, K_2CO_3, 3 h, -78 ºC; (iii) CH_3MgCl, Et_2O/THF, 16 h, rt; (iv) Phosphorochloridite, toluene, py, DMAP cat., 16 h, 80 ºC.

3.4.2.2. Inclusion of the ligand in the supramolecular metallocage and preparation of encapsulated Ir-complex

The tetragonal prismatic nanocage **1**·$(BArF)_8$ was synthetized as previously described.[5] Cage **1**·$(BArF)_8$ showed to be able to accommodate pyridine-containing ligands[6] due to the ability of Zn-porphyrins to interact with pyridine moieties.[10-11] Therefore, we try to perform the inclusion of ligand **L17** in the nanocage **1**·$(BArF)_8$ using the conditions previously developed in Ribas' group.[6] High-resolution mass spectrometry (HR-MS) analysis of the host-guest compound confirms the formation of host-guest complex **L17**⊂**1**·$(BArF)_8$ in a 1:1 stoichiometry (Figure 3.4.3).

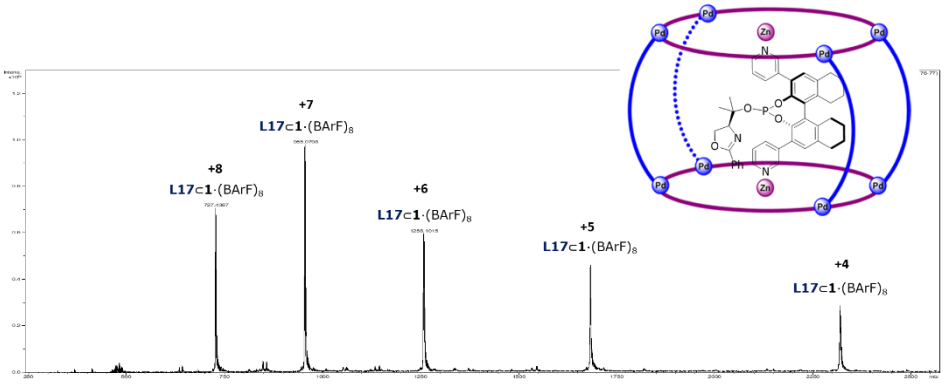


Figure 3.4.3. HRMS spectra of **L17**⊂**1**·$(BArF)_8$ host-guest complex.

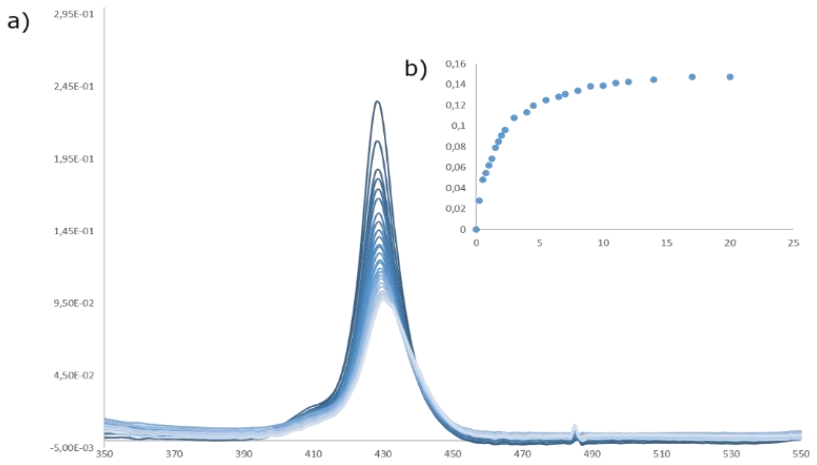


Figure 3.4.4. a) UV-vis monitoring of the titration of **1**·$(BArF)_8$ nanocapsule with phosphite-oxazoline ligand **L17**; b) Absorbance variation of the Soret band versus different concentrations of the ligand.

UV-vis titration experiments indicated an interaction between the supramolecular cage **1**·(BArF)$_8$ and **L17** (Figure 3.4.4) by the change in the absorbance of the Soret band of porphyrins. From this data, we also obtained a binding constant of (5.4±0.18)·10^6 M^{-1}. This high binding constant suggests that ligand **L17** is bonded in a ditopic fashion inside the nanocage **1**·(BArF)$_8$,[6,10] thus phosphite-oxazoline ligand **L17** is located in the middle of the supramolecular cage.

Once we confirmed that the ligand was successfully entrapped, we next studied its coordination to iridium. Initially, we used [Ir(cod)$_2$]BAr$_F$ as iridium source. However, we observed that this Ir-precursor cannot be stabilized inside the nanocage. This is most likely due to the highly cationic nature of the cage which hampers the introduction of a cationic host. We then used a neutral iridium complex, the dicarbonyl(2,4-pentanedionato)iridium. The reaction of the encapsulated ligand with [Ir(acac)(CO)$_2$] under and atmosphere of hydrogen led to the selective formation of a single complex, corresponding to [Ir(**L17**)(acac)]⊂**1**·(BArF)$_8$ (Figure 3.4.5). In addition, no peaks attributed to empty nanocapsule were detected in the HR-MS analysis, which further confirms the formation of the host-guest complex [Ir(**L17**)(acac)]⊂**1**·(BArF)$_8$ in a 1:1 stoichiometry.

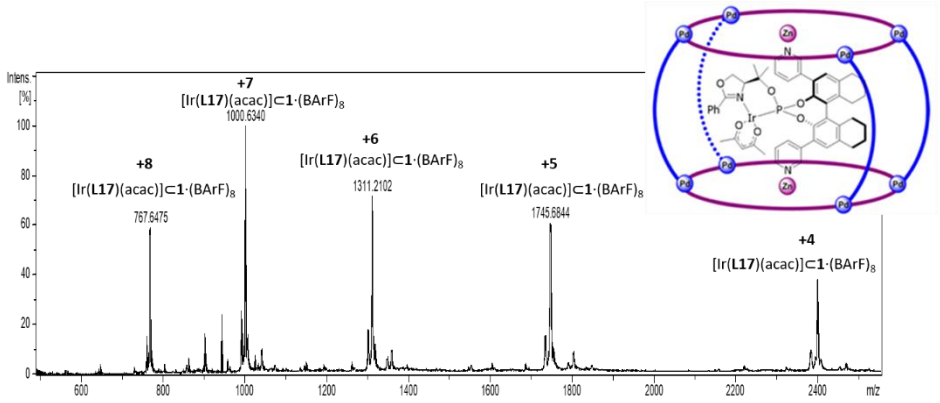


Figure 3.4.5. HRMS spectra of [Ir(**L17**)(acac)]⊂**1**·(BArF)$_8$ host-guest complex.

3.4.3. Conclusions and Future work

We reported the successful inclusion of [Ir(**L17**)(acac)] in the supramolecular metallocage **1**·(BArF)$_8$. The metallocage is constituted for two opposed Zn-porphyrin building blocks, linked by four bridging macrocyclic walls which assembles the cage structure through Pd-carboxylate coordination bonds. From the high binding constant extracted from the inclusion of the free phosphite-oxazoline ligand **L17** in the nanocage, we can conclude that the *meta*-pyridine groups of the biaryl phosphite moiety interact with Zn-porphyrins building blocks of the supramolecular metallocage **1**·(BArF)$_8$ in a ditopic fashion. These satisfactory results will allow to further apply this entrapped

catalyst precursor in the asymmetric hydrogenation of minimally functionalized olefins in the near future.

3.4.4. Experimental Section

3.4.4.1. General considerations

All reactions were carried out by using standard Schlenk techniques under an argon, nitrogen or hydrogen atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridite was easily prepared in one step from the corresponding *meta*-pyridine binaphthol.[10] Intermediates **2**-**4**[9] and molecular cage **1**·$(BArF)_8$[5] were prepared as reported previously. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H and ^{13}C assignments were made based on the results of ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments. High resolution mass spectra (HR-MS) were obtained on a Bruker MicroTOF-Q-II, using acetonitrile as the mobile phase. UV-Vis spectroscopy was performed on an Agilent 8452 UV-vis spectrophotometer with 1 cm quartz cell.

3.4.4.2. Preparation of phosphite-oxazoline ligand L17

The corresponding phosphorochloridite (0.55 mmol) produced *in situ* was dissolved in toluene (2 mL), and pyridine (0.08 mL, 1.0 mmol) was added. The hydroxyl-oxazoline compound **4** (102.6 mg, 0.50 mmol) was azeotropically dried with toluene (3x3 mL) and then dissolved in toluene (2 mL) to which pyridine (0.08 mL, 1.0 mmol) and catalytic DMAP (6.7 mg, 0.055 mmol) was added. The phosphorochloridite solution was then transferred slowly to the hydroxyl-oxazoline solution. The reaction mixture was stirred at 80 °C for 16 h, after which the triethylamine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography on neutral silica (CH_2Cl_2/NEt_3= 1:0.1 as eluent) to produce the corresponding ligand as a white solid. Yield: 80 mg (25%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 143.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.78 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.15-1.52 (m, 8H, CH_2), 2.16-2.33 (m, 3H, CH_2), 2.44-2.66 (m, 5H, CH_2), 3.79-3.87 (m, 2H, CH_2-O), 3.99 (dd, 1H, CH-N, $^{3}J_{H\text{-}H}$= 10.0 Hz, $^{3}J_{H\text{-}H}$= 7.2 Hz), 6.74-6.80 (m, 2H, CH=), 6.96-7.02 (m, 5H, CH=), 7.70-7.74 (m, 1H, CH=), 7.78-7.81 (m, 1H, CH=), 7.92-7.94 (m, 2H, CH=), 8.44 (dd, 1H, CH=, $^{3}J_{H\text{-}H}$= 5.7 Hz, $^{4}J_{H\text{-}H}$= 1.7 Hz), 8.48 (dd, 1H, CH=, $^{3}J_{H\text{-}H}$= 5.7 Hz, $^{4}J_{H\text{-}H}$= 1.7 Hz), 9.14 (dd, 1H, CH=, $^{4}J_{H\text{-}H}$= 2.3 Hz, $^{4}J_{H\text{-}H}$= 1.8 Hz), 9.16 (dd, 1H, CH=, $^{4}J_{H\text{-}H}$= 2.3 Hz, $^{4}J_{H\text{-}H}$= 1.8 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 22.2 (CH_3), 22.3 (CH_3), 22.4 (CH_2), 22.8 (CH_2), 26.4 (CH_2), 27.7 (CH_2), 28.9 (CH_2), 68.3 (CH_2-O), 75.3 (CH-N), 81.2 (CMe_2), 122.5-150.7 (aromatic carbons), 164.3 (C=N).

3.4.4.3. Preparation of L17 ⊂ 1·$(BAr_F)_8$

In a nitrogen atmosphere, **1**·$(BArF)_8$ nanocapsule (9 mg, 1.9 μmols) was dissolved in 300 μL of CH_3CN. Then, a solution of **L17** (1.3 mg, 1.9 μmols) dissolved in 1200 μL CH_3CN was added. The mixture was stirred at room temperature for 5 min. After the reaction time, the mixture was filtered through cotton and recrystallized by diethyl ether diffusion. A quantitative yield was obtained.

3.4.4.4. Preparation of [Ir(L17)(acac)] ⊂ 1·$(BAr_F)_8$

In an atmosphere of H_2, **1**·$(BArF)_8$ (16 mg, 3.5 μmol) was dissolved in a 1:1 mixture of CH_2Cl_2/CH_3CN (1.2 mL). Then, the phosphite-oxazoline ligand **L17** (2.4 mg, 3.5 μmols) and [Ir(acac)$(CO)_2$] (1.4 mg, 3.5 μmols) were sequentially added. The mixture was left at room temperature for 16 h. A quantitative yield was obtained.

3.4.5. Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P), European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D.).

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3.5. Highly enantioselective hydrogenation of unfunctionalized olefins using Ir-P*-aminophosphine-oxazoline catalysts

Biosca, M.; Salomó, E.; Orgué, S.; Flores-Gaspar, A.; Riera, A.; Verdaguer, X.; Pàmies, O.; Diéguez, M. *Chem Commun*. **2015**, *51*, 3455 and m*anuscript submitted to Adv. Synth. Catal.*

In collaboration with the group of Prof. A. Riera (University of Barcelona).

Abstract: Air stable and readily available Ir-catalyst precursors modified with MaxPHOX-type ligands have been successfully applied in the challenging asymmetric hydrogenation of tetrasubstituted olefins under mild reaction conditions. Gratifyingly, these catalyst precursors are not only able to efficiently hydrogenate a range of indene derivatives (ee's up to 96%) but also 1,2-dihydro-naphthalene derivatives and acyclic olefins (ee's up to 99%), which both constitute the most challenging substrates for this transformation. In addition, preliminary results of their application in the hydrogenation of α,β-unsaturated esters showed enantioselectivities up to >99% ee.

3.5.1. Introduction

Asymmetric hydrogenation is one of the most common, reliable and environmentally friendly industrial processes for the preparation of chiral compounds, such as drugs and crop protecting chemicals.[1] Its strategic relevance has spurred research in both academia and industry over the last decades. Nowadays an important number of Rh-, Ru- and Ir-catalysts exist for the asymmetric hydrogenation of a broad range of substrates.[2] However, for some substrates such as tetrasubstituted olefins, attaining high activity and enantioselectivity is still a challenge. Their reduction would open up opportunities to simultaneously generate two vicinal tertiary stereocenters, which are present in many natural and high-valued products.[3] Achieving high enantiocontrol is even more difficult if the olefin lacks a coordinative group that can assist in the transfer of the chiral information from the catalyst to the product.[2] The asymmetric hydrogenation of tetrasubstituted unfunctionalized olefins is therefore underdeveloped compared to the asymmetric hydrogenation of olefins that contain a coordinative functional group.[3] To date, high catalytic performance have been reported in only four publications and with a limited substrate scope. In 1999 Buchwald *et al*. reported the first successful asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins.[4] Although high enantioselectivities were achieved for substituted indenes using the zirconozene catalyst **1** (Figure 3.5.1; ee's in the range 52–99%), the high catalyst loading (8 mol%), high H_2 pressure (typically >110 bar) and the low stability of the catalyst hampered their broad use. In addition, enantioselectivity was negatively affected by substituents other than a methyl in the benzylic position of the substrate.[5]

Pfaltz *et al*. made an important breakthrough by using stable Ir/P,N-catalysts for asymmetric hydrogenation of unfunctionalized olefins.[2g] They found that the optimum ligand structures for tri- and tetrasubstituted olefins differed strongly. Using Ir-catalysts **2**, containing ligands that form a 5-membered chelate ring, a wide range of indenes were hydrogenated with ee's in the range 94–96% (Figure 3.5.1).[6] Improving previous results, catalysts **2** allowed asymmetric hydrogenation under milder reaction conditions and lower catalyst loading (typically 1-2 mol%) which was highly advantageous for sustainable industrial processes. They also found catalysts **2** performance to be less dependent on the substituents in the benzylic position of the substrate. Nevertheless, ee's diminished for non-cyclic olefins and specially for 1,2-dihydro-naphthalenes (ee's between 89–97% and up to 77%, respectively).

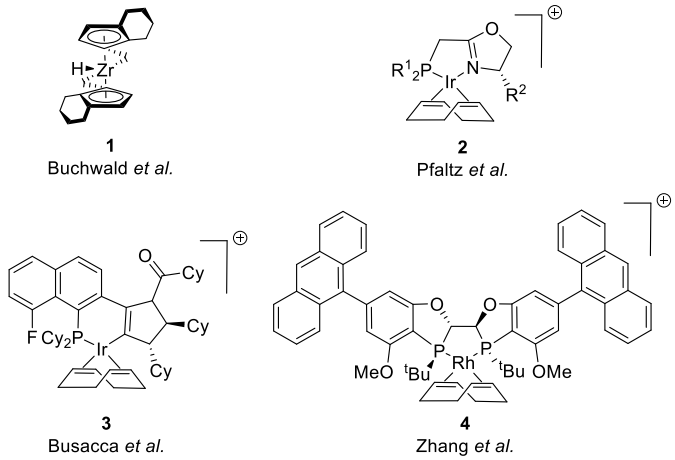


Figure 3.5.1. Most successful catalysts for the asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins.

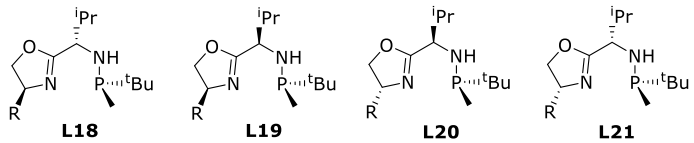
In 2013 Busacca *et al*. found that the Ir-catalyst **3** could hydrogenate two cyclic substrates with ee's up to 96% at low catalyst loading. Two inconveniences were that low temperature (0 °C) was required and the difficult preparation of the 1,8-disubstituted naphthalene core of the ligand.[7] In 2017, Zhang *et al.* reported a Rh-catalyst **4** (Figure 3.5.1), containing a P*-stereogenic diphosphine ligand synthesized in nine steps,[8] that provided 85–95% ee's in the asymmetric hydrogenation of indenes.[9] In contrast to Ir-catalysts, their Rh-catalyst required high catalyst loading (10 mol%), 60 °C and longer reaction times (4 days).

Despite of the relevance of the four mentioned advances, the substrate scope for the asymmetric hydrogenation of tetrasubstituted olefins remains limited. Research for stable, easy to synthesize, catalytic systems for the asymmetric hydrogenation of cyclic and acyclic unfunctionalized tetrasubstituted olefins under mild reaction conditions is still needed. Over the last decade, our group developed Ir/biaryl phosphite-N catalyst libraries that became the state-of-art for the Ir-hydrogenation of unfunctionalized

olefins.[10] Improving previous results, we could efficiently reduce a broad range of *E*- and *Z*-trisubstituted unfunctionalized olefins and the more challenging disubstituted ones. Mechanistic studies confirmed that the bulky and flexible biaryl phosphite group was responsible for the high substrate scope. However, the bulkiness of the phosphite moiety made these catalysts inefficient for the asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins.

The combination of the advantageous reaction conditions of Pfaltz's Ir/phosphine-N catalysts and Zhang's P*-stereogenic concept could be expected to lead to improved stereocontrol (thanks to the fact that the bulky P*-stereogenic group would allow the chiral center be closer to the metal center) in the asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins under mild reaction conditions. This development was however delayed by the difficulty of synthesizing bulky P-stereogenic phosphines in optically pure form. Fortunately, Riera, Verdaguer, *et al*. recently presented a novel, straightforward synthetic route that solved this problem and allowed the synthesis of a library of P*-stereogenic aminophosphine-oxazoline (MaxPHOX) ligands in which both enantiomeric series are equally available.[11,12]

We report here the asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins using Ir-complexes containing MaxPHOX ligands **L18**-**L21a**-**c** as precatalysts (Figure 3.5.2). Ligands **L18**-**L21a**-**c** contemplate the four diastereomeric possibilities of varying the configuration of substituents at the oxazoline and at the alkyl backbone chain, while maintaining the configuration of the P-stereogenic center (**L18**-**L21**). We also studied the effect of increasing the steric bulk of the oxazoline substituent (**a**-**c**).



a R= Ph; **b** R= ^{i}Pr; **c** R= ^{t}Bu

Figure 3.5.2. Chiral aminophosphine-oxazoline ligands **L18**-**L21a**-**c**.

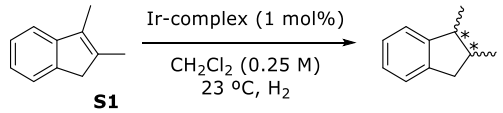
3.5.2. Results and Discussion

3.5.2.1. Asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins

Initially, we explored the asymmetric hydrogenation of 2,3-dimethyl-1*H*-indene **S1** with ligands **L18**–**L21a-c** (Table 3.5.1). **S1** was chosen as the model substrate since it could be compared with previous catalysts **1**-**4** results. For the initial reaction conditions, we tested ligands **L18**-**L21a**-**c** in the optimal mild reaction conditions from the previous study with Ir-catalysts **2**.[6] The reactions were therefore carried out at room

temperature using 1 mol% of the catalyst under 50 bar of H_2 in dichloromethane. The reactions proceeded smoothly to provide the *cis*-diastereoisomer only. It was observed that both the diastereomeric backbone of the ligand and the oxazoline substituent (entries 1–6) had a remarkable effect on the enantioselectivity. Catalyst precursor Ir/**L18b** provided the highest enantioselectivity of the series (entry 2, ee up to 93%). Interestingly, lowering the hydrogen pressure the enantioselectivity increased (see entries 2, 7 and 8).[13] Enantioselectivities up to 95% ee were achieved at only 10 bars of H_2, while maintaining the full conversion (entry 8) under mild reaction conditions. This result is comparable to the best one reported in the literature.

Table 3.5.1. Asymmetric hydrogenation of 2,3-dimethyl-1*H*-indene **S1** using Ir-catalyst precursors [Ir(cod)(**L18**-**L21a**-**c**)]BAr_F.



S1

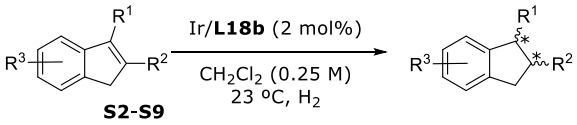
Entry	L	P_{H2} (bar)	% Conv[a]	% ee[b]
1	**L18a**	50	100	83 (*S*,*S*)
2	**L18b**	50	100	93 (*R*,*R*)
3	**L18c**	50	100	90 (*R*,*R*)
4	**L19b**	50	100	63 (*R*,*R*)
5	**L20b**	50	100	82 (*S*,*S*)
6	**L21b**	50	100	74 (*S*,*S*)
7	**L18b**	75	100	92 (*R*,*R*)
8[c]	**L18b**	10	100	95 (*R*,*R*)

[a] Conversions were measured by ^{1}H NMR spectroscopy after 24 h; [b] Enantiomeric excesses determined by chiral GC; [c] Reaction performed using 2 mol% of catalysts.

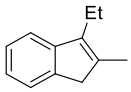
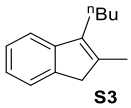
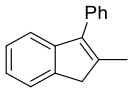
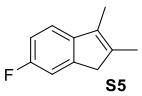
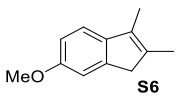
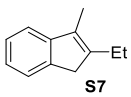
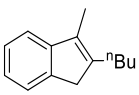
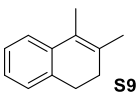
We further studied the performance of **L18b** in the reduction of other indenes (**S2**–**S8**) and of the demanding 3,4-dimehtyl-1,2-dihydronaphthalene **S9** (Table 3.5.2). Substrates **S2**–**S8** contemplate several substituents at both benzylic (**S2**–**S4**) and vinylic position (**S7**–**S8**) and several substituents at the 6-position of the indene (**S5**–**S6**). We found that ligand **L18b** tolerated well variations of the alkyl substituent at both the benzylic (Table 4.5.1 entry 8 and Table 4.5.2 entries 1-2) and vinylic positions (Table 4.5.2, entries 6 and 7). The only exception was substrate **S4** with a phenyl substituent at the benzylic position that led to somewhat lower enantioselectivity (entry 3). The results also indicated that conversion and yields were comparable for substrates **S5** and **S6** (entries 4–5) that contain a different substituent at the 6-position of the indene, although enantioselectivity was slightly better for the methoxy substituted indene **S6** (entry 5). We should highlight the high enantioselectivity achieved in the hydrogenation of 3,4-dimehtyl-1,2-dihydronaphthalene **S9** (entry 8), one of the most

challenging substrates for this reaction. This result improves the previous result by Pfaltz[6] and is comparable to Busacca's result[7] but requires a lower temperature.

Table 3.5.2. Asymmetric hydrogenation of several indenes **S2**-**S8** and 1,2-dihydro-naphthalene **S9**.



S2-**S9**

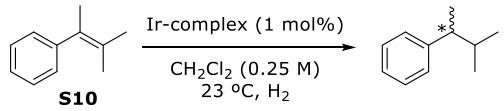
Entry	Substrate	% Conv (% Yield)[a]	% ee[b]
1	 **S2**	100 (98)	95 (*R*,*R*)
2	 **S3**	100 (96)	96 (*R*,*R*)
3[c]	 **S4**	45 (-)[d]	82 (*S*,*R*)
4	 **S5**	100 (94)	85 (*R*,*R*)
5	 **S6**	100 (96)	91 (*R*,*R*)
6	 **S7**	100 (91)	92 (*R*,*R*)
7	 **S8**	100 (92)	91 (*R*,*R*)
8[c]	 **S9**	100 (93)	89 (*R*,*R*)

[a] Conversions were measured by ^{1}H NMR spectroscopy after 24 h. [b] Enantiomeric excesses determined by chiral GC; [c] Reaction performed using 75 bar of H_2; [d] Isolated yield not calculated.

Encouraged by the previous results, we finally turned our attention to the asymmetric hydrogenation of the most challenging class of tetrasubstituted olefins – the acyclic

ones. So far, only the catalytic systems **2** have been successful but enantioselectivity was only high (97%) in the asymmetric hydrogenation of **S12** (Figure 3.5.3).[6] We first tested Ir-precatalysts with ligands **L18**-**L21a**–**c** in the asymmetric hydrogenation of 3-methylbut-2-en-2-yl)benzene **S10** as a model substrate (Table 3.5.3). The results indicated again that the diastereomeric ligand backbone and the oxazoline substituent affected significatively (entries 1–6). However, in contrast to what it was observed for cyclic olefins, catalyst precursor Ir/**L19b** provided the highest enantioselectivity of the series (entry 2). This result clearly shows the importance of using a modular scaffold to build a catalyst. Again, there is a positive effect on enantioselectivity when the hydrogen pressure is lowered (entries 2, 7–9). Enantioselectivities increased up to an unprecedented 98% ee when the reduction was done at only 2 bars of H_2 (entry 9).

Table 3.5.3. Asymmetric hydrogenation of (3-methylbut-2-en-2-yl)benzene S10 using Ir-catalyst precursors with ligands **L18**-**L21a**-**c**.

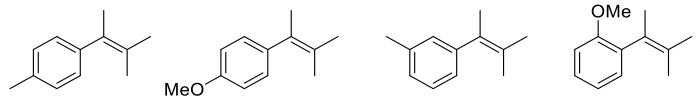


S10

Entry	L	P_{H2} (bar)	% Conv[a]	%ee[b]
1	**L18b**	75	85	33 (*S*)
2	**L19b**	75	100	85 (*S*)
3	**L20b**	75	100	44 (*R*)
4	**L21b**	75	100	25 (*R*)
5	**L19c**	75	85	44 (*R*)
6	**L19a**	75	100	75 (*R*)
7	*enant*-**L19b**	50	100	90 (*R*)
8[c]	*enant*-**L19b**	10	100	93 (*R*)
9[c,d]	*enant*-**L19b**	2	100	98 (*R*)

[a] Conversions were measured by ^{1}H NMR spectroscopy after 24 h; [b] Enantiomeric excesses determined by chiral GC; [c] Reaction performed using 2 mol% of catalysts; [d] Conversion measured after 36 h.

Under the mild optimal conditions found we further extended our work to the asymmetric hydrogenation of other acylic tetrasubstituted olefins **S11**-**S14** (Figure 3.5.3). Advantageously, we found that the catalytic performance of **L19b** was neither affected by the introduction of *para*-, *meta*- and even *ortho*-substituents at the phenyl groups of the substrate, nor by the nature of these substituents. A range of substituted acyclic tetrasubstituted olefins were therefore hydrogenated in high yields and with excellent enantioselectivities (ee's ranging from 97% to 99%; Figure 3.5.3). These results surpass the best ones reported so far.



S11
96% Yield
97% (*R*) ee

S12
97% Yield
98% (*R*) ee

S13
95% Yield
99% (*R*) ee

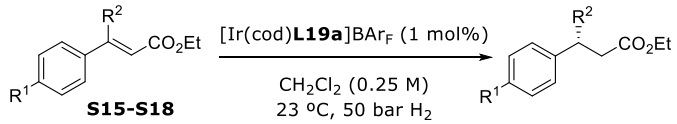
S14
93% Yield
98% (*R*) ee

Figure 3.5.3. Asymmetric hydrogenation of several acyclic tetrasubstituted olefins **S11**-**S14**. Reactions carried out using 2 mol% of *enant*-**L19b** at 2 bars of hydrogen at 23 ºC for 36 hours.

3.5.2.2. Asymmetric hydrogenation of α,β-unsaturated esters

With iridium complex Ir/**L19a**, we also perform a preliminary study of its performance in the asymmetric hydrogenation of α,β-unsaturated esters (Table 3.5.4).[14] Reduction of ethyl *trans*-β-methylcinnamate under standard non-optimized conditions (50 bar of hydrogen in dichloromethane with 1 mol% of Ir/**L19a** as the catalyst) produced the (*R*)-hydrogenated product in 95% ee (entry 1). Under the same reaction conditions, hydrogenation of the isopropyl and cyclohexyl β-substituted cinnamates afforded the reduced products in 97% ee (entries 2 and 3). Finally, *para*-methyl-substituted methylcinnamate afforded the reduced compound with complete selectivity (>99% ee, entry 4).

Table 3.5.4. Asymmetric hydrogenation of α,β-unsaturated esters using complex Ir/**L19a** as the catalyst.



S15-S18

Entry	L	R^1	R^2	% Conv[a]	%ee[b]
1	**S15**	H	Me	100	95 (*R*)
2	**S16**	H	^{i}Pr	100	97 (*R*)
3	**S17**	H	Cy	100	97 (*R*)
4	**S18**	Me	Me	100	>99 (*R*)

[a] Conversions were measured by ^{1}H NMR analysis of the crude reaction; [b] Enantiomeric excesses determined by chiral HPLC.

3.5.3. Conclusions

We reported a Ir/P*-stereogenic P,N-catalyst library with a simple modular architecture for the successful asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins. These air stable catalysts can be easily prepared in a few steps from readily available sources. Improving previous results, these catalysts are able to efficiently reduce indenes and the challenging 1,2-dihydronaphthalene derivatives (ee's

up to 96%) and also a range of the most elusive acyclic olefins with unprecedented enantioselectivity (ee's up to 99%) under mild reaction conditions. Interestingly, the reactions could be performed at low pressure with no loss of catalytic performance. In addition, preliminary results of their application in the hydrogenation of α,β-unsaturated esters showed enantioselectivities up to >99% ee. These results show that the readily available, air stable, modular catalysts MaxPHOX are useful for the challenging enantioselective hydrogenation of unfunctionalized olefins.

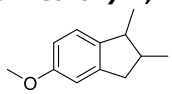
3.5.4. Experimental Section

3.5.4.1. General considerations

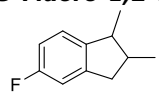
All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. All reagents were used as received. Substrates **S1**-**S14**,[4] **S15**,[15] **S16**-**S17**[14a] and **S18**[15] were prepared following the reported procedures. Ir-catalyst precursors containing ligands **L18**-**L21a**–**c** were prepared as previously reported.[11] ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C). ^{1}H and ^{13}C assignments were made based on ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC.

3.5.4.2. General procedure for the hydrogenation reactions

The alkene (1 mmol) and Ir complex (2 mol%) were dissolved in CH_2Cl_2 (2 mL) in a high-pressure autoclave. The autoclave was purged four times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 mL) and filtered through a short plug of Celite. Conversions were determined by ^{1}H NMR and enantiomeric excesses by chiral GC or chiral HPLC (for hydrogenation products from **S1**-**S4**, **S7**-**S9** and **S11**-**S14** see previous Section 3.3.4.8 and for hydrogenation product from **S10** and **S15-S18** see previous Section 3.2.4.6).

5-Methoxy-1,2-dimethyl-2,3-dihydro-1H-indene.[9]  Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, Isotherm at 150 ºC). t_R 5.3 (*R*); t_R 5.4 (*S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (d, 3H, CH_3, *J*= 6.9 Hz), 1.11 (d, 3H, CH_3, *J*= 7.2 Hz), 2.46-2.65 (m, 2H, CH_2 ring), 2.90-3.02 (m, 1H, CH, MeCH), 3.06-3.17 (m, 1H, CH, MeCH), 3.80 (s, 3H, CH3, MeO), 6.73 (dd, 1H, CH=, Ar, *J*= 8.2 Hz, *J*= 2.4 Hz), 6.78 (d, 1H, CH=, *J*= 2.4 Hz), 7.08 (d, 1H, CH=, Ar, *J*= 8.2 Hz).

5-Fluoro-1,2-dimethyl-2,3-dihydro-1H-indene.[9] Enantiomeric excess determined by GC using Chiraldex β-DM (100 kPa H_2, Isotherm at 90 ºC). t_R 15.5 (*R*); t_R 17.4 (*S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, 3H, CH_3, *J*= 6.9 Hz), 1.10 (d, 3H, CH_3, *J*= 7.2 Hz), 2.49-2.64 (m, 2H, CH_2 ring), 2.89-3.00 (m, 1H, CH, MeCH), 3.07-3.14 (m, 1H, CH, MeCH), 6.81-6.89 (m, 2H, CH=, Ar), 7.08 (dd, 1H, CH=, Ar, *J*= 8.1 Hz, *J*= 5.3 Hz).



3.5.5. Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P and CTQ2014-56361-P), IRB Barcelona, European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2014SGR670), and the ICREA Foundation (ICREA Academia award to M.D). IRB Barcelona is the recipient of a Severo Ochoa Award of Excellence from MINECO. E.S. thanks MINECO for a fellowship.

3.5.6. References

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3.6. Screening of a phosphite-sulfoximine ligand library in the asymmetric Ir-hydrogenation of minimally functionalized olefins

Biosca, M.; Pàmies, O.; Diéguez, M. *Preliminary results.*

Abstract: A new family of phosphite-sulfoximine ligands was prepared in four synthetic steps. These ligands allow the study of the replacement of commonly used oxazoline moiety by a more robust sulfoximine group. The iridium complexes of these phosphite-sulfoximine ligands were evaluated in the asymmetric reduction of several minimally functionalized olefins, including di-, tri- and tetrasubstituted examples. By carefully selecting the ligand parameters, high enantioselectivities were obtained in the hydrogenation of relevant substrates such as trisubstituted α,β-unsaturated enones, esters and δ-lactams (ee's up to 97%) and in the reduction of a trisubstituted alkenyl boronic ester (>99% ee).

3.6.1. Introduction

The high degree of enantiopurity required in life-science products have stimulated the development and industrial application of asymmetric catalysis. Asymmetric hydrogenation is a fundamental strategy for the preparation of these enantiopure compounds due to the high enantioselectivities achieved, the use of low catalyst loadings, the quantitative yields obtained, its perfect atom economy, and the general mild reaction conditions used.[1]

In this field, the hydrogenation of olefins containing an adjacent good coordinating group (e.g. dehydroamino acids) catalyzed by Rh- and Ru-catalyst precursors with diphosphine ligands has a long successful history. However, the hydrogenation of olefins without the presence of an adjacent good coordinating group, the so-called minimally functionalized olefins, has been less developed.[1-2] For this later class of substrates, Ir-P,N complexes have emerged as efficient catalysts.[3] In the last years, the composition of these ligands has been extended by introducing different P-donor groups (or carbene analogues) other than phosphines and N-donor groups other than oxazolines (such as pyridine, oxazole, thiazole …), and by modifying the chiral backbone.[3i,4] However, most of the chiral catalysts developed are still highly substrate-dependent and the development of efficient chiral ligands that tolerate a broader range of substrates remains a challenge. In an effort to overcome this limitation, our group has shown the benefits of introducing a π-acceptor biaryl-phosphite moiety in the ligand design.[5] The presence of a flexible biaryl phosphite group allows the catalyst to adapt its chiral pocket to the steric requirements of the substrate, facilitating for instance the successful hydrogenation of 1,1'-disubstituted olefins.[3d] Nevertheless, this approach is not general enough and further efforts to overcome the substrate limitation are still needed.

Sulfoximine-based compounds have proved to be very efficient as chiral ligands in several catalytic processes (such as Cu-catalyzed Diels–Alder reaction, Pd-catalyzed allylic substitution, Mg-catalyzed 1,3-dipolar cycloaddition,…).[6] Nevertheless, their use in the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins has been overlooked. Thus, to our knowledge there are only two examples in the literature.[7] In these reports, Bolm *et al.* described the use of phosphine-sulfoximine ligands in the Ir-catalyzed asymmetric hydrogenation of several α,β-unsaturated ketones. These Ir-P,N catalyst precursors were only effective in the reduction of a limited series of β,β' disubstituted enones (ee's up to 97%), since the enantiocontrol was highly dependent on subtle variations on the nature of the β'-substituent.[7a] Moderate enantioselectivities (up to 55% ee) were achieved in the hydrogenation of α-substituted enones.[7b]

In this section we present the synthesis of phosphite-sulfoximine ligands **L22**-**L24a**-**c** and their application in the Ir-catalyzed asymmetric hydrogenation of several minimally functionalized olefins. Ligands **L22**-**L24a**-**c** combine the robustness of the sulfoximine group with the flexibility and modularity of the biaryl phosphite moiety. Moreover, in the sulfoximine group the N-donor atom is directly attached to the stereogenic sulfur atom providing an additional chiral element in close proximity to the metal center. These ligands therefore allow to study the effect of introducing different substituents in the aryl group of the backbone (**L22** vs **L23**), changing the configuration of the biaryl phosphite moiety (**a**-**c**) and the rigidity of the ligand backbone (**L22**-**L23** vs **L24**).

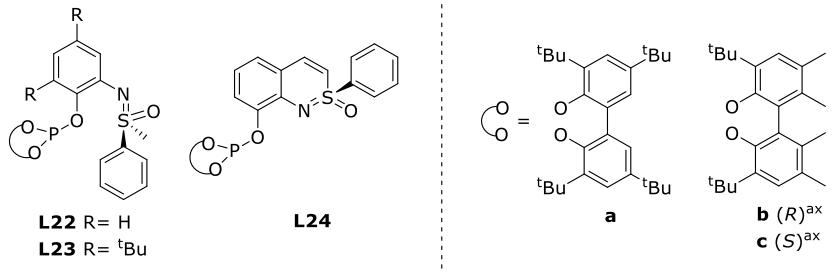


Figure 3.6.1. Phosphite-sulfoximine ligands **L22**-**L24a**-**c**.

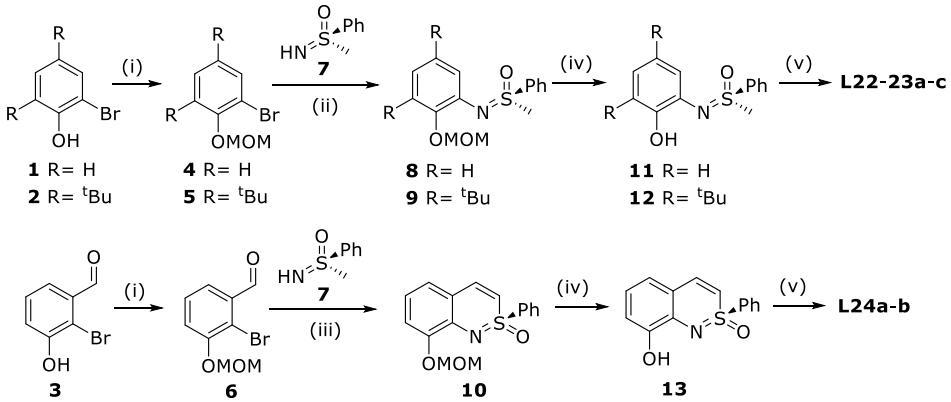
3.6.2. Results and Discussions

3.6.2.1. Synthesis of ligands

The synthesis of ligands **L22**-**L24a**-**c** is summarized in Scheme 3.6.1. They were synthesized in four steps from readily available compounds **1**-**3**. The first step consists in the protection of the hydroxyl group under basic conditions using methoxymethyl chloride (MOMCl; step i) to yield intermediates **4**-**6**. Then, they are coupled with the enantiopure sulfoximine **7**[8] (steps ii and iii). It should be noted that for compound **6**,

the coupling of **6** with sulfoximine **7** is followed by a cyclization reaction which allows the formation of benzothiazine **10** (step iii). Then, the deprotection of intermediates **8**-**10** was achieved quantitatively by treatment with HCl to give the desired hydroxyl-sulfoximines **11**-**13** (step iv). The last step of the ligand synthesis consisted in the coupling of the appropriate hydroxyl-sulfoximine intermediate (**11**-**13**) with the desired phosphorochloridite ($ClP(OR)_2$; $(OR)_2$= **a**-**c**; step v).

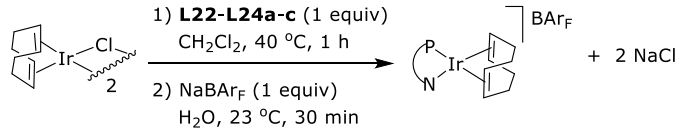
All ligands were stable during purification on neutral alumina under an atmosphere of argon and all were isolated as white or yellow solids. The ligands were stable in air and very stable to hydrolysis, so further manipulation/storage was carried out in air. HRMS-ESI spectra were consistent with the assigned structures. The ligands were also characterized by $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. The spectral assignments, based on ^1H-^1H and ^{13}C-^1H correlation measurements, were as expected for these C_1-symmetric ligands.



Scheme 3.6.1. Synthesis of sulfoximine-phosphite ligands **L22**-**L24a**-**c**. (i) MOMCl, NEt_3, THF, rt, 2-16 h; (ii) **7**, CuI, DMEDA, NaI, Cs_2CO_3, toluene, 110 ºC, 40-80 h; (iii) **7**, $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, toluene, reflux, 48 h; (iv) ^{i}PrOH/HCl/THF (2:1:1), rt, 3 h; (v) $ClP(OR)_2$; $(OR)_2$= **a**-**c**, Py, toluene, rt, 18 h.

3.6.2.2. Synthesis of Ir-catalyst precursors

The [Ir(cod)(**L22**-**L24a**-**c**)]BAr_F catalyst precursors were prepared by treating 0.5 equivalent of $[Ir(\mu\text{-}Cl)(cod)]_2$ with an equimolar amount of the appropriate phosphite-sulfoximine ligand (**L22**-**L24a**-**c**) in dichloromethane at 40 ºC for 1 h. Then, the Cl^-/BAr_F^- counterion exchange was performed by reaction with sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate ($NaBAr_F$; 1 equiv) in water (Scheme 3.6.2). The catalyst precursors were obtained in pure form as air-stable orange solids, so they were further manipulated and stored in air.



Scheme 3.6.2. Synthesis of [Ir(cod)(**L22**-**L24a**-**c**)]BAr_F catalyst precursors.

The HRMS-ESI spectra show the heaviest ions at m/z which correspond to the loss of the BAr_F anion from the molecular species. The complexes were also characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments, made using ^1H–^1H and ^{13}C–^1H correlation measurements, were as expected for these C_1-symmetric iridium complexes. It should be pointed out that for complexes containing ligands **L22** and **L23**, two species in solution are present. The 2D DOSY $^{31}P\{^1H\}$ NMR experiments showed that these two species have the same diffusion coefficient, which indicates that they must be isomers. A possible explanation for that behavior could be that the 6-memberred chelate ring on ligands **L22** and **L23** adopts two different stable conformations. Further proof could be found in the fact that for complexes containing ligands **L24**, which has a rigid ligand backbone, only one species in solution has been detected.

3.6.2.3. Asymmetric Ir-catalyzed hydrogenation of trisubstituted minimally functionalized olefins

As previously mentioned, the asymmetric hydrogenation of minimally functionalized olefins is highly dependent on the substrate geometry and its substitution pattern.[3] In general, the hydrogenation of *E*-trisubstituted olefins proceeds with higher enantioselectivities than the reduction of *Z*-olefins. In order to evaluate the potential of ligands **L22**-**L24a**-**c** in the reduction of olefins with different geometries, we initially tested them in the asymmetric hydrogenation of model substrates *E*-2-(4-methoxyphenyl)-2-butene **S1** and *Z*-2-(4-methoxyphenyl)-2-butene **S2**. The results, which are found in Table 3.6.1, indicated that the enantioselectivities are affected by the configuration of the biaryl phosphite moiety, the substituents on the aryl group of the ligand backbone as well as by the rigidity of the ligand backbone.

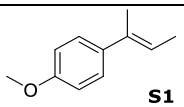
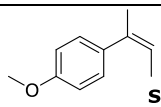
The effect of the configuration of the biaryl phosphite moiety on catalytic performance was studied with ligands **L22a**-**c** (entries 1-3). The results indicated that the ligand backbone is not able to control the tropoisomerism of the biaryl phosphite moiety **a** upon coordination to iridium (entry 1 vs 2 and 3). The presence of a chiral enantiopure biaryl phosphite moiety is therefore necessary to maximize enantioselectivities. The results also indicated that there is a cooperative effect between the configuration of the sulfoximine group and that of the biaryl phosphite moiety that results in a matched combination for ligands **L22b** that contains an (*R*)-biaryl phosphite group (entry 2).

The introduction of bulky *tert*-butyl substituents in the aryl group of the ligand backbone (ligand **L23a**) had a negative effect in the asymmetric induction for both substrates **S1** and **S2** (entry 1 vs 4).

Finally, the use of ligands **L24**, with a more rigid ligand backbone, also led to lower enantioselectivities than ligands **L22** (entries 1-2 vs 5-6).

In summary the highest enantioselectivities (ee's up to 80% and 61 for **S1** and **S2**, respectively) were achieved using ligand **L22b**, which contains the optimal combination of the ligand parameters.

Table 3.6.1. Ir-catalyzed hydrogenation of **S1** and **S2** using **L22**-**L24a**-**c**.[a]

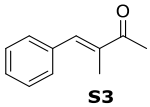
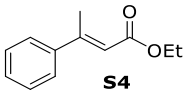
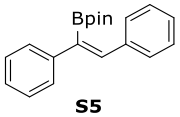
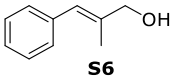
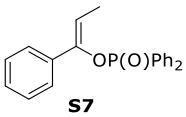
		 **S1**		 **S2**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L22a**	100	48 (*S*)	100	33 (*R*)
2	**L22b**	100	80 (*S*)	100	61 (*R*)
3	**L22c**	100	30 (*R*)	100	21 (*R*)
4	**L23a**	100	21 (*S*)	100	13 (*R*)
5	**L24a**	100	32 (*R*)	100	21 (*S*)
6	**L24b**	100	61 (*R*)	100	5 (*S*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (50 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^1H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by GC analysis.

To further study the potential of ligands **L22**-**L24a**-**c**, we next screened them in the asymmetric hydrogenation of other trisubstituted olefins containing poorly coordinative groups (**S3**-**S8**; Figure 3.6.2). The hydrogenation of these substrates is important since the corresponding hydrogenated products are relevant intermediates for the preparation of more complex chiral frameworks through their functionalization. The results are summarized in Table 3.6.2 (for a complete series of results, see Table SI-1 in Supporting Information at the end of this chapter). The results indicated that the ligand parameters must be correctly selected to enhance the enantioselectivity for each particular substrate.

We were pleased to find out that the reduction of α,β-unsaturated enone **S3** proceeded with high enantiocontrol using [Ir(cod)(**L24b**)]BAr_F catalyst precursor (96% ee, entry 1). Interestingly, we could also efficiently hydrogenate α,β-unsaturated ester **S4** using Ir/**L22b** catalytic system (97% ee, entry 2). Excellent enantiocontrol was also obtained in the reduction of alkenyl boronic ester **S5** (>99 % ee, entry 3). Nevertheless, the new catalytic systems are less efficient in transferring the chiral information in the hydrogenation of allylic alcohol **S6**, enol phosphinate **S7** and also for the more elusive α,β-unsaturated amide **S8** (entries 4-6).

Table 3.6.2. Selected results for the asymmetric hydrogenation of **S3-S8** using [Ir(cod)(**L22**-**L24a**-**c**)]BAr_F catalyst precursors.[a]

Entry	Ligand	Substrate	% Conv[b]	% ee[c]
1	**L24b**	 **S3**	100	96 (*R*)
2	**L22b**	 **S4**	100	97 (*S*)
3[d]	**L22a**	 **S5**	100	>99 (-)
4	**L22b**	 **S6**	100	60 (*S*)
5	**L22c**	 **S7**	86	48 (*R*)
6[d]	**L22b**	 **S8**	70	75 (*S*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (50 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^1H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by HPLC analysis; [d] Reaction carried out for 18 h.

Encouraged by the satisfactory results achieved in the hydrogenation of α,β-unsaturated enone and ester (**S3** and **S4**) and α,β-unsaturated amide **S8**, we next studied the substrate scope for these substrate types. The results are found in Figure 3.6.2. A range of α,β-unsaturated enones (**S9**-**S14**) were hydrogenated with high enantioselectivities (ee's ranging from 95% to 97%). Remarkably, the enantioselectivities do not depend on the electronic nature of the substrate phenyl ring or the nature of the ketone substituent. These results are noteworthy not only because they are among the best reported for these substrates (surpassing the results achieved using previously described phosphine-sulfoximine analogues); but also because the hydrogenation of α-substituted enones have been less studied than other trisubstituted olefins, despite their hydrogenation is a simple way to obtain ketones with a stereogenic center in the α-position to the carbonyl moiety.[4j,4q,4s,9]

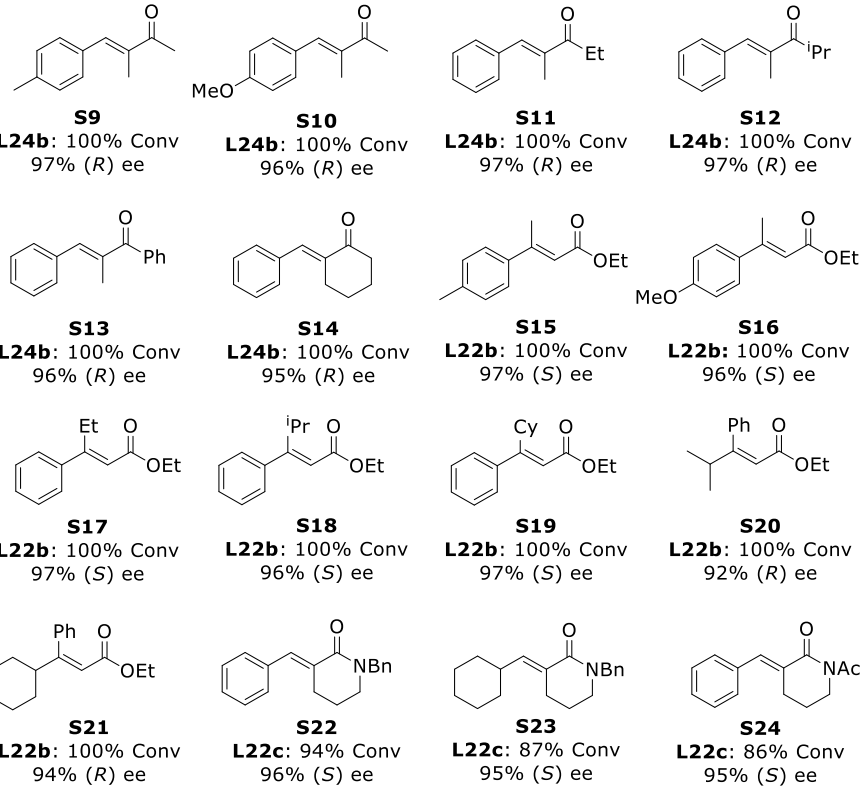


Figure 3.6.2. Results for the hydrogenation of trisubstituted olefins **S9**-**S24** using [Ir(cod)(**L22**-**L24a**-**c**)]BAr_F catalyst precursors. Reaction conditions: Catalyst precursor (2 mol%), CH_2Cl_2, H_2 (50 bar), 4 h (for **S9**-**S21**) or 18 h (for **S22**-**S24**).

We next studied the reduction of several α,β-unsaturated esters, including more challenging examples with *Z*-geometry (**S15**-**S21**). High enantioselectivities were achieved in all cases (ee's ranging from 92% to 97%). Owing the importance of the resulting chiral carboxylic ester derivatives, which are present in many relevant product, these results are remarkable.[10]

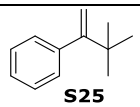
Finally, the effectiveness of the new catalytic systems were also evaluated in the hydrogenation of α,β-unsaturated δ-lactams (**S22**-**S24**). Chiral δ-lactams with stereogenic centers in the α-position are present in several natural products and they could also be useful fragments in synthetic chemistry.[4w,10b,11] We were pleased to see that high enantioselectivities were obtained independently of the nature of the protecting group of the amide and the nature of the substituent on the β-position (ee's up to 96%).

3.6.2.4. Asymmetric Ir-catalyzed hydrogenation of di- and tetrasubstituted minimally functionalized olefins

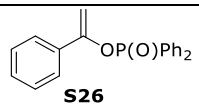
We next screened ligands **L22**-**L24a**-**c** in the asymmetric reduction of much more challenging substrates, di- and tetrasubstituted olefins. As previously mentioned, terminal olefins have been not successfully hydrogenated until very recently and the reduction of tetrasubstituted olefins is still a challenge.[3]

First, we tested the catalytic performance of phosphite-sulfoximine ligands **L22**-**L24a**-**c** in the hydrogenation of two terminal olefins, the model substrate 3,3-dimethyl-2-phenyl-1-butene (**S25**) and the enol phosphinate (**S26**). As shown in Table 3.6.3, the enantioselectivities are again highly affected by the configuration of the biaryl phosphite moiety, the substituents on the aryl group of the ligand backbone and the rigidity of the ligand backbone as in the case of trisubstituted substrates. However, the effects of the configuration of the phosphite moiety and the rigidity of the ligand backbone on enantioselectivity are different from those observed for **S1** and **S2**. Thus, in contrast to **S1** and **S2**, the best enantioselectivities were obtained with ligands that contain an (*S*)-biaryl phosphite group (**c**, entry 3 vs 2). The results also indicated that for both substrates (**S25** and **S26**), the presence of a more rigid ligand backbone has a positive effect on enantioselectivity (entries 5-6 vs 1-2). Enantioselectivities up to 86% ee for **S25** and up to 48% ee for **S6** were achieved using [Ir(cod)(**L24b**)]BAr_F and [Ir(cod)(**L22c**)]BAr_F catalyst precursors, respectively (entries 3 and 6).

Table 3.6.3. Ir-catalyzed hydrogenation of **S25** and **S26** using **L22**-**L24a**-**c**.[a]



S25



S26

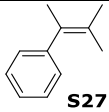
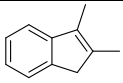
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L22a**	100	48 (*R*)	35	9 (*S*)
2	**L22b**	100	0	100	4 (*R*)
3	**L22c**	100	70 (*R*)	36	48 (*S*)
4	**L23a**	100	14 (*R*)	16	4 (*R*)
5	**L24a**	100	75 (*S*)	100	25 (*S*)
6	**L24b**	100	86 (*S*)	76	34 (*S*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (1 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^{1}H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by GC (for **S25**) or HPLC (for **S26**) analysis.

Concerning the tetrasubstituted substrates, we explored the asymmetric reduction of acyclic and cyclic tetrasubstituted olefins (**S27** and **S28**, respectively). The results, which are shown in Table 3.6.4, follow a similar trend than in the hydrogenation of trisubstituted olefins. Thus, the best enantioselectivities (ee's up to 42% and 40% for

S27 and **S28**, respectively) were achieved with [Ir(cod)(**L22b**)]BAr_F catalyst precursor (entry 2).

Table 3.6.4. Ir-catalyzed hydrogenation of **S27** and **S28** using **L22**-**L24a**-**c**.[a]

		 **S27**		 **S28**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L22a**	45	6 (*S*)	67	36 (*S*,*S*)
2	**L22b**	30	42 (*R*)	43	40 (*S*,*S*)
3	**L22c**	34	30 (*S*)	70	4 (*R*,*R*)
4	**L23a**	13	6 (*R*)	28	35 (*S*,*S*)
5	**L24a**	20	10 (*S*)	26	8 (*S*,*S*)
6	**L24b**	16	10 (*R*)	13	4 (*R*,*R*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (50 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^1H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by GC analysis.

3.6.3. Conclusions

Six new Ir-catalyst precursors, containing phosphite-sulfoximine ligands, were synthetized in five steps. These ligands combine the robustness of the sulfoximine group with the flexibility and modularity of the biaryl phosphite moiety. These ligands therefore allow to study the effect of introducing different substituents in the aryl group of the ligand backbone (**L22** vs **L23**), changing the configuration of the biaryl phosphite moiety (**a**-**c**) and the rigidity of the ligand backbone (**L22**-**L23** vs **L24**). Their Ir/**L22**-**L24a**-**c** catalytic systems were screened in the asymmetric hydrogenation of several minimally functionalized olefins with different geometries and substitution patterns, including di-, tri- and tetrasubstituted olefins. The catalytic results indicated that enantioselectivity is highly affected by the ligand parameters as well as by the type of substrate employed. Although, moderate enantioselectivities were obtained in the reduction of most of the substrates screened, the novel catalyst precursors have shown their effectiveness in the hydrogenation of relevant substrates such as trisubstituted α,β-unsaturated enones, esters and δ-lactams (ee's up to 97%) and in the reduction of a trisubstituted alkenyl boronic ester (>99% ee), with enantioselectivities comparable to the best one reported.

3.6.4. Experimental Section

3.6.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[12] ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H, ^{13}C, and ^{31}P assignments were made on the basis of ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC and ^{1}H-^{31}P gHMBC experiments. Substrates **S1**-**S2**,[13] **S3**,[14] **S4**,[15] **S6**,[16] **S7**,[17] **S8**,[18] **S9**-**S13**,[4j] **S14**,[19] **S15**-**S16**,[15] **S17**-**S21**,[10b] **S22**-**S24**,[20] **S25**,[21] **S26**[17] and **S27**-**S28**[22] were prepared following the reported procedures and **S5** was commercially available. Hydroxyl-sulfoximine **13**[23] and sulfoximine **7**[8] were prepared as previously described.

3.6.4.2. General procedure for the preparation of compounds 4-5

A flame dried Schlenk flushed with argon was charged with compound **1**-**2** (10 mmol, 1 eq.) which was dissolved in dry THF (25 mL) along with dry triethylamine (49.6 mmol, 6.8 mL, 5 eq.), and a stir bar. MOMCl (20 mmol, 1.5 mL, 2 eq.) was added dropwise resulting in the formation of a white precipitate. The reaction was allowed to stir during 4 h for compound **1**, and 16 h for compound **2**. The reaction was taken up in water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (94% (petroleum ether): 6% (ethyl acetate) for **4** and 100% (petroleum ether) for **5**).

1-Bromo-2-(methoxymethoxy)benzene (4): Yield: 1.73 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.52 (s, 3H, CH_3), 5.26 (s, 2H, CH_2), 6.88 (ddd, 1H, CH=, $^{3}J_{H\text{-}H}$= 7.9 Hz, $^{3}J_{H\text{-}H}$= 7.4 Hz, $^{4}J_{H\text{-}H}$= 1.5 Hz), 7.15 (dd, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.3 Hz, $^{4}J_{H\text{-}H}$= 1.5 Hz), 7.24 (ddd, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.3 Hz, $^{3}J_{H\text{-}H}$= 7.4 Hz, $^{4}J_{H\text{-}H}$= 1.6 Hz), 7.55 (dd, 1H, CH=, $^{3}J_{H\text{-}H}$= 7.9 Hz, $^{4}J_{H\text{-}H}$= 1.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 56.3 (CH_3), 95.0 (CH_2), 112.9 (C), 116.2 (CH=), 123.1 (CH=), 128.5 (CH=), 128.5 (CH=), 133.4 (CH=), 153.8 (C).

1-Bromo-3,5-di-*tert*-butyl-2-(methoxymethoxy)benzene (5): Yield: 1.97 g (60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.29 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 9H, CH_3, ^{t}Bu), 3.69 (s, 3H, CH_3), 5.21 (s, 2H, CH_2), 7.30 (d, 1H, CH=, $^{4}J_{H\text{-}H}$= 2.4 Hz), 7.39 (d, 1H, CH=, $^{4}J_{H\text{-}H}$= 2.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 30.8 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 35.9 (C, ^{t}Bu), 57.7 (CH_3), 99.3 (CH_2), 117.5 (C), 123.9 (CH=), 128.7 (CH=), 144.4 (CH=), 147.5 (CH=), 150.5 (C).

3.6.4.3. General procedure for the preparation of compounds 8-9

Under an argon atmosphere a dry flamed Schlenk flask was charged with the MOM-protected hydroxyl-aryl bromide **4**-**5** (2.0 equiv, 5.0 mmol), CuI (0.1 equiv, 0.25 mmol, 47.5 mg), DMEDA (0.2 equiv, 0.5 mmol, 44.1 mg) and NaI (4.0 equiv, 10 mmol, 1.5 g). Then, degassed toluene (50 mL) was added, and the resulting heterogeneous mixture was heated to 110 °C for 20 h for **4** and 40 h for **5**. Then, sulfoximine **7** (1.0 equiv, 2.5 mmol, 0.4 g) and Cs_2CO_3 (2.5 equiv, 12.5 mmol, 4.0 g) were added and the mixture was kept at 110 °C for additional 20 h for **4**, and 40 h for **5**. Subsequently, the mixture was cooled to room temperature, and extracted with dichloromethane and an aqueous ammonia solution. The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel with 100% ethyl acetate afforded compounds **8**-**9**.

(*S*)-((2-(Methoxymethoxy)phenyl)imino)(methyl)(phenyl)-λ⁶-sulfanone (8): Yield: 619.1 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.21 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 5.16 (d, 2H, CH_2, $^2J_{H-H}$= 6.6 Hz), 5.21 (d, 2H, CH_2, $^2J_{H-H}$= 6.6 Hz), 6.75 (td, 1H, CH=, $^3J_{H-H}$= 7.6 Hz, $^4J_{H-H}$= 1.5 Hz), 6.82 (td, 1H, CH=, $^3J_{H-H}$= 7.6 Hz, $^4J_{H-H}$= 1.7 Hz), 7.03 (dd, 1H, CH=, $^3J_{H-H}$= 8.0 Hz, $^4J_{H-H}$= 1.5 Hz), 7.08 (dd, 1H, CH=, $^3J_{H-H}$= 7.8 Hz, $^4J_{H-H}$= 1.7 Hz), 7.43-7.58 (m, 3H, CH=), 8.00 (dd, 2H, CH=, $^3J_{H-H}$= 8.4 Hz, $^4J_{H-H}$= 1.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 46.2 (CH_3), 56.1 (CH_3), 95.5 (CH_2), 116.9 (CH=), 122.5 (CH=), 122.7 (CH=), 124.6 (CH=), 128.4 (CH=), 129.4 (CH=), 133.1 (CH=), 135.0 (C), 140.1 (C), 150.7 (C).

(*S*)-((2,3-Di-*tert*-butyl-6-(methoxymethoxy)phenyl)imino)(methyl)-(phenyl)-λ⁶-sulfanone (9): Yield: 585.2 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.11 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 9H, CH_3, ^{t}Bu), 3.23 (CH_3), 3.70 (CH_3), 5.31 (d, 1H, CH_2, $^2J_{H-H}$= 4.5 Hz), 5.44 (d, 1H, CH_2, $^2J_{H-H}$= 4.5 Hz), 6.87 (dd, 2H, CH=, $^3J_{H-H}$= 8.2 Hz, $^4J_{H-H}$= 2.4 Hz), 7.46-7.61 (m, 3H, CH=), 7.98-8.07 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 30.7 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 45.6 (CH_3), 57.5 (CH_3), 98.4 (CH_2), 117.5 (CH=), 119.4 (CH=), 128.5 (CH=), 129.4 (CH=), 133.0 (CH=), 137.0 (C), 139.6 (C), 141.8 (C), 145.2 (C), 147.1 (C).

3.6.4.4. General procedure for the preparation of compounds 11-12

The corresponding compound **8** or **9** (1 equiv, 2.0 mmol) was added to a solution of 2-propanol (50 equiv, 7.7 mL, 100 mmol), HCl (25 equiv, 12.1 N, 4.1 mL, 50 mmol) and THF (25 equiv, 4.1 mL, 50 mmol). The mixture was stirred at room temperature for 3 h. The mixture was diluted with water (10 mL) and extracted with ether (3 × 10 mL). The combined organic layers were washed with 5% (w/w) $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo* affording pure hydroxy-sulfoximine **11**-**12**.

(*S*)-((2-Hydroxyphenyl)imino)(methyl)(phenyl)-λ⁶-sulfanone (11): Yield: 474.8 mg (96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.32 (s, 3H, CH_3), 6.57 (td, 1H, CH=, $^{3}J_{H-H}$= 7.6 Hz, $^{4}J_{H-H}$= 1.6 Hz), 6.80-6.86 (m, 3H, CH=), 7.50-7.67 (m, 3H, CH=), 7.90-7.97 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 46.0 (CH_3), 113.9 (CH=), 119.9 (CH=), 120.9 (CH=), 122.8 (CH=), 128.3 (CH=), 129.8 (CH=), 131.8 (C), 133.7 (CH=), 138.2 (C), 149.9 (C).

(*S*)-((2,3-Di-*tert*-butyl-6-hydroxyphenyl)imino)(methyl)(phenyl)-λ⁶-sulfanone (12): Yield: 675.9 mg (94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.14 (s, 9H, CH_3, ^{t}Bu), 1.26 (s, 9H, CH_3, ^{t}Bu), 4.11 (s, 3H, CH_3), 6.96 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.06 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.59 (t, 2H, CH=, $^{3}J_{H-H}$= 7.7Hz), 7.71 (t, 1H, CH=, $^{3}J_{H-H}$= 7.4 Hz), 8.16 (d, 2H, CH=, $^{3}J_{H-H}$= 7.9 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 29.3 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 42.5 (CH_3), 121.0 (CH=), 123.4 (CH=), 129.9 (CH=), 130.1 (CH=), 131.7 (C), 136.1 (CH=), 138.3 (C), 142.2 (C), 148.0 (C).

3.6.4.5. General procedure for the preparation of ligands L22-L24a-c

To a solution of *in situ* generated phosphorochloridite (0.55 mmol) in dry toluene (3 mL), pyridine (0.08 mL, 1.0 mmol) was added. Then, this solution was placed in a -78 ºC bath and a solution of the hydroxyl-sulfoximine (0.50 mmol) and pyridine (0.08 mL, 1.0 mmol) in toluene (3 mL) was added dropwise. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered under argon, and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral alumina and dry toluene (1% NEt_3) as eluent system) to afford the corresponding phosphite-sulfoximine as white solids for **L22**-**23a**-**c** or as yellow solid for **L24a**-**b**.

L22a: Yield: 174.9 mg (51%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 137.8 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.45 (s, 18H, CH_3, ^{t}Bu), 1.79 (s, 9H, CH_3, ^{t}Bu), 1.81 (s, 9H, CH_3, ^{t}Bu), 2.88 (s, 3H, CH_3), 6.68-6.77 (m, 2H, CH=), 6.98-7.00 (m, 1H, CH=), 7.11-7.30 (m, 3H, CH=), 7.79 (s, 2H, CH=), 8.13 (s, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 31.1 (CH_3, ^{t}Bu), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 2.6 Hz), 31.3 (CH_3, ^{t}Bu), 34.4 (d, C, ^{t}Bu, J_{C-P}= 3.0 Hz), 35.4 (C, ^{t}Bu), 45.0 (CH_3), 121.9-146.6 (aromatic carbons). MS HR-ESI [found 708.3250, $C_{41}H_{52}NO_4PS$ $(M-Na)^+$ requires 708.3247].

L22b: Yield: 120.3 mg (40%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 132.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.24 (s, 9H, CH_3, ^{t}Bu), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.77 (s, 6H, CH_3), 2.36 (s, 3H, CH_3), 6.49-6.53 (m, 1H, CH=), 6.57-6.60 (m, 1H, CH=), 6.82-6.84 (m, 1H, CH=), 6.89-6.92 (m, 3H, CH=), 7.00-7.11 (m, 1H, CH=), 7.30 (s, 1H, CH=), 7.41-7.44 (m, 1H, CH=), 7.91-7.94 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.3 (CH_3), 16.5 (CH_3), 20.1 (CH_3), 31.1 (CH_3, ^{t}Bu, J_{C-P}=

5.1 Hz), 31.8 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 44.7 (CH_3), 121.9-146.1 (aromatic carbons). MS HR-ESI [found 652.2624, $C_{37}H_{44}NO_4PS$ $(M\text{-}Na)^+$ requires 652.2621].

L22c: Yield: 66.2 mg (22%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 130.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.54 (s, 9H, CH_3, ^{t}Bu), 1.75 (s, 9H, CH_3, ^{t}Bu), 1.78 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.08 (s, 6H, CH_3), 2.68 (s, 3H, CH_3), 6.47-6.51 (m, 1H, CH=), 6.53-6.57 (m, 1H, CH=), 6.92-7.05 (m, 5H, CH=), 7.11-7.13 (m, 1H, CH=), 7.26 (s, 1H, CH=), 7.34 (s, 1H, CH=), 7.35-7.37 (m, 1H, CH=), 8.01-8.04 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.4 (CH_3), 16.6 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.2 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.5 Hz), 31.7 (s, CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 45.1 (CH_3), 121.9-145.7 (aromatic carbons). MS HR-ESI [found 652.2623 $C_{37}H_{44}NO_4PS$ $(M\text{-}Na)^+$ requires 652.2621].

L23a: Yield: 39.9 mg (10%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 131.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.08 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 18H, CH_3, ^{t}Bu), 2.66 (s, 3H, CH_3), 6.84-7.07 (m, 4H, CH=), 7.26 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.2 Hz), 7.43 (d, 1H, $^4J_{H\text{-}H}$= 2.4 Hz), 7.57 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.4 Hz), 7.67 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.5 Hz), 7.71 (d, 1H, CH=, $^4J_{H\text{-}H}$= 2.4 Hz), 7.95-7.98 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 30.4 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.1 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.5 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 44.2 (CH_3), 116.7-150.4 (aromatic carbons). MS HR-ESI [found 820.4501, $C_{49}H_{68}NO_4PS$ $(M\text{-}Na)^+$ requires 820.4499].

L24a: Yield: 160.0 mg (46%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 138.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.22 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 5.65 (d, 1H, CH=, $^3J_{H\text{-}H}$= 9.5 Hz), 6.57-6.71 (m, 2H, CH=), 6.75 (d, 1H, CH=, $^3J_{H\text{-}H}$= 9.5 Hz), 6.84-7.01 (m, 3H, CH=), 7.05-7.11 (m, 1H, CH=), 7.32 (dd, 2H, CH=, $^3J_{H\text{-}H}$= 6.5 Hz, $^4J_{H\text{-}H}$= 2.1 Hz), 7.56 (dd, 2H, CH=, $^3J_{H\text{-}H}$= 12.1 Hz, $^4J_{H\text{-}H}$= 2.1 Hz), 7.72 (dd, 2H, CH=, $^3J_{H\text{-}H}$= 7.3 Hz, $^4J_{H\text{-}H}$= 1.1 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 31.1 (CH_3, ^{t}Bu), 31.2 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 2.3 Hz), 34.3 (d, C, ^{t}Bu, $J_{C\text{-}P}$= 4.2 Hz), 35.4 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 110.6 (CH=), 137.7 (CH=), 117.7-146.3 (aromatic carbons). MS HR-ESI [found 718.3092, $C_{42}H_{50}NO_4PS$ $(M\text{-}Na)^+$ requires 718.3090].

L24b: Yield: 165.2 mg (54%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 133.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.49 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.68 (s, 9H, CH_3, ^{t}Bu), 1.70 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 5.74 (d, 1H, CH=, $^3J_{H\text{-}H}$= 9.8 Hz), 6.62 (t, 1H, CH=, $^3J_{H\text{-}H}$= 7.1 Hz), 6.72 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.8 Hz), 6.83 (d, 1H, CH=, $^3J_{H\text{-}H}$= 9.8 Hz), 6.88-6.94 (m, 3H, CH=), 7.19 (s, 1H, CH=), 7.25 (s, 1H, CH=), 7.30 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.7 Hz), 7.76-7.86 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.3 (CH_3), 16.5 (CH_3), 20.1 (CH_3), 31.2 (d, CH3, ^{t}Bu, $J_{C\text{-}P}$= 5.2 Hz), 31.8 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 111.2 (CH=), 137.4 (CH=), 118.0-145.6 (aromatic carbons). MS HR-ESI [found 662.2467, $C_{38}H_{42}NO_4PS$ $(M\text{-}Na)^+$ requires 662.2464].

3.6.4.6. General procedure for the preparation of [Ir(cod)(L22-L24a-c)]BAr_F

The corresponding ligand (0.074 mmol) was dissolved in CH_2Cl_2 (5 mL) and [Ir(μ-Cl)(cod)]$_2$ (25.0 mg, 0.037 mmol) was added. The reaction mixture was heated to reflux at 40 °C for 1 h. After 5 min at rt, $NaBAr_F$ (77.2 mg, 0.080 mmol) and water (5 mL) were added and the reaction mixture was stirred vigorously for 30 min at rt. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ filtered through a plug of Celite and the solvent was evaporated to give the product as an orange solid.

[Ir(cod)(L22a)]BAr_F: Yield: 124 mg (91%). Major isomer (57%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 122.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.27 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 9H, CH_3, ^{t}Bu), 1.57-1.67 (m, 2H, CH_2, cod), 1.92-2.16 (m, 2H, CH_2, cod), 2.28-2.35 (m, 3H, CH_2, cod), 2.49-2.52 (m, 1H, CH_2, cod), 3.12 (s, 3H, CH_3), 3.91 (m, 1H, CH=, cod), 4.57 (m, 1H, CH=, cod), 5.42 (m, 1H, CH=, cod), 6.15 (m, 1H, CH=, cod), 6.39-8.45 (m, 25H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 25.9 (CH_2, cod), 29.8 (CH_2, cod), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 32.3 (CH_2, cod), 34.9-35.8 (C, ^{t}Bu), 36.9 (CH_2, cod), 44.1 (CH_3), 65.3 (CH=, cod), 66.7 (CH=, cod), 99.8 (d, CH=, cod, $J_{C\text{-}P}$= 20.1 Hz), 109.2 (d, CH=, cod, $J_{C\text{-}P}$= 12.9 Hz), 117.8-150.2 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.8 Hz). Minor isomer (43%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 120.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.05-1.26 (m, 2H, CH_2, cod), 1.14 (s, 9H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.73 (s, 9H, CH_3, ^{t}Bu), 1.67-1.71 (m, 3H, CH_2, cod), 1.91 (m, CH=, cod), 2.08-2.24 (m, 2H, CH_2, cod), 2.50 (m, 1H, CH_2, cod), 3.95 (CH_3), 3.89 (m, 1H, CH=, cod), 4.41 (m, 1H, CH=, cod), 6.08 (m, 1H, CH=, cod), 7.11-8.02 (m, 25H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 24.6 (CH_2, cod), 29.0 (CH_2, cod), 30.1 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 33.2 (CH_2, cod), 34.9-35.8 (C, ^{t}Bu), 50.0 (CH_3), 54.5 (CH=, cod), 66.3 (CH=, cod), 99.7 (d, CH=, cod, $J_{C\text{-}P}$= 22.5 Hz), 108.1 (d, CH=, cod, $J_{C\text{-}P}$= 13.8 Hz), 117.8-150.2 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.8 Hz). MS HR-ESI [found 986.3919, $C_{49}H_{64}IrNO_4PS$ $(M\text{-}BAr_F)^+$ requires 986.3923].

[Ir(cod)(L22b)]BAr_F: Yield: 122 mg (92%). Major isomer (80%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 121.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.15 (s, 9H, CH_3, ^{t}Bu), 1.43-1.46 (m, 1H, CH_2, cod), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.70-1.82 (m, 1H, CH_2, cod), 1.71 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 2.05-2.08 (m, 1H, CH_2, cod), 2.25-2.33 (m, 3H, CH_2, cod), 2.28 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.50-2.54 (m, 1H, CH_2, cod), 2.33 (m, 1H, CH=, cod), 4.01 (s, 3H, CH_3), 4.32 (m, 1H, CH=, cod), 5.46 (m, 1H, CH=, cod), 6.58 (m, 1H, CH=, cod), 6.71-7.89 (m, 23H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.9 (CH_3), 17.0 (CH_3), 20.0 (CH_3), 20.6 (CH_3), 25.8 (CH_2, cod), 29.8 (CH_2, cod), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 32.6 (CH_2, cod), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 37.5 (CH_2, cod), 49.6 (CH_3),

54.9 (CH=, cod), 68.8 (CH=, cod), 100.0 (d, CH=, cod, $J_{C\text{-}P}$= 21.3 Hz), 108.6 (d, CH=, cod, $J_{C\text{-}P}$= 14.1 Hz), 117.8-145.3 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.9 Hz). Minor isomer (20%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 119.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.28 (s, 9H, CH_3, ^{t}Bu), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.70 (s, 3H, CH_3), 1.73-1.93 (m, 4H, CH_2, cod), 1.95 (s, 3H, CH_3), 2.00-2.30 (m, 4H, CH_2, cod), 2.30 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.55 (s, 3H, CH_3), 4.10 (m, 1H, CH=, cod), 4.14 (m, 1H, CH=, cod), 4.74 (m, 1H, CH=, cod), 5.89 (m, 1H, CH=, cod), 6.46-7.80 (m, 23H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.8 (CH_3), 16.9 (CH_3), 20.7 (CH_3), 20.9 (CH_3), 25.8 (CH_2, cod), 30.4 (CH_2, cod), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.9 (CH_2, cod), 32.3 (CH_2, cod), 35.8 (C, ^{t}Bu), 44.6 (CH_3), 53.8 (CH=, cod), 63.1 (CH=, cod), 100.0 (CH=, cod), 109.0 (d, CH=, cod, $J_{C\text{-}P}$= 14.4 Hz), 121.8-147.3 (aromatic carbons), 162.1 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.9 Hz). MS HR-ESI [found 930.3293, $C_{45}H_{61}IrNO_4PS$ $(M\text{-}BAr_F)^+$ requires 930.3297].

[Ir(cod)(L22c)]BAr_F: Yield: 126 mg (95%). Major isomer (80%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 121.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.17-1.28 (m, 2H, CH_2, cod), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.54 (m, 1H, CH=, cod), 1.69 (s, 9H, CH_3, ^{t}Bu), 1.74 (s, 3H, CH_3), 1.90-2.13 (m, 2H, CH_2, cod), 2.21-2.29 (m, 2H, CH_2, cod), 2.40-2.44 (m, 2H, CH_2, cod), 1.98 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.06 (m, 1H, CH=, cod), 5.31 (m, 1H, CH=, cod), 6.11 (m, 1H, CH=, cod), 6.53-8.50 (m, 23H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.4 (CH_3), 16.5 (CH_3), 20.2 (CH_3), 20.5 (CH_3), 25.2 (CH_2, cod), 29.6 (CH_2, cod), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 32.1 (CH_2, cod), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 36.8 (CH_2, cod), 49.5 (CH_3), 55.1 (CH=, cod), 68.8 (CH=, cod), 99.6 (d, CH=, cod, $J_{C\text{-}P}$= 21.3 Hz), 108.0 (d, CH=, cod, $J_{C\text{-}P}$= 14.1 Hz), 117.4-144.9 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.9 Hz). Minor isomer (20%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 119.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.00-1.11 (m, 2H, CH_2, cod), 1.11 (s, 9H, CH_3, ^{t}Bu), 1.22-1.25 (m, 2H, CH_2, cod), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.68-1.72 (m, 1H, CH_2, cod), 1.85 (s, 3H, CH_3), 2.10-2.21 (m, 3H, CH_2, cod), 2.24 (s, 3H, CH_3), 2.33 (s, 6H, CH_3), 3.07 (s, 3H, CH_3), 3.89 (m, 1H, CH=, cod), 4.26 (m, 1H, CH=, cod), 4.43 (m, 1H, CH=, cod), 6.05 (m, 1H, CH=, cod), 6.96-7.93 (m, 23H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.4 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 25.5 (CH_2, cod), 28.2 (CH_2, cod), 29.3 (CH_2, cod), 30.9 (CH_3, ^{t}Bu), 31.7 (CH_2, cod), 34.9 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 36.8 (CH_2, cod), 44.1 (CH_3), 54.4 (CH=, cod), 68.4 (CH=, cod), 99.6 (CH=, cod), 108.3 (d, CH=, cod, $J_{C\text{-}P}$= 21.5 Hz), 121.2-146.8 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.9 Hz). MS HR-ESI [found 930.3294 $C_{45}H_{56}IrNO_4PS$ $(M\text{-}BAr_F)^+$ requires 930.3297].

[Ir(cod)(L23a)]BAr_F: Yield: 138 mg (95%). Major isomer (78%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 117.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.15 (s, 9H, CH_3, ^{t}Bu), 1.17 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 1H, CH_2, cod), 1.74 (s, 9H, CH_3, ^{t}Bu), 1.92-2.00 (m, 3H, CH_2, cod), 2.03 (m, 1H, CH=, cod), 2.30-2.34 (m, 2H, CH_2, cod), 2.40-2.58 (m, 2H, CH_2, cod), 2.90 (s, 3H,

CH_3), 3.97 (m, 1H, CH=, cod), 4.63 (m, 1H, CH=, cod), 6.20 (m, 1H, CH=, cod), 7.02-8.43 (m, 23H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 22.7 (CH_2, cod), 24.7 (CH_2, cod), 30.0 (CH_2, cod), 30.6 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.9 (CH_2, cod), 43.3 (CH_3), 52.7 (CH=, cod), 66.4 (CH=, cod), 101.3 (d, CH=, cod, $J_{C\text{-}P}$= 20.5 Hz), 107.9 (d, CH=, cod, $J_{C\text{-}P}$= 14.3 Hz), 117.4-149.7 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.7 Hz). Minor isomer (22%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 118.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.01 (s, 9H, CH_3, ^{t}Bu), 1.14-1.25 (m, 3H, CH_2, cod), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 2.08-2.15 (m, 3H, CH_2, cod), 2.32-2.45 (m, 2H, CH_2, cod), 2.60 (m, 1H, CH=, cod), 3.97 (s, 3H, CH_3), 4.49 (m, 1H, CH=, cod), 5.72 (m, 1H, CH=, cod), 6.36 (m, 1H, CH=, cod), 6.39-7.81 (m, 23H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 22.6 (CH_2, cod), 25.7 (CH_2, cod), 29.5 (CH_2, cod), 29.7 (CH_3, ^{t}Bu), 30.8 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 36.5 (CH_2, cod), 49.5 (CH_3), 55.4 (CH=, cod), 68.1 (CH=, cod), 103.3 (CH=, cod), 109.0 (CH=, cod), 1204-149.7 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.7 Hz). MS HR-ESI [found 1098.5170, $C_{57}H_{80}IrNO_4PS$ $(M\text{-}BAr_F)^+$ requires 1098.5175].

[Ir(cod)(L24a)]BAr$_F$: Yield: 125 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 116.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.26-1.28 (m, 1H, CH_2, cod), 1.38 (s, 18H, CH_3, ^{t}Bu), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.66-1.68 (m, 1H, CH_2, cod), 1.92-2.10 (m, 3H, CH_2, cod), 2.18-2.27 (m, 2H, CH_2, cod), 2.43-2.46 (m, 1H, CH_2, cod), 3.07 (m, 1H, CH=, cod), 3.55 (m, 1H, CH=, cod), 5.80 (m, 1H, CH=, cod), 6.48 (m, 1H, CH=, cod), 6.68-7.71 (m, 26H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 26.2 (CH_2, cod), 28.6 (CH_2, cod), 29.7 (CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 34.8 (d, C, ^{t}Bu, $J_{C\text{-}P}$= 4.2 Hz), 35.6 (d, C, ^{t}Bu, $J_{C\text{-}P}$= 7.1 Hz), 36.2 (CH_2, cod), 56.7 (CH=, cod), 61.6 (CH=, cod), 107.8 (d, CH=, cod, $J_{C\text{-}P}$= 16.9 Hz), 110.7 (d, CH=, cod, $J_{C\text{-}P}$= 14.1 Hz), 116.1 (CH=), 130.1 (CH=), 117.5-149.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.8 Hz). MS HR-ESI [found 996.3762, $C_{50}H_{62}IrNO_4PS$ $(M\text{-}BAr_F)^+$ requires 996.3766].

[Ir(cod)(L24b)]BAr$_F$: Yield: 124 mg (94%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 113.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.28 (m, 1H, CH_2, cod), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.79 (s, 3H, CH_3), 1.73-1.95 (m, 2H, CH_2, cod), 1.85 (s, 3H, CH_3), 2.13-2.22 (m, 3H, CH_2, cod), 2.30 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.42 (m, 1H, CH_2, cod), 3.01 (m, 1H, CH=, cod), 3.59 (m, 1H, CH=, cod), 5.75 (m, 1H, CH=, cod), 6.39 (m, 1H, CH=, cod), 6.66-7.71 (m, 26H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.4 (CH_3), 16.5 (CH_3), 20.3 (CH_3), 26.0 (CH_2, cod), 28.5 (CH_2, cod), 31.2 (CH_2, cod) 31.6 (CH_3, ^{t}Bu), 32.4 (CH_3, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.2 (CH_2, cod), 56.8 (CH=, cod), 62.1 (CH=, cod), 107.4 (d, CH=, cod, $J_{C\text{-}P}$= 14.8 Hz), 109.4 (d, CH=, cod, $J_{C\text{-}P}$=

17.8 Hz), 115.7 (CH=), 130.2 (CH=), 117.4-144.7 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz). MS HR-ESI [found 940.3138, $C_{46}H_{54}IrNO_4PS$ $(M\text{-}BAr_F)^+$ requires 940.3140].

3.6.4.7. General procedure for the asymmetric hydrogenation

The alkene (0.5 mmol) and Ir complex (2 mol%) were dissolved in CH_2Cl_2 (2 mL) and placed in a high-pressure autoclave. The autoclave was purged 4 times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized, and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short plug of Celite. Conversions were determined by ^1H NMR and enantiomeric excesses were determined by chiral GC or chiral HPLC (for hydrogenation products from **S1**-**S3**, **S5**-**S7**, **S10**-**S11**, **S14** and **S25**-**S26** see previous Section 3.1.4.5, for hydrogenation products from **S4**, **S8**, **S12**-**S13**, **S15**-**S24** and **S27** see previous Section 3.2.4.6 and for hydrogenation products from **S9** and **S28** see previous Section 3.3.4.8).

3.6.5. Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P), European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D.).

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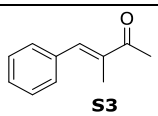
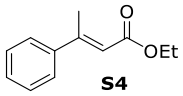
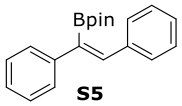
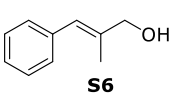
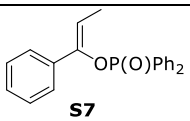
3.6.7. Supporting Information

3.6.7.1. Table SI.1. Full set of results for the asymmetric hydrogenation of trisubstituted olefins S3-S8[a]

	 **S3**		 **S4**		 **S5**	
Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b,d]	% ee[c]
L22a	85	13 (*S*)	100	61 (*S*)	56	>99 (-)
L22b	90	76 (*S*)	100	97 (*S*)	45	99 (-)
L22c	80	57 (*R*)	100	31 (*R*)	39	60 (-)
L23a	24	11 (*S*)	100	57 (*S*)	23	99 (-)
L24a	100	73 (*R*)	100	28 (*R*)	41	65 (-)
L24b	100	96 (*R*)	100	38 (*R*)	29	66 (-)
	 **S6**		 **S7**		 **S8**	
Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b,d]	% ee[c]
L22a	100	41 (*S*)	26	25 (*R*)	65	35 (*R*)
L22b	100	60 (*S*)	19	48 (*R*)	55	37 (*R*)
L22c	100	48 (*R*)	11	17 (*S*)	70	75 (*S*)
L23a	100	60 (*S*)	6	8 (*R*)	15	18 (*R*)
L24a	100	25 (*R*)	56	5 (*S*)	100	16 (*S*)
L24b	100	33 (*R*)	35	13 (*S*)	100	48 (*S*)

[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor at 50 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by HPLC; [d] Reaction carried out for 18 h.

3.7. Synthesis of novel cationic phosphonite-pyridine ligands for Ir-catalyzed enantioselective hydrogenation of minimally functionalized olefins

Biosca, M.; Alcarazo, M.; Pàmies, O.; Diéguez, M. *Preliminary results.*

In collaboration with the group of Prof. M. Alcarazo (University of Göttingen).

Abstract: A new class of heterodonor cationic phosphonite-pyridine ligands **L25**-**L26** have been synthetized and characterized. Both ligands shared a TADDOL skeleton which is cheap and easy to tune. Both ligands differ from the substituents on the positively charged moiety at phosphorous. Moreover, this cationic group confers to the resulting ligand strong π-acceptor properties. Ligands **L25**-**L26** are designed for their specific application in the enantioselective hydrogenation of minimally functionalized olefins.

3.7.1. Introduction

The asymmetric hydrogenation of olefins by transition metal catalysts is one of the most powerful mild and clean chemical transformation that allows the achievement of chiral compounds in excellent chemo-, regio- and enantioselectivities. The preparation of these chiral compounds is of great importance in several relevant fields such as pharmaceutical, agrochemical, fine chemicals and natural product chemistry.[1] This field has been dominated by the Rh/Ru-catalyzed asymmetric reduction of alkenes bearing a good coordinating group close to C=C bonds, which its chelating ability is key in transferring the chiral information from the catalysts to the product. Nowadays, a remarkable range of ligands are being applied to transform a broad range of functionalized substrates. In contrast, the hydrogenation of olefins without good coordinating groups is less developed. The first successful ligand applied in this process was the phosphine-oxazoline ligand (PHOX) developed by Pfaltz.[2] Since then, the research in this field has been focused on the development of new Ir-catalysts modified with heterodonor ligands in order to increase the range of successfully hydrogenated substrates. This modifications were mainly based on the replacement of the phosphine moiety by a phosphinite or carbene group and the oxazoline moiety by other N-, S- and O-donor groups.[3] However, despite the success of some of these modifications, there are still some substrate classes whose hydrogenation is still not solved. Therefore, more research is needed to find more versatile catalytic systems. Our group has shown that the presence of a π-acceptor biaryl phosphite moiety in the ligand design provided greater substrate versatility than previous catalytic systems developed.[4] The flexible biaryl phosphite group allows the perfectly embedding of the substrate into the chiral pocket of the catalyst and moreover its different electronic properties compared to the

N-donor group provides an efficient differentiation between coordination positions, which reduces the number of reaction intermediates and allows a better stereocontrol.

In this context, the unique structure of α-cationic phosphorus confers to the resulting ligand strong π-acceptor properties, which frequently surpass those of traditional π-acceptor ligands such as phosphites. In these ligands, at least one of the three substituents on phosphorus corresponds to a cationic group, which is attached without any spacer to the phosphorus atom. This property has demonstrated to be beneficial in several catalytic transformations such as Au-catalyzed cycloisomerization, Pd-catalyzed alkynylation, Pt-catalyzed hydrogenation, among others.[5] The potential of this class of ligands although have been not tested in the Ir-catalyzed hydrogenation of minimally functionalized olefins, the more π-acceptor character of these entities can provide more dissimilar electronic properties between their two coordinating functionalities, which could improve the results obtained until now in this process.

Having this in mind, we synthetized the novel cationic phosphonite-pyridine ligands **L25**-**L26** (Figure 3.7.1) to further study the effect of the introduction of more dissimilar electronic functionalities in this process. Ligands **L25**-**L26** with a common TADDOL-based cationic phosphonite moiety differs in the substituent of the N-group of the imidazole.

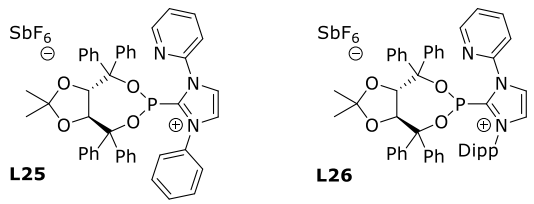
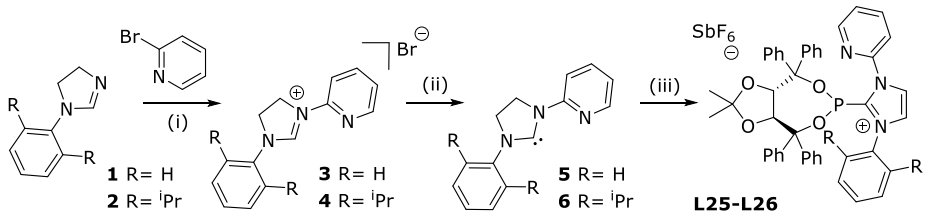


Figure 3.7.1. Novel cationic phosphonite-pyridine ligands **L25**-**L26**. (Dipp= 2,6-diisopropylphenyl).

3.7.2. Results and Discussions

3.7.2.1. Synthesis of ligands

The synthetic route for the synthesis of cationic phosphonite-pyridine ligands is showed in Scheme 3.7.1. These ligands are easily accessible from 1-phenyl-4,5-dihydro-1*H*-imidazole **1** and 1-(2,6-diisopropylphenyl)-4,5-dihydro-1*H*-imidazole **2**.[3d] The first step of the synthesis consists in the coupling of **1**-**2** with 2-bromopyridine to obtain the corresponding imidazolium salt **3**-**4** (step i).[6] Then, imidazolium salts **3**-**4** were deprotonated using sodium hydride (step ii) and subsequently, the appropriate free carbene **6**-**7** was coupled with the TADDOL-based phosphorochloridite affording the corresponding cationic phosphonite-pyridine ligand **L25**-**L26** (step iii).



Scheme 3.7.1. Synthesis of cationic phosphonite-pyridine ligands **L25**-**L26**. (i) 2-bromopyridine, 150 ºC-170 ºC, 3-4 days; (ii) NaH, THF, rt, 16 h; (iii) Phosphorochloridite, $NaSbF_6$, Et_2O, -78 ºC to rt, 18 h.

After purification on silica at -10 ºC, both ligands were obtained as pale-yellow solids. Ligands **L25**-**L26** were characterized by $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy and HRMS-ESI. All data were in agreement with assigned structures. The spectra assignments were supported by the information obtained from ^1H-^1H and ^1H-^{13}C correlation measurements. The ^1H and ^{13}C NMR spectra were as expected for these C_1-ligands.

3.7.3. Conclusions and future work

Novel chelating cationic ligands composed by a cationic TADDOL-based phosphonite moiety and a pyridine group (**L25**-**L26**) have been successfully synthetized. The synthesis of these ligands has been confirmed by ^{31}P, ^1H and ^{13}C NMR and HRMS-ESI. In all spectra the expected signals for each ligand have appeared. The unique electronic characteristic of these ligand structures lead us to think that they can be optimal ligands for a future application in the asymmetric hydrogenation of minimally functionalized olefins.

3.7.4. Experimental Section

3.7.4.1. General considerations

All reactions were carried out under atmosphere of argon using Schlenk techniques and to manipulate and weight compounds which are sensible to water or air glovebox techniques were used. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding TADDOL compound.[7] ^1H, ^{13}C, and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H, ^{13}C and ^{31}P assignments were made on the basis of ^1H-^1H gCOSY and ^1H-^{13}C gHSQC. Compounds **1**-**2**[3d] and imidazolium salts **3**-**4**[6] are prepared as previously described.

3.7.4.2. General procedure for the preparation of free carbenes 5-6

In a flame dried Schlenck, the corresponding imidazolium salt (0.5 mmol, 1 equiv.) was dried *in vacuo* for 30 min. Then, NaH (13.2 mg, 0.55 mmol, 1.1 equiv) was added. The mixture was dissolved in THF (0.2M respect to the imidazolium salt) and stirred for 16 h at room temperature. After this time, the resulting suspension was filtered under argon atmosphere, using a cannula fitted with a glass-fiber filter. The filtrate was evaporated affording the desired product **5-6**.

3-Phenyl-1-(pyridin-2-yl)-4,5-dihydro-1*H*-imidazol-3-ium-2-ide (5):[8] Yield: 78 mg (70%), brown oil. ^{1}H-NMR (400 MHz, C_6D_6): δ= 6.50 (m, 1H), 6.89 (d, 1H, *J*= 1.9 Hz), 7.10 (m, 1H), 7,14 (m, 3H), 7.79 (m, 2H), 8.20 (m, 1H), 8.26 (d, 1H, *J*= 1,9 Hz), 8.76 (m, 1H).

3-(2,6-Diisopropylphenyl)-1-(pyridin-2-yl)-4,5-dihydro-1*H*-imidazol-3-ium -2-ide (6): Yield: 129 mg (84%), brown solid. ^{1}H-NMR (400 MHz, C_6D_6): δ= 1.07 (d, 6H, *J*= 6.8 Hz), 1,18 (d, 6H, *J* = 6.8 Hz), 2,90 (m, 2H), 6.52 (m, 1H), 6.58 (d, 1H, *J*= 1.8 Hz), 7.08-7.04 (m, 2H), 7.14 (s, 2H), 7.26 (m, 1H), 8.21 (m, 1H), 8.38 (d, 1H, *J*= 1.7 Hz), 8.74 (m, 1H).

3.7.4.3. General procedure for the preparation of ligands cationic phosphinite-pyridine ligands L25-L26

The desired chlorophosphite (0.5 mmol, 1 equiv.) and $NaSbF_6$ (388 mg, 1.5 mmol, 3 equiv.) were suspended in Et_2O (0.087 M), cooled to -78 ºC with dry ice and a solution of the free carbene **5**-**6** (223.3 mg, 1 mmol, 2 equiv. of **5** and 153.7 mg, 0.5 mmol, 1 equiv. of **6**) in Et_2O (0.14 M) was added dropwise. The reaction mixture was stirred in this bath for 16 h, allowing to reach room temperature slowly. After this time, the bath was removed, and the reaction was stirred at room temperature for 2 h. Next, the solvent was removed *in vacuo* and DCM was added. The resulting suspension was filtered under an argon atmosphere, using a cannula fitted with a glass-fiber filter and the remaining solid was washed three times with more portions of DCM. The filtrate was evaporated affording a pale-brown solid that was further purified by flash chromatography at -10 ºC (DCM/EtOAc; 95/5) to obtain the corresponding cationic phosphonite-pyridine ligand **L25**-**L26** as a pale-yellow solid.

L25: Yield: 219 mg (46%). ^{31}P NMR (162 MHz, CD_3CN): δ= 145.8 (s). ^{1}H NMR (400 MHz, CD_3CN): δ= 0.18 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 4.71 (d, 1H, CH, *J*= 8.4 Hz), 5.10 (dd, 1H, CH, *J*= 8.0 Hz, *J*= 5.6 Hz), 6.79 (d, 2H, CH=, *J*= 6.8 Hz), 7.01 (m, CH=, 2H), 7.22-7.43 (m, 16H, CH=), 7.52-7.76 (m, 8H, CH=), 7.83 (s, 1H, CH=), 8.04 (m, 2H, CH=), 8.52 (m, 1H, CH=). ^{13}C NMR (101 MHz, CD_3CN): δ= 25.8 (CH_3), 28.3 (CH_3), 83.3 (CH), 83.5 (d, CH, $J_{C\text{-}P}$= 4.0 Hz), 87.2 (d, C, $J_{C\text{-}P}$= 5.3 Hz), 87.3 (C), 114.5-150.9

(aromatic carbons). MS HR-ESI [found 716.2678, $C_{45}H_{39}N_3O_4P$ $(M\text{-}SbF_6)^+$ requires 716.2673].

L26: Yield: 52 mg (10%). ^{31}P NMR (162 MHz, CD_3CN): δ= 149.7 (s). ^1H-NMR (400 MHz, CD_3CN): δ= 0,09 (s, 3H, CH_3), 0.29(d, 3H, CH_3, ^{i}Pr, J=6.7), 0.94 (d, 3H, CH_3, ^{i}Pr, J=6.7), 1.01 (d, 3H, CH_3, ^{i}Pr, J= 6.7 Hz), 1.07 (d, 3H, CH_3, ^{i}Pr, J= 6.7 Hz), 1.26 (s, 3H, CH_3), 2.14 (m, 1H, CH, ^{i}Pr), 2.23 (m, 1H, CH, ^{i}Pr), 4.78 (d, 1H, CH, J= 8.2 Hz), 4.92 (dd, 1H, CH, J= 7.9 Hz, $J_{H\text{-}P}$= 5.4 Hz), 6.18 (m, 3H, CH=), 7.02-7.52 (m, 19H, CH=), 7.75 (t, 1H, CH=, J= 7.9 Hz), 7.84-7.97 (m, 3H, CH=), 8.05 (m, 1H, CH=), 8.14 (m, 1H, CH=), 8.88 (m, 1H, CH=). ^{13}C NMR (101 MHz, CD_3CN): δ= 21.5 (CH_3), 22.5 (CH_3), 25.1 (CH_3), 25.6 (CH_3), 26.0 (CH_3), 27.6 (CH_3), 29.7 (CH), 30.1 (d, CH, $J_{C\text{-}P}$= 5.6 Hz), 83.2 (CH), 83.7 (d, C, $J_{C\text{-}P}$= 4.0 Hz), 86.9 (C), 87.1 (d, C, $J_{C\text{-}P}$= 5.0 Hz), 114.3-151.3 (aromatic carbons). MS HR-ESI [found 800.3612, $C_{51}H_{51}N_3O_4P$ $(M\text{-}SbF_6)^+$ requires 800.3612].

3.5.5. Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P), European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D.).

3.5.6. References

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3.8. Chiral ferrocene-based P-S ligands for Ir-catalyzed hydrogenation of minimally functionalized olefins. Scope and limitations

Biosca, M.; Coll, M.; Lagarde, F.; Brémond, E.; Routaboul, L.; Manoury, E.; Pàmies, O.; Poli, R.; Diéguez, M. *Tetrahedron* **2016**, *72*, 2623.

In collaboration with the group of Prof. R. Poli (CNRS, Toulouse).

Abstract: A family of 12 modular ferrocenyl planar chiral phosphine-thioethers (P,S) has been studied in the asymmetric hydrogenation of minimally functionalized alkenes. These ligands differ by the substituent on sulfur or by the linker between the ferrocene moiety and the sulfur atom (no linker, methylene or methyl substituted methylene linker bearing an additional element of chirality). The cationic iridium(cod) complexes of the different P,S-ligands have been efficiently synthesized. For the majority of the ligands, coordination yielded only a single diasteroisomer with full control of the absolute configuration on sulfur. The different iridium complexes have been used in the hydrogenation of various di-, tri-, and tetrasubstituted minimally functionalized olefins. Conversions and enantioselectivities are highly dependent on the ligand and substrate structure. Full conversions and low-to-excellent enantioselectivities could be obtained (maximum ee from 14 to 94% for 1,1'-disubstituted alkenes, from 17 to 99% for trisubstituted olefins, and 34% for the tetrasubstituted alkene).

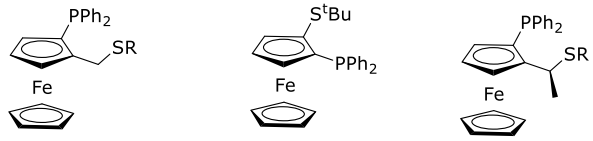
3.8.1. Introduction

One of the most challenging tasks of organic chemistry is the synthesis of chiral compounds, which are necessary intermediates in the preparation of a wide range of pharmaceutical, agrochemical, fine chemical, and natural products.[1] Up to date, asymmetric hydrogenation, the atom-economical addition of H_2 to a C=X (X= C, N or O) bond to obtain chiral compounds is one of the most efficient, sustainable, and straightforward chirality-generating process.[1-2] For the enantioselective hydrogenation of minimally functionalized olefins, Ir-complexes with chiral P,N-ligands have shown to be effective catalysts that complement the well-developed Rh/Ru-catalysts for functionalized olefins.[3] Since the application of Ir-phosphine-oxazoline PHOX chiral catalysts in 1998 by Pfaltz *et al.*,[4] researchers have focused on Ir-catalysts based on a wide range of P-oxazoline ligands.[5] These new Ir-catalysts have significantly broadened the substrate scope. Despite the advances in Ir-based P,N catalysts, their activity and selectivity for reducing some significant minimally functionalized olefins still needs to be improved, especially since the demand for new optically active chiral centers has moved researchers into the Ir-catalyzed asymmetric reduction of more "exotic" substrates. This

will require novel, highly efficient chiral ligands that are easier to handle, readily accessible, and that enhance the application range. In this respect, research has progressed to heterodonor P,X-ligands bearing more robust X-donor groups than oxazolines (pyridines,[6] amides,[7] thiazoles,[5v,8] thiazolines,[9] oxazoles,[10] etc.). Some of us have recently described the successful use of non-N-donor heterodonor ligands, the phosphorus-thioether ligands, for the enantioselective Ir-catalyzed reduction of minimally functionalized olefins.[11] Ir-complexes modified with two families of P-thioether ligands efficiently catalyzed the hydrogenation of a large range of olefins, with results comparable to the best ones reported in the literature. Despite this success, other thioether-P ligands have not yet been reported and research is in progress to study the possibilities of this new class of ligands for this process.

Some of us have been involved for several years in the development of chiral ferrocene-based ligands for asymmetric catalysis.[12] Ferrocene-based ligands have been successfully employed in asymmetric catalysis for more than three decades.[13] They are particularly interesting because of the facile introduction of different chiralities (planar and central), their particular stereoelectronic properties, and their high stability. Although they have emerged as a privileged ligand structures for asymmetric catalysis, their use in the Ir-catalyzed hydrogenation of minimally functionalized olefins has been scarce.[14]

Because we are interested in more versatile and robust Ir-catalysts, we took one further step and tested ligands that incorporate the advantages of ferrocenes and the robustness of the thioether moiety. To this end, we tested a family of modular ferrocene phosphine-thioether ligands **L27**-**L38** (Figure 3.8.1) in the Ir-catalyzed hydrogenation of 34 minimally functionalized alkenes, including concrete examples with neighboring polar groups. The selection of chiral ligands contemplates systematic variations of the electronic and steric properties of the thioether moiety (ligands **L27**-**L35**),[15] the removal of the methylene spacer between the ferrocene and the thioether groups (ligand **L36**),[16] as well as introducing a second stereogenic center in the methylene spacer (ligands **L37**-**L38**)[17].



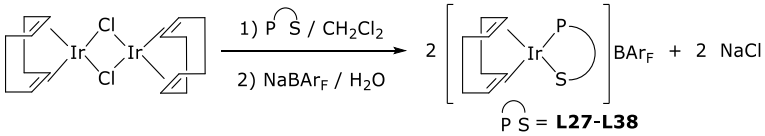
L27 R= Et **L32** R= Ph **L36** **L37** R= Ph
L28 R= ^{i}Pr **L33** R= Bn **L38** R= 2,6-Me_2-C_6H_3
L29 R= Cy **L34** R= 1-Naphthyl
L30 R= ^{t}Bu **L35** R= 2,6-Me_2-C_6H_3
L31 R= Ad

Figure 3.8.1. Ferrocene-based phosphine-thioether ligands **L27**-**L38**.

3.8.2. Results and Discussion

3.8.2.1. Synthesis of Ir-catalyst precursors

The Ir-catalyst precursors were prepared in a two-step, one-pot procedure (Scheme 3.8.1). In the first step, the appropriate ligand reacts with 0.5 equivalent of [Ir(μ-Cl)(cod)]$_2$ for 1 h at reflux. Then, Cl^-/BAr_F^- counterion exchange was achieved by a reaction with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$; 1 equiv) in the presence of water at room temperature. The iridium catalyst precursors were isolated in pure form as air-stable orange solids in excellent yields (89-91%).



Scheme 3.8.1. Preparation of Ir-catalyst precursors [Ir(cod)(**L27**-**L38**)]BAr_F.

The elemental analyses were in agreement with the assigned structures. The HRMS-ESI spectra of [Ir(cod)(**L27**-**L38**)]BAr_F displayed the heaviest ions at m/z which correspond to the loss of the BAr_F anion from the molecular species. Crystals suitable for X-ray diffraction analysis of [Ir(cod)(**L30**)]BAr_F complex were also obtained in order to determine the coordination mode of the ferrocene-based phosphine-thioether ligands (Figure 3.8.2). The six-membered chelate ring adopted a boat conformation, with the thioether substituent in an equatorial position and the sulfur in an (*R*)-configuration as has already been observed for similar complexes.[18]

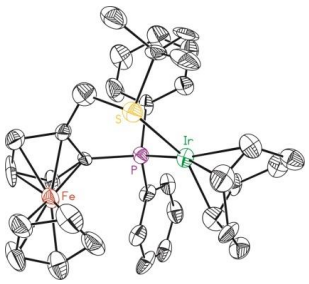


Figure 3.8.2. X-ray structure of [Ir(cod)(**L30**)]BAr_F (CCDC 1033867) (the hydrogen atoms and BAr_F^- anion have been omitted for clarity).

The ^1H, ^{13}C, and ^{31}P NMR spectra show the expected pattern for these C_1-complexes. The VT-NMR spectra in CD_2Cl_2 (+35 to -75 °C) indicate the presence of a single isomer in all cases except for [Ir(cod)(**L34**)]BAr_F and [Ir(cod)(**L38**)]BAr_F that were mixtures of two isomers in equilibrium at a ratio of 1:2 and 1:6, respectively. These isomers may be attributed to the two possible diastereoisomers formed when the thioether

coordinates to the metal atom (note that the coordinated S atom is a stereogenic center), to different conformers for the six-membered chelate ring, or to both. To obtain the spatial orientation of the thioether substituent and the conformation adopted by the six-membered chelate ring we initially performed NOESY experiments of [Ir(cod)(**L30**)]BAr_F and [Ir(cod)(**L38**)]BAr_F. Since the NOE contacts for Ir/**L30** were not conclusive, we studied the [Ir(cod)(**L35**)]BAr_F analogue instead.

For complex [Ir(cod)(**L35**)]BAr_F and the major isomer of [Ir(cod)(**L38**)]BAr_F, the NOE indicated interactions between one of the methyl groups of the thioether xylyl substituent and the phenyl group of the phosphine moiety and of that same methyl group with either the methyl substituent (for Ir/**L38**) or one of the hydrogen atoms (for Ir/**L35**) at the alkyl backbone chain (Figure 3.8.3a). In addition, the NOE indicated interactions of the other xylyl methyl group with the other hydrogen of the alkyl backbone chain and with the unsubstituted cyclopentadiene ring. These interactions can be explained assuming an equatorial disposition of the thioether group and a boat conformation of the six-membered chelate ring with an (*R*)-configuration of the sulfur atom (Figure 3.8.3a), as in the X-ray structure of [Ir(cod)(**L30**)]BAr_F (see Figure 3.8.2).

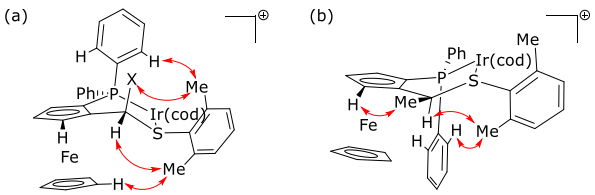
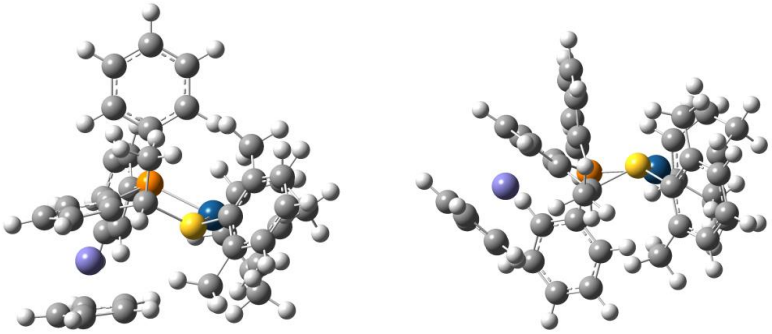


Figure 3.8.3. Main NOE contacts for (a) [Ir(cod)(**L35**)]BAr_F (X= H) and major isomer of [Ir(cod)(**L38**)]BAr_F (X= Me) and (b) minor isomer of [Ir(cod)(**L38**)]BAr_F.

For the minor isomer of [Ir(cod)(**L38**)]BAr_F, we found NOE interactions between one of the xylyl methyl groups and the phenyl group of the phosphine moiety and with the hydrogen at the alkyl backbone chain (Figure 3.8.3b). We also observed NOE contacts between the methyl substituent at the alkyl backbone chain and the substituted cyclopentadiene ring. All these NOE contacts are in agreement with a boat conformation of the six-membered chelate ring and the thioether substituent in an equatorial disposition but, in contrast to previous isomers, with an (*S*)-configuration of the sulfur atom (Figure 3.8.3b). The assignments of the isomers of [Ir(cod)(**L38**)]BAr_F were further confirmed by DFT studies. Figure 3.8.4 shows these calculated structures and the relative values of the formation enthalpy, being the isomer with an (*R*)-configuration of the sulfur atom the most stable. Complexes [Ir(cod)(**L34**)]BAr_F and [Ir(cod)(**L38**)]BAr_F are the first examples of incomplete control of the sulfur chirality upon coordination for ferrocenyl phosphine-thioethers with this type of backbone: only one diastereoisomer was observed for all previously reported complexes, whatever the metal or the oxidation state.[18-19]



Major isomer (0 kJ/mol) **Minor isomer** (11.8 kJ/mol)

Figure 3.8.4. Calculated structures (DFT) for cationic species of complex [Ir(cod)(**L38**)]BAr_F and their relative formation enthalpies.

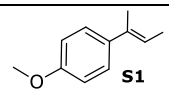
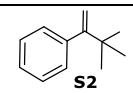
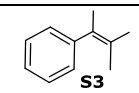
3.8.2.2. Asymmetric Ir-catalyzed hydrogenation

Asymmetric hydrogenation of minimally functionalized olefins is highly sensitive to the steric demands of the substrate.[3] Unlike trisubstituted olefins, 1,1'-disubstituted olefins have not been successfully hydrogenated until very recently.[3e,3h] This is because the catalyst must control not only the face selectivity coordination (only two substituents compared with the three in trisubstituted olefins), but also the isomerization of the olefins to form the more stable *E*-trisubstituted substrates, which are hydrogenated to form the opposite enantiomer. Tetrasubstituted olefins also remain an unsolved class of substrate.[3f,3h] The only Ir-catalysts that react with them with high yields and enantioselectivities contain the less bulky phosphanylmethyloxazoline ligands reported by Pfaltz.[20] In order to evaluate the efficiency of ferrocene-based P,S-ligands **L27**-**L38** in the hydrogenation of olefins with different steric demands, we initially tested them in the asymmetric reduction of the model tri-, di-, and tetrasubstituted substrates **S1-S3** (Table 3.8.1).

Although low-to-moderate enantioselectivities were achieved in the reduction of tetrasubstituted substrate **S3**, high enantioselectivities were obtained in the hydrogenation of model tri- and disubstituted substrates (ee's up to 85% and 82% for **S1** and **S2**, respectively). The results also indicated that the ligand components need to be properly tuned for each substrate to maximize the enantioselectivities. For instance, while for **S1** the best enantioselectivities were obtained with ligand **L38** (entry 12), containing both planar and central chirality and a bulky 2,6-dimethylphenyl thioether substituent, the highest enantioselectivities for **S2** were achieved with ligands **L32** and **L36** (entries 4 and 10), containing only planar chirality and a bulky *tert*-butyl thioether group. Interestingly, for disubstituted substrate **S2** both enantiomers of the hydrogenated products could be obtained in high enantioselectivity by simply selecting the planar chirality. We also studied the reaction of model substrates **S1** and **S2** at low

catalyst loading (0.25 mol%) using ligand **L38**, and the enantioselectivities and conversion (95% for **S1** and 99% for **S2**) were maintained (entry 13).

Table 3.8.1. Ir-catalyzed hydrogenation model substrates **S1**-**S3**[a]

		 **S1**		 **S2**		 **S3**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L27**	100	25 (*S*)	100	22 (*S*)	75	9 (*R*)
2	**L28**	100	0	100	30 (*S*)	<5	nd
3	**L29**	100	10 (*S*)	100	33 (*S*)	<5	nd
4	**L30**	100	50 (*R*)	100	81 (*S*)	70	32 (*R*)
5	**L31**	100	46 (*S*)	100	73 (*S*)	60	34 (*R*)
6	**L32**	100	11 (*S*)	100	34 (*S*)	85	6 (*R*)
7	**L33**	100	30 (*S*)	100	16 (*S*)	35	8 (*R*)
8	**L34**	100	24 (*S*)	100	32 (*S*)	65	6 (*R*)
9	**L35**	100	50 (*R*)	100	26 (*S*)	49	10 (S)
10	**L36**	100	15 (*S*)	100	82 (*R*)	95	4 (*R*)
11	**L37**	100	29 (*S*)	100	3 (*R*)	100	9 (*R*)
12	**L38**	100	85 (*S*)	100	46 (*R*)	100	12 (S)
13[d]	**L38**	95	84 (*S*)	99	46 (*R*)	-	-

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (1 mol%), H_2 (100 bar for **S1** and **S3**; 1 bar for **S2**), CH_2Cl_2 (2 mL), RT; [b] Conversion measured by ^{1}H-NMR after 4 h (for **S1** and **S2**) and after 18 h (for **S3**); [c] Enantiomeric excess determined by GC; [d] Reactions carried out at 0.25 mol% of Ir-catalyst precursor.

We next evaluated the new Ir/**L27**-**L38** catalyst precursors in the hydrogenation of a selected range of trisubstituted substrates, most of them with neighbouring polar groups. The reduction of substrates with neighbouring polar groups has a large interest because they are relevant intermediates for the synthesis of highly valued chemicals. The most remarkable results are shown in Figure 3.8.5 (see Supporting Information at the end of this chapter for a complete set of results).

We first considered the reduction of aryl/alkyl substrates with *Z*-geometry **S4**-**S6**, which are usually hydrogenated less enantioselectively than *E*-trisubstituted olefins like **S1**.[3] Unfortunately, as previous studies had already suggested, enantiocontrol was only moderate (ee's up to 46%). On the other hand, [Ir(cod)(**L30**)]BAr_F was very efficient in the reduction of several α,β-unsaturated esters **S7**-**S11**.[21] The ee's were between 95-98% and quite independent on the electronic nature of the substrate phenyl ring and on the substituent *cis* to the ester group. Being able to hydrogenate α,β-unsaturated esters at such high ee's is of great importance because chiral carboxylic ester derivatives with tertiary benzylic aliphatic stereogenic centres are found in many fragrances, pharmaceuticals, and natural products.[22] This methodology represents a more

sustainable route for producing these chiral carboxylic esters than other common methods such as the Co-catalyzed asymmetric conjugated reduction of α,β-unsaturated esters using sodium borohydride[23] and the Cu- and Rh-catalyzed 1,4-reduction using very moisture-sensitive hydrosilane reagents[24].

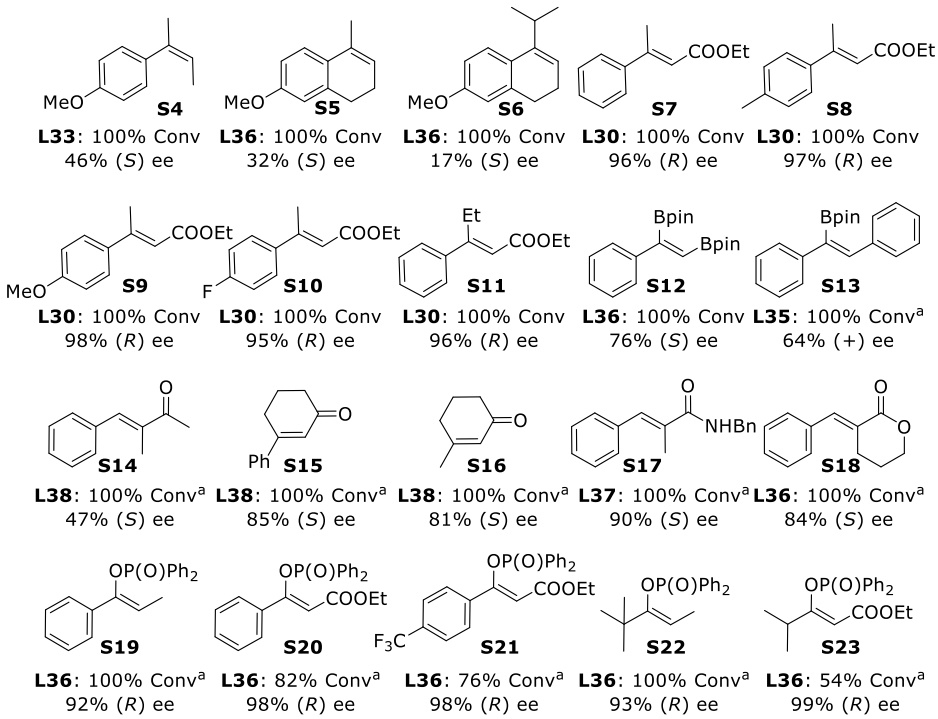


Figure 3.8.5. Selected results for the hydrogenation of trisubstituted olefins **S4**-**S23** using [Ir(cod)(**L27**-**L38**)]BAr_F catalyst precursors. Reaction conditions: Catalyst precursor (1 mol%), CH_2Cl_2 as solvent, H_2 (100 bar), 4 h. [a] Reaction carried out for 18 h.

We then studied the reduction of alkenylboronic esters **S12** and **S13** which would form versatile chiral C-B bonds that can later become C-N, C-O, and C-C bonds. The hydrogenation of alkenes containing one or two pinacolato-boron groups proceeded smoothly with enantioselectivities as high as 76% ee. Another important class of substrates that is receiving much attention are the α,β-unsaturated enones. The hydrogenation of these substrates is an elegant path for obtaining ketones with a stereogenic center in the α-position of the carbonyl moiety. Nonetheless, they have been less studied and less successfully hydrogenated than other trisubstituted olefins.[5i,5u,v,25] The hydrogenation of the model α,β-unsaturated enone **S14** proceeded with moderate enantiocontrol (ee's up to 47%). However, it was very interesting to find that enantioselectivities increased up to 85% in the hydrogenation of more challenging cyclic enones **S15** and **S16**.[5v] These latter results prompted us to focus on the hydrogenation of other difficult olefins, such as enamide **S17**,[26] lactone **S18**[27] and enol phosphinates **S19**-**S23**[28]. Very few catalytic systems can provide high

enantioselectivities for these substrates so it was remarkable that we could achieve high-to-excellent enantioselectivities in all of them by carefully tuning the ligand components. Thus, in the reduction of enamide **S17** and lactone **S18**, the highest enantioselectivities (up to 90% ee) were achieved using [Ir(cod)(**L37**)]BAr_F and [Ir(cod)(**L36**)]BAr_F, respectively. [Ir(cod)(**L36**)]BAr_F was also extremely efficient in the reduction of a range of sterically demanding enol phosphinates, including examples of pure alkyl-substituted enol phosphinates (Figure 3.8.5; **S19**-**S23**), providing comparable high enantioselectivities to those achieved with the best ones reported (ee's between 92-99%). The effective hydrogenation of this type of substrates opens up an appealing route for obtaining chiral organophosphinates, which can be easily transformed into high-value compounds such as alcohols and phosphines.

Then we focused our attention on extending the range of disubstituted substrates (Figure 3.8.6). Our results with several α-alkylstyrenes bearing decreasingly sterically demanding alkyl substituents (**S2**, **S24**, and **S25**) indicated that enantioselectivity is affected by the nature of the alkyl chain (ee's ranging from 14% to 82%). A plausible explanation is the competition between direct hydrogenation and isomerization. This is supported by the fact that the hydrogenation of substrate **S2** bearing a *tert*-butyl group, which cannot isomerize, provides the highest enantioselectivity. We then tested a wide range of α-*tert*-butylstyrene type substrates (**S26**-**S32**) to evaluate how the electronic and steric properties of the aryl group of the substrate affected the catalytic performance. The highest enantioselectivities (up to 90% ee) of the series were achieved in the reduction of substrates containing electrondonating groups at the *para*-position of the aryl group (substrates **S26** and **S27**).

Finally, we studied whether the excellent enantioselectivities obtained in the hydrogenation of trisubstituted enol phosphinates (**S19**-**S23**, Figure 3.8.5) are maintained for the even more demanding disubstituted analogues **S33** and **S34**. Again, [Ir(cod)(**L36**)]BAr_F was able to successfully hydrogenate these substrates with excellent enantioselectivities comparable to the best ones reported.[29]

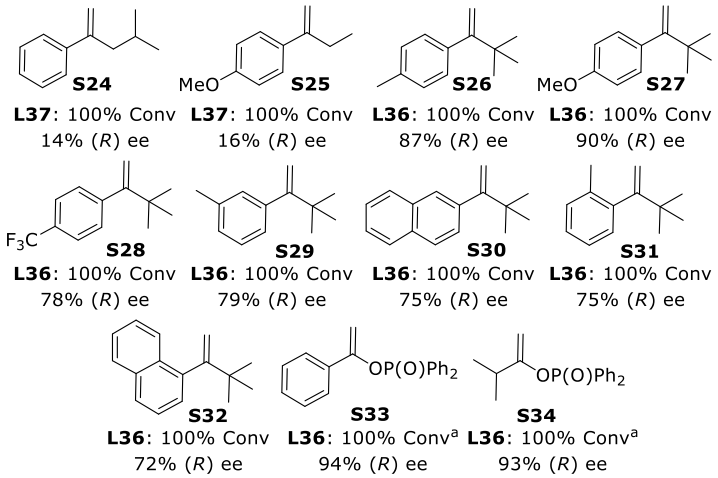


Figure 3.8.6. Selected results for the hydrogenation of 1,1-disubstituted olefins **S24**-**S34** using [Ir(cod)(**L27**-**L38**)]BAr_F catalyst precursors. Reaction conditions: Catalyst precursor (1 mol %), CH_2Cl_2 as solvent, H_2 (1bar), 4 h. [a] Reactions carried out for 18 h.

3.8.3. Conclusions

Stable cationic iridium(cod) complexes with different P,S-ligands proved to be good precatalysts for the asymmetric hydrogenation of minimally functionalized olefins in terms of activities and enantioselectivities. For many substrates, the ligand fine tuning, thanks to its high modularity, enabled achieving good to excellent levels of enantioselectivity, underlining their promising potential. Therefore, these new Ir-catalysts compete well with the state-of-art not only for model trisubstituted α,β-unsaturated esters **S7**-**S11**,[21] but also for demanding di- and tri-substituted enol phosphinates **S19**-**S23**[28] and **S33**-**S34**[29]. In addition promising high enantioselectivities have been achieved for challenging cyclic enones **S15**-**S16**,[5v] and alkenes bearing benzyl amide[26] (**S17**) and δ-lactone[27] (**S18**) groups.

3.8.4. Experimental Section

3.8.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphine-thioether ligands **L37**[17b] and **L38**[30] were prepared as previously reported. Substrates **S1**,[31] **S2**,[32] **S3**,[33] **S4**,[31] **S5**-**S6**,[34] **S7**-**S10**,[35] **S11**,[21a] **S14**,[36] **S15**,[37] **S17**,[38] **S18**,[27a] **S19**-**S23**,[28a] **S24**,[39] **S25**,[40] **S26**-**S32**[32] and **S33**-**S34**[28a] were prepared following the reported procedures and **S12**-**S13** and **S16** were commercially available. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded using a 400 MHz or a 300 MHz spectrometer. Chemical shifts are

relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H and ^{13}C assignments were made on the basis of ^1H-^1H gCOSY and ^1H-^{13}C gHSQC. Geometries of isomers of [Ir(cod)(**L38**)]BAr_F were optimized using the Gaussian 09 program,[41] employing the B3LYP[42] density functional and the LANL2DZ[43] basis set for iridium and iron and the 6-31G* basis set for all other elements.[44] Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters of dichloromethane.[45] The complexes were treated with the charge +1 and in singlet state. No symmetry constraints were applied. The energies were further refined by applying dispersion correction using the DFT-D3[46] model. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + E_{DFTD3.}$

3.8.4.2. General procedure for the preparation of ligands L27-L38

Ligands **L27**-**L30** and **L32**-**L33** were prepared as previously reported.[15a] The ligands **L31**, **L34**, and **L35** were prepared using the same method. In a Schlenk tube, enantiomerically pure (*R*)-(2-diphenylthiophosphinoferrocenyl)methanol (100 mg, 0.23 mmol)[12c] was dissolved in 2 mL of dry dichloromethane. A 54% solution of fluoroboric acid in ether (100 μL, 0.724 mmol) was then added. After 1 min stirring, the corresponding thiol (0.724 mmol) was added. After 1 min of stirring, the crude materials were filtered on silica gel with ether as an eluent. After evaporation of the solvent, a yellow oil was obtained, which was extracted in pentane to yield, after evaporation, the protected ligand **L31-S**, **L34-S** or **L35-S**.

Then, in a Schlenk tube, the corresponding protected ligand **L31-S**, **L34-S** or **L35-S** (0.23 mmol) was dissolved in 5 mL of toluene with 0.2 mL of tris-(dimethylamino)phosphine (5 equiv)[15a]. The solution was kept at reflux overnight. After cooling back to rt, the solution was evaporated on vacuum line. The crude materials were purified, under argon, by flash chromatography on silica gel using dichloromethane as an eluent, to obtain the desired ligand, which was immediately engaged in the coordination reaction.

L31-S: Yield: 131 mg (97%). ^{31}P NMR (121 MHz, $CDCl_3$): δ= 41.7 (s). ^1H NMR (300 MHz, $CDCl_3$): δ= 1.63 (m, 6H, CH_2, Ad), 1.75 (m, 6H, CH_2, Ad), 1.97 (m, 3H, CH, Ad), 3.72 (s, 1H, CH=, Cp), 3.90 (br d, 1H, CH_2, $^2J_{H\text{-}H}$= 13.0 Hz), 3.98 (br d, 1H, CH_2, $^2J_{H\text{-}H}$= 13.0 Hz), 4.29 (s, 1H, CH=, Cp), 4.36 (s, 5H, CH=, Cp), 4.66 (s, 1H, CH=, Cp), 7.55-7.35 (m, 6H, CH=), 7.66 (m, 2H, CH=), 7.86 (m, 2H, CH=). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 23.7 (CH_2), 29.7 (CH, Ad), 36.3 (CH_2, Ad), 43.3 (CH_2, Ad), 44.8 (C, Ad), 69.0 (d, CH=, Cp, $J_{C\text{-}P}$= 10.5 Hz), 70.9 (Cp), 73.4 (d, CH=, Cp, $J_{C\text{-}P}$= 9.3 Hz), 74.0 (d, C, Cp, $J_{C\text{-}P}$= 94.6 Hz) 74.2 (d, CH=, Cp, $J_{C\text{-}P}$= 12.7 Hz), 90.2 (d, C, Cp, $J_{C\text{-}P}$= 12.0 Hz), 128.0 (d, CH=, $J_{C\text{-}P}$= 12.4 Hz), 128.1 (d, CH=, $J_{C\text{-}P}$= 12.5 Hz), 131.1 (d, CH=, $J_{C\text{-}P}$= 3.0 Hz), 131.2 (d, CH=, $J_{C\text{-}P}$= 3.0 Hz), 132.1 (d, CH=, $J_{C\text{-}P}$= 10.6 Hz), 132.3 (d, CH=, $J_{C\text{-}P}$= 10.6 Hz), 133.6 (d, C, $J_{C\text{-}P}$=

86.0 Hz), 134.6 (d, C, $J_{C\text{-}P}$= 87.1 Hz). MS HR-ESI [found 582.1273, $C_{33}H_{35}PS_2Fe$ (M)+ requires 582.1267].

L31: Yield: 114 mg (92%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= -23.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.64 (m, 6H, CH_2, Ad), 1.77 (m, 6H, CH_2, Ad), 1.98 (m, 3H, CH, Ad), 3.62 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 13.2 Hz, $J_{H\text{-}P}$= 2.4 Hz), 3.73 (b, 1H, CH=, Cp), 3.75 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 13.2 Hz), 4.02 (s, 5H, CH=, Cp), 4.26 (m, 1H, CH=, Cp), 4.55 (m, 1H, CH=, Cp), 7.1-7.3 (m, 5H, CH=), 7.40 (m, 3H, CH=), 7.57 (m, 2H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 24.5 (d, CH_2, $J_{C\text{-}P}$= 12.2 Hz), 29.8 (CH, Ad), 36.5 (CH_2, Ad), 43.4 (CH_2, Ad), 44.9 (C, Ad), 69.5 (CH=, Cp), 70.0 (CH=, Cp), 71.1 (d, CH=, Cp, $J_{C\text{-}P}$= 3.8 Hz), 71.5 (d, C, Cp, $J_{C\text{-}P}$= 3.8 Hz) 75.7 (d, CH=, Cp, $J_{C\text{-}P}$= 10.2 Hz), 91.3 (d, C, Cp, $J_{C\text{-}P}$= 25.1 Hz), 125.4 (C), 127.8 (CH=), 128.0 (d, CH=, $J_{C\text{-}P}$= 6.0 Hz), 128.3 (d, CH=, $J_{C\text{-}P}$= 7.6 Hz), 128.4 (C), 129.2 (d, CH=, $J_{C\text{-}P}$= 6.2 Hz), 132.6 (d, CH=, $J_{C\text{-}P}$= 17.5 Hz), 135.3 (d, CH=, $J_{C\text{-}P}$= 21.3 Hz), 137.7 (d, C, $J_{C\text{-}P}$= 8.3 Hz), 140.0 (d, C, $J_{C\text{-}P}$= 9.1 Hz). MS HR-ESI [found 550.1546, $C_{33}H_{35}FePS$ (M)+ requires 550.1547].

L34-S: Yield: 110 mg (83%).^{31}P NMR (121 MHz, $CDCl_3$): δ= 41.4 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ= 3.83 (m, 1H, CH=, Cp), 4.26 (s, 1H, CH=, Cp), 4.29 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 13.0 Hz), 4.32 (s, 5H, CH=, Cp) 4.42 (s, 1H, CH=, Cp), 4.60 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 13.0 Hz), 7.55-7.35 (m, 10H, CH=), 7.9-7.7 (m, 6H, CH=), 8.23 (m, 1H, CH=). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 33.5 (CH_2), 69.2 (d, CH=, Cp, $J_{C\text{-}P}$= 10.4 Hz), 71.0 (CH=, Cp), 73.8 (d, CH=, Cp, $J_{C\text{-}P}$= 9.2 Hz), 74.1 (d, C, Cp, $J_{C\text{-}P}$= 96.3 Hz), 74.6 (d, CH=, Cp, $J_{C\text{-}P}$= 12.7 Hz), 88.8 (d, C, Cp, $J_{C\text{-}P}$= 12.0 Hz), 125.4 (CH=), 125.5 (CH=), 126.1 (CH=), 126.2 (CH=), 127.3 (CH=), 128.1 (d, CH=, $J_{C\text{-}P}$= 12.6 Hz), 128.2 (d, CH=, $J_{C\text{-}P}$= 12.7 Hz), 128.4 (CH=), 128.9 (CH=), 131.3 (d, 2C, $J_{C\text{-}P}$= 2.7 Hz), 132.1 (d, CH=, $J_{C\text{-}P}$= 10.8 Hz), 132.2 (d, CH=, $J_{C\text{-}P}$= 10.7 Hz), 132.9 (C), 133.6 (d, C, $J_{C\text{-}P}$= 70.2 Hz), 133.9 (C), 134.0 (C), 134.5 (d, C, $J_{C\text{-}P}$= 71.0 Hz). MS HR-ESI [found 574.0642, $C_{33}H_{27}PS_2Fe$ (M)+ requires 574.0641], 415.0364 (M-S(naphthyl), 100 %).

L34: Yield: 92 mg (89%).^{31}P NMR (162 MHz, $CDCl_3$): δ= -24.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.86 (m, 1H, CH=, Cp), 4.04 (s, 5H, CH=, Cp), 4.21 (b, 2H, CH_2), 4.29 (m, 1H, CH=, Cp), 4.43 (m, 1H, CH=, Cp), 7.33 (m, 5H, CH=), 7.4-7.5 (m, 4H, CH=), 7.53 (m, 3H, CH=), 7.61 (m, 2H, CH=), 7.76 (m, 1H, CH=), 7.85 (m, 1H, CH=), 8.30 (m, 1H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 34.6 (d, CH_2, $J_{C\text{-}P}$= 12.2 Hz), 69.8 (CH=, Cp), 70.0 (CH=, Cp), 71.6 (d, CH=, Cp, $J_{C\text{-}P}$= 3.8 Hz), 71.8 (d, CH=, Cp, $J_{C\text{-}P}$= 3.8 Hz), 76.1 (d, C, Cp, $J_{C\text{-}P}$= 8.4 Hz), 89.9 (d, C, Cp, $J_{C\text{-}P}$= 25.9 Hz), 125.6 (d, CH=, $J_{C\text{-}P}$= 6.8 Hz), 126.3 (d, CH=, $J_{C\text{-}P}$= 20.6 Hz), 127.6 (CH=), 128.1 (CH=), 128.2 (d, CH=, $J_{C\text{-}P}$= 6.1 Hz), 128.4 (d, CH=, $J_{C\text{-}P}$= 5.9 Hz), 128.6 (CH=), 129.3 (CH=), 132.6 (CH=), 132.7 (CH=), 133.2 (C), 134.0 (C), 134.3 (C), 135.1 (CH=), 135.4 (CH=), 137.6 (d, C, $J_{C\text{-}P}$= 7.6 Hz), 139.7 (d, C, $J_{C\text{-}P}$= 9.1 Hz). MS HR-ESI [found 542.0919, $C_{33}H_{27}FePS$ (M)+ requires 542.0921].

L35-S: Yield: 118 mg (93%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 41.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.42 (s, 6H, CH_3), 3.78 (m, 1H, CH=, Cp), 3.86 (d, 1H, CH_2, $^{2}J_{H-H}$= 12.7 Hz), 4.30 (m, 1H, CH=, Cp), 4.33 (d, 1H, CH_2, $^{2}J_{H-H}$= 12.7 Hz), 4.34 (s, 5H, CH=, Cp), 4.45 (m, 1H, CH=, Cp), 7.0-7.2 (m, 3H, CH=), 7.4-7.6 (m, 6H, CH=), 7.7-7.8 (m, 2H, CH=),7.8-7.9 (m, 2H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.2 (CH_3), 33.6 (CH_2) 69.2 (d, CH=, Cp, J_{C-P}= 10.3 Hz), 70.9 (CH=, Cp), 73.3 (d, CH=, Cp, J_{C-P}= 9.2 Hz), 74.4 (d, C, Cp, J_{C-P}= 95.1 Hz), 74.5 (d, CH=, Cp, J_{C-P}= 12.5 Hz), 89.6 (d, C, Cp, J_{C-P}= 12.2 Hz), 128.0 (CH=), 128.1 (CH=), 128.1 (CH=), 128.2 (CH=), 131.2 (d, CH=, J_{C-P}= 3.5 Hz), 131.3 (d, CH=, J_{C-P}= 3.5 Hz), 132.1 (d, CH=, J_{C-P}= 10.8 Hz), 132.3 (d, CH=, J_{C-P}= 10.7 Hz), 133.5 (d, C, J_{C-P}= 85.5 Hz), 134.2 (C), 134.4 (d, C, J_{C-P}= 86.6 Hz), 143.2 (C).

L35: Yield: 101 mg (91%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= -24.0 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.43 (s, 6H, CH_3), 3.46 (d, 1H, CH_2, $^{2}J_{H-H}$= 11.2 Hz), 3.79 (b, 1H, CH=, Cp), 3.84 (d, 1H, CH_2, $^{2}J_{H-H}$= 11.2 Hz), 4.00 (s, 5H, CH=, Cp), 4.27 (b, 1H, CH=, Cp), 4.37 (b, 1H, CH=, Cp), 7.07 (m, 3H, CH=), 7.39 (m, 5H, CH=), 7.55 (m, 3H, CH=), 7.59 (m, 2H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.0 (CH_3), 34.3 (d, CH_2, J_{C-P} = 12.9 Hz) 69.6 (CH=, Cp), 69.7 (CH=, Cp), 71.3 (b, CH=, Cp), 75.9 (d, C, Cp, J_{C-P}= 7.6 Hz), 90.4 (d, C, Cp, J_{C-P}= 25.9 Hz), 127.8 (CH=), 127.9 (CH=), 128.0 (CH=), 128.1 (CH=), 128.2 (CH=), 129.1 (CH=), 132.5 (d, CH=, J_{C-P}= 18.2 Hz), 134.2 (C), 135.2 (d, CH=, J_{C-P}= 21.3 Hz), 137.6 (d, C, J_{C-P}= 8.3 Hz), 139.7 (d, C, J_{C-P}= 9.1 Hz), 143.1 (C). MS HR-ESI [found 520.1074, $C_{31}H_{29}FePS$ (M)+ requires 520.1077].

3.8.4.3. General procedure for the preparation of [Ir(cod)(L27-L38)]BAr$_F$

The corresponding ligand (0.074 mmol) was dissolved in CH_2Cl_2 (5 mL) and [Ir(μ-Cl)(cod)]$_2$ (25.0 mg, 0.037 mmol) was added. The reaction mixture was refluxed at 40 ºC for 1 hour. After 5 min at room temperature, NaBAr$_F$ (77.2 mg, 0.080 mmol) and water (5 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$. Evaporation of the solvent gave a brown-orange solid, which was purified by flash chromatography on neutral silica (dichloromethane/petroleum ether (1/1) as eluent) to produce the corresponding complex as an orange solid.

[Ir(cod)(L27)]BAr$_F$: Yield: 105.9 mg (89%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 9.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.12 (t, 3H, CH_3, $^{3}J_{H-H}$= 7.6 Hz), 1.56 (m, 1H, CH_2, cod), 1.71 (m, 1H, CH_2, cod), 2.06 (m, 1H, CH_2, cod), 2.32 (m, 1H, CH_2, cod), 2.45 (m, 3H, CH_2, cod), 2.64 (m, 1H, CH_2, Et), 2.78 (d, CH_2-S, 1H, $^{2}J_{H-H}$= 12.4 Hz), 2.91 (m, 1H, CH_2, Et), 3.47 (m, 1H, CH=, cod), 3.57 (m, 1H, CH=, cod), 4.00 (d, 1H, CH_2-S, $^{2}J_{H-H}$= 12.4 Hz), 4.05 (s, 1H, CH=, Cp), 4.41 (m, 1H, CH=, Cp), 4.47 (s, 6H, CH=, Cp), 4.63 (m, 1H, CH=, cod), 4.94 (m, 1H, CH=, cod), 7.3-7.8 (m, 22H, CH=). ^{13}C NMR (100 MHz,

$CDCl_3$): δ= 14.6 (CH_3), 27.4 (CH_2, cod), 29.2 (CH_2, cod), 31.2 (CH_2), 31.6 (CH_2, cod), 33.7 (CH_2, Et), 35.0 (CH_2, cod), 63.7 (d, C, Cp, $^1J_{C\text{-}P}$= 63.6 Hz), 68.8 (d, CH=, Cp, $J_{C\text{-}P}$= 5.2 Hz), 70.9 (CH=, cod and CH=, Cp), 72.3 (CH=, cod), 73.2 (CH=, Cp), 76.0 (d, CH=, Cp, $J_{C\text{-}P}$= 7.0 Hz), 84.3 (d, C, Cp, $^2J_{C\text{-}P}$= 15.5 Hz), 90.5 (d, CH=, cod, $J_{C\text{-}P}$= 14.6 Hz), 90.7 (d, CH=, cod, $J_{C\text{-}P}$= 14.6 Hz), 117.4 (b, CH=, BAr_F), 120.4-134.2 (aromatic carbons), 134.7 (b, CH=, BAr_F), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 48.8 Hz). MS HR-ESI [found 745.1336, $C_{65}H_{49}BF_{24}FeIrPS$ $(M\text{-}BAr_F)^+$ requires 745.1332]. Elemental analysis calcd (%) for $C_{65}H_{49}BF_{24}FeIrPS$: C, 48.55; H, 3.07; S, 1.99; found: C, 48.34; H, 3.06; S, 1.95.

[Ir(cod)(L28)]BAr_F: Yield: 108.0 mg (90%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 9.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.18 (d, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 1.41 (d, 3H, 3H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.8 Hz), 1.62 (m, 1H, CH_2, cod), 1.78 (m, 1H, CH_2, cod), 2.17 (m, 2H, CH_2, cod), 2.41 (m, 1H, CH_2, cod), 2.51 (m, 2H, CH_2, cod), 2.57 (m, 1H, CH_2, cod), 2.84 (d, 3H, CH_2-S, $^2J_{H\text{-}H}$= 11.6 Hz), 3.24 (q, 1H, CH, ^{i}Pr, $^2J_{H\text{-}H}$= 6.8 Hz), 3.55 (m, 1H, CH=, cod), 3.59 (m, 1H, CH=, Cp), 4.05 (d, 1H, CH_2-S, $^2J_{H\text{-}H}$= 11.6 Hz), 4.08 (s, 1H, CH=, Cp), 4.47 (s, 1H, CH=, Cp), 4.54 (s, 5H, CH=, Cp), 4.57 (s, 1H, CH=, Cp), 4.81 (m, 1H, CH=, cod), 5.04 (m, 1H, CH=, cod), 7.4-7.8 (m, 22H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 21.7 (CH_3, ^{i}Pr), 23.1 (CH_3, ^{i}Pr), 24.8 (b, CH_2S), 27.3 (CH_2, cod), 29.0 (CH_2, cod), 31.5 (CH_2, cod), 35.2 (b, CH_2, cod), 43.3 (CH, ^{i}Pr), 63.7 (d, C, Cp, $^1J_{C\text{-}P}$= 63.9 Hz), 68.7 (d, CH=, Cp, $J_{C\text{-}P}$= 6.2 Hz), 69.9 (CH=, cod), 71.0 (CH=, Cp), 71.5 (CH=, cod), 73.4 (d, CH=, Cp, $^3J_{C\text{-}P}$= 2.1 Hz), 76.2 (d, CH=, Cp, $J_{C\text{-}P}$= 6.1 Hz), 84.0 (d, C, Cp, $^2J_{C\text{-}P}$= 16.0 Hz), 90.3 (d, CH=, cod, $J_{C\text{-}P}$= 11.4 Hz), 90.8 (d, CH=, cod, $J_{C\text{-}P}$= 11.4 Hz), 117.4 (b, CH=, BAr_F), 120.4-134.2 (aromatic carbons), 134.7 (b, CH=, BAr_F), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 50.1 Hz). MS HR-ESI [found 759.1485, $C_{66}H_{51}BF_{24}FeIrPS$ $(M\text{-}BAr_F)^+$ requires 759.1489]. Elemental analysis calcd (%) for $C_{66}H_{51}BF_{24}FeIrPS$: C, 48.87; H, 3.17; S, 1.98; found: C, 48.69; H, 3.15; S, 1.95.

[Ir(cod)(L29)]BAr_F: Yield: 111.9 mg (91%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 9.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.14 (m, 2H, CH_2), 1.51 (m, 4H, CH_2), 1.76 (m, 1H, CH_2), 1.91 (m, 2H, CH_2), 2.09 (m, 1H, CH_2), 2.17 (m, 2H, CH_2), 2.43 (m, 1H, CH_2), 2.51 (m, 2H, CH_2), 2.57 (m, 1H, CH_2), 2.85 (m, 1H, CH-S), 2.90 (d, 1H, CH_2-S, $^2J_{H\text{-}H}$= 10.8 Hz), 3.51 (m, 1H, CH=, cod), 3.54 (m, 1H, CH=, cod), 4.06 (d, 1H, CH_2-S, $^2J_{H\text{-}H}$= 10.8 Hz), 4.08 (s, 1H, CH=, Cp), 4.46 (b, 1H, CH=, Cp), 4.53 (s, 6H, CH=, Cp), 4.76 (m, 1H, CH=, cod), 5.04 (m, 1H, CH=, cod), 7.4-7.8 (m, 22H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 24.4 (CH_2), 26.0 (d, CH_2-S, $^3J_{C\text{-}P}$= 3.8 Hz), 27.1 (CH_2), 27.3 (CH_2), 28.7 (CH_2), 29.7 (CH_2), 31.5 (CH_2), 32.3 (CH_2), 34.1 (CH_2), 35.2 (d, CH_2-S, $^3J_{C\text{-}P}$= 3.8 Hz), 51.9 (CH-S), 64.2 (d, C, Cp, $^1J_{C\text{-}P}$= 63.8 Hz), 68.6 (d, CH=, Cp, $J_{C\text{-}P}$= 6.1 Hz), 69.6 (CH=, cod), 71.0 (CH=, Cp), 71.3 (CH=, cod), 73.3 (d, CH=, Cp, $J_{C\text{-}P}$= 3.1 Hz), 76.1 (d, CH=, Cp, $J_{C\text{-}P}$= 6.9 Hz), 84.4 (d, C, Cp, $^2J_{C\text{-}P}$= 16.7 Hz), 90.2 (d, CH=, cod, $J_{C\text{-}P}$= 11.4 Hz), 90.7 (d, CH=, cod, $J_{C\text{-}P}$= 11.4 Hz), 117.4 (b, CH=, BAr_F), 120.4-134.3 (aromatic carbons), 134.7 (b, CH=, BAr_F), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 50.1 Hz). MS HR-

ESI [found 799.1779, $C_{69}H_{55}BF_{24}FeIrPS$ $(M\text{-}BAr_F)^+$ requires 799.1802]. Elemental analysis calcd (%) for $C_{69}H_{55}BF_{24}FeIrPS$: C, 49.86; H, 3.34; S, 1.93; found: C, 49.76; H, 3.31; S, 1.90.

[Ir(cod)(L30)]BAr$_F$: Yield: 108.9 mg (90%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 10.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.35 (s, 9H, CH_3, ^{t}Bu), 1.52 (m, 1H, CH_2, cod), 1.69 (m, 1H, CH_2, cod), 2.18 (m, 2H, CH_2, cod), 2.37 (m, 1H, CH_2, cod), 2.53 (m, 3H, CH_2, cod), 2.80 (d, 1H, CH_2-S, $^2J_{H\text{-}H}$= 12.0 Hz), 3.51 (m, 2H, CH=, cod), 4.15 (d, 1H, CH_2-S, $^2J_{H\text{-}H}$= 12.0 Hz), 4.17 (s, 1H, CH=, Cp), 4.48 (s, 1H, CH=, Cp), 4.56 (m, 6H, CH=, Cp), 5.35 (m, 1H, CH=, cod), 5.45 (m, 1H, CH=, cod), 7.4-7.8 (m, 22H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 27.4 (CH_2, cod), 28.4 (d, CH_2, cod, $J_{C\text{-}P}$= 2.4 Hz), 30.3 (d, CH_2-S, $^3J_{C\text{-}P}$= 4.6 Hz), 31.8 (CH_3, ^{t}Bu), 32.1 (d, CH_2, cod, $J_{C\text{-}P}$= 2.3 Hz), 35.7 (d, CH_2, cod, $J_{C\text{-}P}$= 4.7 Hz), 59.1 (C, ^{t}Bu), 62.6 (d, C, Cp, $^1J_{C\text{-}P}$= 60.4 Hz), 68.2 (CH=, cod), 69.0 (d, CH=, Cp, $J_{C\text{-}P}$= 6.2 Hz), 69.1 (CH=, cod), 71.1 (CH=, Cp), 73.9 (d, CH=, Cp, $J_{C\text{-}P}$= 3.1 Hz), 76.5 (d, CH=, Cp, $J_{C\text{-}P}$= 7.0 Hz), 84.8 (d, C, Cp, $^2J_{C\text{-}P}$= 16.3 Hz), 89.8 (d, CH=, cod, $J_{C\text{-}P}$= 10.9 Hz), 90.5 (d, CH=, cod, $J_{C\text{-}P}$= 11.6 Hz), 117.6 (b, CH=, BAr_F), 120.6-134.3 (aromatic carbons), 134.9 (b, CH=, BAr_F), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 50.4 Hz). MS HR-ESI [found 773.1644, $C_{67}H_{53}BF_{24}FeIrPS$ $(M\text{-}BAr_F)^+$ requires 773.1645]. Elemental analysis calcd (%) for $C_{67}H_{53}BF_{24}FeIrPS$: C, 49.19; H, 3.27; S, 1.96; found: C, 49.11; H, 3.25; S, 1.95. Suitable crystals for X-ray diffraction were achieved by slow diffusion of petroleum ether to an isopropanol solution.

[Ir(cod)(L31)]BAr$_F$: Yield: 114.2 mg (90%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 10.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.28 (m, 1H, CH), 1.48 (m, 1H, CH_2, cod), 1.59-1.72 (m, 6H, CH_2), 1.84 (m, 4H, CH_2), 2.05-2.17 (m, 6H, CH_2), 2.19 (m, 3H, CH_2, cod), 2.33 (m, 1H, CH_2, cod), 2.53 (m, 2H, CH_2, cod), 2.58 (m, 1H, CH_2, cod), 2.82 (d, 1H, CH_2-S, $^2J_{H\text{-}H}$= 12.4 Hz), 4.17 (s, 1H, CH=, Cp), 3.48 (m, 2H, CH=, cod), 4.13 (d, 1H, CH_2-S, $^2J_{H\text{-}H}$= 12.4 Hz), 4.18 (b, 1H, CH=, Cp), 4.46 (b, 1H, CH=, Cp), 4.51 (b, 1H, CH=, Cp), 4.55 (s, 5H, CH=, Cp), 5.49 (m, 2H, CH=, cod), 7.4-7.8 (m, 22H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.6 (CH_2, Ad), 27.2 (CH_2, cod), 27.8 (d, CH_2, cod, $J_{C\text{-}P}$= 4.6 Hz), 27.9 (CH_2-S), 30.5 (CH_2, Ad), 32.0 (CH_2, cod), 35.3 (CH_2, Ad), 35.6 (d, CH_2, cod, $J_{C\text{-}P}$= 4.5 Hz), 43.9 (CH_2, Ad), 62.7 (d, C, Cp, $^1J_{C\text{-}P}$= 63.8 Hz), 67.4 (CH=, cod), 68.6 (CH=, cod), 68.7 (d, CH=, Cp, $J_{C\text{-}P}$= 6.0 Hz), 70.9 (CH=, Cp), 73.6 (d, CH=, Cp, $J_{C\text{-}P}$= 3.8 Hz), 76.2 (d, CH=, Cp, $J_{C\text{-}P}$= 7.6 Hz), 84.7 (d, C, Cp, $^2J_{C\text{-}P}$= 16.7 Hz), 89.7 (d, CH=, cod, $J_{C\text{-}P}$= 10.6 Hz), 90.5 (d, CH=, cod, $J_{C\text{-}P}$= 12.2 Hz), 117.4 (b, CH=, BAr_F), 120.4-134.4 (aromatic carbons), 134.7 (b, CH=, BAr_F), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 50.2 Hz). MS HR-ESI [found 851.2112, $C_{73}H_{59}BF_{24}FeIrPS$ $(M\text{-}BAr_F)^+$ requires 851.2115]. Elemental analysis calcd (%) for $C_{73}H_{59}BF_{24}FeIrPS$: C, 51.15; H, 3.47; S, 1.87; found: C, 51.11; H, 3.44; S, 1.85.

[Ir(cod)(L32)]BAr$_F$: Yield: 109.1 mg (89%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 8.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.72 (m, 2H, CH_2, cod), 1.96 (m, 1H, CH_2-S, cod), 2.24 (m, 1H, CH_2, cod), 2.46 (m, 2H, CH_2, cod), 2.57 (m, 2H, CH_2, cod), 3.31 (d, 1H, CH_2, $^2J_{H-H}$= 12.8 Hz), 3.70 (m, 1H, CH=, cod), 3.72 (m, 1H, CH=, cod), 3.94 (m, 1H, CH=, cod), 4.17 (s, 1H, CH=, Cp), 4.43 (d, 1H, CH_2, $^2J_{H-H}$= 12.8 Hz), 4.51 (s, 1H, CH=, Cp), 4.59 (s, 1H, CH=, Cp), 4.65 (s, 5H, CH=, Cp), 4.88 (m, 1H, CH=, cod), 7.3-7.8 (b, 27H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 27.1 (CH_2, cod), 29.8 (d, CH_2, cod, J_{C-P}= 2.4 Hz), 30.9 (d, CH_2, cod, J_{C-P}= 2.4 Hz), 34.8 (d, CH_2, cod, J_{C-P}= 4.6 Hz), 38.7 (d, CH_2-S, $^3J_{C-P}$= 3.5 Hz), 64.2 (d, C, Cp, $^1J_{C-P}$= 63.6 Hz), 68.6 (d, CH=, Cp, J_{C-P}= 7.0 Hz), 70.9 (CH=, cod), 71.1 (CH=, Cp), 72.9 (CH=, cod), 73.5 (d, CH=, Cp, J_{C-P}= 3.2 Hz), 76.2 (d, CH=, Cp, J_{C-P}= 6.2 Hz), 84.0 (d, C, Cp, $^2J_{C-P}$= 16.3 Hz), 90.8 (d, CH=, cod, J_{C-P}= 11.7 Hz), 94.4 (d, CH=, cod, J_{C-P}= 10.8 Hz), 117.4 (b, CH=, BAr_F), 120.4-134.2 (aromatic carbons), 134.7 (b, CH=, BAr_F), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49.6 Hz). MS HR-ESI [found 793.1330, $C_{69}H_{49}BF_{24}FeIrPS$ (M-BAr_F)$^+$ requires 793.1332]. Elemental analysis calcd (%) for $C_{69}H_{49}BF_{24}FeIrPS$: C, 50.04; H, 2.98; S, 1.94; found: C, 49.98; H, 2.96; S, 1.92.

[Ir(cod)(L33)]BAr$_F$: Yield: 112.5 mg (91%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 8.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.71 (m, 2H, CH_2, cod), 1.85 (m, 1H, CH_2, cod), 2.21 (m, 2H, CH_2, cod), 2.41 (m, 1H, CH_2, cod), 2.54 (m, 3H, CH_2, cod), 2.67 (d, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz), 3.64 (m, 1H, CH=, cod), 3.72 (m, 1H, CH=, cod), 3.76 (d, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz), 3.83 (d, 1H, CH_2-Ph, $^2J_{H-H}$= 13.2 Hz), 4.11 (s, 1H, CH=, Cp), 4.22 (d, 1H, CH_2-Ph, $^2J_{H-H}$= 13.2 Hz), 4.41 (s, 1H, CH=, Cp), 4.42 (s, 1H, CH=, Cp), 4.47 (s, 5H, CH=, Cp), 4.90 (m, 1H, CH=, cod), 5.13 (m, 1H, CH=, cod), 7.1-7.8 (b, 27H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 27.9 (d, CH_2, cod, J_{C-P}= 1.6 Hz), 29.6 (d, CH_2, cod, J_{C-P}= 2.4 Hz), 31.8 (d, CH_2, cod, J_{C-P}= 2.3 Hz), 32.8 (d, CH_2-S, J_{C-P}= 4.7 Hz), 35.1 (d, CH_2, cod, J_{C-P}= 4.7 Hz), 44.5 (CH_2-Ph), 64.5 (d, C, Cp, $^1J_{C-P}$= 63.6 Hz), 69.1 (d, CH=, Cp, J_{C-P}= 7.0 Hz), 71.2 (CH=, Cp), 72.1 (CH=, cod), 73.4 (CH=, cod), 73.5 (d, CH=, Cp, J_{C-P}= 3.9 Hz), 76.2 (d, CH=, Cp, J_{C-P}= 7.0 Hz), 84.3 (d, $^2J_{C-P}$ = 16.3 Hz, C, Cp), 90.7 (d, CH=, cod, J_{C-P}= 11.6 Hz), 91.2 (d, CH=, cod, J_{C-P}= 11.6 Hz), 117.6 (b, CH=, BAr_F), 120.6-134.2 (aromatic carbons), 135.0 (b, CH=, BAr_F), 161.8 (q, C-B, BAr_F, $^1J_{C-B}$ = 49.7 Hz). MS HR-ESI [found 807.1488, $C_{70}H_{51}BF_{24}FeIrPS$ (M-BAr_F)$^+$ requires 807.1489]. Elemental analysis calcd (%) for $C_{70}H_{51}BF_{24}FeIrPS$: C, 50.34; H, 3.08; S, 1.92; found: C, 50.27; H, 3.06; S, 1.89.

[Ir(cod)(L34)]BAr$_F$: Yield: 114.9 mg (91%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 6.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.62 (m, 3H, CH_2, cod), 1.78 (m, 2H, CH_2, cod), 2.28 (m, 3H, CH_2, cod and CH_2-S), 2.46 (m, 1H, CH_2, cod, and CH_2-S), 3.71 (m, 1H, CH=, Cp), 3.86 (m, 1H, CH=, cod), 4.04 (m, 1H, CH=, cod), 4.26 (m, 1H, CH=, cod), 4.51 (m, 1H, CH=, Cp), 4.59 (s, 1H, CH=, Cp), 4.69 (s, 5H, CH=, Cp), 4.70 (m, 1H, CH=, cod), 7.4-7.9 (b, 29H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 27.8 (b, CH_2, cod), 29.7

(b, CH_2, cod), 30.2 (b, CH_2, cod), 31.4 (CH_2-S), 33.4 (CH_2-S), 64.3 (d, C, Cp, $^1J_{C\text{-}P}$= 64.2 Hz), 68.7 (d, CH=, Cp, $J_{C\text{-}P}$= 6.4 Hz), 71.3 (CH=, Cp and CH=, cod), 73.8 (CH=, cod), 76.3 (d, CH=, Cp, $J_{C\text{-}P}$= 5.9 Hz), 84.9 (d, C, Cp, $^2J_{C\text{-}P}$= 20.4 Hz), 90.9 (d, CH=, cod, $J_{C\text{-}P}$= 10.8 Hz), 95.0 (d, CH=, cod, $J_{C\text{-}P}$= 12.2 Hz), 117.4 (b, CH=, BAr_F), 120.4-134.2 (aromatic carbons), 134.8 (b, CH=, BAr_F), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.4 Hz). MS HR-ESI [found 843.1487, $C_{73}H_{51}BF_{24}FeIrPS$ $(M\text{-}BAr_F)^+$ requires 843.1489]. Elemental analysis calcd (%) for $C_{73}H_{51}BF_{24}FeIrPS$: C, 51.39; H, 3.01; S, 1.88; found: C, 51.33; H, 2.99; S, 1.85. Major isomer (66%): ^{31}P NMR (162 MHz, $CDCl_3$, 228 K): δ= 6.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$, 228 K): δ= 1.5-2.5 (b, 8H, CH_2, cod), 3.64 (m, 2H, CH=, cod), 3.70 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 12.0 Hz), 3.88 (m, 1H, CH=, cod), 3.99 (b, 1H, CH=, Cp), 4.17 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 12.0 Hz), 4.50 (b, 1H, CH=, Cp), 4.60 (m, 1H, CH=, Cp), 4.63 (b, 1H, CH=, cod), 4.67 (s, 5H, CH=, Cp), 6.6-8.5 (m, 29H, CH=). Minor isomer (33%): ^{31}P NMR (162 MHz, $CDCl_3$, 228 K): δ= 8.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$, 228 K): δ= 1.5-2.7 (b, 8H, CH_2, cod), 3.28 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 12.0 Hz), 3.64 (m, 2H, CH=, cod), 3.94 (m, 1H, CH=, cod), 4.20 (b, 1H, CH=, Cp), 4.45 (b, 1H, CH=, Cp), 4.60 (b, 1H, CH=, Cp), 4.73 (s, 5H, CH=, Cp), 4.88 (m, 1H, CH=, cod), 6.6-8.5 (m, 29H, CH=).

[Ir(cod)(L35)]BAr_F: Yield: 113.4 mg (91%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 5.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.76 (m, 2H, CH_2, cod), 2.06 (m, 1H, CH_2, cod), 2.20 (s, 3H, CH_3), 2.29 (m, 3H, CH_2, cod), 2.41 (m, 1H, CH_2, cod), 2.56 (m, 1H, CH_2, cod), 2.78 (s, 3H, CH_3), 3.42 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 13.2 Hz), 3.70 (m, 1H, CH=, cod), 3.83 (m, 1H, CH=, cod), 3.92 (m, 2H, CH=, cod and Cp), 3.99 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 13.2 Hz), 4.51 (m, 2H, CH=, cod and Cp), 4.65 (s, 6H, CH=, Cp), 7.1-7.8 (b, 25H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.9 (CH_3), 23.1 (CH_3), 27.9 (b, CH_2, cod), 30.6 (b, CH_2, cod), 30.8 (d, CH_2, cod, $J_{C\text{-}P}$= 2.3 Hz), 33.9 (d, CH_2, cod, $J_{C\text{-}P}$= 4.6 Hz), 35.2 (b, CH_2-S), 64.1 (d, C, Cp, $^1J_{C\text{-}P}$= 63.9 Hz), 68.5 (CH=, cod), 68.7 (d, CH=, Cp, $J_{C\text{-}P}$= 6.1 Hz), 71.2 (CH=, Cp), 73.0 (CH=, cod), 73.9 (d, CH=, Cp, $J_{C\text{-}P}$= 2.1 Hz), 76.3 (d, CH=, Cp, $J_{C\text{-}P}$= 7.8 Hz), 85.3 (d, C, Cp, $^2J_{C\text{-}P}$= 16.0 Hz), 89.9 (d, CH=, cod, $J_{C\text{-}P}$= 12.2 Hz), 94.2 (d, CH=, cod, $J_{C\text{-}P}$= 11.4 Hz), 117.4 (b, CH=, BAr_F), 120.4-134.0 (aromatic carbons), 134.7 (b, CH=, BAr_F), 140.3 (C), 142.0 (C), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.6 Hz). MS HR-ESI [found 821.1642, $C_{71}H_{53}BF_{24}FeIrPS$ $(M\text{-}BAr_F)^+$ requires 821.1645]. Elemental analysis calcd (%) for $C_{71}H_{53}BF_{24}FeIrPS$: C, 50.64; H, 3.17; S, 1.90; found: C, 50.61; H, 3.16; S, 1.88.

[Ir(cod)(L36)]BAr_F: Yield: 108.0 mg (90%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 25.0 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.09 (s, 9H, CH_3, ^{t}Bu), 1.68 (m, 1H, CH_2, cod), 1.84 (m, 1H, CH_2, cod), 2.16 (m, 2H, CH_2, cod), 2.32 (m, 1H, CH_2, cod), 2.42 (m, 1H, CH_2, cod), 2.52 (m, 2H, CH_2, cod), 3.79 (m, 1H, CH=, cod), 4.32 (s, 5H, CH=, Cp), 4.49 (b, 1H, CH=, Cp), 4.60 (m, 1H, CH=, cod), 4.79 (m, 1H, CH=, cod), 4.95 (b, 1H, CH=, Cp), 5.21 (s, 1H, CH=, Cp), 5.54 (s, 1H, CH=, cod), 7.3-7.8 (m, 22H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 27.4 (d, CH_2, cod, $J_{C\text{-}P}$= 2.3 Hz), 29.1 (d, CH_2, cod, $J_{C\text{-}P}$= 2.2 Hz), 31.0 (CH_3, ^{t}Bu), 33.2 (b, CH_2, cod), 35.5 (d, CH_2, cod, $J_{C\text{-}P}$= 4.5 Hz), 61.8 (C, ^{t}Bu), 70.8 (CH=,

Cp), 71.7 (CH=, cod), 72.7 (CH=, Cp), 73.2 (CH=, cod), 73.6 (d, CH=, Cp, $J_{C\text{-}P}$= 9.1 Hz), 79.2 (d, C, Cp, $^{1}J_{C\text{-}P}$= 62.1 Hz), 80.2 (d, CH=, Cp, $J_{C\text{-}P}$= 14.5 Hz), 85.2 (d, C, Cp, $^{2}J_{C\text{-}P}$= 26.4 Hz), 86.4 (d, CH=, cod, $J_{C\text{-}P}$= 14.5 Hz), 94.3 (d, CH=, cod, $J_{C\text{-}P}$= 9.9 Hz), 117.4 (b, CH=, BAr_F), 120.4-133.1 (aromatic carbons), 134.7 (b, CH=, BAr_F), 161.7 (q, C-B, BAr_F, $J_{C\text{-}B}$= 49.4 Hz). MS HR-ESI [found 759.1484, $C_{66}H_{51}BF_{24}FeIrPS$ $(M\text{-}BAr_F)^+$ requires 759.1489]. Elemental analysis calcd (%) for $C_{66}H_{51}BF_{24}FeIrPS$: C, 48.87; H, 3.17; S, 1.98; found: C, 48.81; H, 3.15; S, 1.94.

[Ir(cod)(L37)]BAr_F: Yield: 111.2 mg (90%). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 3.9 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.71 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$= 6.8 Hz), 1.69 (m, 2H, CH_2, cod), 2.01 (m, 1H, CH_2, cod), 2.17 (m, 1H, CH_2, cod), 2.42 (m, 2H, CH_2, cod), 2.46 (m, 1H, CH_2, cod), 2.56 (m, 1H, CH_2, cod), 3.48 (m, 1H, CH=, cod), 3.54 (m, 1H, CH=, cod), 4.11 (s, 1H, CH=, Cp), 4.32 (m, 1H, CH=, cod), 4.50 (s, 7H, CH=, Cp), 4.61 (q, 1H, CH, $^{3}J_{H\text{-}H}$= 6.8 Hz), 4.72 (m, 2H, CH=, cod), 7.5-7.8 (b, 22H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.9 (CH_2, cod), 29.7 (CH_2, cod), 31.0 (CH_2, cod), 34.9 (CH_2, cod), 47.7 (CH), 63.5 (d, C, Cp, $^{1}J_{C\text{-}P}$= 61.5 Hz), 69.1 (d, CH=, Cp, $J_{C\text{-}P}$= 6.9 Hz), 70.9 (CH=, cod), 71.5 (CH=, Cp), 72.1 (CH=, cod), 74.1 (CH=, cod), 74.5 (d, CH=, Cp, $J_{C\text{-}P}$= 6.1 Hz), 90.8 (d, C, Cp, $^{2}J_{C\text{-}P}$= 16.7 Hz), 93.4 (d, CH=, cod, $J_{C\text{-}P}$= 10.6 Hz), 93.8 (d, CH=, cod, $J_{C\text{-}P}$= 10.6 Hz), 117.4 (b, CH=, BAr_F), 120.4-134.2 (aromatic carbons), 134.7 (b, CH=, BAr_F), 135.0 (CH=, Cp), 161.7 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$= 49.8 Hz). MS HR-ESI [found 807.1488, $C_{70}H_{51}BF_{24}FeIrPS$ $(M\text{-}BAr_F)^+$ requires 807.1489]. Elemental analysis calcd (%) for $C_{70}H_{51}BF_{24}FeIrPS$: C, 50.34; H, 3.08; S, 1.92; found: C, 50.31; H, 3.06; S, 1.90.

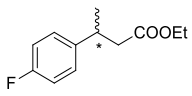
[Ir(cod)(L38)]BAr_F: Yield: 111.9 mg (89%). Major isomer (85%): ^{31}P NMR (162 MHz, $CDCl_3$): δ= 3.0 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.71 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$= 6.8 Hz), 1.83 (m, 2H, CH_2, cod), 2.10 (m, 1H, CH_2, cod), 2.30 (m, 1H, CH_2, cod), 2.39 (m, 2H, CH_2, cod), 2.46 (m, 1H, CH_2, cod), 2.57 (m, 1H, CH_2, cod), 2.62 (s, 3H, CH_3-Ar), 2.79 (s, 3H, CH_3-Ar), 3.36 (m, 1H, CH=, cod), 3.58 (m, 1H, CH=, cod), 4.00 (m, 1H, CH=, cod), 4.11 (b, 1H, CH=, Cp), 4.52 (s, 6H, CH=, Cp), 4.62 (m, 2H, CH and CH=, Cp), 4.64 (m, 1H, CH=, cod), 7.2-7.7 (m, 25H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 21.2 (CH_3), 23.1 (CH_3-Ar), 24.8 (CH_3-Ar), 26.8 (CH_2, cod), 29.8 (CH_2, cod), 31.2 (CH_2, cod), 34.8 (d, CH_2, cod, $J_{C\text{-}P}$= 3.2 Hz), 47.0 (CH), 63.8 (d, C, Cp, $^{1}J_{C\text{-}P}$= 61.5 Hz), 69.0 (d, CH=, Cp, $J_{C\text{-}P}$= 6.9 Hz), 69.7 (CH=, cod), 70.3 (CH=,cod), 71.4 (CH=, Cp), 74.3 (d, CH=, Cp, $J_{C\text{-}P}$= 6.9 Hz), 74.8 (d, CH=, Cp, $J_{C\text{-}P}$= 3.8 Hz), 90.8 (d, C, Cp, $^{2}J_{C\text{-}P}$= 16.8 Hz), 92.6 (d, CH=, cod, $J_{C\text{-}P}$= 11.4 Hz), 94.2 (d, CH=, cod, $J_{C\text{-}P}$= 10.6 Hz), 117.4 (b, CH=, BAr_F), 120.4-134.7 (aromatic carbons), 134.7 (b, CH=, BAr_F), 140.4-143.9 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^{1}J_{C\text{-}B}$= 49.4 Hz). Minor isomer (15%): ^{31}P NMR (162 MHz, $CDCl_3$): δ= 5.7 ppm (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.35 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$= 6.8 Hz), 1.92 (m, 1H, CH_2, cod), 2.11 (m, 1H, CH_2, cod), 2.23 (s, 3H, CH_3-Ar), 2.2-2.6 (m, 6H, CH_2, cod), 2.74 (s, 3H, CH_3-Ar), 3.63 (m, 2H, CH and CH=, cod), 3.75 (m, 2H, CH=, cod), 3.93 (m, 1H, CH=, Cp), 4.52 (b, 1H, CH=, cod), 4.56 (m, 1H, CH=, Cp), 4.66 (s,

5H, CH=, Cp), 4.73 (m, 1H, CH=, Cp), 7.2-7.7 (m, 25H, CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 17.1 (CH_3), 22.8 (CH_3-Ar), 23.7 (CH_3-Ar), 27.6 (CH_2, cod), 29.6 (CH_2, cod), 34.3 (d, CH_2, cod, J_{C-P}= 3.3 Hz), 42.8 (CH), 64.8 (d, C, Cp, $^1J_{C-P}$= 60.8 Hz), 69.3 (b, CH=, Cp), 71.1 (CH=, Cp), 72.3 (CH=,cod), 74.4 (d, CH=, Cp, J_{C-P}= 5.8 Hz), 75.2 (d, CH=, Cp, J_{C-P}= 3.2 Hz), 89.3 (d, C, Cp, $^2J_{C-P}$= 19.1 Hz), 90.1 (d, CH=, cod, J_{C-P}= 10.4 Hz), 95.7 (d, CH=, cod, J_{C-P}= 14.3 Hz), 134.7 (b, CH=, BAr_F), 140.4-143.9 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.4 Hz). MS HR-ESI [found 835.1801, $C_{72}H_{55}BF_{24}FeIrPS$ $(M\text{-}BAr_F)^+$ requires 835.1802]. Elemental analysis calcd (%) for $C_{72}H_{55}BF_{24}FeIrPS$: C, 50.93; H, 3.26; S, 1.89; found: C, 50.88; H, 3.24; S, 1.84.

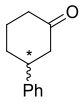
3.8.4.4. General procedure for the hydrogenation of olefins

The alkene (0.5 mmol) and Ir complex (1 mol%) were dissolved in CH_2Cl_2 (2 mL) in a high-pressure autoclave, which was purged four times with hydrogen. Then, it was pressurized to the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short Celite plug. Conversion were determined by ^{1}H NMR and enantiomeric excesses were determined by chiral GC or chiral HPLC (for hydrogenation products from **S1**-**S2**, **S4**-**S6**, **S12**-**S14** and **S19**-**S34** see previous Section 3.1.4.5 and for hydrogenation products from **S3**, **S7**-**S9**, **S11** and **S17**-**S18** see previous Section 3.2.4.6).

Ethyl 3-(4-fluorophenyl)butanoate.[47] Enantiomeric excess determined by HPLC using Chiracel AS-H column (hexane/2-propanol=99.5/0.5, 1 mL/min, 254 nm). t_R 25.8 min (*R*); t_R 26.2 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.15 (t, 3H, *J*= 7.2 Hz), 1.28 (d, 3H, *J*= 6.8 Hz), 2.54 (m, 2H), 3.25 (m, 1H), 4.07 (m, 2H), 6.9-7.2 (m, 4H).



3-Phenylcyclohexanone.[5v] Enantiomeric excess determined by GC using Chiradex B-DM column (82.5 kPa H_2, 50 °C for 2 min, 1 °C/min until 175 °C). t_R 87.8 min (*R*); t_R 88.5 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.82 (m, 2H), 2.12 (m, 2H), 2.3-2.7 (m, 4H), 3.02 (m, 1H), 7.0-7.5 (m, 5H)



3-Methylcyclohexanone. [5v] Enantiomeric excess determined by GC using Chiradex B-DM column (82.5 kPa H_2, 60 °C for 30 min, 3 °C/min until 175 °C). t_R 14.4 min (*R*); t_R 14.6 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.97 (d, 3H, *J*= 6.4 Hz), 1.28 (m, 1H), 1.61 (m, 1H), 1.89 (m, 4H), 2.24 (m, 3H).

3.8.5. Acknowledgements

We thank the Spanish Government for providing grant CTQ2013-40568, the Catalan Government for grant 2014SGR670, and the ICREA Foundation for providing M. Diéguez

and O. Pàmies with financial support through the ICREA Academia awards. We also thank the Centre National de la Recherche Scientifique, the Institut Universitaire de France, and the Laboratoire Européen Associé "Laboratoire Trans-Pyrénéen: de la Molécule aux Matériaux" for additional support.

3.8.6. References

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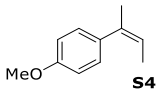
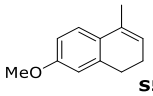
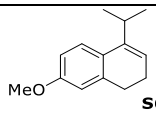
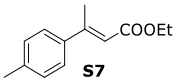
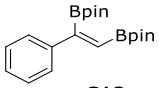
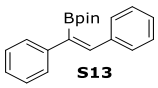
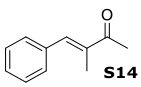
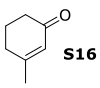
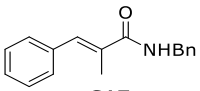
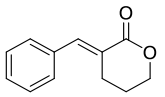
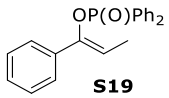
3.8.7. Supporting Information

3.8.7.1. Table SI.1. Complete series of results for the asymmetric hydrogenation of trisubstituted olefins S4-S19

	 **S4**		 **S5**		 **S6**		 **S7**	
Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
L27	100	36 (*S*)	100	28 (*S*)	100	22 (*S*)	100	50 (*S*)
L28	100	20 (*S*)	100	15 (*S*)	100	12 (*S*)	100	4 (*R*)
L29	100	17 (*S*)	100	11 (*S*)	100	15 (*S*)	100	3 (*R*)
L30	100	5 (*S*)	100	20 (*R*)	100	14 (*R*)	100	96 (*R*)
L31	100	9 (*R*)	100	16 (*S*)	100	14 (*S*)	100	58 (*S*)
L32	100	26 (*S*)	100	19 (*S*)	100	8 (*S*)	100	40 (*S*)
L33	100	46 (*S*)	100	27 (*R*)	100	12 (*R*)	100	21 (*S*)
L34	100	20 (*S*)	100	20 (*S*)	100	11 (*S*)	100	33 (*S*)
L35	100	0	100	19 (S)	100	12 (S)	100	34 (*R*)
L36	100	40 (*S*)	100	32 (*S*)	100	17 (*S*)	100	92 (*S*)
L37	100	20 (*S*)	100	15 (*R*)	100	2 (*R*)	100	92 (*S*)
L38	100	35 (*R*)	100	28 (*R*)	100	14 (*R*)	100	92 (*R*)
	 **S12**		 **S13**		 **S14**		 **S16**	
Ligand	% Conv[b]	% ee[c]	% Conv[b,d]	% ee[c]	% Conv[b,d]	% ee[c]	% Conv[b,d]	% ee[c]
L27	100	43 (*R*)	100	50 (+)	100	21 (*S*)	100	14 (*R*)
L28	100	57 (*R*)	100	48 (+)	100	5 (*S*)	100	9 (*R*)
L29	100	62 (*R*)	100	43 (+)	100	7 (*S*)	100	4 (*R*)
L30	100	44 (*R*)	100	62 (+)	100	18 (*S*)	100	56 (*R*)
L31	100	57 (*S*)	69	55 (+)	100	11 (*S*)	100	21 (*S*)
L32	100	70 (*R*)	100	61 (+)	100	14 (*S*)	100	19 (*R*)
L33	100	45 (*R*)	100	50 (+)	100	21 (*S*)	100	11 (*R*)
L34	100	80 (*R*)	100	48 (+)	100	20 (*S*)	100	13 (*R*)
L35	100	70 (*S*)	100	64 (+)	100	11 (*S*)	100	9 (R)
L36	100	76 (*S*)	100	50 (+)	100	6 (*R*)	100	70 (*S*)
L37	100	28 (*R*)	100	32 (+)	100	33 (*S*)	100	12 (*R*)
L38	100	21 (*S*)	50	8 (-)	100	47 (*S*)	100	81 (*S*)

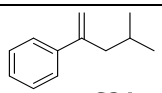
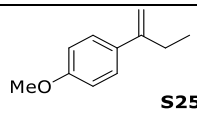
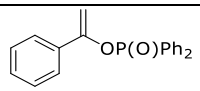
[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 1 mol% of Ir-catalyst precursor at 100 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by GC or HPLC; [d] Reaction carried out for 18 h.

3.8.7.1. Table SI.1. Complete series of results for the asymmetric hydrogenation of trisubstituted olefins S4-S19 (continuation)

	 **S17**		 **S18**		 **S19**	
Ligand	% Conv[b,d]	% ee[c]	% Conv[b,d]	% ee[c]	% Conv[b,d]	% ee[c]
L27	100	10 (*R*)	100	20 (*S*)	100	18 (*R*)
L28	100	38 (*R*)	100	28 (*S*)	100	5 (*R*)
L29	100	38 (*R*)	100	23 (*S*)	100	4 (*R*)
L30	100	50 (*S*)	100	66 (*S*)	100	3 (*R*)
L31	100	66 (*R*)	100	70 (*R*)	100	21 (*R*)
L32	100	2 (*S*)	100	5 (*S*)	100	5 (*R*)
L33	100	14 (*S*)	100	16 (*S*)	100	14 (*R*)
L34	100	44 (*R*)	100	24 (*S*)	100	51 (*R*)
L35	100	20 (R)	100	30 (*R*)	100	76 (*R*)
L36	100	85 (*R*)	100	84 (*S*)	100	92 (*R*)
L37	100	90 (*S*)	100	50 (*S*)	100	68 (*S*)
L38	100	50 (*R*)	100	64 (*R*)	100	30 (*R*)

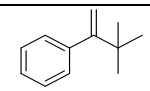
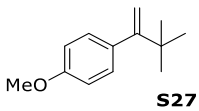
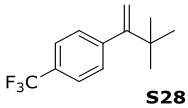
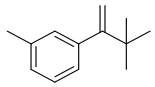
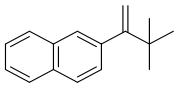
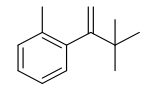
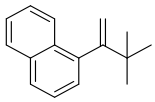
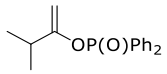
[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 1 mol% of Ir-catalyst precursor at 100 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by GC or HPLC; [d] Reaction carried out for 18 h.

3.8.7.2. Table SI.2. Complete series of results for the asymmetric hydrogenation of 1,1-disubstituted olefins S24-S25 and S33

	 **S24**		 **S25**		 **S33**	
Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b,d]	% ee[c]
L27	100	7 (*S*)	100	8 (*S*)	100	16 (*S*)
L28	100	5 (*S*)	100	5 (*S*)	100	8 (*S*)
L29	100	2 (*R*)	100	2 (*S*)	100	2 (*S*)
L30	100	8 (*S*)	100	13 (*S*)	100	30 (*S*)
L31	100	3 (*S*)	100	1 (*S*)	100	12 (*S*)
L32	100	8 (*S*)	100	8 (*S*)	100	5 (*S*)
L33	100	4 (*R*)	100	9 (*R*)	100	8 (*S*)
L34	100	11 (*S*)	100	10 (*S*)	100	16 (*S*)
L35	100	4 (S)	100	7 (S)	100	12 (*S*)
L36	100	2 (*S*)	100	0 (*S*)	100	94 (*R*)
L37	100	14 (*R*)	100	16 (*R*)	100	92 (*S*)
L38	100	6 (*R*)	100	10 (*R*)	100	49 (*R*)

[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 1 mol% of Ir-catalyst precursor at 1 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by GC or HPLC; [d] Reaction carried out at 50 bar of H_2.

3.8.7.3. Table SI.3. Complete series of results for the asymmetric hydrogenation of 1,1-disubstituted olefins S26-S32 and S34

	L30		L36		L38	
Ligand	% Conv[b]	% ee[c]	% Conv[b,d]	% ee[c]	% Conv[b,d]	% ee[c]
 **S26**	100	86 (*S*)	100	87 (*R*)	100	43 (*R*)
 **S27**	100	88 (*S*)	100	90 (*R*)	100	51 (*R*)
 **S28**	100	75 (*S*)	100	78 (*R*)	100	39 (*R*)
 **S29**	100	77 (*S*)	100	79 (*R*)	100	39 (*R*)
 **S30**	100	74 (*S*)	100	75 (*R*)	100	33 (*R*)
 **S31**	100	72 (*S*)	100	75 (*R*)	100	29 (*R*)
 **S32**	100	69 (*S*)	100	72 (*R*)	100	29 (*R*)
 **S34**	100[d]	34 (*S*)	100[d]	93 (*R*)	100[d]	39 (*R*)

[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 1 mol% of Ir-catalyst precursor at 1 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by GC or HPLC; [d] Reaction carried out at 50 bar of H_2.

3.9. Ir-catalyzed asymmetric hydrogenation with simple cyclohexane-based P/S ligands: In situ HP-NMR and DFT calculations for the characterization of reaction intermediates

Borràs, C.; Biosca, M.; Pàmies, O.; Diéguez, M. *Organometallics* **2015**, *34*, 5321.

Abstract: We report a reduced but structurally valuable phosphite/phosphinite-thioether ligand library for the Ir-hydrogenation of 40 minimally functionalized alkenes, including relevant examples with poorly coordinative groups. We found that enantiomeric excesses are mainly dependent on the substrate structure and on some ligand parameters (i.e. the type of thioether/phosphorus moieties and the configuration of the phosphite group), whereas the substituents of the biaryl phosphite moiety had little impact. By tuning the ligand parameters, we were able to find highly selective catalysts for a range of substrates (ee's up to 99%). These phosphite/ phosphinite-thioether ligands have a simple backbone and thus yield simple NMR spectra that reduce signal overlap and facilitate the identification of relevant intermediates. Therefore, by combining HP-NMR spectroscopy and theoretical studies, we were also able to identify the catalytically competent Ir-dihydride alkene species, which made it possible to explain the enantioselectivity obtained.

3.9.1. Introduction

Over the last four decades, the increasing demand for enantiopure compounds for agrochemicals, pharmaceuticals and materials has stimulated the search for efficient methodologies for their preparation.[1] Because of its high selectivity and perfect atom-economic nature, transition metal-catalyzed asymmetric hydrogenation is one of the most powerful and versatile approaches for preparing a wide range of enantiopure compounds.[1-2] This field has been dominated by the Rh/Ru-catalyzed asymmetric hydrogenation of substrates with a good coordination group close to the C-C double bond.[1-3] Today, an impressive range of ligands are being applied to transform a wide range of functionalized substrates. In contrast, the asymmetric hydrogenation of substrates that do not have an adjacent coordinative polar group - minimally functionalized olefins – is much less developed, despite the fact that it constitutes an easy way to create complex compounds from simple olefins.[4] In this respect, Ir-catalyzed asymmetric hydrogenation has emerged as an effective and easy method for reducing minimally functionalized olefins. Since Pfaltz applied Ir/phosphine-oxazoline PHOX chiral catalysts in 1998,[5] some of the most efficient reported chiral ligands have been mixed P-oxazoline ligands. Several successful phosphine/phosphinite/carbene-oxazoline ligands have been prepared by modifying the chiral backbone.[6] Our group has contributed to the Ir-hydrogenation of minimally functionalized olefins with an

improved series of ligands. We have shown that phosphite groups improve the ligand's efficiency. Mixed phosphite-oxazoline ligands have been shown to be exceptionally effective, providing better substrate versatility than earlier Ir-phosphinite/phosphine-oxazoline catalysts.[7] Despite the advances achieved with Ir/P-oxazoline catalysts, the activity and enantioselectivity in the reduction of some relevant minimally functionalized olefins still need to be improved. To this end, research has progressed towards mixed ligands with groups that are more robust than oxazolines (pyridines,[8] amides,[9] thiazoles,[10] oxazoles,[11] etc). In this context, we recently reported the use of non-N-donor mixed ligands – phosphite/phosphinite-thioether – in the enantioselective Ir-catalyzed reduction of minimally functionalized olefins.[12] The coordination of the thioether moiety to the iridium not only exerts steric and electronic effects by means of the change in the thioether groups, but also creates a new stereogenic center with a substituent that is very close to the iridium atom and therefore strongly shields one of the faces of the coordination sphere. In this context, two families of Ir/P,S-catalysts were shown to hydrogenate a large variety of olefins with enantioselectivities comparable to the best ones reported to date.[12b,c] Despite this success, the performance of this new class of ligands must be further studied for this process by screening new readily accessible thioether-containing ligands and studying the species responsible for the catalytic performance under hydrogenation conditions. No experimental studies of the mechanism and the nature of the relevant catalytic intermediates under hydrogenation conditions have yet been carried out. The mechanistic proposals using phosphorus-thioether ligands are based on our previous work using DFT investigation.[12c] Therefore, in this paper we report a reduced but structurally valuable library of phosphite/phosphinite-thioether ligands **L39**-**L40a**-**g**[13] (Figure 3.9.1) for the Ir-hydrogenation of 40 minimally functionalized alkenes, including some specific examples with poorly coordinative groups. We also investigated the key iridium intermediate complexes under hydrogenation conditions to explain the origin of the enantioselectivity. By combining high pressure NMR (HP-NMR) spectroscopy and theoretical studies we were able to identify the catalytically competent Ir-dihydride alkene species.

Phosphite/phosphinite-thioether ligands **L39**-**L40a**-**g** have been selected for this work because they have the following advantages: (a) they are synthesized in only two steps from commercially accessible cyclohexene oxide, (b) they benefit from the robustness of the thioether group, (c) a simple tuning of the thioether and phosphite/phosphinite moieties (**a**-**g**) provides control over the chiral cavity, and (d) their backbone is simple, thus yielding simple NMR spectra that reduce the overlap signals and facilitate the identification of relevant intermediates by HP-NMR. For the purpose of this work, only two thioether substituents, *tert*-butyl and 2,6-dimethylphenyl, were used because previous work with Ir/P-thioether catalysts showed that these bulky substituents made it possible to achieve high enantioselectivities.[12b,c]

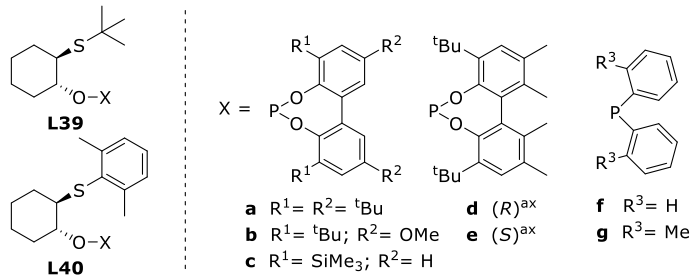


Figure 3.9.1. Phosphite/phosphinite-thioether ligands **L39**-**L40a**-**g**.

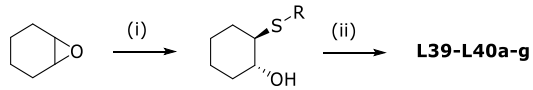
3.9.2. Results and Discussion

3.9.2.1. Synthesis of ligands

The synthesis of ligands **L39**-**L40a**-**g** is shown in Scheme 3.9.1. The new ligands **L39**-**L40a**-**e** and **L39**-**L40f**-**g** are prepared in only two steps from readily available cyclohexene oxide. The first step (step i) consists of the enantioselective desymmetrization of cyclohexene oxide with the corresponding thiol using (*R*)-GaLibis(binaphtoxide) complex (GaLB-(*R*)), in keeping with Shibasaki's method.[14] Desymmetrization using *tert*-butylthiol provided the desired cyclohexanol-thioether **1** in >99% ee.[13a,b] However, desymmetrization using 2,6-dimethylbenzenethiol led to poor enantiocontrol (43% ee). Further enantiomer resolution by using semipreparative chiral HPLC gave access to both enantiomers of the corresponding hydroxyl-thioether (**2** and *ent*-**2**). In the last step of the ligand synthesis process (step ii), cyclohexanol-thioether intermediates **1**-**2** were functionalized with different phosphite (**a**-**e**) or phosphinite moieties (**f**-**g**). Therefore, treating enantiopure hydroxyl-thioethers **1**-**2** with 1 equiv. of either the appropriate *in situ* formed phosphorochloridite ($ClP(OR)_2$, $(OR)_2$=**a**-**e**) or the required chlorophosphine ($ClPR_2$, R= **f**-**g**) provided the desired phosphite-thioether (**L39**-**L40a**-**e**) and phosphinite-thioether (**L39**-**L40f**-**g**) ligands.

All ligands were isolated in good yields as white solids (phosphite-thioether ligands **L39**-**L40a**-**e**) or colorless oils (phosphinite-thioether ligands **L39**-**L40f**-**g**) after purification on neutral alumina. They were found to be stable in air and resistant to hydrolysis, so they were further manipulated and stored in air. The elemental analyses and mass spectrometry were in agreement with the assigned structures. The ligands were also further characterized by $^{31}P\{^1H\}$, ^1H, and $^{13}C\{^1H\}$ NMR spectroscopy. The spectral assignments were based on information from bidimensional ^1H-^1H and ^{13}C-^1H experiments. The $^{31}P\{^1H\}$ NMR spectra showed one singlet for each compound. The expected diastereoisomeric mixtures using tropoisomeric biphenyl phosphite moieties (**a**-**c**) were not detected by low-temperature $^{31}P\{^1H\}$ NMR, which is consistent with the fast ring inversions in the biphenylphosphorus moieties on the NMR time-scale.[15] ^1H and $^{13}C\{^1H\}$ NMR spectra showed the expected pattern for the cyclohexane backbone

and the phosphite/phosphinite moieties. Concerning the protons of the cyclohexane ring, we found the signals of the corresponding diastereomeric methylene protons and the expected two signals for the methine protons. The methine protons adjacent to the sulfur atom appear at a lower chemical shift than the methine protons adjacent to the oxygen atom because the sulfur atom is less electron withdrawing than the oxygen atom. Finally, the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra also showed the expected pattern for the thioether groups.



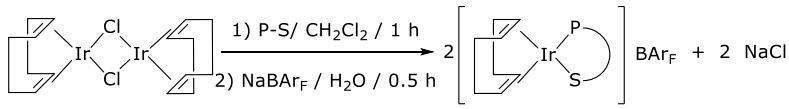
1 (1*R*,2*R*); R= ^{t}Bu
2 (1*R*,2*R*); R= 2,6-(Me)$_2$-Ph

Scheme 3.9.1. Synthesis of ligands **L39-L40a**-**g**; (i) GaLB-(*R*), RSH, toluene, molecular sieves 4 Å. For compounds **2** and *ent*-**2** semipreparative chiral HPLC was further needed; (ii) ClP(OR)$_2$, Py, toluene or ClPR$_2$, NEt$_3$, toluene.

3.9.2.2. Synthesis of Ir-catalyst precursors

The reaction of the corresponding phosphite/phosphinite-thioether ligand **L39**-**L40a**-**g** with [Ir(μ-Cl)(cod)]$_2$ in dichloromethane for one hour followed by *in situ* chlorine abstraction with NaBAr$_F$ produced the desired cationic catalyst precursors [Ir(cod)(**L39**-**L40a**-**g**)]BAr$_F$ (**3**-**12**; Scheme 3.9.2). These complexes were obtained in excellent yields and in pure form as orange-red solids. They were stable to air, so they were further manipulated and stored in air.

The complexes were characterized by elemental analysis, mass spectrometry and $^{31}P\{^{1}H\}$, ^{1}H, and $^{13}C\{^{1}H\}$ NMR spectroscopy. For all complexes, the elemental analysis of C, H, and S matched with the expected stoichiometry. The TOF-MS (ESI+) spectra show the highest ions at m/z, which correspond to the loss of the non-coordinated BAr$_F$ anion from the mononuclear species [Ir(cod)(**L39**-**L40a**-**g**)]BAr$_F$. The $^{31}P\{^{1}H\}$ NMR spectra exhibited a sharp signal in all cases. However, for complexes **3**-**5**, the ^{31}P VT-NMR spectra (+35 °C to -80 °C) showed that the signals became broader when the temperature was lowered. This behavior has been attributed to the tropoisomerization of the biphenyl phosphite moieties (**a**-**c**), which led to a mixture of diastereoisomeric species in solution. This is supported by the fact that the $^{31}P\{^{1}H\}$ VT-NMR spectra of related complexes containing ligands with enantiomerically pure biphenyl moieties (**L39**-**L40d**-**e**) showed a single isomer in all cases, which rules out the possibility of the S-coordination being responsible for the diastereoisomeric species in complexes [Ir(cod)(**L39a**-**c**)]BAr$_F$.



3 P-S = **L39a** **8** P-S = **L39f**
4 P-S = **L39b** **9** P-S = **L40d**
5 P-S = **L39c** **10** P-S = **L40e**
6 P-S = **L39d** **11** P-S = **L40f**
7 P-S = **L39e** **12** P-S = **L40g**

Scheme 3.9.2. Synthesis of [Ir(cod)(**L39**-**L40a**-**g**)]BAr_F (**3**-**12**).

Crystals suitable for X-ray diffraction analysis of the [Ir(**L39a**)(cod)]BAr_F complex were obtained by means of the slow diffusion of diethyl ether in a chloroform solution (Figure 3.9.2). It should be pointed out that only the diastereoisomer containing an (*R*)-disposition of the biaryl phosphite group crystallized out of the two observed diastereoisomers in solution (see above).

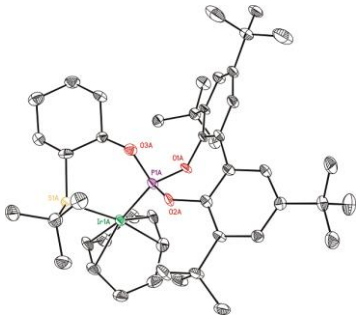


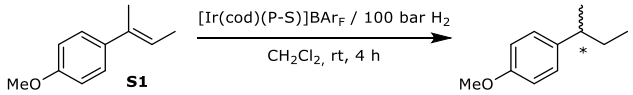
Figure 3.9.2. X-Ray structure of [Ir(**L39a**)(cod)]BAr_F complex **3** (hydrogens and BAr_F anion have been omitted for clarity).

The crystal structure clearly indicates the bidentate coordination of the P,S-ligand through both donor atoms with a twist-boat conformation of the chelate ring. As expected, the large variations in the Ir-carbon bond distances *trans* the phosphite and thioether (c.a. 0.1 Å) point to the difference in *trans* influence between the two donor groups. The structure also shows a pseudoaxial disposition of the thioether substituent as previously observed by the analogue rhodium complex ([Rh(cod)(**L39f**)]BF_4).[13c] However, this behavior contrasts with the pseudoequatorial disposition of the thioether substituent in our previous Ir-structures containing arylglycidol-derived phosphite-thioether ligands, which also form a six-membered chelate ring.[12c] For this latter case, Ir/phosphite-thioether catalysts have always provided much lower enantioselectivities in the reduction of minimally functionalized olefins than related Ir/phosphinite-thioether analogues, in which the thioether substituent adopts a pseudoaxial disposition. This, together with the fact that phosphite-thioether ligand reported in the present paper provided high enantioselectivities in several substrates (see below), could indicate that the disposition of the thioether substituent in the catalyst precursors has a relevant effect on the stereochemical outcome of the reaction.[16]

3.9.2.3. Asymmetric hydrogenation

Initially we tested the capacity of ligands **L39**-**L40a**-**g** by applying them in the reduction of the trisubstituted substrate **S1** model (Table 3.9.1). Excellent activities were obtained in all cases. However, the value of enantioselectivity depended on the type of thioether/phosphorus moieties and the configuration of the phosphite group, while the substituents of the biaryl phosphite moiety had little impact.

Table 3.9.1. Ir-catalyzed hydrogenation of **S1** using ligand library **L39**-**L40a**-**g**.[a]



Entry	L	% Conv[a]	% ee[b]
1	**L39a**	100	19 (*R*)
2	**L39b**	100	18 (*R*)
3	**L39c**	100	18 (*R*)
4	**L39d**	100	42 (*S*)
5	**L39e**	100	86 (*R*)
6	**L39f**	100	60 (*R*)
7	**L40d**	100	5 (*S*)
8	**L40e**	100	36 (*R*)
9	**L40f**	100	69 (*R*)
10	**L40g**	100	61 (*R*)
11[c]	**L39e**	100	86 (*S*)
12[d]	**L39e**	81	85 (*R*)

[a] Reaction conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%); [b] Conversion and enantiomeric excesses determined by chiral GC; [c] Reaction carried out using 0.25 mol% of Ir-catalyst precursor; [d] PC as solvent.

The effect on enantioselectivity of replacing the phosphite moiety with a phosphinite group depends on the thioether substituent. Thus, while for ligands **L39**, containing a *tert*-butyl thioether substituent, the addition of a phosphinite led to lower enantioselectivities (Table 3.9.1, entries 5 vs. 6), enantioselectivities increased for ligands **L40** with a 2,6-dimethylphenyl group (Table 3.9.1, entries 8 vs. 9). The results also show that a chiral phosphite moiety is needed for high enantioselectivity (entries 1-3 vs. 4-5). This indicates that, in contrast to previous xylofuranoside-based thioether-phosphite ligands,[12b] the simple cyclohexane-backbone is not able to control the tropoisomerization of the biaryl phosphite groups (**a**-**c**) in the active species, as has been found for [Ir(cod)(**L39a**-**c**)]BAr_F precatalysts (see above). Therefore, it is not surprising that low enantioselectivities were obtained for this substrate with Ir/**L39a**-**c** catalysts (entries 1-3). We also found a cooperative effect between the configuration

of the cyclohexane-backbone and the configuration of the biaryl phosphite group (entries 4, 5, 7 and 8). This led to a matched combination with ligands containing an (*S*)-biaryl phosphite moiety (**e**; entries 5 and 8). The best enantioselectivity was therefore obtained with ligand **L39e** (ee's up to 86%; entry 5).

We also performed this reaction at a low catalyst loading (0.25 mol%) using Ir/**L39e**, which provided the best result, and enantioselectivity was maintained (Table 3.9.1, entry 11). Advantageously, the use of propylene carbonate (PC) as an environmentally friendly alternative solvent[17] to dichloromethane didn´t affected the stereochemical outcome of the reaction (entry 12).

To further establish the scope of Ir/**L39**-**L40a**-**g** catalysts, we chose a representative family of substrates, some of which contain neighboring polar groups. The results are summarized in Figure 3.9.3 (for a full set of results see Supporting Information at the end of this chapter). We found that the ligand parameters must be selected specifically for each substrate with the aim of obtaining the highest enantioselectivity. We initially considered the reduction of substrates **S2**-**S3**, which are related to **S1**. We found that enantioselectivities are relatively unaffected by varying the electronic and steric properties of the substrate (ee's between 85% and 92%). For both substrates the highest enantioselectivities were also obtained with Ir/**L39e** catalyst. The reduction of more challenging *Z*-isomers (model **S4** and **S5**), which are hydrogenated much less enantioselectively than *E*-isomers, also proceeded smoothly. We were pleased to see that for the more demanding *Z*-substrate **S5**, enantioselectivity (87% ee) was higher than for the *Z*-**S4** model.

We then went on to study the reduction of a range of key trisubstituted olefins with poorly coordinative groups. Their hydrogenation is of particular importance because they can be further converted into relevant intermediates for synthesizing more complex chiral molecules. Interestingly, the hydrogenation of a very large series of α,β-unsaturated esters **S6**-**S13** proceeded with high enantioselectivities (ee's up to 98%), comparable to the best reported to date.[18] However, unlike previous **S1**-**S4** substrates, the effect of the ligand parameters on enantioselectivity is slightly different. Therefore, regardless of the thioether substituent, the presence of a biaryl phosphite moiety is highly beneficial and the tropoisomerization of the flexible biaryl phosphite moieties (**a**-**c**) is efficiently controlled (see Supporting Information at the end of this chapter). The best enantioselectivities were obtained using the Ir/**L39a**-**c** and Ir/**L39e** catalytic systems. Advantageously, the ee's were independent of the electronic nature of the substrate phenyl ring (**S6**-**S8**) and the steric nature of the alkyl substituent (**S6**, **S9**-**S11**). Also noteworthy were the high enantioselectivities obtained using more demanding *Z*-isomers (**S12** and **S13**). Being able to reduce such a range of α,β-unsaturated esters with these high ee's is highly significant because the resulting chiral carboxylic ester derivatives are present in many relevant products. This method is a more sustainable way to prepare these chiral carboxylic esters than other regular

methodologies.[19] Another relevant set of substrates that is receiving much consideration are the α,β-unsaturated enones. In the reduction of a range of α,β-unsaturated enones **S14**-**S17**, the highest enantioselectivities (ee's up to 92%) were obtained with Ir/**L39f** catalyst, which contains a diphenylphosphinite moiety with a *tert*-butyl thioether substituent. The reduction of these kinds of olefins is an elegant route for producing ketones with a chiral center in the α position of the carbonyl moiety. Nevertheless, they have been less investigated and hydrogenated with less success than other trisubstituted olefins.[6i,6q,r,20]

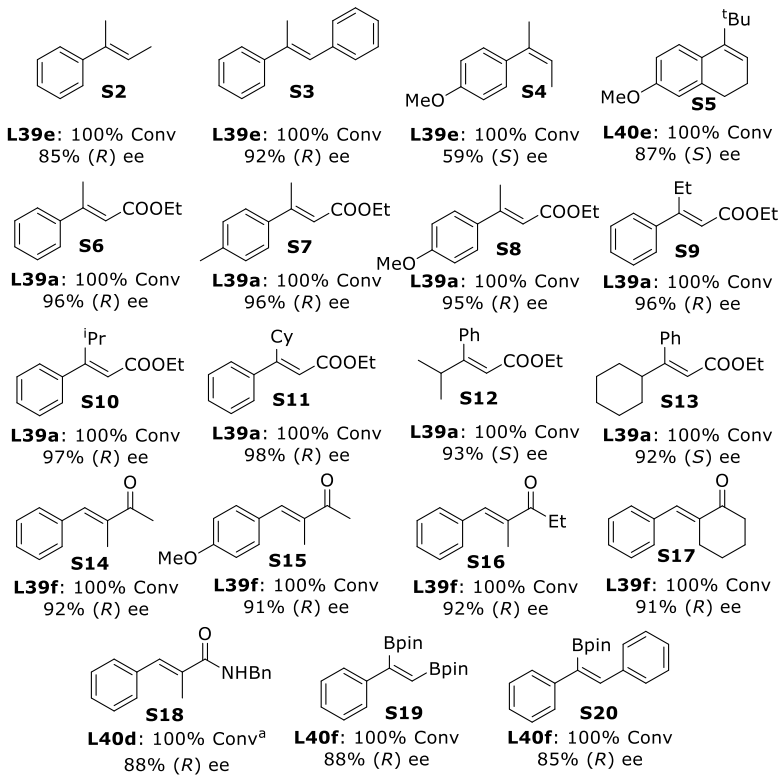


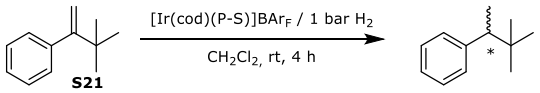
Figure 3.9.3. Asymmetric hydrogenation of trisubstituted substrates **S2**-**S20**. Reaction conditions: Catalyst precursor (1 mol%), CH_2Cl_2, H_2 (100 bar), 4 h. [a] Reactions carried out for 18 h.

These last results encouraged us to move on to the hydrogenation of other difficult olefins, such as enamide **S18**[21] and alkenylboronic esters **S19**-**S20**.[22] Few catalysts can afford high enantioselectivities for these alkenes, so it was noteworthy that we could reach high enantioselectivities in all of them by carefully modification of the ligand parameters. In the reduction of enamide **S18**, the highest enantioselectivities (up to 88% ee) were therefore achieved using [Ir(cod)(**L40d**)]BAr_F, while for alkenylboronic esters the best enantioselectivities (ee's up to 85%) were obtained with [Ir(cod)(**L40f**)]BAr_F. The reduction of enamides and alkenylboronic esters is also of

great interest because hydrogenated products can easily be transformed into high-value compounds such us benzylic acid derivatives and chiral boron compounds.

Finally, we focused on the reduction of a more demanding type of substrate: 1,1'-disubstituted olefins. Unlike trisubstituted olefins, 1,1'-disubstituted olefins have not been successfully hydrogenated until very recently.[4a,e,h] This is because most of the successful catalysts developed for the reduction of trisubstituted substrates fail either to control the face-selective coordination of the less hindered disubstituted substrate or to suppress the isomerization of the olefin that leads to the formation of the more stable *E*-trisubstituted substrates, which in turn form the opposite enantiomer when hydrogenated. With the aim of evaluating the efficiency of ligands **L39**-**L40a**-**g** in hydrogenating this kind of substrate, we first studied the reduction of the model substrate **S21**. The results are shown in Table 3.9.2. We found that the substituents of the biaryl phosphite moiety have little impact on selectivity and that the presence of a chiral phosphite moiety (**d**-**e**) is needed for high enantioselectivity. However, in contrast to trisubstituted olefins, the best enantioselectivity was obtained with the ligand containing an (*R*)-biaryl phosphite moiety and 2,6-Me_2-C_6H_3 thioether substituent (ligand **L40d**, ee's up to 97%; entry 7). Interestingly, we also found that the configuration of the biaryl phosphite moiety controls the sense of enantioselectivity; therefore, both enantiomers of the reduction product can be obtained in high enantioselectivities under mild reaction conditions (entries 7 and 8).

Table 3.9.2. Ir-catalyzed hydrogenation of **S21** using ligand library **L39**-**L40a**-**g**.[a]

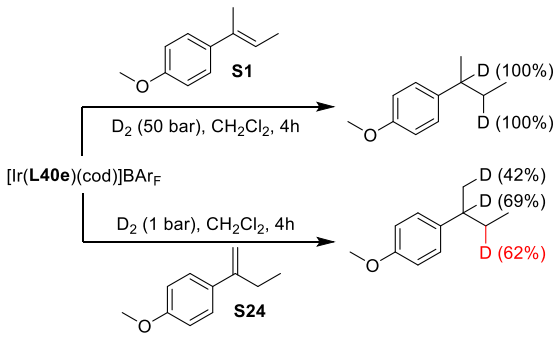


Entry	L	% Conv[a]	% ee[b]
1	**L39a**	100	30 (*S*)
2	**L39b**	100	28 (*S*)
3	**L39c**	100	27 (*S*)
4	**L39d**	100	90 (*S*)
5	**L39e**	100	85 (*R*)
6	**L39f**	100	29 (*S*)
7	**L40d**	100	97 (*S*)
8	**L40e**	100	90 (*R*)
9	**L40f**	100	65 (*S*)
10	**L40g**	100	84 (*S*)

[a] Reaction conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%); [b] Conversion and enantiomeric excesses determined by chiral GC.

The scope of Ir/**L39**-**L40a**-**g** catalysts was further studied by using other 1,1'-disubstituted substrates (Figure 3.9.4, **S22**-**S40** and Supporting Information at the end of this chapter for a full set of results).

Our results with several α-alkylstyrenes with different sterically demanding alkyl groups (**S21-S24**) showed that enantioselectivity is influenced by the alkyl substituents (ee's ranging from 34% to 97%). This behavior may be due to a competition between direct hydrogenation and isomerization. In line with this, the hydrogenation of **S21** with a *tert*-butyl group, which cannot isomerize, provided the highest enantioselectivity. However, face selectivity problems cannot be ignored.[4h] To address this issue, we carried out deuterium labeling experiments (Scheme 3.9.3) in which we reduced **S1** and **S24** with deuterium. In contrast to **S1**, the hydrogenation of **S24** led to the addition of deuterium not only at the expected positions (direct incorporation to the double bond), but also at the allylic position, which is in agreement of a competing isomerization pathway.[23] Accordingly, the mass spectra data of the corresponding deuterated product from **S24** showed species with more than two incorporated deuteriums (see Supporting Information).



Scheme 3.9.3. Deuterium labeling experiments of substrates **S1** and **S24**. The percentage of incorporation of deuterium atoms is shown in brackets. The results of the indirect addition of deuterium due to the isomerization process are shown in red.

We next screened a wide range of α-*tert*-butylstyrene type substrates (**S25**-**S31**) to evaluate how the steric and electronic properties of the aryl group of the substrate affected enantioselectivity. Advantageously, we found that enantioselectivity (ee's up to 99%) is relatively insensitive to changes in the electronic and steric properties of the aryl group. *N*-containing heterocycles are present in many relevant compounds such us pharmaceuticals and natural products. We were pleased to see that we could also obtained high enantioselectivities in both enantiomers of the reduction products of 2-(3,3-dimethylbut-1-en-2-yl)pyridine (**S32**).

Finally, due to the importance of chiral borane compounds, we wanted to see if the high enantioselectivities achieved in the reduction of trisubstituted alkenylboronic esters (Figure 3.9.3, substrate **S19**-**S20**) were retained for the even more challenging

terminal analogues. The hydrogenation of such compounds using Ir-catalyst has recently emerged as a more sustainable alternative to the existing synthetic routes.[12c,22a] However, high levels of enantioselectivity have only been obtained for alkyl-substituted terminal boronic esters such as **S33**-**S36**, and the hydrogenation of aryl-substituted boronic esters such as **S37** has yielded much lower enantioselectivities.[12c,22a] Despite the moderate enantioselectivities achieved in the reduction of **S33**-**S36** using our new Ir/**L39**-**L40a**-**g** catalytic systems, we were pleased to find that a range of aryl-substituted terminal boronic esters **S37**-**S40** could be efficiently reduced using the Ir/**L40e** catalytic system. Interestingly, the substitution pattern in the aryl ring did not affect the stereochemical outcome of the reaction. This constitutes an important finding that overcomes the limitations previously encountered in the reduction of terminal aryl-substituted boronic esters and nicely complements the current state-of-art.

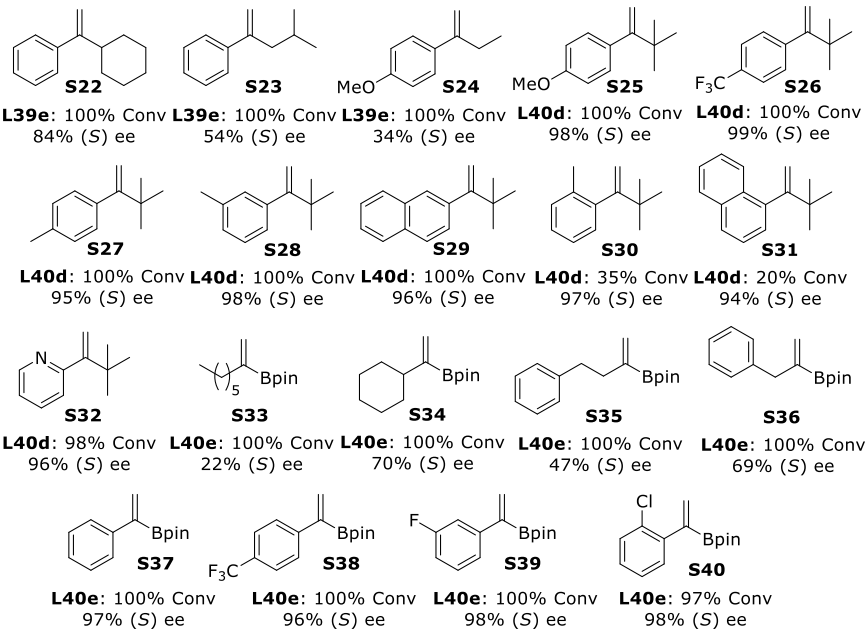


Table 3.9.4. Asymmetric hydrogenation of 1,1'-disubstituted olefins **S22**-**S40**. Reaction conditions: Catalysts precursor (1 mol%), CH_2Cl_2, H_2 (1 bar), 4 h.

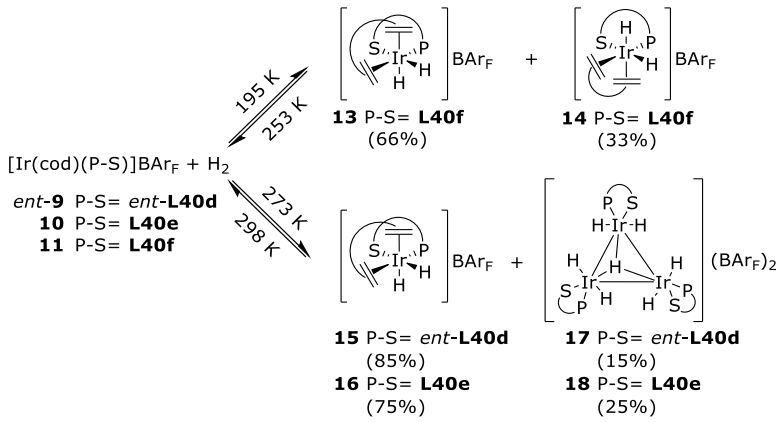
In summary by efficiently selecting the ligand parameters of this reduced and simple readily available phosphite/phosphinite-thioether ligand family, we could obtain highly selective catalysts for a range of substrates, with enantioselectivities comparable in most cases to the best ones reported.

3.9.2.4. Mechanistic studies: study of reaction intermediates by in situ HP-NMR and theoretical studies

Computational and experimental research with P,N- and C,N-ligands showed that the hydrogenation of minimally functionalized olefins proceeds via and Ir^{III}/Ir^{V} migratory-insertion/reductive-elimination catalytic cycle.[7e,24] Very recently, Pfaltz *et al*., based on mechanistic studies under hydrogenation conditions, was able to detect the Ir(III) dihydride alkene intermediates responsible for the catalytic performance for the first time.[25] They found that, similarly to the classical Halpern-mechanism for asymmetric hydrogenation with Rh-catalysts, the minor intermediate, which is less stable, is converted to the major product enantiomer.

Similarly, our previous DFT investigations using Ir/P,S-ligands also agree with Ir^{III}/Ir^{V} pathway, with migratory insertion of the hydride as an enantioselective-determining step.[12c] However, there is a lack of experimental evidences to support the calculations. On the basis of these previous studies and in an effort to rationalize the enantioselectivity achieved with the Ir/P-thioether catalysts reported in this manuscript, we performed an HP-NMR study of the iridium intermediates formed under hydrogenation conditions, with the aim of identifying the catalytically competent Ir-dihydride alkene species.

For this study, we initially investigated the oxidative addition of hydrogen to the iridium catalyst precursors [Ir(cod)(P-S)]BAr_F (P-S= **L40f,** *ent*-**L40d** and **L40e**; Scheme 3.9.4). As models, we took complexes containing phosphinite-thioether ligand **L40f** and the phosphite-thioether ligands *ent*-**L40d** and **L40e**, respectively. These ligands contain different P-donor groups that can provide insight into their previously observed substantial effect on enantioselectivity (see above).



Scheme 3.9.4. Oxidative addition of H_2 to [Ir(cod)(P-S)]BAr_F complexes **11**, *ent*-**9** and **10**.

Bubbling H_2 in a CD_2Cl_2 solution of [Ir(cod)(**L40f**)]BAr_F (**11**) at -78 °C led to the formation of two dihydride species **13** and **14** in a 2:1 ratio (Scheme 3.9.4), which are

unstable when warming up. The equilibrium shifts back to the starting olefin complex **11** at -20 °C. Both isomers of [Ir(H)$_2$(cod)(**L40f**)]BAr$_F$ showed small phosphorus-hydride coupling constants ($^2J_{P\text{-}H} \leq 21.2$ Hz) that indicate that all the hydrides are *cis* to the phosphorus atom (Table 3.9.3).[13c,26]

Table 3.9.3. $^{31}P\{^1H\}$ and ^1H NMR data at the hydride region of dihydride species [Ir(H)$_2$(cod)(**L40f**)]BAr$_F$ (**13** and **14**), [Ir(H)$_2$(cod)(*ent*-**L40d**)]BAr$_F$ **15** and [Ir(H)$_2$(cod)(**L40e**)]BAr$_F$ **16**.

Compound	H^a	H^b	$^{31}P\{^1H\}$
[Ir(H)$_2$(cod)(**L40f**)]BAr$_F$ (**13**)	-12.2 (d, $^2J_{P\text{-}H}$=18 Hz)	-14.4 (d, $^2J_{P\text{-}H}$=16.8 Hz)	86.2 (s)
[Ir(H)$_2$(cod)(**L40f**)]BAr$_F$ (**14**)	-12.3 (d, $^2J_{P\text{-}H}$=21.2 Hz)	-15.9 (d, $^2J_{P\text{-}H}$=16.8 Hz)	87.5 (s)
[Ir(H)$_2$(cod)(*ent*-**L40d**)]BAr$_F$ (**15**)	-12.4 (d, $^2J_{P\text{-}H}$=22.4 Hz)	-14.7 (s)	73.4 (s)
[Ir(H)$_2$(cod)(**L40e**)]BAr$_F$ (**16**)	-12.43 (d, $^2J_{P\text{-}H}$=21.6 Hz)	-14.63 (s)	86.1 (s)

The 3D structure of both isomers of [Ir(H)$_2$(cod)(**L40f**)]BAr$_F$ were assigned by DFT and NMR studies. Table 3.9.4 shows the calculated DFT relative energies of the four possible isomers with all the hydrides *cis* to the phosphinite group. These four structures result from the up or down relative position of one of the hydrides and the two possible configurations at the sulfur center (the S atom becomes a stereogenic center upon coordination to the metal).

Table 3.9.4. Calculated energies (in kJ/mol) for dihydride complexes **13**-**16** containing ligands **L40f**, *ent*-**L40d** and **L40e**, respectively.

Intermediate	L40f	L40d	L40e
 **A** *S* config on sulfur	0	0	0
 **B** *R* config on sulfur	20	18	29
 **C** *S* config on sulfur	25	27	35
 **D** *R* config on sulfur	12	29	30

The DFT calculations indicate that the most stable isomer **13** corresponds to intermediate **A** in which the hydride *trans* to the olefin (H^a) is pointing down with an (*S*)-configuration at the S atom (Figure 3.9.5a). The minor isomer **14** has been assigned to intermediate **D** with the hydride *trans* to the olefin (H^a) pointing up and an (*R*)-configuration at the S atom (Figure 3.9.5a). The assignments of the major and minor isomers of [Ir(H)$_2$(cod)(**L40f**)]BAr$_F$ were further confirmed by NOE experiments. The major isomer **13** therefore showed NOE contacts between the hydride *trans* to the olefin and the methine proton adjacent to the P group, while for the minor isomer **14** this NOE interaction appeared with the methine proton adjacent to the thioether group (Figure 3.9.5b). The agreement between the NMR elucidation and the DFT calculations of structures of **13** and **14** validates the computational model used. The observed results may be compared with those obtained from the oxidative addition of H_2 to [Ir(cod)(**L39f**)]SbF_6, whose ligand differs from (**11**) by a *tert*-butyl thioether group instead of a 2,6-dimethylphenyl thioether moiety.[13c] The use of Evans and colleagues' ligand leads to a single dihydride species with high thermal stability which has the same structure of the major isomer **13**.

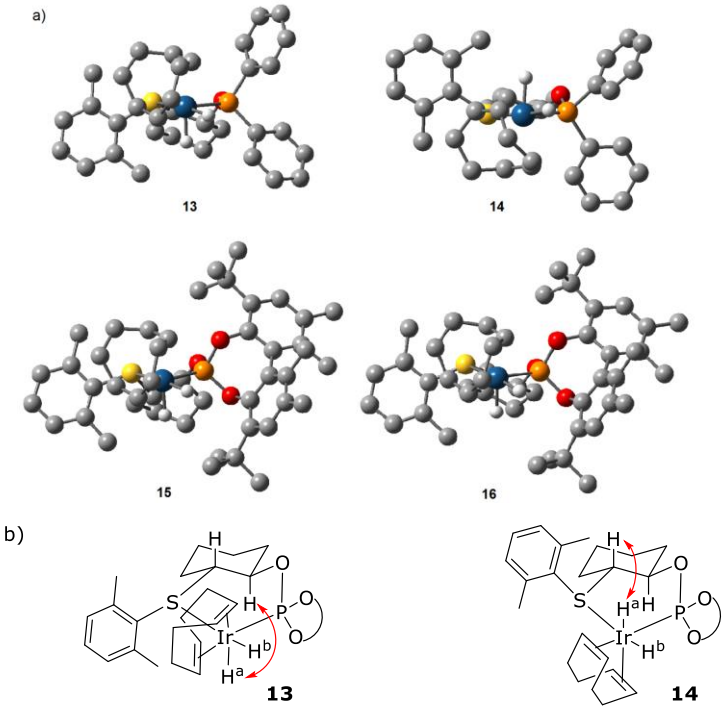
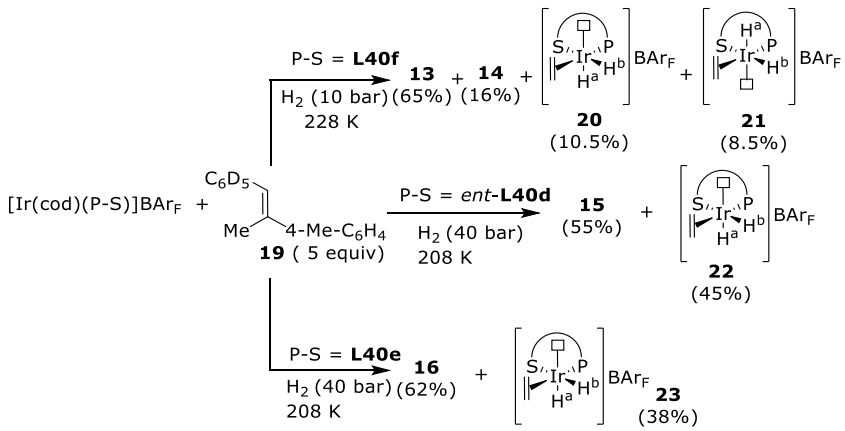


Figure 3.9.5. a) Calculated structures of dihydride [Ir(H)$_2$(cod)(P-S)]BAr$_F$ complexes **13**-**16** (hydrogen atoms and BAr$_F$ anion have been omitted for clarity); b) Relevant NOE contacts from the NOESY experiment of dihydride [Ir(H)$_2$(cod)(P-S)]BAr$_F$ complexes **13** and **14**.

We next studied the oxidative addition of H_2 to [Ir(cod)(P-S)]BAr_F precursors containing phosphite-thioether ligands *ent*-**L40d** and **L40e** (compounds *ent*-**9** and **10**). Only one dihydride intermediate was detected for each and required up to 0 ºC to push the equilibrium to the expected dihydride species (Scheme 3.9.4). The observed results contrast with [Ir(H)$_2$(cod)(**L40f**)]BAr_F where two dihydride species were observed and required -78 °C. Again, the NMR spectra of the dihydride intermediates of each complex indicated that they are *cis* to the phosphorus atom (Table 3.9.3). The final assignments of these dihydride intermediates were performed by DFT studies (Table 3.9.4). As observed for the previous diphosphinite analogue [Ir(H)$_2$(cod)(**L40f**)]BAr_F, dihydride compounds **15** and **16** correspond to intermediate **A** in which the hydride *trans* to the olefin (H^a) is pointing down with an (*S*)-configuration at the S atom (Figure 3.9.5a). It should be noted, that at 0 ºC the cyclooctadiene of the catalyst precursors *ent*-**9** and **10** also hydrogenated, resulting in the concomitant formation of other species, that have been assigned to catalytically inactive trinuclear iridium hydrido species [Ir$_3$(μ_3-H)(H)$_6$(P-S)$_3$](BAr_F)$_2$ **17** and **18** (Scheme 3.9.4).[27,28] These trinuclear iridium hydrido species **17** and **18** showed the expected pattern of the hydrides. Thus, for instance, for **17** the bridging μ_3 hydride signal appeared at -5.62 ppm as quadruplet due to the coupling with the three phosphorus atoms, while the terminal hydride resonances appeared at -13.58 ppm and at -33.72 ppm as a singlet and a broad signal, respectively. The hydride resonances for **18** appeared at -4.48, -14.53 and -36.94 ppm, respectively.



Scheme 3.9.5. Reactivity of [Ir(cod)(P-S)]BAr_F complexes with olefin **19** under hydrogenation conditions.

We next investigated the reactivity of iridium precatalysts [Ir(cod)(**L40f**)]BAr_F **11**, [Ir(cod)(*ent*-**L40d**)]BAr_F *ent*-**9** and [Ir(cod)(**L40e**)]BAr_F **10** with H_2 in the presence of an alkene (Scheme 3.9.5). The alkene used was *E*-1-methyl-4-(1-phenylprop-1-en-2-

yl)benzene-D_5 **19**, in accordance with the methodology recently described by Pfaltz and colleagues.[25]

Under 10 bar of H_2 at -45 ºC, the reaction of **11** with five equiv. of **19** led to the formation of four dihydride complexes in a ratio 6:1.5:1:0.8 (Scheme 3.9.5). The two most abundant complexes were unambiguously assigned to the two dihydrides **13** and **14** described above. The minor isomers were assigned to the elusive dihydride intermediate species [Ir(H)$_2$(**19**)(**L40f**)]BAr$_F$ **20** and **21**, in which the alkene is coordinated (Table 3.9.5).

Table 3.9.5. $^{31}P\{^1H\}$ and ^1H NMR data at the hydride region of dihydride alkene species [Ir(H)$_2$(**19**)(**L40f**)]BAr$_F$ (**20** and **21**), [Ir(H)$_2$(**19**)(*ent*-**L40d**)]BAr$_F$ **22** and [Ir(H)$_2$(**19**)(**L40e**)]BAr$_F$ **23**.

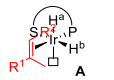
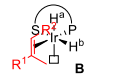
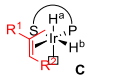
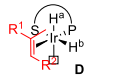
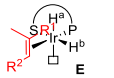
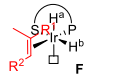
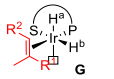
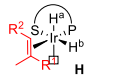
Compound	H[a]	H[b]	$^{31}P\{^1H\}$
[Ir(H)$_2$(**19**)(**L40f**)]BAr$_F$ (**20**)	-28.52 (d, $^2J_{P\text{-}H}$= 26 Hz)	-16.41 (d,$^2J_{P\text{-}H}$= 17.2 Hz)	75.2 (s)
[Ir(H)$_2$(**19**)(**L40f**)]BAr$_F$ (**21**)	-25.59 (d, $^2J_{P\text{-}H}$= 27.6 Hz)	-16.23 (d, $^2J_{P\text{-}H}$= 15.6 Hz)	84.1 (s)
Ir(H)$_2$(**19**)(*ent*-**L40d**)]BAr$_F$ (**22**)	-25.67 (d, $^2J_{P\text{-}H}$= 34.8 Hz)	-16.19 (s)	76.3 (s)
[Ir(H)$_2$(**19**)(**L40e**)]BAr$_F$ (**23**)	-27.22 (d, $^2J_{P\text{-}H}$= 32.1 Hz)	-16.74 (d, $^2J_{P\text{-}H}$= 7.2 Hz)	77.4 (s)

The alkene coordination to iridium in these dihydride intermediate species **20** and **21** was verified by ^1H NMR, which showed a significant low-frequency shift of the olefinic proton of the alkene **19** from 6.82 to *ca* 4.8 ppm. Interestingly, in the ^1H-NMR spectra of species **20** and **21** one of the hydrides appeared high-field shifted (between -25.6 and -28.5 ppm). This is characteristic of a hydride ligand positioned *trans* to the coordination site which is either vacant or engaged in a C-H agostic interaction.[25] As for [Ir(H)$_2$(cod)(**L40f**)]BAr$_F$ complexes **13** and **14**, dihydride alkene intermediate species **20** and **21** also show a small phosphorus-hydride coupling constant ($^2J_{P\text{-}H} \leq$ 27.6 Hz), which indicates that all the hydrides are *cis* to the phosphorus atom. This behavior is not unexpected because early theoretical calculations on Ir(III) dihydride alkene intermediates showed the alkene coordinated *trans* to the phosphorus donor group.[24]

On the other hand, the reaction of iridium precatalysts [Ir(cod)(*ent*-**L40d**)]BAr$_F$ and [Ir(cod)(**L40e**)]BAr$_F$ with five equiv. of **19** under optimized reaction conditions (40 bar of H_2 at -65 ºC) led to the formation for each complex of two hydride species at a ratio of 1.2:1 and 1.6:1, respectively (Scheme 3.9.5). In both cases, the major isomers were assigned to the corresponding dihydride complexes [Ir(H)$_2$(cod)(P-S)]BAr$_F$ **15**

and **16**, whereas the minor isomers were attributed to [Ir(H)$_2$(**19**)(P-S)]BAr$_F$ intermediate species (**22** and **23**) in which the alkene is coordinated (Table 3.9.5).

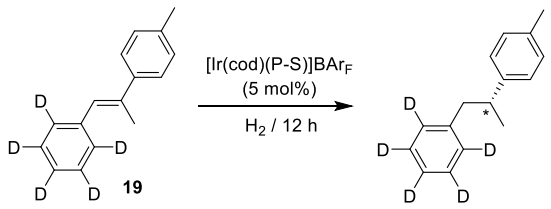
Table 3.9.6. Calculated energies (in kJ/mol) for dihydride olefin complexes **20**-**23** containing ligands **L40f**, *ent*-**L40d** and **L40e**, respectively.

Intermediate	L40f	L40d	L40e	Intermediate	L40f	L40d	L40e
 **A** *R* config on sulfur	0.9	13.2	2.2	 **I** *R* config on sulfur	16.1	20.8	13.0
 **B** *S* config on sulfur	16.2	21.7	20.3	 **J** *S* config on sulfur	15.4	19.3	21.4
 **C** *R* config on sulfur	48.3	11.8	12.0	 **K** *R* config on sulfur	0	12.9	0
 **D** *S* config on sulfur	26.5	6.7	24.1	 **L** *S* config on sulfur	5.7	0	7.3
 **E** *R* config on sulfur	-	44.4	32.0	 **M** *R* config on sulfur	-	33.3	25.8
 **F** *S* config on sulfur	35.4	33.5	49.2	 **N** *S* config on sulfur	17.8	19.7	22.6
 **G** *R* config on sulfur	18.3	29.9	30.1	 **O** *R* config on sulfur	18.9	31.1	31.1
 **H** *S* config on sulfur	36.1	36.9	47.3	 **P** *S* config on sulfur	32.8	32.5	37.1

The assignments of the 3D structure of both isomers of [Ir(H)$_2$(**19**)(**L40f**)]BAr$_F$ **20** and **21** and of the isomer of each complex of [Ir(H)$_2$(**19**)(*ent*-**L40d**)]BAr$_F$ **22** and [Ir(H)$_2$(**19**)(**L40e**)]BAr$_F$ **23** were performed by DFT studies. Unfortunately, due to signal overlap in the ^{1}H NMR, these studies could not be validated by NOE experiments. The DFT relative energies of the sixteen possible isomers with all the hydrides *cis* to the phosphinite/phosphite group are shown in Table 3.9.6. These isomers result from varying the relative position of one of the hydrides, the coordination of two enantiotopic olefin faces, the two possible configurations at the sulfur center and the relative

position of the vacant site (up or down). The results indicate that the observed major (**20**) and minor (**21**) isomers of the olefinic dihydride intermediates [Ir(H)$_2$(**19**)(**L40f**)]BAr$_F$ adopt structures **K** and **A**, respectively, while intermediates **22** adopts an **L** structure and intermediate **23** adopts a **K** structure.

With these mechanistic results in hand, we next screened precatalysts [Ir(cod)(**L40f**)]BAr$_F$ **11**, [Ir(cod)(*ent*-**L40d**)]BAr$_F$ *ent*-**9** and [Ir(cod)(**L40e**)]BAr$_F$ **10** with substrate **19** under the conditions used for the HP-NMR analysis. The results are shown in Scheme 3.9.6. For precatalyst [Ir(cod)(**L40f**)]BAr$_F$ **11** the configuration of the product obtained from hydrogenation is (*R*) (Scheme 3.9.6), which requires coordination of the substrate as determined for the minor isomer **21**. This result therefore indicates that the hydrogenation of substrate **19** with the Ir/**L40f** catalytic system follows the Halpern-type mechanism in which the less stable isomer **21** reacts faster than the major intermediate **20**, and it is converted into the major product enantiomer. The same behavior is obtained using precatalysts [Ir(cod)(*ent*-**L40d**)]BAr$_F$ *ent*-**9** and [Ir(cod)(**L37e**)]BAr$_F$ **10**. Thus, the configuration of the hydrogenated products is (*R*), while the expected from the detected isomers of **22** and **23** is (*S*).



P-S	p_{H2} (bar)	T (K)	%ee
L40f	10	228	65 (*R*)
ent-**L40d**	40	208	8 (*R*)
L40e	40	208	34 (*R*)

Scheme 3.9.6. Asymmetric hydrogenation of **19** using precatalysts [Ir(cod)(**L40f**)]BAr$_F$ **11**, [Ir(cod)(*ent*-**L40d**)]BAr$_F$ *ent*-**9** and [Ir(cod)(**L40e**)]BAr$_F$ **10** under HP-NMR conditions.

From this we can conclude that in order to obtain the highest enantioselectivity the amount of the minor faster reacting isomer has to be enhanced and/or the energy difference, and therefore the reaction rates, between both TS resulting from the major and minor isomers observed has to be increased. Accordingly, the lowest enantioselectivities obtained with precatalysts [Ir(cod)(*ent*-**L40d**)]BAr$_F$ *ent*-**9** and [Ir(cod)(**L40e**)]BAr$_F$ **10** in comparison with [Ir(cod)(**L40f**)]BAr$_F$ **11** can been explained by the lower population of the faster reacting olefinic dihydride isomer.

3.9.3. Conclusions

We report a reduced but structurally valuable phosphite/phosphinite-thioether ligand library for the Ir-hydrogenation of 40 minimally functionalized alkenes, including some relevant examples with poorly coordinative groups. These phosphite/phosphinite-thioether ligands are synthesized in only two steps from commercially accessible cyclohexene oxide. They also benefit from the robustness of the thioether group and the additional control of the chiral cavity by tuning the thioether and phosphite/phosphinite moieties. With a simple tuning of these ligand parameters we developed highly selective catalysts for a range of substrates with enantioselectivities up to 99% ee, including a variety of olefins that have recently caught attention because their hydrogenated compounds can lead to high-value chemicals. Moreover, these catalysts extend the state-of-art with the successful reduction, for the first time, of terminal aryl-substituted boronic esters. It is also remarkable that these thioether-phosphite/phosphinite ligands have a simple backbone and thus their NMR spectra are simple, with reduced signal overlap, which facilitates the identification of relevant intermediates. Therefore, by combining HP-NMR spectroscopy and theoretical studies, we were able to identify the catalytically competent Ir-dihydride alkene species, which made it possible to explain the enantioselectivity obtained. We found that, similarly to the classical Halpern-mechanism for asymmetric hydrogenation with Rh-catalysts, the minor intermediate, which is less stable, is converted to the major product enantiomer.

3.9.4. Experimental Section

3.9.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and $^{13}C\{^{1}H\}$) as an internal standard or H_3PO_4 (^{31}P) as an external standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC and NOESY experiments. The GaLB-(*R*) solution was prepared in accordance with a method published in the literarure.[14] Phosphorochloridites were easily prepared in one step from the corresponding biphenols.[29] Enantiopure hydroxyl-thioether compound **1**,[13b] thioether-phosphinite ligand **L39f**[13b] and *E*-1-methyl-4-(1-phenylprop-1-en-2-yl)benzene-D_5 **19**[25] were prepared as previously described. Substrates **S1**,[30] **S2**,[31] **S4**,[30] **S5**,[32] **S6**-**S8**,[33] **S9**-**S13**,[10i] **S14**,[34] **S15**-**S16**,[6i] **S17**,[35] **S18**,[36] **S21**,[37] **S22**,[38] **S23**,[39] **S24**,[40] **S25**-**S31**,[37] **S32**[7c] and **S33**-**S36**[22a] were prepared

following the reported procedures and **S3**, **S19**-**S20** and **S37**-**S40** were commercially available.

3.9.4.2. Computational details

The geometries of all intermediates were optimized using the Gaussian 09 program,[41] employing the B3LYP[42] density functional and the LANL2DZ[43] basis set for iridium and the 6-31G* basis set for all other elements.[44] Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[45] The complexes were treated with charge +1 and in the single state. No symmetry constraints were applied. The energies were further refined by performing single point calculations using the above mentioned parameters, with the exception that the 6-311+G**[46] basis set was used for all elements except iridium, and by applying dispersion correction using DFT-D3[47] model. All energies reported are Gibbs free energies at 298.15 K and calculated as Greported = $G_{6\text{-}31G^*}$ + ($E_{6\text{-}311+G^{**}}$ - $E_{6\text{-}31G^*}$) + E_{DFTD3}.

3.9.4.3. Preparation of (1*R*, 2*R*)-2-(2,6-dimethylphenylthio)cyclohexanol 2

A mixture of a 0.05 M solution of GaLB-(*R*) (2.0 mL, 0.10 mmol) and powdered MS 4Å (200 mg) was stirred at room temperature for 30 min and then evaporated *in vacuo* to remove THF. Toluene (2.0 mL) and cyclohexene oxide (101 µL, 1.00 mmol) were added to the residue, and then 2,6-dimethylbenzenethiol (160 µL, 1.20 mmol) was added in one portion. The mixture was stirred at room temperature for 9 h, then diluted with diethyl ether (30 mL), and filtered over a celite pad. The filtrate was washed successively with 5% aq. citric acid (10 mL), sat. aq. $NaHCO_3$ (10 mL), and brine (10 mL), dried over $MgSO_4$ and then evaporated *in vacuo.* The residue was purified by flash chromatography (SiO_2, hexane/acetone (20:1)) to yield the desired thioether-alcohol as a mixture of enantiomers. Further enantiomeric resolution by using semipreparative chiral HPLC (Daicel CHIRACEL OD, 3% 2-propanol in hexanes, 5 mL·min^{-1}, 23 min (**2**)) gave access to desired enantiomer hydroxyl-thioether **2** as a white solid.

(1*R*,2*R*)-2-(2,6-dimethylphenylthio)cyclohexanol (2): Yield: 69 mg (29%). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.16 (m, 1H, CH_2), 1.24 (m, 2H, CH_2), 1.31 (m, 1H, CH_2), 1.63 (m, 1H, CH_2), 1.73 (m, 1H, CH_2), 1.88 (m, 1H, CH_2), 2.12 (m, 1H, CH_2), 2.58 (s, 6H, CH_3-Ph), 2.63 (b, 1H, OH), 2.72 (m, 1H, CH-O), 3.56 (m, 1H, CH-S), 7.13 (b, 3H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 22.6 (CH_3), 24.2 (CH_2), 25.8 (CH_2), 32.5 (CH_2), 34.1 (CH_2), 56.4 (CH-O), 73.9 (CH-S), 128.3 (CH=), 132.0 (C), 143.5 (CH=). MS HR-ESI [found 236.1232, $C_{14}H_{20}OS$ requires 236.1235]. Elemental analysis calcd (%) for $C_{14}H_{20}OS$: C 71.14, H 8.53, S 13.56; found: C 71.07, H 8.56, S 13.48.

3.9.4.4. General procedure for the preparation of the thioether-phosphite ligands L39-L40a-e

The corresponding phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (3.8 mmol, 0.3 mL) was added. The corresponding hydroxyl-thioether (1 mmol) was azeotropically dried with toluene (3x1 mL) and dissolved in toluene (5 mL) to which pyridine (3.8 mmol, 0.3 mL) was added. The solution was transferred slowly at 0 ºC to the phosphorochloridite solution. The reaction mixture was stirred overnight at 80 ºC, and the pyridine salts were removed by filtration. The evaporation of the solvent yielded a white foam, which was purified by flash chromatography in alumina (eluent: toluene/triethylamine – 100:1) to produce the corresponding ligand as a white solid.

L39a: Yield: 423 mg (67%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 146.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.23 (b, 2H, CH_2), 1.26 (s, 9H, CH_3, S^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.55 (m, 1H, CH_2), 1.69 (m, 3H, CH_2), 1.72 (s, 18H, CH_3, ^{t}Bu), 1.84 (m, 2H, CH_2), 2.38 (m, 1H, CH_2), 3.19 (b, 1H, CH-S), 4.75 (b, 1H, CH-O), 7.42 (m, 2H, CH=), 7.69 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 20.2 (CH_2), 22.1 (CH_2), 29.2 (b, CH_2), 29.8 (b, CH_2), 30.9 (CH_3, S^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 43.0 (CH-S), 44.2 (C, S^{t}Bu), 76.7 (b, CH-O, $^2J_{C\text{-}P}$= 7.7 Hz), 123.9-146.2 (aromatic carbons). MS HR-ESI [found 649.3811, $C_{38}H_{59}O_3PS$ $(M\text{-}Na)^+$ requires 649.3815]. Elemental analysis calcd (%) for $C_{38}H_{59}O_3PS$: C 72.80, H 9.49, S 5.11; found: C 72.71, H 9.44, S 5.06.

L39b: Yield: 410 mg (71%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 146.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.22 (s, 9H, CH_3, S^{t}Bu), 1.32 (b, 2H, CH_2), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.63 (b, 3H, CH_2), 1.83 (m, 1H, CH_2), 1.94 (m, 1H, CH_2), 2.31 (m, 1H, CH_2), 3.14 (b, 1H, CH-S), 3.31 (s, 3H, CH_3-O), 3.34 (s, 3H, CH_3-O), 4.73 (b, 1H, CH-O), 6.65-7.18 (4H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 20.1 (CH_2), 21.9 (CH_2), 29.4 (b, CH_2), 29.6 (b, CH_2), 30.8 (CH_3, ^{t}Bu), 30.9 (CH_3, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 43.0 (CH-S), 44.0 (C, S^{t}Bu), 54.6 (CH_3-O), 54.7 (CH_3-O), 76.6 (d, CH-O, $^2J_{C\text{-}P}$= 8.6 Hz), 113.0-155.9 (aromatic carbons). MS HR-ESI [found 597.2768, $C_{32}H_{47}O_5PS$ $(M\text{-}Na)^+$ requires 597.2774]. Elemental analysis calcd. (%) for $C_{32}H_{47}O_5PS$: C 66.87, H 8.24, S 5.58; found: C 66.85, H 8.22, S 5.55.

L39c: Yield: 343 mg (63%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 142.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.44 (s, 9H, $SiMe_3$), 0.47 (s, 9H, $SiMe_3$), 1.13 (s, 9H, CH_3, S^{t}Bu), 1.25 (m, 2H, CH_2), 1.48-1.72 (b, 5H, CH_2), 2.21 (m, 1H, CH_2), 2.97 (m, 1H, CH-S), 4.52 (m, 1H, CH-O), 7.03-7.42 (6H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 0.0 ($SiMe_3$), 0.1 ($SiMe_3$), 20.8 (CH_2), 22.5 (CH_2), 29.7 (b, CH_2), 30.4 (b, CH_2), 31.0 (CH_3, ^{t}Bu), 43.0 (CH-S), 44.5 (C, S^{t}Bu), 76.9 (d, CH-O, $^2J_{C\text{-}P}$= 3.1 Hz), 124.5-155.2 (aromatic carbons). MS HR-ESI [found 569.2098, $C_{28}H_{43}O_3PSSi_2$ $(M\text{-}Na)^+$ requires 569.2101]. Elemental

analysis calcd. (%) for $C_{28}H_{43}O_3PSSi_2$: C 61.50, H 7.93, S 5.86; found: C 61.47, H 7.92, S 5.83.

L39d: Yield: 399 mg (69%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 143.7 (s). ^1H NMR (400 MHz, C_6D_6): δ= 1.21 (s, 9H, CH_3, S^{t}Bu), 1.30 (b, 2H, CH_2), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.62 (b, 3H, CH_2), 1.66 (s, 9H, CH_3, ^{t}Bu), 1.70 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.93 (b, 2H, CH_2), 2.04 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.32 (m, 1H, CH_2), 3.05 (b, CH-S), 4.76 (m, 1H, CH-O), 7.24 (s, 1H, CH=), 7.25 (s, 1H, CH=).^{13}C NMR (C_6D_6): δ= 16.2 (CH_3), 16.4 (CH_3), 19.5 (CH_2), 19.9 (CH_3), 20.0 (CH_3), 21.2 (CH_2), 27.8 (b, CH_2), 28.2 (b, CH_2), 30.8 (CH_3, S^{t}Bu), 31.2 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.5 Hz), 31.6 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 43.0 (CH-S), 43.9 (C, S^{t}Bu), 76.1 (d, CH-O, $^2J_{C\text{-}P}$= 14.7 Hz), 125.2-145.8 (aromatic carbons). MS HR-ESI [found 593.3187, $C_{34}H_{51}O_3PS$ $(M\text{-}Na)^+$ requires 593.3189]. Elemental analysis calcd. (%) for $C_{34}H_{51}O_3PS$: C 71.54, H 9.01, S 5.62; found: C 71.52, H 8.99, S 5.58.

L39e: Yield: 404 mg (70%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 133.6 (s). ^1H NMR (400 MHz, C_6D_6): δ= 1.19 (s, 9H, CH_3, S^{t}Bu), 1.26 (b, 1H, CH_2), 1.56 (b, 1H, CH_2) 1.60 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.60-1.75 (b, 5H, CH_2), 1.69 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.27 (m, 1H, CH_2), 3.19 (m, 1H, CH-S), 4.48 (m, 1H, CH-O), 7.22 (s, 1H, CH=), 7.24 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.8 (CH_3), 17.2 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_2), 22.6 (CH_2), 29.8 (CH_2), 30.3 (CH_2), 31.6 (CH_3, S^{t}Bu), 31.9 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.6 Hz), 32.1 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 43.6 (CH-S), 44.5 (C, S^{t}Bu), 77.6 (d, CH-O, $^2J_{C\text{-}P}$= 2.1 Hz), 128-146.7 (aromatic carbons). MS HR-ESI [found 593.3183, $C_{34}H_{51}O_3PS$ $(M\text{-}Na)^+$ requires 593.3189]. Elemental analysis calcd. (%) for $C_{34}H_{51}O_3PS$: C 71.54, H 9.01, S 5.62; found: C 71.50, H 9.02, S 5.59.

L40d: Yield: 392 mg (63%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 141.7 (s). ^1H NMR (400 MHz, C_6D_6): δ= 1.19 (m, 1H, CH_2), 1.26 (m, 1H, CH_2), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.57 (b, 3H, CH_2), 1.68 (s, 6H, CH_3), 1.89 (m, 1H, CH_2), 2.01 (b, 1H, CH_2), 2.03 (s, 3H, CH_3-Ph), 2.05 (s, 3H, CH_3-Ph), 2.19 (m, 1H, CH_2), 2.45 (s, 6H, CH_3), 3.20 (m, 1H, CH-S), 4.60 (m, 1H, CH-O), 6.93-7.20 (m, 5H, CH=). ^{13}C NMR (100.6 Hz, C_6D_6): δ= 16.9 (CH_3), 17.1 (CH_3), 20.7 (CH_3), 21.2 (CH_2), 22.2 (CH_2), 22.9 (CH_3-Ph), 27.7 (b, CH_2), 29.3 (b, CH_2), 31.7 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.3 Hz), 32.6 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 52.2 (CH-S), 76.2 (d, CH-O, $^2J_{C\text{-}P}$= 15.3 Hz), 126.0-146.4 (aromatic carbons). MS HR-ESI [found 641.3186, $C_{38}H_{51}O_3PS$ $(M\text{-}Na)^+$ requires 641.3189]. Elemental analysis calcd. (%) for $C_{38}H_{51}O_3PS$: C 73.75, H 8.32, S 5.18; found: C 73.72, H 8.31, S 5.16.

L40e: Yield: 344 mg (56%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 137.0 (s). ^1H NMR (400 MHz, C_6D_6): δ= 1.31 (m, 1H, CH_2), 1.42 (m, 1H, CH_2), 1.75 (m, 1H, CH_2), 1.81 (s, 9H, CH_3, ^{t}Bu), 1.83 (s, 9H, CH_3, ^{t}Bu), 1.84 (b, 3H, CH_2), 1.94 (s, 3H, CH_3), 2.01 (s,

3H, CH_3), 2.18 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.75 (s, 6H, CH_3-Ph), 3.51 (m, 1H, CH-S), 4.79 (m, 1H, CH-O), 7.17-7.50 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.2 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 21.0 (CH_2), 21.2 (CH_2), 22.3 (CH_3-Ph), 28.3 (b, CH_2), 30.2 (b, CH_2), 31.2 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.4 Hz), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 51.4 (CH-S), 75.2 (d, CH-O, $^2J_{C\text{-}P}$= 1.8 Hz), 125.3-143.2 (aromatic carbons). MS HR-ESI [found 641.3184, $C_{38}H_{51}O_3PS$ $(M\text{-}Na)^+$ requires 641.3189]. Elemental analysis calcd. (%) for $C_{38}H_{51}O_3PS$: C 73.75, H 8.32, S 5.18; found: C 73.72, H 8.30, S 5.15.

3.9.4.5. General procedure for the preparation of the thioether-phosphinite ligands L40f-g

The corresponding thioether-hydroxyl compound (0.5 mmol) and DMAP (6.7 mg, 0.055 mmol) were dissolved in toluene (1 ml), and triethylamine was added (0.09 ml, 0.65 mmol) at rt, followed by the addition of the corresponding chlorophosphine (0.55 mmol) via syringe. The reaction was stirred for 20 min at rt. The solvent was removed *in vacuo*, and the product was purified by flash chromatography on alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as a colorless oil.

L40f: Yield: 307 mg (73%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 108.8 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.85 (m, 1H, CH_2), 1.01 (m, 1H, CH_2), 1.32 (m, 2H, CH_2), 1.44 (m, 2H, CH_2), 1.71 (m, 1H, CH_2), 2.02 (m, 1H, CH_2), 2.46 (s, 6H, CH_3-Ph), 3.17 (m, 1H, CH-S), 4.03 (m, 1H, CH-O), 6.9-7.7 (m, 13H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 22.2 (CH_3-Ph), 22.8 (b, CH_2), 23.7 (b, CH_2), 30.2 (b, CH_2), 32.5 (b, CH_2), 52.0 (CH-S), 81.1 (d, CH-O, $^2J_{C\text{-}P}$= 21.4 Hz), 127.3-143.8 (aromatic carbons). MS HR-ESI [found 443.1563, $C_{26}H_{29}OPS$ $(M\text{-}Na)^+$ requires 443.1569]. Elemental analysis calcd. (%) for $C_{26}H_{29}OPS$: C 74.26, H 6.95, S 7.62; found: C 74.33, H 6.96, S 7.59.

L40g: Yield: 363 mg (81%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 95.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.95 (m, 1H, CH_2), 1.09 (m, 1H, CH_2), 1.37 (m, 2H, CH_2), 1.49 (m, 2H, CH_2), 1.76 (m, 1H, CH_2), 2.05 (m, 1H, CH_2), 2.28 (s, 3H, CH_3-Ph), 2.38 (s, 3H, CH_3-Ph), 2.42 (s, 6H, CH_3-Ph), 3.09 (m, 1H, CH-S), 4.00 (m, 1H, CH-O), 6.80-7.80 (m, 11H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 20.2 (CH_3-Ph), 20.5 (CH_3-Ph), 22.1 (CH_3-Ph), 22.5 (b, CH_2), 23.3 (b, CH_2), 29.7 (b, CH_2), 31.6 (b, CH_2), 52.0 (CH-S), 80.1 (d, CH-O, $^2J_{C\text{-}P}$= 16.2 Hz), 125.7-143.3 (aromatic carbons). MS HR-ESI [found 471.1878, $C_{28}H_{33}OPS$ $(M\text{-}Na)^+$ requires 471.1882]. Elemental analysis calcd. (%) for $C_{28}H_{33}OPS$: C 74.97, H 7.41, S 7.15; found: C 75.08, H 7.42, S 7.10.

3.9.4.6. General procedure for the preparation of [Ir(cod)(P-S)]BAr_F (P-S=L39-L40a-g).

The corresponding ligand (0.074 mmol) was dissolved in CH_2Cl_2 (5 mL) and [Ir(μ-Cl)(cod)]$_2$ (25.0 mg, 0.037 mmol) was added. The reaction mixture was refluxed at 50 ºC for 1 hour. After 5 min at room temperature, $NaBAr_F$ (77.2 mg, 0.080 mmol) and water (5 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of silica and the solvent was evaporated, resulting in the product as a red-orange solid.

[Ir(cod)(L39a)]BAr_F (3): Yield: 123 mg (93%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 99.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.33 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, S^{t}Bu), 1.76 (b, 2H, CH_2), 1.82 (b, 2H, CH_2), 1.95 (m, 2H, CH_2), 2.01 (m, 2H, CH_2, cod), 2.14 (m, 2H, CH_2), 2.21 (m, 2H, CH_2, cod), 2.30 (m, 2H, CH_2, cod), 2.38 (m, 2H, CH_2, cod), 2.72 (m, 1H, CH-S), 4.21 (m, 1H, CH-O), 4.61 (b, 1H, CH=, cod), 4.88 (m, 2H, CH=, cod), 5.76 (b, 1H, CH=, cod), 6.97-7.76 (m, 16H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 23.9 (CH_2), 25.8 (CH_2), 26.8 (b, CH_2, cod), 29.9 (b, CH_2, cod), 30.3 (b, CH_2, cod), 31.2 (CH_2), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 32.0 (CH_3, S^{t}Bu), 33.6 (b, CH_2, cod), 34.9 (b, CH_2, cod), 35.7 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 47.6 (CH-S), 58.8 (C, S^{t}Bu), 77.4 (CH=, cod), 78.0 (CH-O), 78.0 (b, CH=, cod), 99.4 (d, CH=, cod, $J_{C\text{-}P}$= 20.4 Hz), 110.7 (d, CH=, cod, $J_{C\text{-}P}$= 14.0 Hz), 117.7 (b, CH=, BAr_F), 120.6-131.2 (aromatic carbons), 134.9 (b, CH=, BAr_F), 138.1-149.3 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.4 Hz). MS HR-ESI [found 927.4487, $C_{46}H_{71}IrO_3PS$ (M-BAr_F)$^+$ requires 927.4491]. Elemental analysis calcd. (%) for $C_{78}H_{83}BF_{24}IrO_3PS$: C 52.32, H 4.67, S 1.79; found: C 52.29, H 4.66, S 1.75.

[Ir(cod)(L39b)]BAr_F (4): Yield: 116 mg (90%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 102.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.44 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.79 (m, 4H, CH_2), 2.00 (m, 2H, CH_2, cod), 2.11 (m, 2H, CH_2, cod), 2.20 (m, 2H, CH_2), 2.12 (m, 2H, CH_2, cod), 2.29 (m, 2H, CH_2, cod), 2.32 (m, 2H, CH_2), 2.75 (m, 1H, CH-S), 3.80 (s, 3H, CH_3-O), 3.84 (s, 3H, CH_3-O), 4.24 (m, 1H, CH-O), 4.77 (b, 2H, CH=, cod), 4.91 (m, 1H, CH=, cod), 5.73 (b, 1H, CH=, cod), 6.52-7.70 (m, 16H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 23.8 (CH_2), 25.8 (CH_2) 27.2 (CH_2, cod), 29.9 (CH_2, cod), 30.7 (CH_2), 31.2 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 33.9 (b, CH_2, cod), 34.1 (b, CH_2, cod), 35.2 (CH_2), 35.9 (C, ^{t}Bu), 36.1 (C, ^{t}Bu), 47.7 (CH-S), 55.8 (CH_3-O), 55.9 (CH_3-O), 58.5 (C, S^{t}Bu), 75.8 (CH=, cod), 77.4 (CH-O), 79.5 (CH=, cod), 99.7 (d, CH=, cod, $J_{C\text{-}P}$= 19.5 Hz), 111.0 (d, CH=, cod, $J_{C\text{-}P}$= 13.3 Hz), 112.9-115.6 (aromatic carbons), 117.6 (b, CH=, BAr_F), 120.6-131.9 (aromatic

carbons), 135.0 (b, CH=, BAr_F), 140.4-157.3 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$= 49.4 Hz). MS HR-ESI [found 875.3447, $C_{40}H_{59}IrO_5PS$ $(M\text{-}BAr_F)^+$ requires 875.3450]. Elemental analysis calcd. (%) for $C_{72}H_{71}BF_{24}IrO_5PS$: C 49.75, H 4.12, S 1.84; found: C 49.61, H 4.10, S 1.79.

[Ir(cod)(L39c)]BAr_F (5): Yield: 115 mg (91%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 99.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.44 (s, 18H, CH_3, $SiMe_3$), 1.57 (s, 9H, CH_3, S^tBu), 1.79 (b, 4H, CH_2, CH_3), 1.96 (m, 2H, CH_2, cod), 2.09 (m, 2H, CH_2, cod), 2.20 (m, 4H, CH_2, cod), 2.66 (m, 1H, CH-S), 4.14 (m, 1H, CH=, cod), 4.69 (b, 1H, CH=, cod), 4.92 (m, 2H, CH=, cod, CH-O), 5.90 (b, 1H, CH=, cod), 7.23-7.70 (m, 18H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 0.7 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 24.1 (CH_2), 25.9 (CH_2), 26.8 (CH_2, cod), 30.3 (CH_2, cod), 31.2 (CH_2), 31.7 (CH_3, S^tBu), 33.4 (d, CH_2, cod, J_{C-P}= 6.2 Hz), 34.7 (d, CH_2, cod, J_{C-P}= 5.5 Hz), 34.9 (CH_2), 47.6 (CH-S), 58.8 (C, S^tBu), 76.9 (CH=, cod), 77.4 (CH-O), 78.5 (CH=, cod), 99.9 (d, CH=, cod, J_{C-P}= 20.4 Hz), 111.6 (d, CH=, cod, J_{C-P}= 14.1 Hz), 117.6 (b, CH=, BAr_F), 120.7-133.1 (aromatic carbons), 134.9 (b, CH=, BAr_F), 135.8-154.1 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$ = 49.2 Hz). MS HR-ESI [found 847.2773, $C_{36}H_{55}IrO_3PSSi_2$ $(M\text{-}BAr_F)^+$ requires 847.2777]. Elemental analysis calcd. (%) for $C_{68}H_{67}BF_{24}IrO_3PSSi_2$: C 47.75, H 3.95, S 1.87; found: C 47.68, H 3.92, S 1.84.

[Ir(cod)(L39d)]BAr_F (6): Yield: 119 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 99.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.38 (b, 2H, CH_2), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.56 (m, 2H, CH_2), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.75 (b, 6H, CH_2), 1.84 (s, 3H, CH_3), 2.10-2.20 (b, 6H, CH_2), 2.23 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.69 (m, 1H, CH-S), 4.24 (m, 1H, CH=, cod), 4.36 (m, 1H, CH=, cod), 4.91 (m, 2H, CH=, cod, CH-O), 5.59 (m, 1H, CH=, cod), 7.17-7.70 (m, 14H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.4 (CH_3-Ph), 16.7 (CH_3-Ph), 20.3 (CH_3-Ph), 20.6 (CH_3-Ph), 23.7 (CH_2), 25.8 (CH_2), 27.8 (b, CH_2), 29.2 (CH_2), 31.2 (CH_3, ^{t}Bu), 31.2 (b, CH_2), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 33.2 (b, CH_2), 34.7 (b, CH_2), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 47.7 (CH-S), 57.6 (C, S^tBu), 74.1 (b, CH=, cod), 77.7 (b, CH=, cod), 81.6 (CH-O), 99.2 (d, CH=, cod, J_{C-P}= 19.7 Hz), 110.4 (d, CH=, cod, J_{C-P}= 14.0 Hz), 117.6 (b, CH=, BAr_F), 123.3-134.4 (aromatic carbons), 134.9 (b, CH=, BAr_F), 135.9-143.9 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$= 49.4 Hz). MS HR-ESI [found 871.3861, $C_{42}H_{63}IrO_3PS$ $(M\text{-}BAr_F)^+$ requires 871.3865]. Elemental analysis calcd. (%) for $C_{74}H_{75}BF_{24}IrO_3PS$: C 51.25, H 4.36, S 1.85; found: C 51.05, H 4.34, S 1.82.

[Ir(cod)(L39e)]BAr_F (7): Yield: 118 mg (92%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 94.6 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.39-1.62 (b, 4H, CH_2), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.60-1.90 (m, 6H, CH_2), 1.62 (s, 3H, CH_3), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.85 (s, 3H, CH_3), 2.10-2.40 (b, 6H, CH_2), 2.25 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.81 (m, 1H, CH-S), 4.12 (m, 1H, CH=, cod), 4.55 (m, 1H, CH=, cod), 4.92 (m, 2H, CH=, cod, CH-O), 5.98 (m, 1H, CH=, cod), 7.12-7.70 (m, 14H, CH=). ^{13}C NMR (100.6

MHz, $CDCl_3$): δ= 16.7 (CH_3-Ph), 20.2 (CH_3-Ph), 20.7 (CH_3-Ph), 24.4 (CH_2), 25.1 (CH_2), 25.8 (b, CH_2), 30.1 (CH_2), 30.8 (CH_3, ^{t}Bu), 31.6 (b, CH_2), 32.0 (CH_3, ^{t}Bu), 32.2 (CH_3, ^{t}Bu), 33.7 (b, CH_2), 34.2 (b, CH_2), 34.7 (b, CH_2), 35.2 (C, ^{t}Bu), 36.4 (C, ^{t}Bu), 46.8 (CH-S), 57.9 (C, S^{t}Bu), 61.9 (b, CH=, cod), 63.4 (b, CH=, cod), 79.6 (CH-O), 97.6 (d, CH=, cod, $J_{C\text{-}P}$= 18.4 Hz), 110.2 (d, CH=, cod, $J_{C\text{-}P}$= 16.1 Hz), 117.7 (b, CH=, BAr_F), 120.6-134.6 (aromatic carbons), 134.9 (b, CH=, BAr_F), 137.2-144.2 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.4 Hz). MS HR-ESI [found 871.3863, $C_{42}H_{63}IrO_3PS$ (M-BAr_F)$^+$ requires 871.3865]. Elemental analysis calcd. (%) for $C_{74}H_{75}BF_{24}IrO_3PS$: C 51.25, H 4.36, S 1.85; found: C 51.11, H 4.35, S 1.82.

[Ir(cod)(L39f)]BAr_F (8): Yield: 103 mg (91%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 100.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.24 (s, 9H, CH_3, S^{t}Bu), 1.37 (m, 2H, CH_2), 1.49 (m, 2H, CH_2), 1.79 (m, 2H, CH_2, cod), 1.86 (m, 2H, CH_2), 2.03 (m, 2H, CH_2, cod), 2.17 (m, 2H, CH_2, cod), 2.28 (m, 2H, CH_2, cod), 2.37 (m, 2H, CH_2), 2.76 (m, 1H, CH-S), 3.37 (b, 1H, CH-O), 4.20 (m, 2H, CH=, cod), 4.81 (m, 1H, CH=, cod), 5.48 (b, 1H, CH=, cod), 7.16-7.70 (m, 22H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 24.3 (CH_2), 25.9 (CH_2), 28.0 (CH_2, cod), 31.3 (CH_3, S^{t}Bu), 31.8 (CH_2), 34.0 (CH_2, cod), 35.0 (CH_2, cod), 35.4 (CH_2), 48.7 (CH-S), 59.4 (C, S^{t}Bu), 74.7 (CH=, cod), 77.4 (CH-O), 83.3 (CH=, cod), 96.1 (d, CH=, cod, $J_{C\text{-}P}$= 13.3 Hz), 104.8 (d, CH=, cod, $J_{C\text{-}P}$= 11.8 Hz), 117.6 (b, CH=, BAr_F), 120.7-134.7 (aromatic carbons), 134.9 (b, CH=, BAr_F), 135.3 (C), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.2 Hz). MS HR-ESI [found 673.2239, $C_{30}H_{41}IrOPS$ (M-BAr_F)$^+$ requires 673.2245]. Elemental analysis calcd. (%) for $C_{62}H_{53}BF_{24}IrOPS$: C 48.48, H 3.48, S 2.09; found: C 48.21, H 3.46, S 2.02.

[Ir(cod)(L40d)]BAr_F (9): Yield: 125 mg (95%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 88.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.15 (m, 1H, CH_2), 1.27 (b, 1H, CH_2), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.62 (m, 1H, CH_2), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.74 (m, 2H, CH_2), 1.76 (s, 6H, CH_3), 1.84 (m, 3H, CH_2), 1.97 (m, 4H, CH_2, cod), 2.01 (m, 4H, CH_2, cod), 2.26 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.26 (b, 1H, CH-S), 3.53 (m, 1H, CH=, cod), 4.40 (m, 1H, CH=, cod), 4.54 (m, 2H, CH=, cod), 4.74 (m, 1H, CH-O), 7.20-7.71 (m, 17H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.6 (CH_3), 16.6 (CH_3), 20.3 (CH_3-Ph), 20.3 (CH_3-Ph), 23.6 (CH_3), 23.8 (CH_3), 25.4 (CH_2), 27.6 (b, CH_2, cod), 29.3 (CH_2), 29.7 (CH_2), 31.6 (CH_3, ^{t}Bu), 31.8 (b, CH_2, cod), 32.3 (CH_3, ^{t}Bu), 33.7 (b, CH_2, cod), 34.8 (b, CH_2), 34.9 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 50.9 (d, CH=, cod, $J_{C\text{-}P}$= 5.4 Hz), 66.9 (CH-S), 76.9 (CH-O), 82.1 (b, CH=, cod), 102.4 (d, CH=, cod, $J_{C\text{-}P}$= 15.6 Hz), 104.0 (d, CH=, cod, $J_{C\text{-}P}$= 14.8 Hz), 117.4 (b, CH=, BAr_F), 120.4-134.1 (aromatic carbons), 134.8 (b, CH=, BAr_F), 135.7-144.9 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.0 Hz). MS HR-ESI [found 919.3858, $C_{46}H_{63}IrO_3PS$ (M-BAr_F)$^+$ requires 919.3865]. Elemental analysis calcd. (%) for $C_{78}H_{75}BF_{24}IrO_3PS$: C 52.56, H 4.24, S 1.80; found: C 52.34, H 4.22, S 1.77.

[Ir(cod)(L40e)]BAr$_F$ (10): Yield: 122 mg (93%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 88.8 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.38 (s, 9H, CH_3, ^{t}Bu), 1.55 (m, 2H, CH_2, cod), 1.57 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.72 (b, 2H, CH_2), 1.75 (s, 3H, CH_3), 1.81 (m, 2H, CH_2, cod), 1.90-2.03 (m, 6H, CH_2), 2.10 (m, 2H, CH_2, cod), 2.17 (s, 3H, CH_3-Ph), 2.20 (s, 3H, CH_3-Ph), 2.25 (m, 2H, CH_2, cod), 2.42 (s, 3H, CH_3), 2.68 (m, 1H, CH-S), 2.88 (s, 3H, CH_3), 3.25 (m, 1H, CH=, cod), 3.81 (m, 1H, CH=, cod), 4.32 (m, 1H, CH=, cod), 4.46 (m, 1H, CH-O), 4.86 (m, 1H, CH=, cod), 7.07-7.64 (m, 17H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3-Ph), 20.4 (CH_3-Ph), 22.6 (CH_3), 22.8 (CH_3), 25.4 (CH_2), 26.5 (b, CH_2, cod), 29.7 (CH_2), 29.9 (CH_2), 30.3 (CH_2), 31.4 (b, CH_2, cod), 31.7 (CH_3, ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 34.2 (b, CH_2, cod), 34.6 (b, CH_2, cod), 34.8 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 52.6 (CH=, cod), 66.2 (CH-S), 76.2 (CH-O), 78.3 (b, CH=, cod), 102.3 (d, CH=, cod, $J_{C\text{-}P}$= 14.1 Hz), 105.3 (d, CH=, cod, $J_{C\text{-}P}$= 16.4 Hz), 117.5 (b, CH=, BAr$_F$), 120.4-134.4 (aromatic carbons), 134.8 (b, CH=, BAr$_F$), 135.4-143.5 (aromatic carbons), 161.5 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$= 49.2 Hz). MS HR-ESI [found 919.3861, $C_{46}H_{63}IrO_3PS$ (M-BAr$_F$)$^+$ requires 919.3865]. Elemental analysis calcd. (%) for $C_{78}H_{75}BF_{24}IrO_3PS$: C 52.56, H 4.24, S 1.80; found: C 52.38, H 4.23, S 1.79.

[Ir(cod)(L40f)]BAr$_F$ (11): Yield: 107 mg (91%). ^{31}P NMR (C_6D_6): δ= 99.0 (s). ^{1}H NMR (C_6D_6): δ= 1.27 (b, 2H, CH_2), 1.56 (m, 2H, CH_2, cod), 1.68 (b, 2H, CH_2), 1.83 (m, 2H, CH_2, cod), 1.91 (m, 2H, CH_2, cod), 2.08 (m, 2H, CH_2, cod), 2.36 (m, 4H, CH_2), 2.63 (s, 3H, CH_3-Ph), 3.05 (s, 3H, CH_3-Ph), 3.12 (b, 1H, CH=, cod), 3.43 (m, 2H, CH-S, CH=, cod), 3.70 (b, 2H, CH-O, CH=, cod) 5.01 (b, 1H, CH=, cod), 7.17-8.03 (m, 25H, CH=). ^{13}C NMR (C_6D_6): δ= 22.8 (CH_3-Ph), 23.5 (CH_3-Ph), 25.4 (CH_2), 27.5 (b, CH_2, cod), 29.7 (b, CH_2), 30.2 (CH_2), 30.3 (CH_2), 31.2 (b, CH_2, cod), 33.0 (b, CH_2, cod), 35.0 (b, CH_2, cod), 51.3 (CH=, cod), 67.4 (CH-S), 75.9 (CH-O), 77.8 (CH=, cod), 94.1 (d, CH=, cod, $J_{C\text{-}P}$= 9.4 Hz), 98.5 (d, CH=, cod, $J_{C\text{-}P}$= 13.2 Hz), 117.5 (b, CH=, BAr$_F$), 120.4-133.9 (aromatic carbons), 134.8 (b, CH=, BAr$_F$), 134.9-143.2 (aromatic carbons), 161.5 (q, C-B, BAr$_F$, $^1J_{C\text{-}B}$= 49.4 Hz). MS HR-ESI [found 721.2240, $C_{34}H_{41}IrOPS$ (M-BAr$_F$)$^+$ requires 721.2245]. Elemental analysis calcd. (%) for $C_{66}H_{53}BF_{24}IrOPS$: C 50.04, H 3.37, S 2.02 found: C 49.98, H 3.35, S 1.98.

[Ir(cod)(L40g)]BAr$_F$ (12): Yield: 112 mg (94%). ^{31}P NMR (C_6D_6): δ= 101.6 (s). ^{1}H NMR (C_6D_6): δ= 1.40 (m , 2H, CH_2), 1.50 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.79-2.01 (m, 6H, CH_2, cod), 2.08 (s, 3H, CH_3), 2.17 (m, 4H, CH_2, cod), 2.41 (s, 3H, CH_3), 2.56 (b, 1H, CH=, cod), 2.82 (s, 3H, CH_3-Ph), 2.90 (s, 3H, CH_3-Ph), 3.08 (b, 1H, CH-S), 3.47 (m, 1H, CH=, cod), 3.66 (m, 2H, CH-O, CH=, cod), 4.70 (b, 1H, CH=, cod), 6.62-8.95 (m, 23H, CH=). ^{13}C NMR (C_6D_6): δ= 21.7 (d, CH_3, $J_{C\text{-}P}$= 3.0 Hz), 22.5 (d, CH_3-Ph, $J_{C\text{-}P}$= 7.0 Hz), 22.7 (d, CH_3-Ph, $J_{C\text{-}P}$= 3.0 Hz), 23.4 (b, CH_3), 25.5 (CH_2), 27.8 (b, CH_2, cod), 29.6 (CH_2), 29.7 (CH_2), 30.3 (CH_2), 31.2 (CH_2, cod), 33.0 (CH_2, cod), 35.7 (d, CH_2, cod, $J_{C\text{-}P}$= 7.0 Hz), 50.8 (CH=, cod), 68.0 (CH-S), 76.5 (CH-O), 78.8 (b,

CH=, cod), 96.9 (d, CH=, cod, $J_{C\text{-}P}$= 9.4 Hz), 98.1 (d, CH=, cod, $J_{C\text{-}P}$= 13.3 Hz), 117.5 (b, CH=, BAr_F), 120.5-133.9 (aromatic carbons), 134.8 (b, CH=, BAr_F), 139.9-143.4 (aromatic carbons), 161.5 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.2 Hz). MS HR-ESI [found 749.2553, $C_{36}H_{45}IrOPS$ $(M\text{-}BAr_F)^+$ requires 749.2558]. Elemental analysis calcd. (%) for $C_{68}H_{57}BF_{24}IrOPS$: C 50.66, H 3.56, S 1.99 found: C 50.34, H 3.53, S 1.93.

3.9.4.7. In situ preparation of $[Ir(H)_2(cod)(L39\text{-}L40a\text{-}g)]BAr_F$

In a typical experiment hydrogen was bubbled through a CD_2Cl_2 solution of the desired $[Ir(cod)(P,S)]BAr_F$ catalyst precursor (6.2 mmol) to the desired temperature for 15-30 min. The reaction mixture was analyzed by NMR spectroscopy at the desired temperature.

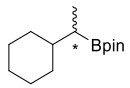
3.9.4.8. In situ HP-NMR hydrogenation experiments using *E*-1-methyl-4-(1-phenylprop-1-en-2-yl)benzene-D_5 19

The desired $[Ir(cod)(P\text{-}S)]BAr_F$ catalyst precursor (6.2 μmol) and *E*-1-methyl-4-(1-phenylprop-1-en-2-yl)benzene-D_5 (5.9 mg, 27.7 μmol, 4.5 equiv.) were added to an oven-dried Schlenk tube and dissolved in CD_2Cl_2 (0.6 ml). The solution was transferred to a HP-NMR sapphire tube (ϕ= 5 mm) and cooled to 195 K. The HP-NMR was pressurized to the desired pressure of hydrogen gas. The reaction mixture was analyzed by NMR spectroscopy at the desired temperature.

3.9.4.9. General procedure for the hydrogenation of olefins

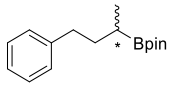
The alkene (0.5 mmol) and Ir-complex (2 mol%) were dissolved in CH_2Cl_2 (2 mL) in a high-pressure autoclave, which was purged four times with hydrogen. It was then pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short Celite plug. The enantiomeric excess was determined by chiral GC or chiral HPLC and conversions were determined by ^1H NMR. (for hydrogenation products from **S1**-**S5**, **S14**-**S17**, **S19**-**S31**, **S33**, **S37** see previous Section 3.1.4.5, for hydrogenation products from **S6**-**S13**, **S18**, **S38**-**S40** see previous Section 3.2.4.6 and for hydrogenation product from **S32** see previous Section 3.3.4.8).

2-(1-Cyclohexylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. [22a] Enantiomeric excess were determined after oxidation/acetylation of the pinacolborane derivative to the corresponding trifluoroacetylated compound using sodium perborate monohydrate (75 mg, 0.75 mmol) in a THF/H_2O solution (1:1, 4 mL). After 1 h, the reaction mixture was extracted with DCM (3×1 mL), dried with $MgSO_4$ and filtrated. To the filtrate acetic anhydride (240 μL,



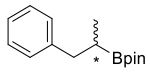
2.5 mmol), NEt_3 (700 μL, 5 mmol) and a pinch of DMAP (c.a. 1 mg) was added. After 12 h, the volatiles were removed under vacuum. Enantiomeric excess determined by GC using HP CHIRAL 20B column (1.5 mL/min H_2, 50 °C, 1 ºC/min to 230 ºC). t_R 49.8 min (*S*); t_R 52.5 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.23 (m, 12H), 0.8-1.4 (b, 10H), 1.5-1.8 (b, 5H).

2-(4-Phenylbutan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. [22a] Enantio-



meric excess were determined after oxidation of the pinacolborane derivative to the corresponding alcohol using sodium perborate monohydrate (75 mg, 0.75 mmol) in a THF/H_2O solution (1:1, 4 mL). Enantiomeric excess determined by HPLC using Chiracel IB column (hexane/2-propanol=90/10, 1 mL/min, 254 nm). t_R 5.4 min (*R*); t_R 6.1 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.01 (m, 3H), 1.2-1.3 (m, 13H), 1.54 (m, 1H), 1.72 (m, 1H), 2.61 (t, 2H, *J*= 8.0 Hz), 7.16 (m, 2H), 7.28 (m, 3H).

2-(1-Phenylpropan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. [22a] Enantio-



meric excess were determined after oxidation of the pinacolborane derivative to the corresponding alcohol using sodium perborate monohydrate (75 mg, 0.75 mmol) in a THF/H_2O solution (1:1, 4 mL). Enantiomeric excess determined by GC using Chiralsil-Dex CB column (80 kPa H_2, 90 °C for 15 min, 10 °C/min, to 180 °C). t_R 13.3 min (*R*); t_R 13.8 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 0.97 (d, 3H, *J*= 7.2 Hz), 1.18 (s, 6H), 1.19 (s, 6H), 1.35 (m, 1H), 2.54 (dd, 1H, *J*= 8.4 Hz, *J*= 13.2 Hz), 2.80 (dd, 1H, *J*= 7.6 Hz, *J*= 13.2 Hz), 7.16 (m, 1H), 7.22 (m, 4H).

3.9.5. Acknowledgments

Financial support from the Spanish Government (CTQ2013-40568P), the Catalan Government (2014SGR670), the ICREA Foundation (ICREA Academia awards to M. Diéguez and O. Pàmies) is gratefully acknowledged.

3.9.6. References

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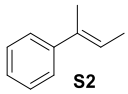
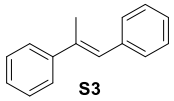
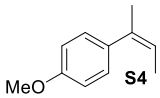
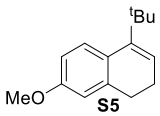
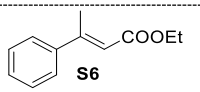
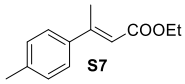
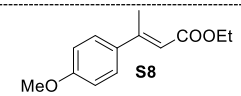
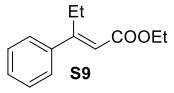
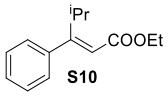
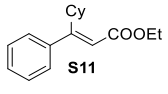
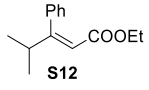
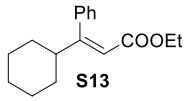
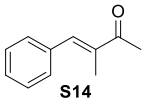
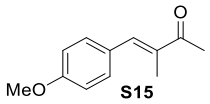
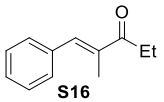
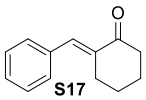
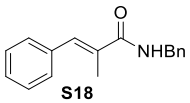
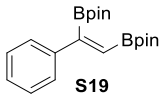
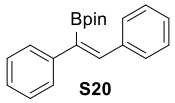
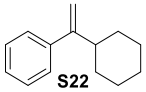
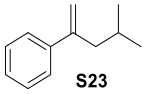
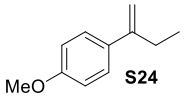
3.9.7. Supporting Information

3.9.7.1. Table SI.1. Complete series of results for the Ir-catalyzed hydrogenation of S2-S20, S22-S24 and S33-S37 using [Ir(cod)(L39-L40a-g)]BAr_F catalyst precursors

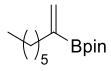
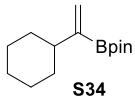
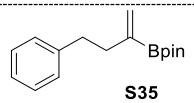
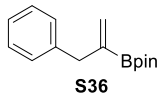
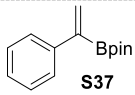
Substrate	% ee									
	L39a	L39b	L39c	L39d	L39e	L39f	L40d	L40e	L40f	L40g
 S2	15 (*R*)	16 (*R*)	15 (*R*)	43 (*S*)	85 (*R*)	63 (*R*)	7 (*R*)	34 (*R*)	70 (*R*)	63 (*R*)
 S3	18 (*R*)	17 (*R*)	19 (*R*)	39 (*S*)	92 (*R*)	69 (*R*)	4 (*R*)	42 (*R*)	76 (*R*)	67 (*R*)
 S4	26 (*S*)	25 (*S*)	25 (*S*)	29 (*R*)	59 (*S*)	8 (*S*)	4 (*S*)	32 (*S*)	2 (*S*)	28 (*R*)
 S5	4 (*R*)	13 (*S*)	4 (*R*)	17 (*R*)	48 (*S*)	11 (*R*)	60 (*R*)	87 (*S*)	7 (*R*)	33 (*S*)
 S6	96 (*R*)	96 (*R*)	96 (*R*)	90 (*R*)	94 (*R*)	79 (*R*)	92 (*R*)	95 (*R*)	88 (*R*)	67 (*R*)
 S7	96 (*R*)	95 (*R*)	95 (*R*)	91 (*R*)	95 (*R*)	76 (*R*)	94 (*R*)	91 (*R*)	84 (*R*)	72 (*R*)
 S8	95 (*R*)	95 (*R*)	95 (*R*)	90 (*R*)	93 (*R*)	79 (*R*)	92 (*R*)	89 (*R*)	87 (*R*)	75 (*R*)
 S9	96 (*R*)	96 (*R*)	95 (*R*)	92 (*R*)	92 (*R*)	81 (*R*)	94 (*R*)	92 (*R*)	89 (*R*)	76 (*R*)
 S10	97 (*R*)	96 (*R*)	96 (*R*)	89 (*R*)	92 (*R*)	80 (*R*)	93 (*R*)	90 (*R*)	88 (*R*)	74 (*R*)
 S11	98 (*R*)	97 (*R*)	97 (*R*)	92 (*R*)	97 (*R*)	82 (*R*)	94 (*R*)	93 (*R*)	82 (*R*)	73 (*R*)
 S12	93 (*S*)	92 (*S*)	93 (*S*)	89 (*S*)	92 (*S*)	80 (*S*)	92 (*S*)	91 (*S*)	83 (*S*)	73 (*S*)

Full conversions were achieved in all cases

3.9.7.1. Table SI.1. Complete series of results for the Ir-catalyzed hydrogenation of S2-S20, S22-S24 and S33-S37 using [Ir(cod)(L39-L40a-g)]BAr_F catalyst precursors (continuation)

Substrate	% ee									
	L39a	L39b	L39c	L39d	L39e	L39f	L40d	L40e	L40f	L40g
 S13	92 (*S*)	92 (*S*)	91 (*S*)	88 (*S*)	91 (*S*)	83 (*S*)	90 (*S*)	92 (*S*)	79 (*S*)	69 (*S*)
 S14	18 (*R*)	20 (*R*)	19 (*R*)	21 (*S*)	71 (*R*)	92 (*R*)	82 (*R*)	33 (*R*)	61 (*R*)	34 (*R*)
 S15	19 (*R*)	20 (*R*)	20 (*R*)	23 (*S*)	75 (*R*)	91 (*R*)	79 (*R*)	30 (*R*)	59 (*R*)	29 (*R*)
 S16	18 (*R*)	18 (*R*)	19 (*R*)	19 (*S*)	73 (*R*)	92 (*R*)	81 (*R*)	32 (*R*)	60 (*R*)	33 (*R*)
 S17	20 (*R*)	21 (*R*)	20 (*R*)	29 (*S*)	65 (*R*)	91 (*R*)	68 (*R*)	7 (*S*)	40 (*R*)	35 (*R*)
 S18	15 (*S*)	13 (*S*)	16 (*S*)	4 (*R*)	4 (*S*)	68 (*S*)	88 (*R*)	9 (*S*)	3 (*S*)	2 (*S*)
 S19	39 (*R*)	40 (*R*)	40 (*R*)	68 (*R*)	70 (*R*)	39 (*R*)	55 (*R*)	76 (*R*)	88 (*R*)	56 (*R*)
 S20	47 (*R*)	46 (*R*)	48 (*R*)	60 (*R*)	72 (*R*)	46 (*R*)	52 (*R*)	73 (*R*)	85 (*R*)	41 (*R*)
 S22	19 (*S*)	17 (*S*)	20 (*S*)	32 (*R*)	84 (*S*)	83 (*S*)	63 (*S*)	48 (*R*)	33 (*S*)	53 (*S*)
 S23	15 (*S*)	17 (*S*)	16 (*S*)	29 (*R*)	54 (*S*)	48 (*S*)	19 (*S*)	26 (*R*)	19 (*S*)	29 (*S*)
 S24	10 (*S*)	8 (*S*)	19 (*S*)	21 (*R*)	34 (*S*)	42 (*S*)	48 (*S*)	28 (*R*)	50 (*S*)	51 (*S*)

3.9.7.1. Table SI.1. Complete series of results for the Ir-catalyzed hydrogenation of S2-S20, S22-S24 and S33-S37 using [Ir(cod)(L39-L40a-g)]BAr_F catalyst precursors (continuation)

Substrate	% ee									
	L39a	L39b	L39c	L39d	L39e	L39f	L40d	L40e	L40f	L40g
 **S32**	29 (*S*)	30 (*S*)	29 (*S*)	89 (*S*)	84 (*R*)	33 (*S*)	96 (*S*)	93 (*R*)	64 (*S*)	79 (*S*)
 **S33**	7 (*R*)	4 (*R*)	9 (*R*)	11 (*R*)	9 (*S*)	22 (*R*)	14 (*S*)	22 (*S*)	11 (*S*)	2 (*S*)
 **S34**	4 (*R*)	6 (*R*)	5 (*R*)	27 (*R*)	34 (*S*)	11 (*R*)	52 (*R*)	70 (*S*)	13 (*R*)	5 (*R*)
 **S35**	9 (*S*)	7 (*S*)	7 (*S*)	14 (*S*)	26 (*S*)	11 (*S*)	9 (*S*)	47 (*S*)	7 (*S*)	2 (*S*)
 **S36**	9 (*S*)	10 (*S*)	7 (*S*)	41 (*R*)	62 (*S*)	13 (*S*)	9 (*R*)	69 (*S*)	43 (*S*)	36 (*R*)
 **S37**	20 (*S*)	19 (*S*)	21 (*S*)	82 (*R*)	93 (*S*)	24 (*S*)	18 (*R*)	97 (*S*)	58 (*S*)	64 (*R*)

Full conversions were achieved in all cases

3.10. Enantioselective hydrogenation of minimally functionalized olefins and cyclic β-enamides with indene-based Ir-phosphite/phosphinite-thioether catalysts

Margalef, J.; Biosca, M.; Caldentey, X.; Karlsson, E. A.; Rodriguez, C.; Pericàs, M. A.; Pàmies, O.; Diéguez, M. *Preliminary results.*

In collaboration with the group of Prof. M. A. Pericàs (ICIQ, Tarragona).

Abstract: A phosphite/phosphinite-thioether ligand library with an indene-based backbone has been successfully synthetized in only three steps. The ligand design used allowed the systematic variation of the substituents of the thioether and phosphorus groups. Although low-to-moderate enantioselectivities were obtained in the reduction of unfunctionalized *E*- and *Z*-trisubstituted and tetrasubstituted olefins (ee's up to 70% and up to 30%, respectively), high enantioselectivities were achieved with a wide range of trisubstituted substrates with poorly coordinative polar groups (ee's up to 98%). Moreover, this excellent catalytic performance was extended to the more challenging 1,1'-disubstituted olefins and cyclic β-enamides (ee's up to 98% and 95%, respectively).

3.10.1. Introduction

The preparation of compounds of technological interest or possessing biological activity gives rise to the growing demand for enantiomerically pure products. This fact has stimulated the development for highly efficient asymmetric processes that display high selectivity and activity, minimal consumption of energy and minimal generation of byproducts.[1] Asymmetric catalysis is one of the most applied technologies in the formation of chiral molecules because it only uses a small amount of catalyst to produce an extensive amount of the requested target compound thus reducing the formation of byproducts.[1] In this field, asymmetric hydrogenation of olefins using transition metal catalysts has become a powerful tool. This catalytic process is a uniquely mild and clean chemical transformation that allows to obtain chiral compounds in excellent chemo-, regio- and enantioselectivities.[1] Over many years the scope of this reaction has gradually extended in terms of reactant structure and catalyst efficiency. The most studied catalyst for this process are based on Rh- and Ru-catalysts. However, these catalysts are limited in the range of olefins that can be successfully hydrogenated due to Rh- and Ru-catalysts require the presence of a good coordinating group next to the double bond to achieve high levels of asymmetric induction.[1-2] For this reason, the hydrogenation of minimally functionalized olefins with these type of catalysts generally show low reactivities and unsatisfactory enantioselectivities.

To overcome this limitation, Pfaltz *et al*. introduced a new class of hydrogenation catalysts which consist on Ir-complexes modified with chiral P,N-ligands.[3] Since then, a large number of chiral P,N-ligands have been developed and applied in Ir-catalyzed hydrogenation.[4] However, they were highly substrate-dependent and the development of efficient chiral ligands that tolerate a broader range of substrates remained a challenge.[5] Our group discovered that the presence of biaryl-phosphite moieties in these P,N-ligands provided greater substrate versatility than previous Ir-phosphine/phosphinite,N catalyst systems.[6] More recently, our group has also shown that Ir-complexes modified with P,S-ligands, bearing a thioether moiety instead of N-coordinating group, are also highly enantioselective hydrogenation catalysts.[7] Nevertheless, the full potential of the Ir-P,thioether catalytic systems is still understudied, thus the hydrogenation of some important substrate classes was not explored with this type of catalysts. Thus, for example, the hydrogenation of α,β-unsaturated δ-lactams is not tested yet, despite the importance of chiral δ-lactams with stereogenic centers in the α-position which are present in several natural products and they could also be useful fragments in synthetic chemistry.[4v,8]

For these reasons and in order to further study the potential of P,S-ligands in this catalytic process, we report in this section the synthesis and the application of a phosphite/phosphinite-thioether ligand library (**L41**-**L48a**-**f**) in the Ir-catalyzed hydrogenation of minimally functionalized olefins and cyclic β-enamides (Figure 3.10.1). These ligands are synthesized in only three steps from inexpensive indene. They also benefit from the thioether moiety, which is a robust group that allows the introduction of a chiral center in close proximity to the metal center. In addition, their high modularity allows to fine tune the catalyst's chiral environment by systematically varying: (a) the electronic and steric properties of the thioether group (**L41**-**L48**), (b) the configurations of the biaryl phosphite moiety (**a**-**c**), and (c) the phosphorus group (phosphite (**a**-**c**) vs phosphinite groups (**d-f**)).

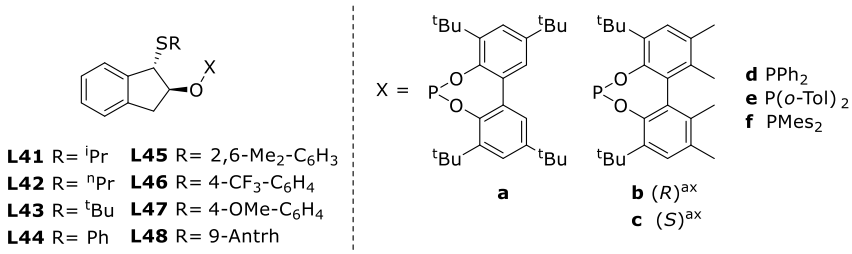


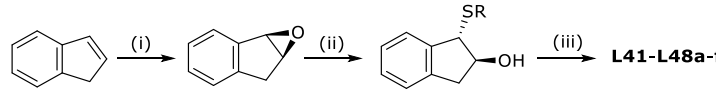
Figure 3.10.1. Phosphite/phosphinite-thioether ligand library **L41**-**L48a**-**f**.

3.10.2. Results and Discussion

3.10.2.1. Synthesis of ligands

Phosphite/phosphinite-thioether ligands **L41**-**L48a**-**f** can be efficiently prepared in three steps as illustrated in Scheme 3.10.1. In the first step, epoxidation of inexpensive indene **1** with bleach using Jacobsen's catalyst, followed by low temperature crystallization, yielded indene oxide with 99% ee (step i).[9] Next, the regio- and stereospecific ring opening of **2** with the corresponding thiol was carried out with sodium hydroxide in a dioxane/water mixture.[10] In order to ensure chemical diversity, eight thiols with markedly different steric and electronic properties were used at this stage. Finally, we took advantage of the hydroxy group in **3**-**10** to establish a representative set of phosphite and phosphinite moieties following standard procedures (step ii).[11] The corresponding thioether-hydroxyl in the presence of base with one equivalent of either the corresponding biaryl phosphorochloridite ($ClP(OR)_2$; $P(OR)_2$ = **a**-**c**) to provide phosphite-thioether ligands (**L41**-**L48a**-**c**) or the desired chlorophosphine ($ClPR_2$; PR_2= **d**-**f**) to achieve the new phosphinite-thioether ligands (**L41**-**L48d**-**f**).

The resulting enantiopure ligands were isolated in good yields as white solids (phosphite-thioether ligands **L41**-**L48a**-**c**) or colorless oils (phosphinite-thioether ligands **L41**-**L48d**-**f**). Phosphite-thioether ligands were found to be stable in air and resistant to hydrolysis, whereas the phosphinite analogues proved less stable, slowly decomposing even when stored at low temperature. All ligands were characterized by $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy and HRMS-ESI. All data were in agreement with assigned structures. The spectra assignments were supported by the information obtained from ^1H-^1H and ^1H-^{13}C correlation measurements. The $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectra showed the expected pattern for the *C1*-ligands.



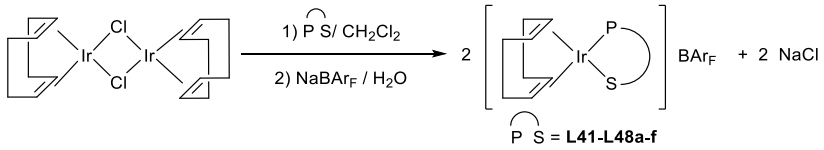
1 **2** **3** R= ^{i}Pr **4** R= ^{n}Pr **5** R= ^{t}Bu **6** R= Ph **7** R=2,6-Me_2-Ph **8** R= 4-CF_3-Ph **9** R= 4-OMe-Ph **10** R= 9-Anth

Scheme 3.10.1. Synthesis of new phosphite/phosphinite-thioether ligands **L41**-**L48a**-**f**; (i) aq. NaOCl, Mn-salen cat., CH_2Cl_2; (ii) RSH, NaOH, dioxane, H_2O, 55 ºC; (iii) $ClP(OR)_2$ (OR= **a**-**c**), pyridine, toluene, 80 °C, 16 h or $ClPR_2$ (R= **d**-**f**), NEt_3, DMAP cat., toluene, 20 min.

3.10.2.2. Synthesis of Ir-catalyst precursors

The catalyst precursors were prepared by treating 0.5 equivalent of $[Ir(\mu\text{-}Cl)(cod)]_2$ with an equimolar amount of the appropriate P,S-ligand (**L41**-**L48a**-**f**) in

dichloromethane under reflux for 1 h. The Cl^-/BAr_F^- counterion exchange was then performed by reaction with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$; 1 equiv) in water (Scheme 3.10.2). The catalyst precursors were obtained in pure form as air-stable red-orange solids.



Scheme 3.10.2. Synthesis of Ir-precursors [Ir(cod)(P-S)]BAr_F (P-S = **L41**-**L48a**-**f**).

The HRMS-ESI spectra show the heaviest ions at m/z which correspond to the loss of the BAr_F anion from the molecular species. The complexes were also characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments, made using ^1H–^1H and ^{13}C–^1H correlation measurements, were as expected for these C_1-symmetric iridium complexes.

3.10.2.3. Asymmetric hydrogenation trisubstituted olefins

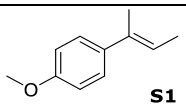
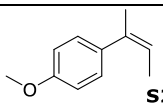
We initially evaluated phosphite/phosphinite-thioether ligands **L41**-**L48a**-**e** in the Ir-catalyzed hydrogenation of model trisubstituted substrates with different geometry, *E*-2-(4-methoxyphenyl)-2-butene **S1** and *Z*-2-(4-methoxyphenyl)-2-butene **S2**. The results are shown in Table 3.10.1. The hydrogenation of both substrates followed similar trends; however, as usually observed, the reduction of substrate **S2** proceeded in lower enantioselectivities.

We first studied the effect of the configuration of the biaryl phosphite group in the asymmetric induction. The results indicated that the presence of chiral biaryl phosphite moiety is necessary to maximize enantioselectivities in both substrates **S1** and **S2** (entries 1 vs 2-3).

The effect of replacing the phosphite moiety by a phosphinite groups depends on the nature of the thioether group. Thus, while for thioether moieties with alkyl substituents (**L41**-**L43**) the replacement of the phosphite by a phosphinite has a negative effect on the enantioselectivity (i.e. entries 2-9), the use of phosphinite moieties in ligands **L44**-**L48**, containing an aryl thioether group, has a positive effect on the enantiocontrol (i.e. entries 11-14). Moreover, the bulkiness of the thioether group also plays an important role, the enhancement of this bulkiness in general provided better results (entries 13-14 vs 19-20).

In summary, the highest enantioselectivities for **S1** and **S2** were obtained with ligands **L48e** and **L48d**, respectively, which contains the optimal combination of ligand parameters (ee's up to 70% and 41%, respectively; entries 19-20).

Table 3.10.1. Ir-catalyzed hydrogenation of **S1** and **S2** using **L41**-**L48a**-**f**.[a]

		 **S1**		 **S2**	
Entry	Ligand	% Conv[b]	%ee[c]	% Conv[b]	% ee[c]
1	**L41a**	100	5 (*R*)	100	2 (*R*)
2	**L41b**	100	48 (*R*)	100	28 (*R*)
3	**L41c**	98	35 (*S*)	100	30 (*S*)
4	**L41d**	100	21 (*S*)	100	0
5	**L41e**	100	33 (*S*)	100	13 (*S*)
6	**L41f**	100	18 (*S*)	100	2 (*R*)
7	**L42b**	100	54 (*R*)	100	17 (*S*)
8	**L43b**	100	61 (*S*)	100	33 (*R*)
9	**L43e**	100	41 (*S*)	100	0
10	**L44b**	100	33 (*S*)	100	20 (*R*)
11	**L45b**	100	38 (*S*)	100	16 (*R*)
12	**L45c**	100	11 (*S*)	100	25 (*R*)
13	**L45d**	100	56 (*S*)	100	35 (*R*)
14	**L45e**	100	60 (*S*)	100	34 (*R*)
15	**L46b**	100	17 (*S*)	100	26 (*R*)
16	**L47b**	100	29 (*S*)	100	28 (*R*)
17	**L48b**	100	39 (*S*)	100	18 (*R*)
18	**L48c**	100	5 (*R*)	100	12 (*R*)
19	**L48d**	100	62 (*S*)	100	41 (*R*)
20	**L48e**	100	70 (*S*)	100	25 (*R*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (100 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^1H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by GC analysis.

To further investigate the potential of phosphite/phosphinite-thioether ligands **L41**-**L48a**-**f**, we selected a representative family of trisubstituted substrates containing poorly coordinative groups. The most relevant results are shown in Figure 3.10.2 (for a complete series of results, see Table SI-1 in Supporting Information at the end of this chapter). The hydrogenation of these olefins is of particular interest because through their functionalization more complex chiral molecules can be obtained. To achieve the highest enantioselectivities, we again found that the ligand components must be correctly selected to suit each substrate.

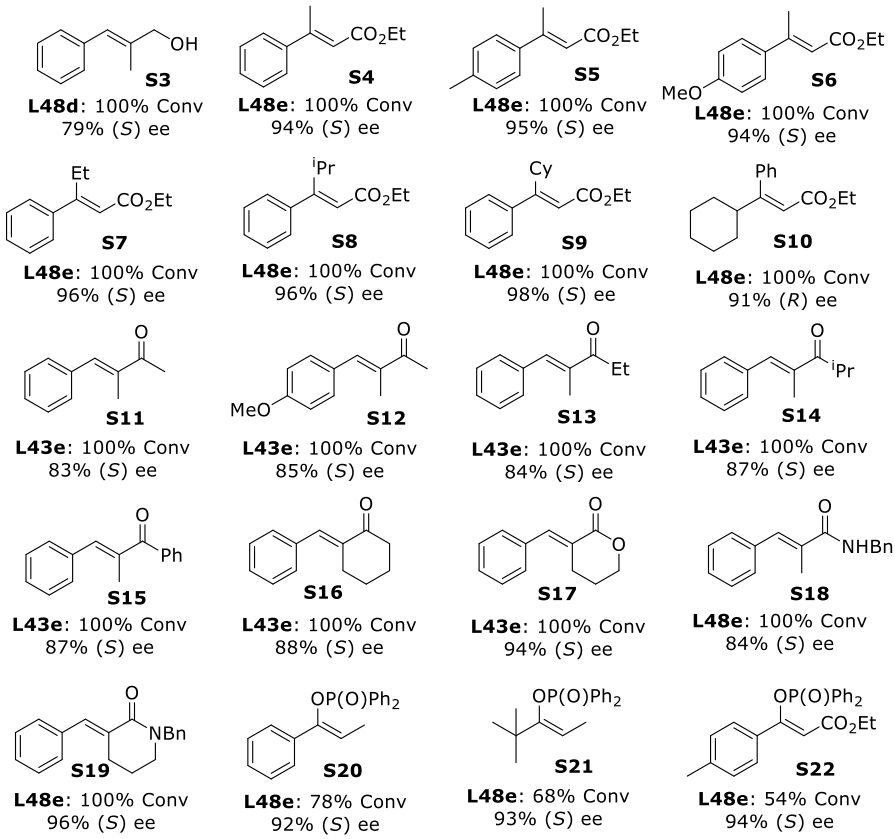


Figure 3.10.2. Selected results for the hydrogenation of trisubstituted olefins **S3**-**S22** by using [Ir(cod)(**L41**-**L48a**-**f**)]BAr_F catalyst precursors. Reaction conditions: Catalyst precursor (2 mol%), CH_2Cl_2, H_2 (100 bar), 4 h (for **S3**-**S16**) or 20 h (for **S17**-**S22**).

We first tested ligands **L41**-**L48a**-**f** in the reduction of allylic alcohol **S3** and a wide range of α,β-unsaturated esters, including a more challenging example with *Z*-geometry (**S4**-**S10**). Although, a moderate enantioselectivity was obtained in the hydrogenation of allylic alcohol **S4** with Ir/**L48d** (79% ee), we were pleased to find out that the reduction of α,β-unsaturated esters **S4**-**S10** proceeds with high enantiocontrol with Ir/**L48e** catalytic system (ee's up to 98%) regardless of the substitution pattern and the olefin geometry. These results are remarkable due to the importance of the resulting chiral carboxylic ester derivatives, which are present in many relevant products.[8d,12]

Then, we focused our attention to the hydrogenation of α,β-unsaturated enones (**S11**-**S16**). Good enantioselectivities were achieved in all cases with Ir/**L43e** (ee's ranging from 83% to 88%), independently of the nature of the alkyl substituent and the electronic nature of the phenyl ring. These results are remarkable not only because of the hydrogenation of these substrates is a simple way to obtain ketones with a stereogenic center in the α-position to the carbonyl moiety, but also because the

hydrogenation of α-substituted enones have been less studied than other trisubstituted olefins.[4i,4p,4r,13]

α,β-Unsaturated lactone **S17**, amide **S18** and lactame **S19** are also challenging substrates whose hydrogenation has been overlooked, despite these frameworks are present in several natural products and have numerous synthetic utilities.[4p,8,14] Gratifyingly, the Ir/**L43e** and Ir/**L48e** catalysts provided good-to-high asymmetric induction in the reduction of these substrates (ee's ranging from 84% to 96%).

Finally, we tested our ligand library in the hydrogenation of enol phosphinates (**S20**-**S22**) whose hydrogenation products can be easily transformed into high valuable compounds such as alcohols and phosphanes.[15] Again, Ir/**L48e** catalytic system is able to provide high enantiocontrol in the hydrogenation of this class of substrates (ee's up to 94%).

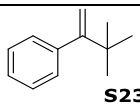
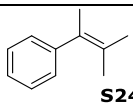
3.10.2.4. Asymmetric hydrogenation of disubstituted and tetrasubstituted olefins

As commented in previous chapters, the hydrogenation of 1,1'-disubsituted olefins usually proceeds in lower asymmetric induction than the reduction of trisubstituted alkenes, due to the enantioselectivity is more difficult to control for the former substrates.[5e,5h] On the other hand, the reduction of tetrasubstituted olefins is still a challenge, only four publications reported a high asymmetric induction with a very limited range of substrates.[16] To evaluate the catalytic performance of ligands **L41**-**L48a**-**f** in the reduction of 1,1'-disubstituted and tetrasubstituted olefins, we chose 3,3-dimethyl-2-phenyl-1-butene (**S23**) and 3-methylbut-2-en-2-yl-benzene (**S24**) as model substrates.

Surprisingly, enantioselectivities for terminal olefin **S23** (Table 3.10.2; ee's up to 97%) were higher than those achieved with trisubstituted substrates **S1** and **S2** (Table 3.10.1; ee's up to 70% and 41%, respectively). The results also indicated that in general the trend of the ligand parameters on the enantioselectivity for **S23** is different than for **S1** and **S2**. Therefore, in contrast to **S1** and **S2**, the use of phosphite moieties instead of phosphinite groups led to higher enantioselectivities (e.g. entries 1 vs 6). The only exception for this general rule can be found in the use of ligands **L48**, which contains a bulkier anthracene thioether moiety, for which similar high levels of enantioselectivity can be achieved using phosphinite-based ligands (**L48d**-**e**, entries 19 and 20 vs 17 and 18). The results also indicated that the sense of enantioselectivity is mainly controlled by the biaryl phosphite moiety. Thus, both enantiomers of the hydrogenated product can be obtained by simply changing the configuration of the phosphite group (e.g. entry 10 vs 11). However, there is cooperative effect between the configuration of the ligand backbone and the biaryl phosphite moiety which depends on the nature of the thioether group. While for ligands with less bulky thioether

substituents the matched combination was achieved with ligands that contain an (*S*)-biaryl phosphite group (e.g. entry 2 vs 3), for ligands with bulkier thioether substituents, the matched combination was obtained with ligands that contain an (R)-biaryl phosphite moiety (e.g. entry 11 vs 12), being the highest enantioselectivities achieved using ligands **L45c** with a 2,6-dimethylphenyl thioether group (97% ee, entry 12).

Table 3.10.2. Ir-catalyzed hydrogenation of **S23** and **S24** using **L41**-**L48a**-**f**.[a]

		 **S23**		 **S24**	
Entry	Ligand	% Conv[b]	%ee[c]	% Conv[b]	% ee[c]
1	**L41a**	100	24 (*S*)	100	15 (*R*)
2	**L41b**	100	82 (*S*)	100	20 (*R*)
3	**L41c**	100	60 (*R*)	100	30 (*S*)
4	**L41d**	100	15 (*S*)	100	28 (*S*)
5	**L41e**	100	9 (*S*)	100	20 (*S*)
6	**L41f**	100	13 (S)	<5	nd
7	**L42b**	100	80 (*S*)	100	21 (*R*)
8	**L43b**	100	50 (*S*)	100	19 (*R*)
9	**L43e**	100	77 (*R*)	100	27 (*S*)
10	**L44b**	100	56 (*S*)	100	11 (*R*)
11	**L45b**	100	66 (*S*)	100	7 (*R*)
12	**L45c**	100	97 (*R*)	100	4 (*S*)
13	**L45d**	100	90 (*R*)	100	11 (*R*)
14	**L45e**	100	87 (*R*)	100	1 (*R*)
15	**L46b**	100	41 (*S*)	100	9 (*R*)
16	**L47b**	100	54 (*S*)	100	6 (*R*)
17	**L48b**	100	56 (*S*)	100	8 (*R*)
18	**L48c**	100	86 (*R*)	100	2 (*R*)
19	**L48d**	100	92 (*R*)	100	4 (*R*)
20	**L48e**	100	94 (*R*)	100	5 (*S*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (1 bar for **S23** and 100 bar for **S24**), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^1H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by GC analysis.

Concerning the reduction of tetrasubstituted acyclic olefin **S24**, only low enantioselectivities could be achieved (ee's up to 30%). The results indicated that the highest enantioselectivities were obtained with ligands that contains alkyl substituents on the thioether moiety, while the type of phosphorus group has a little impact on enantioselectivity.

Encouraged by the high enantioselectivities obtained in the reduction of model 1,1'-disubstituted substrate **S23**, we next studied the catalytic performance of ligands **L41**-**L48a**-**f** in the hydrogenation of other 1,1'-disubstituted substrates. The most noteworthy results are summarized in Figure 3.10.3 (for a complete series of results, see Table SI.2 in the Supporting Information at the end of this chapter). The results indicated that Ir/**L45c** catalyst was able to provide high asymmetric induction in a broad range of 1,1'-disubstituted olefins (**S25**-**S31**; ee's up to 98%), in spite of the variations in the electronic and steric properties of the substituents in the aryl moiety of the substrate.

Finally, we turned our attention in the reduction of 1,1'-disubstiuted enol phosphinates (**S32** and **S33**) to see if the excellent catalytic performance in the reduction of the trisubstituted enol phosphinates was maintained for the even more challenging terminal counterparts. We were pleased to see that catalytic system Ir/**L41f** was able to provide high enantioselectivities in the reduction of this class of substrates (ee's up to 97%).

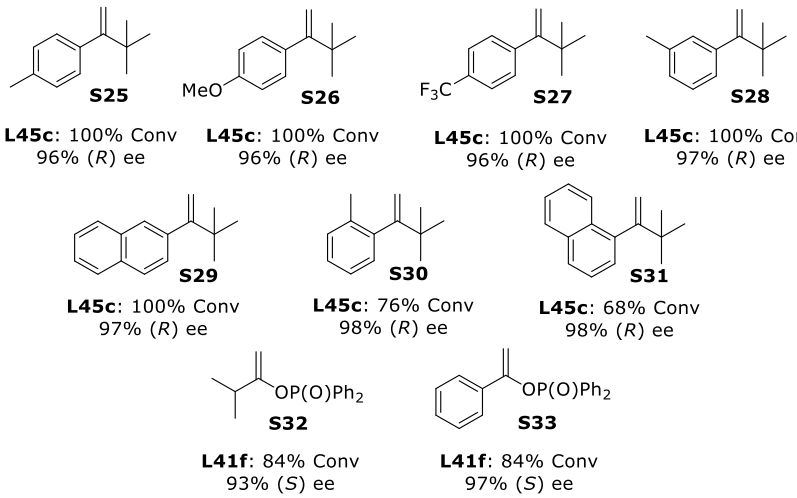
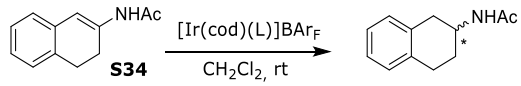


Figure 3.10.3. Selected results for the hydrogenation of trisubstituted olefins **S25**-**S33** by using [Ir(cod)(**L41**-**L48a**-**f**)]BAr_F catalyst precursors. Reaction conditions: Catalyst precursor (2 mol%), CH_2Cl_2, H_2 (1 bar for **S25**-**S31** and 100 bar for **S32** and **S33**), 4 h.

3.10.2.5. Asymmetric hydrogenation of cyclic β-enamides

Finally, we focused on the reduction of challenging cyclic β-enamides, due the hydrogenated products of enamides derived from 2-tetralones and 3-chromanones are key structural units in many therapeutic agents and biologically active natural products.[17] Despite this only few successful examples can be found in the literature and most of them are based on Rh- and Ru-catalyst.[18] However, more recently Ir-catalysts also showed their efficiency in the reduction of this class of substrates.[19]

Table 3.10.3. Ir-catalyzed hydrogenation of **S34** using **L41**-**L48a**-**f**.[a]



Entry	Ligand	% Conv[b]	% ee[b]
1	**L41a**	20	33 (*S*)
2	**L41b**	35	88 (*S*)
3	**L41c**	18	39 (*R*)
4	**L41d**	70	64 (*S*)
5	**L41e**	100	83 (*S*)
6	**L41f**	15	54 (*S*)
7	**L42b**	85	91 (*S*)
8	**L43b**	70	61 (*S*)
9	**L43e**	80	17 (*R*)
10	**L44b**	50	57 (*S*)
11	**L45b**	100	66 (*S*)
12	**L45c**	100	77 (*R*)
13	**L45d**	41	70 (*R*)
14	**L45e**	62	63 (*R*)
15	**L46b**	34	21 (*S*)
16	**L47b**	57	73 (*S*)
17	**L48b**	100	30 (*S*)
18	**L48c**	100	74 (*R*)
19	**L48d**	100	21 (*R*)
20	**L48e**	100	65 (*R*)

[a] Reaction conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (50 bar), CH_2Cl_2 (2 mL), rt, 18 h; [b] Conversion and enantiomeric excesses determined by HPLC.

In order to evaluate the catalytic behavior of ligands **L41**-**L48a**-**f** in the reduction of cyclic β-enamides, we chose *N*-(3,4-dihydronaphthalen-2-yl)acetamide **S34** as model substrate. The results are found in Table 3.10.3 and indicated that again the asymmetric induction is highly affected by the ligand parameters. Thus, they showed that the replacement of the phosphite group by a phosphinite moiety has a negative effect on the enantioselectivity (e.g. entries 2 and 12 vs 4 and 14). In addition, the bulkiness and the electronic nature of the thioether group also play an important role on the enantioselectivity. The presence of electron-poor thioether group (**L46**, entry 15) has a negative influence on enantioselectivity and the bulkiness of the thioether substituents has different effect depending on the configuration of the phosphite group. While for ligands with less bulky thioether substituents the presence of (*R*)-biaryl phosphite moieties results in a matched combination (e.g. **L41b**-**c**, entry 2 vs 3), for ligands **L45**

and **L48b**-**c**, containing bulkier thioether substituents, the matched combination was achieved with (*S*)-biaryl phosphite moieties (entries 10 and 16 vs 11 and 17).

In summary, the highest enantioselectivity was obtained with ligand **L42b**, which combine the less bulky propyl thioether substituent with the presence of a chiral biphenyl phosphite moiety with an (*R*)-configuration (91% ee, entry 7).

We subsequently tested the scope of Ir/**L42b** catalytic systems in the reduction of several cyclic β-enamides (Figure 3.10.3). The high catalytic performance of this catalyst was maintained independently of the different substitution pattern of the 3,4-dihydronaphthalene core. This catalyst precursor (Ir/**L42b**) could also effectively hydrogenate enamide **S40**, derived from 3-chromanone, in high enantioselectivity (95% ee).

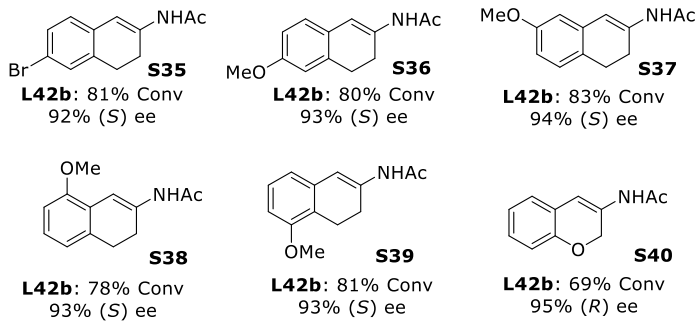


Figure 3.10.3. Results for the hydrogenation of trisubstituted olefins **S35**-**S40** by using [Ir(cod)(**L41**-**L48a**-**f**)]BAr$_F$ catalyst precursors. Reaction conditions: Catalyst precursor (2 mol%), CH_2Cl_2, H_2 (50 bar), 18 h.

3.10.3. Conclusions

An indene-based phosphite/phosphinite-thioether ligand library has been applied in the enantioselective Ir-catalyzed hydrogenation of minimally functionalized olefins and cyclic β-enamides. The new Ir-catalytic systems are prepared in four steps from cheap indene. The highly modularity of these ligands allows us to systematically study the substituents of the thioether and phosphorus groups. With these catalytic systems, the hydrogenation of model *E*-and *Z*-trisubstituted and tetrasubstituted olefins proceed with low-to-moderate asymmetric induction (ee's up to 70%). However, by carefully selecting the ligand components, high enantioselectivities were achieved in several trisubstituted olefins with poorly coordinative neighboring polar groups (ee's up to 98%) as well as in the reduction of more challenging 1,1'-disusbtituted olefins and cyclic β-enamides (ee's up to 98%).

3.10.4. Experimental Section

3.10.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[20] Enantiopure (-)-indene oxide **2**[9] and thioether-phosphinite ligand **L41d**[11b] and **L45d**[11b] were prepared as previously reported. Substrates **S1**-**S2**,[21] **S3**,[22] **S4**-**S6**,[23] **S7**-**S10**,[8d] **S11**,[24] **S12**-**S15**,[4i] **S16**,[25] **S17**,[26] **S18**,[27] **S19**,[26] **S20**-**S22**,[15] **S23**,[28] **S24**,[16a] **S25**-**S31**,[28] **S32**-**S33**,[15] **S34**,[29] **S35**-**S36**,[18j] **S37**,[30] **S38**,[18j] **S39**[18i] and **S40**[18a] were prepared following the reported procedures. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H, ^{13}C and ^{31}P assignments were made on the basis of ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC and ^{1}H-^{31}P gHMBC experiments.

3.10.4.2. General procedure for the preparation of thioether-alcohols 3-10

A solution of indene oxide (2 mmol, 264 mg) in dioxane (4.5 mL/mmol of indene oxide) is treated with the corresponding thiol (3 mmol). Then, a solution of NaOH (3 mmol, 120 mg) in water (0.45 mL/mmol of indene oxide) is added dropwise. The reaction mixture is capped and stirred at 55 °C until the epoxide is consumed according to TLC analysis (*ca*. 45-60 min). After this, the mixture is cooled to rt, diluted with water and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to give a residue that is purified by flash chromatography on silica gel (eluent specified in each case) to give the desired hydroxysulfide.

(*1S*,2*S*)-1-(isopropylthio)-2,3-dihydro-1*H*-inden-2-ol (3): Yield: 308 mg (74%), white solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.34 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.7 Hz), 1.38 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.7 Hz), 2.07 (bs, 1H, OH), 2.86 (dd, 1H, CH_2, $^{2}J_{H-H}$= 16.1 Hz, $^{3}J_{H-H}$= 4.4 Hz), 3.14 (hept, 1H, CH, ^{i}Pr, $^{3}J_{H-H}$= 6.7 Hz), 3.38 (dd, 1H, CH_2, $^{2}J_{H-H}$= 16.1 Hz, $^{3}J_{H-H}$= 6.2 Hz), 4.13 (d, 1H, CH-S, $^{3}J_{H-H}$= 4.1 Hz), 4.46-4.49 (m, 1H, CH-O), 7.22 (bs, 3H, CH=), 7.36 (m , 1H, CH=).^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 23.8 (CH_3), 24.2 (CH_3), 35.5 (CH), 39.9 (CH_2), 55.9 (CH-S), 79.9 (CH-O), 125.1 (CH=), 125.4 (CH=), 127.1 (CH=), 127.9 (CH=), 140.0 (C=), 141.3 (CH).

(1*S*,2*S*)-1-(Propylthio)-2,3-dihydro-1*H*-inden-2-ol (4): Yield: 325 mg (78%), white solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.01 (t, 3H, CH_3, ^{n}Pr, $^{3}J_{H-H}$= 7.3 Hz), 1.66 (sext, 2H, CH_2, ^{n}Pr, $^{3}J_{H-H}$= 7.3 Hz), 2.10 (bs, 1H, OH), 2.53 (dt, 1H, CH_2, $^{2}J_{H-H}$= 12.3 Hz, $^{3}J_{H-H}$= 7.3 Hz), 2.60 (dt, 1H, CH_2, $^{2}J_{H-H}$= 12.3 Hz, $^{3}J_{H-H}$= 7.3 Hz),

2.87 (dd, 1H, CH_2, $^2J_{H-H}$= 16.1 Hz, $^3J_{H-H}$= 4.7 Hz), 3.37 (dd, 1H, CH_2, $^2J_{H-H}$= 16.1 Hz, $^3J_{H-H}$= 6.3 Hz), 4.09 (d, 1H, CH-S, $^3J_{H-H}$= 4.3 Hz), 4.49 (quint, 1H, CH-O, $^3J_{H-H}$= 5.0 Hz), 7.32-7.40 (m, 1H, CH=), 7.20-7.25 (m, 3H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 13.6 (CH_3), 23.2 (CH_2), 33.0 (CH_2), 39.8 (CH_2), 57.0 (CH-S), 79.3 (CH-O), 125.1 (CH=), 125.3 (CH=), 127.1 (CH=), 127.9 (CH=), 140.1 (C=), 140.6 (C=).

(1*S*,2*S*)-1-(*tert*-Butylthio)-2,3-dihydro-1*H*-inden-2-ol (5): Yield: 320 mg (72%), pale orange solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.45 (s, 3H, CH_3, ^{t}Bu), 2.29 (bs, 1H, OH), 2.86 (dd, 1H, CH_2, $^2J_{H-H}$= 15.8 Hz, $^3J_{H-H}$= 5.6 Hz), 3.32 (dd, 1H, CH_2, $^2J_{H-H}$= 15.8 Hz, $^3J_{H-H}$= 6.4 Hz), 4.03 (d, 1H, CH-S, $^3J_{H-H}$= 5.3 Hz), 4.39-4.44 (m, 1H, CH-O), 7.19-7.25 (m, 3H, CH=), 7.38 (m, 1H, CH=), 7.36 (m , 1H, CH=).^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 31.7 (CH_3, ^{t}Bu), 39.9 (CH_2), 43.7 (C, ^{t}Bu), 54.6 (CH-S), 80.8 (CH-O), 124.8 (CH=), 125.6 (CH=), 127.2 (CH=), 127.7 (CH=), 139.7 (C=), 142.0 (C=).

(1*S*,2*S*)-1-(Phenylthio)-2,3-dihydro-1*H*-inden-2-ol (6): Yield: 373 mg (77%), white solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.09 (bs, 1H, OH), 2.82 (dd, 1H, CH_2, $^2J_{H-H}$= 16.3 Hz, $^3J_{H-H}$= 3.5 Hz), 3.32 (dd, 1H, CH_2, $^2J_{H-H}$= 16.3 Hz, $^3J_{H-H}$= 6.2 Hz), 4.50 (dt, 1H, CH-O, $^3J_{H-H}$= 6.2 Hz, $^3J_{H-H}$= 3.4 Hz), 4.55 (d, 1H, CH-S, $^3J_{H-H}$= 3.3 Hz), 7.19-7.24 (m, 4H, CH=), 7.26-7.31 (m, 2H, CH=), 7.34-7.37 (m, 1H, CH=), 7.40-7.43 (m, 2H, CH=).^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 39.9 (CH_2), 59.1 (CH-S), 79.6 (CH-O), 125.2 (CH=), 125.7 (CH=), 126.9 (CH=), 127.2 (CH=), 128.3 (CH=), 129.0 (CH=), 130.9 (CH=), 135.2 (CH=), 139.9 (CH=), 135.2 (C=), 139.9 (C=), 140.6 (C=).

(1*S*,2*S*)-1-((2,6-Dimethylphenyl)thio)-2,3-dihydro-1*H*-inden-2-ol (7): Yield: 427 mg (79%), white solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.75 (bs, 1H, OH), 2.47 (s, 6H, CH_3), 2.82 (dd, 1H, CH_2, $^2J_{H-H}$= 16.6 Hz, $^3J_{H-H}$= 2.1 Hz), 3.52 (dd, 1H, CH_2, $^2J_{H-H}$= 16.6 Hz, $^3J_{H-H}$= 5.5 Hz), 4.32 (d, 1H, CH-S, $^3J_{H-H}$= 2.0 Hz), 4.36 (tt, 1H, CH-O, $^3J_{H-H}$= 5.5 Hz, $^3J_{H-H}$= 2.1 Hz), 6.94 (d, 1H, CH=, $^3J_{H-H}$= 7.5 Hz), 7.06-7.16 (m, 4H, CH=), 7.18-7.26 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.9 (CH_3), 40.3 (CH_2), 58.8 (CH-S), 78.5 (CH-O), 125.3 (CH=), 125.4 (CH=), 126.7 (CH=), 128.1 (CH=), 128.2 (CH=), 128.7 (CH=), 132.0 (CH=), 140.4 (C=), 140.7 (C=), 143.6 (C=).

(1*S*,2*S*)-1-((4-(Trifluoromethyl)phenyl)thio)-2,3-dihydro-1*H*-inden-2-ol (8): Yield: 478 mg (77%), yellow oil. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.06 (d, 1H, OH, $^3J_{H-H}$= 4.9 Hz), 2.91 (dd, 1H, CH_2, $^2J_{H-H}$= 16.5 Hz, $^3J_{H-H}$= 3.5 Hz), 3.42 (dd, 1H, CH_2, $^2J_{H-H}$= 16.5 Hz, $^3J_{H-H}$= 6.0 Hz), 4.55 (m, 1H, CH-O), 4.69 (d, 1H, CH-S, $^3J_{H-H}$= 3.2 Hz), 7.21-7.30 (m, 3H, CH=), 7.36-7.41 (m, 1H, CH=), 7.46-7.57 (m, 4H,

CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 40.2 (CH_2), 58.0 (CH-S), 78.6 (CH-O), 124.1 (CH=), 125.4 (CH=), 125.7 (CH=), 125.8 (q, CH=, $^3J_{H-F}$= 3.8 Hz), 127.4 (CH=), 128.2 (q, C=, $^2J_{H-F}$= 32.8 Hz), 128.7 (CH=), 128.8 (CH=), 139.0 (C=), 140.6 (C=), 141.3 (C=).

(1*S*,2*S*)-1-((4-Methoxyphenyl)thio)-2,3-dihydro-1*H*-inden-2-ol (9): Yield: 541 mg (79%), yellow oil. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 75:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.97 (d, 1H, OH, $^3J_{H-H}$= 5.2 Hz), 2.81 (dd, 1H, CH_2, $^2J_{H-H}$= 16.3, $^3J_{H-H}$= 3.5 Hz), 3.25 (dd, 1H, CH_2, $^2J_{H-H}$= 16.3 Hz, $^3J_{H-H}$= 6.1 Hz), 3.79 (s, 3H, CH_3O), 4.38 (d, 1H, CH-S, $^3J_{H-H}$= 3.3 Hz), 4.50 (tt, 1H, CH-O, $^3J_{H-H}$= 6.1 Hz, $^3J_{H-H}$= 3.5 Hz), 6.82 (d, 2H, CH=, $^3J_{H-H}$= 8.7 Hz), 7.19-7.27 (m, 3H, CH=), 7.35-7.42 (m, 3H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 39.9 (CH_2), 55.3 (CH-S), 60.6 (CH_3O), 78.6 (CH-O), 114.6 (CH=), 124.4 (CH=), 125.2 (CH=), 125.6 (CH=), 127.0 (CH=), 128.1 (CH=), 135.1 (C=), 140.2 (C=), 140.6 (C=), 159.6 (C=).

(1*S*,2*S*)-1-(Anthracen-9-ylthio)-2,3-dihydro-1*H*-inden-2-ol (10): Yield: 308 mg (45%), yellow solid. SiO_2-chromatography (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.33 (d, 1H, OH, $^3J_{H-H}$= 5.1 Hz), 2.80 (dd, 1H, CH_2, $^2J_{H-H}$= 16.4 Hz, $^3J_{H-H}$= 2.6 Hz), 3.58 (dd, 1H, CH_2, $^2J_{H-H}$= 16.4 Hz, $^3J_{H-H}$= 5.6 Hz), 4.40 (m, 1H, CH-O), 4.55 (d, 1H, CH-S, $^3J_{H-H}$= 2.2 Hz), 7.16 (t, 1H, CH=, $^3J_{H-H}$= 7.5 Hz), 7.24 (t, 1H, CH=, $^3J_{H-H}$= 7.5 Hz), 7.25-7.30 (m , 2H, CH=), 7.52 (ddd, 2H, CH=, $^3J_{H-H}$= 8.0 Hz, $^3J_{H-H}$= 6.5 Hz, $^4J_{H-H}$= 1.1 Hz), 7.61 (ddd, 2H, CH=, $^3J_{H-H}$= 8.9 Hz, $^3J_{H-H}$= 6.5 Hz, $^4J_{H-H}$= 1.0 Hz), 8.05 (d, 2H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.54 (s, 1H, CH=), 8.98 (dq, 2H, CH=, $^3J_{H-H}$= 8.9 Hz, $^4J_{H-H}$= 1.0 Hz).^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 40.1 (CH_2), 61.2 (CH-S), 78.7 (CH-O), 125.3 (CH=), 125.4 (CH=), 125.7 (CH=), 126.6 (CH=), 126.9 (CH=), 127.0 (CH=), 127.7 (CH=), 128.4 (CH=), 129.1 (CH=), 129.6 (C=), 131.8 (C=), 134.9 (C=), 140.2 (C=), 140.8 (C=).

3.10.4.3. General procedure for the preparation of phosphite-thioether ligands L41-L48a-c

The corresponding phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.3 mL, 3.9 mmol) was added. The corresponding thioether-hydroxyl compound (1 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.3 mL, 3.9 mmol) was added. The alcohol solution was transferred slowly to a solution of phosphorochloridite. The reaction mixture was stirred at 80 ºC for 90 min, after which the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in silica (Hexane/Toluene/NEt_3 = 7/3/1) to produce the corresponding ligand as a white solid.

L41a: Yield: 320.8 mg (50%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 141.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.09 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.4 Hz), 1.07 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.8 Hz), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 2.90-2.96 (m, 2H, CH_2, CH ^{i}Pr), 3.23 (dd, 1H, CH_2, $^{2}J_{H-H}$= 16.4 Hz, $^{3}J_{H-H}$= 5.6 Hz), 4.57 (b, 1H, CH-S), 5.18 (m, 1H, CH-OP), 6.94-7.12 (m, 3H, CH=), 7.31 (s, 1H, CH=), 7.33 (d, 1H, CH=, $^{4}J_{H-H}$= 2.8 Hz), 7.34 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.57 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.59 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), ^{13}C NMR (100.6 MHz, C_6D_6): δ= 23.4 (CH_3, ^{i}Pr), 23.8 (CH_3, ^{i}Pr), 31.0 (d, CH_3, ^{t}Bu, J_{C-P}= 7.6 Hz), 31.1 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.3 (CH, ^{i}Pr), 39.1 (CH_2), 54.7 (CH-S), 82.8 (CH-OP), 124.1-146.6 (aromatic carbons). MS HR-ESI [found 669.3498, $C_{40}H_{55}O_3PS$ (M-Na)$^{+}$ requires 669.3502].

L41b: Yield: 220.8 mg (37%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 130.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.03 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.8 Hz), 1.23 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.4 Hz), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.71-2.77 (m, 1H, CH, ^{i}Pr), 2.88 (d, 1H, CH_2, $^{2}J_{H-H}$= 16.4 Hz), 3.27 (dd, 1H, CH_2, $^{2}J_{H-H}$= 16.4 Hz, $^{3}J_{H-H}$= 4.8 Hz), 4.81 (b, 1H, CH-S), 4.92 (m, 1H, CH-OP), 6.89-7.12 (m, 3H, CH=), 7.19 (m, 2H, CH=), 7.35 (d, 1H, CH=, $^{3}J_{H-H}$ =8.8 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.3 (CH_3), 16.6 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 23.3 (CH_3, ^{i}Pr), 24.2 (CH_3, ^{i}Pr), 31.3 (CH_3, ^{t}Bu), 31.4 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 34.8 (CH, ^{i}Pr), 39.3 (CH_2), 55.0 (CH-S), 82.9 (CH-OP), 124.9-146.4 (aromatic carbons). MS HR-ESI [found 613.2903, $C_{36}H_{47}O_3PS$ (M-Na)$^{+}$ requires 613.2876].

L41c: Yield: 202.0 mg (34%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.09 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.8 Hz), 1.12 (d, 3H, CH_3, ^{i}Pr, $^{3}J_{H-H}$= 6.8 Hz), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.05 (s, 6H, CH_3), 2.85-2.91 (m, 1H, CH, ^{i}Pr), 3.37 (d, 1H, CH_2, $^{2}J_{H-H}$= 16.4 Hz), 3.38 (dd, 1H, CH_2, $^{2}J_{H-H}$= 16.8 Hz, $^{3}J_{H-H}$= 6.0 Hz), 4.24 (d, 1H, CH-S, $^{3}J_{H-H}$= 4.8 Hz), 5.07-5.11 (m, 1H, CH-OP), 6.95-7.03 (m, 3H, CH=), 7.18 (s, 1H, CH=), 7.23 (2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.3 (CH_3, ^{i}Pr), 16.5 (CH_3, ^{i}Pr), 20.1 (CH_3), 23.5 (CH_3), 23.9 (CH_3), 31.3 (CH_3, ^{t}Bu), 31.4 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 34.6 (C, ^{t}Bu), 34.8 (CH, ^{i}Pr), 39.7 (CH_2), 54.7 (CH-S), 82.7 (d, CH-OP, $^{2}J_{C-P}$= 6.1 Hz), 124.9-145.5 (aromatic carbons). MS HR-ESI [found 613.2869, $C_{36}H_{47}O_3PS$ (M-Na)$^{+}$ requires 613.2876].

L42b: Yield: 352.2 mg (59%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 132.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.82 (pt, 3H, CH_3, Pr, $^{3}J_{H-H}$= 7.2 Hz), 1.41-1.53 (m, 2H, CH_2, Pr), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.23-2.30 (m, 1H, CH_2, Pr), 2.44-2.50 (m, 2H, CH_2, Pr), 2.93 (d, 1H, CH_2, $^{2}J_{H-H}$= 16.8 Hz), 3.25 (dd, 1H, CH_2, $^{2}J_{H-H}$= 16.4 Hz, $^{3}J_{H-H}$= 5.2 Hz), 4.72 (b, 1H, CH-S), 4.90-4.94 (m, 1H, CH-OP), 6.92 (d, 1H, CH=, $^{3}J_{H-H}$= 6.4 Hz), 7.00-

7.03 (m, 2H, CH=), 7.22 (d, 2H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.37 (d, 2H, CH=, $^3J_{H-H}$= 6.8 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 13.2 (CH_3, Pr), 16.2 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 23.0 (CH_2, Pr), 31.3 (CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.4 (CH_3, ^{t}Bu), 33.1 (CH_2, Pr), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 39.2 (d, CH_2, $^3J_{C-P}$= 3.8 Hz), 56.1 (d, CH-S, $^3J_{C-P}$= 3.0 Hz), 82.4 (CH-OP), 124.8-146.1 (aromatic carbons). MS HR-ESI [found 613.2903, $C_{36}H_{47}O_3PS$ $(M-Na)^+$ requires 613.2876].

L43b: Yield: 283.6 mg (47%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 134.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.34 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.71 (d, 1H, CH_2, $^2J_{H-H}$= 16.0 Hz), 3.12 (dd, 1H, CH_2, $^2J_{H-H}$= 16.4 Hz, $^3J_{H-H}$= 5.2 Hz), 4.56 (b, 1H, CH-S), 5.22-5.25 (m, 1H, CH-OP), 6.83 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 6.96-7.21 (m, 1H, CH=), 7.41 (d, 1H, CH=, $^3J_{H-H}$= 7.6 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.3 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.4 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 38.8 (CH_2), 43.5 (C, ^{t}Bu), 54.0 (d, CH-S, $^3J_{C-P}$= 3.8 Hz), 83.7 (CH-OP), 124.7-145.7 (aromatic carbons). MS HR-ESI [found 627.3026, $C_{37}H_{49}O_3PS$ $(M-Na)^+$ requires 627.3032].

L44b: Yield: 284.8 mg (41%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 135.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.44 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.73 (d, 1H, CH_2, $^2J_{H-H}$= 16.8 Hz), 2.93 (dd, 1H, CH_2, $^2J_{H-H}$= 17.2 Hz, $^3J_{H-H}$= 5.6 Hz), 4.95 (b, 1H, CH-S), 5.03-5.06 (m, 1H, CH-OP), 6.80-6.82 (m, 1H, CH=), 6.90-7.01 (m, 5H, CH=), 7.21 (d, 2H, CH=, $^3J_{H-H}$= 3.6 Hz), 7.27-7.29 (m, 3H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.2 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 39.2 (d, CH_2, $^3J_{C-P}$= 3.0 Hz), 58.8 (d, CH-S, $^3J_{C-P}$= 3.8 Hz), 81.6 (d, CH-OP, $^2J_{C-P}$= 4.6 Hz), 124.8-145.7 (aromatic carbons). MS HR-ESI [found 647.2737, $C_{39}H_{45}O_3PS$ $(M-Na)^+$ requires 647.2719].

L45b: Yield: 324.6 mg (42%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 135.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.42 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.31 (s, 6H, CH_3), 2.90 (d, 1H, CH_2, $^2J_{H-H}$= 16.8 Hz), 3.38 (dd, 1H, CH_2, $^2J_{H-H}$= 16.8 Hz, $^3J_{H-H}$= 4.8 Hz), 4.80-4.83 (m, 1H, CH-OP), 4.91 (s, 1H, CH-S), 6.67 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 6.83 (pt, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 6.88-7.03 (m, 5H, CH=), 7.19 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.2 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 21.7 (CH_3), 31.2 (CH_3, ^{t}Bu), 31.3 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 39.3 (d, CH_2, $^3J_{C-P}$= 3.8 Hz), 58.0 (d, CH-S, $^3J_{C-P}$= 3.8 Hz), 81.3 (d, CH-OP, $^2J_{C-P}$= 4.6 Hz), 124.8-145.6 (aromatic carbons). MS HR-ESI [found 675.3026, $C_{41}H_{49}O_3PS$ $(M-Na)^+$ requires 675.3032].

L45c: Yield: 276.4 mg (36%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 137.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.44 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3),

1.74 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.25 (s, 6H, CH_3), 3.19 (d, 1H, CH_2, $^2J_{H-H}$= 16.8 Hz), 3.50 (dd, 1H, CH_2, $^2J_{H-H}$= 17.2 Hz, $^3J_{H-H}$= 4.8 Hz), 4.60 (b, 1H, CH-S), 4.93 (m, 1H, CH-OP), 6.46 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 6.79 (m, 1H, CH=), 6.86-7.22 (m, 6H, CH=), 7.22 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.7 (CH_3), 31.3 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 40.2 (d, CH_2, $^3J_{C-P}$= 3.0 Hz), 57.5 (d, CH-S, $^3J_{C-P}$= 3.8 Hz), 81.0 (d, CH-OP, $^3J_{C-P}$= 7.6 Hz), 124.8-145.5 (aromatic carbons). MS HR-ESI [found 675.3041, $C_{41}H_{49}O_3PS$ $(M-Na)^+$ requires 675.3032].

L46b: Yield: 336.1 mg (52%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 135.6 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.41 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.67 (d, 1H, CH_2, $^2J_{H-H}$= 16.8 Hz), 2.99 (dd, 1H, CH_2, $^2J_{H-H}$= 16.8 Hz, $^3J_{H-H}$= 6.0 Hz), 4.92 (b, 1H, CH-S), 4.96-5.01 (m, 1H, CH-OP), 6.82-6.84 (m, 1H, CH=), 6.99-7.19 (m, 8H, CH=), 7.24-7.26 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.9 (CH_3), 17.1 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 31.9 (d, CH_3, ^{t}Bu, $^3J_{C-P}$= 5.3 Hz), 32.0 (CH_3, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 39.6 (CH_2), 58.3 (d, CH-S, $^3J_{C-P}$= 3.8 Hz), 81.7 (d, CH-OP, $^3J_{C-P}$= 4.6 Hz), 125.7-146.2 (aromatic carbons). MS HR-ESI [found 715.2610, $C_{40}H_{44}F_3O_3PS$ $(M-Na)^+$ requires 715.2593].

L47b: Yield: 321 mg (49%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 135.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.47 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.78 (d, 1H, CH_2, $^2J_{H-H}$= 16.8 Hz), 2.87 (dd, 1H, CH_2, $^2J_{H-H}$= 16.8 Hz, $^3J_{H-H}$= 5.6 Hz), 3.16 (s, CH_3, *p*-OMe) 4.88 (b, 1H, CH-S), 5.04-5.07 (m, 1H, CH-OP), 6.54 (d, 2H, CH=, $^3J_{H-H}$= 8.8 Hz), 6.82 (d, 1H, CH=, $^3J_{H-H}$= 6.8 Hz), 6.96-7.23 (m, 6H, CH=), 7.31 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.7 (CH_3), 16.9 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 31.7 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 39.9 (CH_2), 54.8 (CH_3, *p*-MeO), 60.5 (d, CH-S, $^3J_{C-P}$= 3.8 Hz), 82.4 (d, CH-OP, $^3J_{C-P}$= 4.6 Hz), 114.7-160.4 (aromatic carbons). MS HR-ESI [found 677.2851, $C_{40}H_{47}O_4PS$ $(M-Na)^+$ requires 677.2825].

L48b: Yield: 94.3 mg (27%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 136.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.28 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.91 (d, 1H, CH_2, $^2J_{H-H}$= 16.8 Hz), 3.45 (dd, 1H, CH_2, $^2J_{H-H}$= 16.8 Hz, $^3J_{H-H}$= 5.2 Hz), 4.92-4.95 (m, 1H, CH-OP), 5.22 (b, 1H, CH-S), 6.55-6.63 (m, 2H, CH=), 6.90 (s, 2H, CH=), 7.11-7.28 (m, 6H, CH=), 7.73 (d, 2 H, CH=, $^3J_{H-H}$= 8,0 Hz), 8.16 (s, 1, CH=), 8.96 (d, 2 H, CH=, $^3J_{H-H}$= 8,4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.2 (CH_3), 16.6 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.1 (CH_3, ^{t}Bu), 31.3 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 34.4 (C, ^{t}Bu), 39.7 (CH_2), 60.1 (CH-S), 81.4 (CH-OP), 124.8-145.7 (aromatic carbons). MS HR-ESI [found 747.3048, $C_{47}H_{49}O_3PS$ $(M-Na)^+$ requires 747.3028].

L48c: Yield: 123 mg (34%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 138.1 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.14 (s, 9H, CH_3, ^{t}Bu), 1.19 (s, 9H, CH_3, ^{t}Bu), 1.74 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.06 (d, 1H, CH_2, $^2J_{H-H}$= 17.0 Hz), 3.54 (dd, 1H, CH_2, $^2J_{H-H}$= 17.0 Hz, $^3J_{H-H}$= 4.9 Hz), 4.61 (bs, 1H, CH-S), 4.82 (dd, 1H, CH-OP, $^3J_{C-P}$= 9.0 Hz, $^3J_{H-H}$= 4.9 Hz), 6.64 (d, 1H, CH=, $^3J_{H-H}$= 7.5 Hz), 6.83 (t, 1H, CH=, $^3J_{H-H}$= 7.3 Hz), 7.05-7.20 (m, 4H, CH=), 7.24-7.28 (m, 1H, CH=), 7.45-7.51 (m, 3H, CH=), 7.98-8.01 (m, CH=, 2H), 8.49 (s, 1H, CH=), 8.77-8.80 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.5 (CH_3), 16.7 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 31.1 (d, CH_3, ^{t}Bu, J_{C-P}= 5.2 Hz), 31.2 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.4 (C, ^{t}Bu), 40.0 (d, CH_2-O, $^3J_{C-P}$= 6.1 Hz), 60.0 (d, CH-S, $^3J_{C-P}$= 5.9 Hz), 81.0 (d, CH-OP, $^2J_{C-P}$= 12.0 Hz), 124.9-140.9 (aromatic carbons). MS HR-ESI [found 747.3032, $C_{47}H_{49}O_3PS$ $(M\text{-}Na)^+$ requires 747.3028].

3.10.4.4. General procedure for the preparation of phosphinite-thioether ligands L41-L48d-f.

The corresponding thioether-hydroxyl compound (0.5 mmol) and DMAP (6.7 mg, 0.055 mmol) were dissolved in toluene (1 ml), and triethylamine was added (0.09 ml, 0.65 mmol) at rt, followed by the addition of the corresponding chlorophosphine (0.55 mmol) via syringe. The reaction was stirred for 20 min at rt. The solvent was removed *in vacuo*, and the product was purified by flash chromatography on alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as an oil.

L41e: Yield: 258 mg (61%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 98.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.08 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.21 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 2.37 (s, 3H, CH_3, *o*-Tol), 2.41 (s, 3H, CH_3, *o*-Tol), 2.91-3.01 (m, 2H, CH ^{i}Pr and CH_2), 3.30 (dd, 1H, CH_2, $^2J_{H-H}$= 16.4 Hz, $^3J_{H-H}$= 6.0 Hz), 4.49 (b, 1H, CH-S), 4.82 (m, 1H, CH-OP), 6.91-7.15 (m, 9H, CH=), 7.36 (d, 1H, CH=, $^3J_{H-H}$= 6.8 Hz), 7.52 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 20.3 (d, CH_3, *o*-Tol, $^3J_{C-P}$= 4.0 Hz), 20.5 (d, CH_3, *o*-Tol, $^3J_{C-P}$= 4.4 Hz), 23.2 (CH_3, ^{i}Pr), 23.8 (CH_3, ^{i}Pr), 35.3 (CH, ^{i}Pr), 39.1 (d, CH_2, $^3J_{C-P}$= 6.1 Hz), 54.7 (d, CH-S, $^3J_{C-P}$= 6.1 Hz), 87.7 (d, CH-OP, $^2J_{C-P}$= 20,7 Hz), 124.8-141.4 (aromatic carbons).

L41f: Yield: 129.9 mg (54%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 114.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.11 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.22 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 2.04 (s, 3H, *p*-CH_3, Mes), 2.06 (s, 3H, *p*-CH_3, Mes), 2.39 (s, 12H, *o*-CH_3, Mes), 2.85-2.99 (m, 2H, CH ^{i}Pr, CH_2), 3.33 (dd, 1H, CH_2, $^2J_{H-H}$= 16.4 Hz, $^3J_{H-H}$= 5.6 Hz), 4.46 (b, 1H, CH-S), 4.66 (m, 1H, CH-OP), 6.63 (s, 1H, CH=), 6.64 (s, 1H, CH=), 6.65 (s, 1H, CH=), 6.66 (s, 1H, CH=), 6.94-7.05 (m, 2H, CH=), 7.12 (m, 1H, CH=), 7.31 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 20.6 (*p*-CH_3, Mes), 22.1 (d, *o*-CH_3, Mes, $^3J_{C-P}$= 3.0 Hz), 22.2 (d, *o*-CH_3, Mes, $^3J_{C-P}$= 3.1 Hz), 23.2 (CH_3, ^{i}Pr), 23.9 (CH_3, ^{i}Pr), 35.2

(CH, ^{i}Pr), 38.9 (d, CH_2, $^3J_{C\text{-}P}$= 6.8 Hz), 54.6 (d, CH-S, $^3J_{C\text{-}P}$= 7.6 Hz), 87.6 (d, CH-OP, $^2J_{C\text{-}P}$= 22,1 Hz), 124.7-141.6 (aromatic carbons).

L43e: Yield: 148 mg (31%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 97.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.24 (s, 9H, CH_3, ^{t}Bu), 2.32 (s, 3H, CH_3, *o*-Tol), 2.41 (s, 3H, CH_3, *o*-Tol), 2.92 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 16.4 Hz, $^3J_{H\text{-}H}$= 2.8 Hz), 3.22 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 16.0 Hz, $^3J_{H\text{-}H}$= 5.2 Hz), 4.40 (b, 1H, CH-S), 4.82-4.85 (m, 1H, CH-OP), 6.89-7.12 (m, 9H, CH=), 7.39 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.2 Hz), 7.50-7.54 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 20.2 (d, CH_3, $^3J_{C\text{-}P}$= 15.3 Hz), 20.4 (d, CH_3, $^3J_{C\text{-}P}$= 16.0 Hz), 31.3 (CH_3, ^{t}Bu), 39.0 (d, CH_2, $^3J_{C\text{-}P}$= 6.0 Hz), 43.4 (C, ^{t}Bu), 53.6 (d, CH-S, $^3J_{C\text{-}P}$= 6.8 Hz), 88.5 (d, CH-OP, $^3J_{C\text{-}P}$= 20.6 Hz), 124.6-142.3 (aromatic carbons).

L45e: Yield: 261 mg (54%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 98.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 2.30 (s, 3H, CH_3, *o*-Tol), 2.35 (s, 3H, CH_3, *o*-Tol), 2.44 (s, 6H, CH_3), 3.14 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 16.8 Hz), 3.54 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 16.8 Hz, $^3J_{H\text{-}H}$= 5.2 Hz), 4.78-4.82 (m, 1H, CH-OP), 4.83 (b, 1H, CH-S), 6.91-7.14 (m, 12H, CH=), 7.23 (s, 1H, CH=), 7.32-7.35 (m, 1H, CH=), 7.40-7.44 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 20.1 (d, CH_3, $^3J_{C\text{-}P}$= 6.1 Hz), 20.3 (d, CH_3, $^3J_{C\text{-}P}$= 6.8 Hz), 21.7 (CH_3), 39.4 (d, CH_2, $^3J_{C\text{-}P}$= 6.9 Hz), 58.0 (d, CH-S, $^3J_{C\text{-}P}$= 6.9 Hz), 85.7 (d, CH-OP, $^3J_{C\text{-}P}$= 5.4 Hz), 124.9-143.5 (aromatic carbons).

L48d: Yield: 199 mg (77%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 111.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 2.90 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 16.7 Hz), 3.41 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 16.7 Hz, $3J_{H\text{-}H}$= 5.6 Hz), 4.70-4.74 (m, 1H, CH-OP), 5.04 (b, 1H, CH-S), 6.76-6.99 (m, 10H, CH=), 7.04-7.12 (m, 3H, CH=), 7.18-7.22 (m, 2H, CH=), 7.28-7.32 (m, 3H, CH=), 7.73 (d, 2H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 8.13 (s, 1H, CH=), 9.07 (d, 2H, CH=, $^3J_{H\text{-}H}$= 8.9 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 39.6 (CH_2), 60.4 (CH-S), 85.7 (d, CH-OP, $^2J_{C\text{-}P}$= 19.4 Hz), 125.0-142.1 (aromatic carbons).

L48e: Yield: 212 mg (76%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 98.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.84 (s, 3H, CH_3, *o*-Tol), 2.02 (s, 3H, CH_3, *o*-Tol), 3.00 (d, 1H, CH_2, $^2J_{H\text{-}H}$= 16.7 Hz), 3.51 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 16.7 Hz, $^3J_{H\text{-}H}$= 5.2 Hz), 4.70-4.74 (m, 1H, CH-OP), 5.04 (b, 1H, CH-S), 6.67-7.07 (m, 10H, CH=), 7.12-7.25 (m, 4H, CH=), 7.30-7.34 (m, 2H, CH=), 7.76 (d, 2H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 8.15 (s, 1H, CH=), 9.10 (d, 2H, CH=, $^3J_{H\text{-}H}$= 8.8 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 19.8 (d, CH_3, *o*-Tol, $^3J_{C\text{-}P}$= 20.2 Hz), 20.0 (d, CH_3, *o*-Tol, $^3J_{C\text{-}P}$= 20.4 Hz), 39.3 (d, CH_2, $^3J_{C\text{-}P}$= 6.8 Hz), 60.4 (d, CH-S, $^3J_{C\text{-}P}$= 7.2 Hz), 85.6 (d, CH-OP, $^2J_{C\text{-}P}$= 21.8 Hz), 125.0-141.5 (aromatic carbons).

3.10.4.5. General procedure for the preparation of [Ir(cod)(L38-L45a-g)]BAr_F

The corresponding ligand (0.037 mmol) was dissolved in CH_2Cl_2 (2 mL) and [Ir(μ-Cl)(cod)]$_2$ (12.5 mg, 0.0185 mmol) was added. The reaction mixture was refluxed at 50 ^oC for 1 hour. After 5 min at room temperature, $NaBAr_F$ (38.6 mg, 0.041 mmol) and water (2 mL) were added and the reaction mixture was stirred vigorously for 30 min at room temperature. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered through a plug of celite and the solvent was evaporated to give the product as red-orange solids.

[Ir(cod)(L41a)]BAr_F: Yield: 67 mg (92%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 114.1 (s). ^1H NMR (400 MHz, C_6D_6): δ= 1.36 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.63 (d, 6H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.91-2.10 (m, 5H, CH_2, cod), 2.22-2.27 (m, 3H, CH_2, cod), 3.02 (dd, 1H, CH_2, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 9.6 Hz), 3.26 (dd, 1H, CH_2, $^2J_{H-H}$= 15.2 Hz, $^3J_{H-H}$= 7.6 Hz), 3.68-3.75 (m, 1H, CH, ^{i}Pr), 4.25 (d, 1H, CH-S, $^3J_{H-H}$= 18.8 Hz), 4.47 (b, 1H, CH=, cod), 4.76 (b, 1H, CH=, cod), 4.98-5.07 (m, 1H, CH-OP), 5.09 (b, 1H, CH= cod), 5.43 (b, 1H, CH=, cod), 7.16-7.71 (m, 20H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 24.6 (CH_3, ^{i}Pr), 25.6 (CH_3, ^{i}Pr), 28.4 (b, CH_2, cod), 29.9 (CH_2, cod), 30.9 (b, CH_2, cod), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 33.6 (b, CH_2, cod), 35.0 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 37.5 (d, CH_2, $^3J_{C-P}$= 7.6 Hz), 48.3 (b, CH, ^{i}Pr), 55.0 (CH-S), 75.7 (b, CH=, cod), 78.4 (b, CH=, cod), 82.5 (CH-OP), 100.8 (b, CH=, cod), 104.3 (b, CH=, cod), 117.6-149.1 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz). MS HR-ESI [found 947.4136 $C_{48}H_{67}IrO_3PS$ $(M)^+$ requires 947.4172].

[Ir(cod)(L41b)]BAr_F: Yield: 60 mg (93%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 108.8 (s). ^1H NMR (400 MHz, C_6D_6): δ= 1.03 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.4 Hz), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.50 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.78 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.93-2.15 (m, 6H, CH_2, cod), 2.25 (b, 2H, CH_2, cod), 2.27 (s, 6H, CH_3), 2.89 (dd, 1H, CH_2, $^2J_{H-H}$= 15.2 Hz, $^3J_{H-H}$= 8.8 Hz), 3.35 (dd, 1H, CH_2, $^2J_{H-H}$= 15.6 Hz, $^3J_{H-H}$= 8.4 Hz), 3.61-3.77 (m, 1H, CH, ^{i}Pr), 3.86 (b, 1H, CH=, cod), 4.53 (d, 1H, CH-S, $^3J_{H-H}$= 11.2 Hz), 4.97 (b, 1H, CH=, cod), 5.06-5.13 (m, 2H, CH-OP, CH=, cod), 5.37 (b, 1H, CH=, cod), 7.20-7.70 (m, 18H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.5 (CH_3), 16.8 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 24.7 (CH_3, ^{i}Pr), 24.9 (CH_3, ^{i}Pr), 28.9 (CH_2, cod), 30.0 (CH_2, cod), 31.8 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.3 (CH_2, cod), 32.5 (d, CH_2, cod, J_{C-P}= 4.6 Hz), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 38.2 (d, CH_2, $^3J_{C-P}$= 6.8 Hz), 44.7 (CH, ^{i}Pr), 55.1 (CH-S), 71.9 (CH=, cod), 79.2 (CH-OP), 81.5 (CH=, cod), 98.0 (d, CH=, cod, J_{C-P}= 16.9 Hz), 106.7 (d, CH=, cod, J_{C-P}= 13.2 Hz), 117.4-145.0 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz). MS HR-ESI [found 891.3519, $C_{44}H_{59}IrO_3PS$ $(M)^+$ requires 891.3546].

[Ir(cod)(L41c)]BAr$_F$: Yield: 62 mg (95%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 111.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.43 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.60 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.63 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.77 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.82-1.91 (m, 2H, CH_2, cod), 2.03-2.15 (m, 4H, CH_2, cod), 2.22 (b, 2H, CH_2, cod), 2.28 (s, 6H, CH_3), 3.09 (dd, 1H, CH_2, $^2J_{H-H}$= 15.2 Hz, $^3J_{H-H}$= 9.2 Hz), 3.28 (dd, 1H, CH_2, $^2J_{H-H}$= 15.6 Hz, $^3J_{H-H}$= 8.0 Hz), 3.63-3.70 (m, 1H, CH, ^{i}Pr), 3.85 (b, 1H, CH=, cod), 4.22 (d, 1H, CH-S, $^3J_{H-H}$= 8.8 Hz), 4.86 (b, 1H, CH=, cod), 4.92-4.98 (m, 1H, CH-OP), 5.03 (b, 1H, CH= cod), 5.41 (b, 1H, CH=, cod), 7.22-7.72 (m, 18H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.5 (CH_3), 20.3 (CH_3), 24.0 (CH_3, ^{i}Pr), 25.6 (CH_3, ^{i}Pr), 28.1 (CH_2, cod), 29.7 (CH_2, cod), 30.6 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 33.3 (d, CH_2, cod, J_{C-P}= 4.0 Hz), 34.7 (C, ^{t}Bu), 37.4 (d, CH_2, $^3J_{C-P}$= 8.9 Hz), 48.2 (CH, ^{i}Pr), 54.4 (CH-S), 72.5 (CH=, cod), 79.9 (CH=, cod), 83.0 (d, CH-OP, $^3J_{C-P}$= 5.5 Hz), 99.3 (d, CH=, cod, J_{C-P}= 17.2 Hz), 104.6 (d, CH=, cod, J_{C-P}= 10.8 Hz), 117.4-144.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 50.0 Hz). MS HR-ESI [found 891.3518, $C_{44}H_{59}IrO_3PS$ $(M)^+$ requires 891.3546].

[Ir(cod)(L41d)]BAr$_F$: Yield: 54 mg (93%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 107.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.37 (d, 6H, CH_3, ^{i}Pr, $^3J_{H-H}$= 6.8 Hz), 1.95 -2.15 (m, 8H, CH_2, cod), 2.72 (b, 1H, CH, ^{i}Pr), 3.56 (dd, 1H, CH_2, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 9.2 Hz), 3.53-3.59 (m, 2H, CH_2, CH= cod), 3.85 (b, 1H, CH=, cod), 4.22 (b, 1H, CH-S), 4.99 (b, 1H, CH=, cod), 5.11 (b, 1H, CH-OP), 5.23 (b, 1H, CH=, cod), 7.32-7.74 (m, 26H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 24.4 (CH_3, ^{i}Pr), 24.8 (CH_3, ^{i}Pr), 29.5 (CH_2, cod), 30.5 (CH_2, cod), 31.9 (CH_2, cod), 32.7 (CH_2, cod), 38.0 (d, CH_2, $^3J_{C-P}$= 10.6 Hz), 48.5 (b, CH, ^{i}Pr), 57.2 (CH-S), 98.2 (b, CH=, cod), 106.7 (d, CH=, cod, J_{C-P}= 16.9 Hz), 117.6-136.8 (aromatic carbons), 161.8 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz). MS HR-ESI [found 693.1915, $C_{32}H_{37}IrOPS$ $(M)^+$ requires 693.1926].

[Ir(cod)(L41e)]BAr$_F$: Yield: 54 mg (92%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 116.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.42 (m, 6H, CH_3, ^{i}Pr and CH_3, *o*-Tol), 1.57 (s, 3H, CH_3, *o*-Tol), 1.63 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$= 5.2 Hz), 1.78 (b, CH_2, cod), 2.05-2.36 (m, 6H, CH_2, cod), 2.85 (b, 1H, CH=, cod), 2.97 (b, 1H, CH, ^{i}Pr), 3.18-3.24 (m, 1H, CH_2), 3.41-3.44 (m, 1H, CH_2), 3.82 (b, 1H, CH=, cod), 3.92 (b, 1H, CH-S), 3.99 (b, 1H, CH=, cod), 4.62-4.83 (b, 1H, CH=, cod), 5.09 (b, 1H, CH-OP), 5.35 (b, 1H, CH=, cod), 6.52-8.34 (m, 24H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 21.5 (CH_3, *o*-Tol), 22.2 (CH_3, *o*-Tol), 24.2 (CH_3, ^{i}Pr), 24.4 (CH_3, ^{i}Pr), 27.5 (CH_2, cod), 29.8 (CH_2, cod), 32.2 (CH_2, cod), 34.2 (CH_2, cod), 37.5 (CH_2), 49.8 (b, CH, ^{i}Pr), 57.6 (CH-S), 75.9 (CH=, cod), 77.2 (b, CH-OP), 87.4 (b, CH=, cod), 93.6 (b, CH=, cod), 101.0 (b, CH=, cod), 117.4-143.1 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz). MS HR-ESI [found 721.2243, $C_{34}H_{41}IrOPS$ $(M)^+$ requires 721.2240].

[Ir(cod)(L42b)]BAr$_F$: Yield: 62 mg (93%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 107.9 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.98 (t, 3H, CH_3, Pr, $^3J_{H-H}$= 6.8 Hz), 1.42 (s, 9H, CH_3,

^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.57-1.67 (m, 2H, CH_2, Pr), 1.78 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.94-1.99 (m, 2H, CH_2, cod), 2.04 (m, 2H, CH_2, cod), 2.18 (m, 2H, CH_2, cod), 2.22-2.30 (m, 2H, CH_2, cod), 2.28 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.77-2.81 (m, 2H, CH_2, Pr), 2.95 (dd, 1H, CH_2, $^2J_{H-H}$= 15.2 Hz, $^3J_{H-H}$= 9.2 Hz), 3.34 (dd, 1H, CH_2, $^2J_{H-H}$= 15.6 Hz, $^3J_{H-H}$= 7.6 Hz), 3.44 (b, 1H, CH=, cod), 4.43 (d, 1H, CH-S, $^3J_{H-H}$= 8.8 Hz), 4.93-5.01 (m, 2H, CH-OP and CH= cod), 5.05-5.09 (m, 1H, CH=, cod), 5.31 (b, 1H, CH=, cod), 7.22-7.70 (m, 18H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 13.2 (CH_3, Pr), 16.5 (CH_3), 16.7 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 21.8 (CH_2, Pr), 29.2 (CH_2, cod), 29.5 (CH_2, cod), 31.9 (CH_3, ^{t}Bu, CH_2, cod), 32.3 (CH_3, ^{t}Bu), 33.1 (CH_2, cod), 34.9 (C, ^{t}Bu), 37.3 (CH_2, Pr), 38.1 (d, CH_2, $^3J_{C-P}$= 6.8 Hz), 53.8 (CH-S), 70.9 (CH=, cod), 79.3 (CH-OP), 82.1 (CH=, cod), 98.5 (d, CH=, cod, J_{C-P}= 17.5 Hz), 108.8 (d, CH=, cod, J_{C-P}= 14.6 Hz), 117.4-137.0 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 50.5 Hz). MS HR-ESI [found 889.3509, $C_{44}H_{59}IrO_3PS$ $(M)^+$ requires 889.3523].

[Ir(cod)(L43b)]BAr$_F$: Yield: 60.2 mg (92%). Major isomer (65%): ^{31}P NMR (161.9 MHz, C_6D_6): δ= 107.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.37 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.77 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.00-2.40 (m, 8H, CH_2, cod), 2.26 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.82 (m, 1H, CH_2), 3.41 (m, 1H, CH_2), 3.79 (m, 1H, CH=, cod), 4.78 (m, 1H, CH-S), 4.95 (m, 1H, CH=, cod), 5.24 (m, 1H, CH=, cod), 5.48 (m, 1H, CH=, cod), 5.67 (m, 1H, CH-OP), 7.20-7.80 (m, 18H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.5 (CH_3), 16.7 (CH_3), 20.3 (b, CH_3), 28.4-33.0 (CH_2, cod), 31.6-34.0 (CH_3, ^{t}Bu), 34.5-35.2 (C, ^{t}Bu), 38.4 (CH_2), 58.9 (CH-S), 69.4 (CH=, cod), 79.4 (CH=, cod), 81.0 (CH-OP), 99.4 (d, CH=, cod, J_{C-P}= 14.3 Hz), 110.5 (d, CH=, cod, J_{C-P}= 18.2 Hz), 117.4-135.9 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz). Minor isomer (35%): ^{31}P NMR (161.9 MHz, C_6D_6): δ= 105.6 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.41 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.77 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.00-2.40 (m, 8H, CH_2, cod), 3.12 (s, 3H, CH_3), 3.27 (s, 3H, CH_3), 3.12 (m, 1H, CH_2), 3.27 (m, 1H, CH_2), 4.12 (m, 1H, CH-S), 4.48 (m, 1H, CH=, cod), 4.56 (m, 1H, CH=, cod), 4.94 (m, 1H, CH-OP), 5.48 (m, 1H, CH=, cod), 6.02 (m, 1H, CH=, cod), 7.20-7.80 (m, 18H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.5 (CH_3), 16.7 (CH_3), 20.3 (b, CH_3), 28.4-33.0 (CH_2, cod), 31.6-34.0 (CH_3, ^{t}Bu), 34.5-35.2 (C, ^{t}Bu), 36.9 (CH_2), 49.9 (CH-S), 69.4 (CH=, cod), 81.3 (CH-OP), 82.9 (CH=, cod), 93.5 (b, CH=, cod), 95.7 (b, CH=, cod), 117.4-135.9 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 49.7 Hz). MS HR-ESI [found 905.3711, $C_{45}H_{61}IrO_3PS$ $(M)^+$ requires 905.3703].

[Ir(cod)(L43e)]BAr$_F$: Yield: 52.6 mg (89%). Major isomer (85%): ^{31}P NMR (161.9 MHz, C_6D_6): δ= 116.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.37 (s, 9H, CH_3, ^{t}Bu), 1.70-2.40 (m, 8H, CH_2, cod), 2.27 (s, 3H, CH_3, *o*-Tol), 2.82 (s, 3H, CH_3, *o*-Tol), 2.92 (b, 1H, CH=, cod), 3.28 (dd, 1H, CH_2, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 7.6 Hz), 3.42 (dd, 1H, CH_2, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 9.6 Hz), 3.93 (b, 1H, CH=, cod), 4.21 (d, 1H, CH-S, $^3J_{H-H}$= 9.6 Hz), 4.82

(b, 1H, CH=, cod), 5.08 (m, 1H, CH-OP), 5.47 (b, 1H, CH=, cod), 6.42 (m, 1H, CH=), 7.00-7.80 (m, 22H, CH=), 8.24 (dd, 1H, $^3J_{H-H}$= 17.6 Hz, $^3J_{H-H}$= 7.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 22.4 (CH_3, *o*-Tol), 22.5 (CH_3, *o*-Tol), 27.3 (CH_2, cod), 29.7 (CH_2, cod), 30.0 (CH_2, cod), 31.5 (CH_2, cod), 31.9 (CH_3, ^{t}Bu), 34.0 (C, ^{t}Bu), 37.5 (d, CH_2, $^3J_{C-P}$= 4.2 Hz), 52.5 (CH-S), 74.4 (CH=, cod), 76.6 (CH=, cod), 87.4 (CH-OP), 93.6 (d, CH=, cod, J_{C-P}= 15.2 Hz), 104.0 (d, CH=, cod, J_{C-P}= 16.0 Hz), 117.4-142.9 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 48.8 Hz). Minor isomer (15%): ^{31}P NMR (161.9 MHz, C_6D_6): δ= 115.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.56 (s, 9H, CH_3, ^{t}Bu), 1.70-2.40 (m, 8H, CH_2, cod), 2.29 (s, 3H, CH_3, *o*-Tol), 2.60 (s, 3H, CH_3, *o*-Tol), 2.92 (b, 1H, CH=, cod),3.02 (dd, 1H, CH_2, $^2J_{H-H}$= 15.2 Hz, $^3J_{H-H}$= 8.0 Hz), 3.42 (m, 1H, CH_2), 3.57 (m, 1H, CH=, cod), 4.24 (b, 1H, CH-S), 4.76 (b, 1H, CH=, cod), 5.09 (m, 1H, CH-OP), 5.29 (b, 1H, CH=, cod), 6.60 (m, 1H, CH=), 7.00-7.80 (m, 22H, CH=), 8.65 (dd, 1H, $^3J_{H-H}$= 17.6 Hz, $^3J_{H-H}$= 7.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 22.2 (CH_3, *o*-Tol), 22.7 (CH_3, *o*-Tol), 27.0 (CH_2, cod), 29.3 (CH_2, cod), 29.5 (CH_2, cod), 30.0 (CH_2, cod), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 37.0 (b, CH_2), 52.9 (CH-S), 70.6 (CH=, cod), 76.0 (CH=, cod), 86.4 (CH-OP), 94.2 (b, CH=, cod), 103.8 (b, CH=, cod), 117.4-142.9 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C-B}$= 48.8 Hz). MS HR-ESI [found 735.2398, $C_{35}H_{43}IrOPS$ $(M)^+$ requires 735.2396].

[Ir(cod)(L44b)]BAr_F: Yield: 61 mg (93%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 104.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.49 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.63-1.91 (m, 4H, CH_2, cod), 1.75 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.12-2.35 (m, 4H, CH_2, cod), 2.29 (s, 6H, CH_3), 2.89 (b, 1H, CH=, cod), 3.00 (dd, 1H, CH_2, $^2J_{H-H}$= 14.8 Hz, $^3J_{H-H}$= 9.6 Hz), 3.37 (dd, 1H, CH_2, $^2J_{H-H}$= 15.6 Hz, $^3J_{H-H}$= 8.0 Hz), 4.19 (m, 1H, CH=, cod), 4.67 (m, 1H, CH=, cod), 4.81-4.91 (m, 1H, CH-OP), 5.17 (b, 1H, CH=, cod), 5.21 (d, 1H, CH-S, $^3J_{H-H}$= 9.6 Hz), 6.23-7.74 (m, 23H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.4 (CH_3), 16.6 (CH_3), 20.2 (CH_3), 20.5 (CH_3), 26.4 (CH_2, cod), 29.9 (CH_2, cod), 31.1 (CH_2, cod), 31.8 (CH_3, ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 34.7 (CH_2, cod), 35.0 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 37.8 (d, CH_2, $^3J_{C-P}$= 7.4 Hz), 55.9 (CH-S), 67.9 (CH=, cod), 78.6 (CH=, cod), 79.4 (CH-OP), 101.2 (d, CH=, cod, J_{C-P}= 14.5 Hz), 106.0 (d, CH=, cod, J_{C-P}= 15.3 Hz), 117.4-143.6 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 50.4 Hz). MS HR-ESI [found 923.3367, $C_{47}H_{57}IrO_3PS$ $(M)^+$ requires 923.3366].

[Ir(cod)(L45b)]BAr_F: Yield: 64 mg (95%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 104.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.47 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.65-1.84 (m, 4H, CH_2, cod), 1.76 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 2.13-2.36 (m, 4H, CH_2, cod), 2.29 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 2.72 (m, 1H, CH=, cod), 2.95 (dd, 1H, CH_2, $^2J_{H-H}$= 15.2 Hz, $^3J_{H-H}$= 9.6 Hz), 3.08 (s, 3H, CH_3), 3.38 (dd, 1H, CH_2, $^2J_{H-H}$= 15.2 Hz, $^3J_{H-H}$= 7.6 Hz), 3.92 (m, 1H, CH=, cod), 4.72 (m, 1H, CH=, cod), 4.89 (m, 1H, CH-OP), 5.12 (d, 1H, CH-S, $^3J_{H-H}$= 8.8 Hz), 5.18 (b, 1H, CH=, cod), 6.08-7.70 (m, 21H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3),

20.5 (CH_3), 22.8 (CH_3), 22.9 (CH_3), 25.7 (CH_2, cod), 30.5 (CH_2, cod), 31.0 (CH_2, cod), 31.8 (CH_3, ^{t}Bu), 32.7 (CH_3, ^{t}Bu), 35.0 (CH_2, cod), 35.2 (C, ^{t}Bu), 37.8 (d, CH_2, $^3J_{C\text{-}P}$= 7.6 Hz), 53.7 (CH-S), 66.2 (CH=, cod), 77.7 (CH=, cod), 80.0 (CH-OP), 102.1 (d, CH=, cod, $J_{C\text{-}P}$ =13.8 Hz), 104.6 (d, CH=, cod, $J_{C\text{-}P}$= 16.1 Hz), 117.4-143.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.7 Hz). MS HR-ESI [found 951.3674, $C_{49}H_{61}IrO_3PS$ $(M)^+$ requires 951.3679].

[Ir(cod)(L45c)]BAr_F: Yield: 63 mg (94%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 108.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.41 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.71-1.89 (m, 4H, CH_2, cod), 1.71 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.97-2.20 (m, 4H, CH_2, cod), 2.21 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 2.99-3.08 (m, 2H, CH_2 and CH= cod), 3.31 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 15.6 Hz, $^3J_{H\text{-}H}$= 8.4 Hz), 4.26 (m, 1H, CH=, cod), 4.67 (m, 1H, CH=, cod), 4.74 (m, 1H, CH=, cod), 4.80 (d, 1H, CH-S, $^3J_{H\text{-}H}$ =8.8 Hz), 5.31-5.35 (m, 1H, CH-OP), 5.88-7.63 (m, 21H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.7 (CH_3), 16.8 (CH_3), 20.5 (CH_3), 20.6 (CH_3), 23.5 (CH_3), 24.3 (CH_3), 27.6 (CH_2, cod), 29.8 (d, CH_2, cod, $J_{C\text{-}P}$= 10.0 Hz), 31.8 (CH_3, ^{t}Bu), 32.1 (CH_2, cod), 32.9 (CH_3, ^{t}Bu), 34.2 (CH_2, cod), 35.0 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 37.4 (d, CH_2, $^3J_{C\text{-}P}$= 9.2 Hz), 56.4 (CH-S), 67.3 (CH=, cod), 77.4 (CH=, cod), 86.3 (d, CH-OP, $^2J_{C\text{-}P}$= 6.0 Hz), 103.4 (d, CH=, cod, $J_{C\text{-}P}$= 14.8 Hz), 104.7 (d, CH=, cod, $J_{C\text{-}P}$= 13.9 Hz), 117.6-144.6 (aromatic carbons), 161.9 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 50.1 Hz). MS HR-ESI [found 951.3641, $C_{49}H_{61}IrO_3PS$ $(M)^+$ requires 951.3679].

[Ir(cod)(L45d)]BAr_F: Yield: 55 mg (92%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 114.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.75-1.86 (m, 2H, CH_2, cod), 1.93-2.01 (m, 2H, CH_2, cod), 2.10-2.19 (m, 1H, CH_2, cod), 2.20-2.40 (m, 3H, CH_2, cod), 2.57 (s, 3H, CH_3), 3.02 (s, 3H, CH_3), 3.07 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 15.6 Hz, $^3J_{H\text{-}H}$= 9.6 Hz), 3.19 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 15.6 Hz, $^3J_{H\text{-}H}$= 8.0 Hz), 3.27 (m, 1H, CH=, cod), 3.41 (m, 1H, CH=, cod), 3.97 (m, 1H, CH=, cod), 4.49-4.58 (m, 1H, CH-OP), 5.05 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 8.4 Hz), 5.11 (m, 1H, CH=, cod), 6.09-7.94 (m, 29H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 23.2 (CH_3), 23.6 (CH_3), 27.3 (CH_2, cod), 30.7 (CH_2, cod), 31.0 (CH_2, cod), 33.6 (CH_2, cod), 38.3 (d, CH_2, $^3J_{C\text{-}P}$= 7.6 Hz), 52.9 (CH-S), 69.3 (CH=, cod), 74.9 (CH=, cod), 82.5 (CH-OP), 97.2 (d, CH=, cod, $J_{C\text{-}P}$= 10.0 Hz), 98.6 (d, CH=, cod, $J_{C\text{-}P}$= 13.0 Hz), 117.4-144.7 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.7 Hz). MS HR-ESI [found 755.2085, $C_{37}H_{39}IrOPS$ $(M)^+$ requires 755.2083].

[Ir(cod)(L45e)]BAr_F: Yield: 56 mg (96%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 118.2 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.68-1.85 (m, 2H, CH_2, cod), 1.95-2.19 (m, 2H, CH_2, cod), 2.23 (s, 3H, CH_3), 2.25-2.47 (m, 4H, CH_2, cod), 2.53 (s, 3H, CH_3), 2.92 (s, 4H, CH=, cod and CH_3), 3.03 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 15.6 Hz, $^3J_{H\text{-}H}$= 9.6 Hz), 3.15 (s, 3H, CH_3), 3.15-3.20 (m, 2H, CH= cod, CH_2), 3.75 (m, 1H, CH=, cod), 4.32-4.41 (m, 1H, CH-OP), 5.08 (b, 1H, CH=, cod), 5.24 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 8.4 Hz), 5.89-9.06 (m, 27H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 21.8 (CH_3), 22.3 (d, CH_3, $^3J_{C\text{-}P}$= 6.9 Hz), 23.1 (CH_3),

26.7 (CH_2, cod), 29.9 (CH_2, cod), 31.7 (CH_2, cod), 34.3 (CH_2, cod), 38.3 (d, CH_2, $^3J_{C\text{-}P}$= 7.6 Hz), 52.0 (CH-S), 67.9 (CH=, cod), 77.2 (CH=, cod), 81.4 (CH-OP), 96.5 (d, CH=, cod, $J_{C\text{-}P}$ =9.2 Hz), 96.8 (d, CH=, cod, $J_{C\text{-}P}$= 13.8 Hz), 117.4-143.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.7 Hz). MS HR-ESI [found 783.2401, $C_{39}H_{43}IrOPS$ $(M)^+$ requires 783.2396].

[Ir(cod)(L46b)]BAr_F: Yield: 69 mg (97%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 104.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.49 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.61-1.91 (m, 4H, CH_2, cod), 1.76 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.08-2.38 (m, 4H, CH_2, cod), 2.29 (s, 6H, CH_3), 2.99-3.05 (m, 2H, CH_2 and CH=, cod), 3.39 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 15.2 Hz, $^3J_{H\text{-}H}$= 7.6 Hz), 4.10 (m, 1H, CH=, cod), 4.76 (b, 1H, CH=, cod), 4.84-4.92 (m, 1H, CH-OP), 5.13 (b, 1H, CH=, cod), 5.23 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 9.2 Hz), 6.23-7.89 (m, 22H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.4 (CH_3), 16.6 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 26.6 (CH_2, cod), 29.8 (CH_2, cod), 31.2 (CH_2, cod), 31.8 (CH_3, ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 34.5 (CH_2, cod), 35.0 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 37.7 (CH_2), 56.1 (CH-S), 68.9 (CH=, cod), 79.3 (CH=, cod), 79.7 (CH-OP), 100.9 (d, CH=, cod, $J_{C\text{-}P}$= 13.7 Hz), 105.4 (d, CH=, cod, $J_{C\text{-}P}$= 15.3 Hz), 117.4-143.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.7 Hz). MS HR-ESI [found 991.3222, $C_{48}H_{56}F_3IrO_3PS$ $(M)^+$ requires 991.3240].

[Ir(cod)(L47b)]BAr_F: Yield: 64 mg (95%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 104.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.49 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.65-1.94 (m, 4H, CH_2, cod), 1.75 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.06-2.37 (m, 4H, CH_2, cod), 2.29 (s, 6H, CH_3), 2.86 (m, 1H, CH=, cod), 2.98 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 15.2 Hz, $^3J_{H\text{-}H}$= 9.6 Hz), 3.36 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 15.2 Hz, $^3J_{H\text{-}H}$= 8.0 Hz), 3.84 (s, 3H, CH_3, MeO), 4.28-4.36 (m, 1H, CH=, cod), 4.67 (b, 1H, CH=, cod), 4.79-4.88 (m, 1H, CH-OP), 5.12 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 9.2 Hz), 5.16 (b, 1H, CH=, cod), 6.31-7.70 (m, 22H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.4 (CH_3), 16.6 (CH_3), 20.2 (CH_3), 20.5 (CH_3), 26.3 (CH_2, cod), 30.0 (CH_2, cod), 31.0 (CH_2, cod), 31.8 (CH_3, ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 34.9 (CH_2, cod), 35.0 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 37.8 (d, CH_2, $^3J_{C\text{-}P}$= 8.1 Hz), 55.6 (CH_3, MeO), 56.2 (CH-S), 67.7 (CH=, cod), 78.5 (CH=, cod), 79.4 (CH-OP), 101.3 (d, CH=, cod, $J_{C\text{-}P}$= 14.4 Hz), 106.0 (d, CH=, cod, $J_{C\text{-}P}$= 16.3 Hz), 116.2-163.4 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 50.5 Hz). MS HR-ESI [found 955.3512, $C_{48}H_{56}F_3IrO_3PS$ $(M)^+$ requires 955.3501].

[Ir(cod)(L48b)]BAr_F: Yield: 57.1 mg (89%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=104.4 (s). ^{1}H NMR (400 MHz, C6D6): δ=1.14-1.32 (m, 2H, CH_2, cod), 1.66 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 9H, CH_3, ^{t}Bu), 1.73-1.82 (m, 1H, CH_2, cod), 1.79 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 2.06 (m, 2H, CH_2, cod), 2.12-2.30 1.61-1.91 (m, 4H, CH_2, cod), 2.31 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.78 (m, 1H, CH=, cod), 2.93 (dd, 1H, CH^2, $^2J_{H\text{-}H}$= 15.2 Hz, $^3JH_{\text{-}H}$= 9.2 Hz), 3.39 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 15.6 Hz, $^3J_{H\text{-}H}$= 8.0 Hz), 3.53 (m, 1H, CH=, cod), 4.83 (b, 1H, CH=, cod), 4.99-5.04 (m, 1H, CH-OP), 5.35 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 9.2 Hz), 5.36 (b, 1H, CH=, cod), 5.50-9.47 (m, 27H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=16.5 (CH_3),

16.7 (CH_3), 20.3 (CH_3), 20.6 (CH_3), 24.9 (CH_2, cod), 30.3 (CH_2, cod), 31.0 (CH_2, cod), 31.9 (CH_3, ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 35.1 (CH_2, cod and C, ^{t}Bu), 35.3 (C, ^{t}Bu), 37.7 (CH2), 54.5 (CH-S), 65.8 (CH=, cod), 78.3 (CH=, cod), 79.9 (CH-OP), 103.1 (CH=, cod, $J_{C\text{-}P}$= 13.7 Hz), 105.6 (CH=, cod, $J_{C\text{-}P}$= 16.0 Hz), 117.4-143.9 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.8 Hz). MS HR-ESI [found 1025.3706, $C_{55}H_{61}IrO_3PS$ $(M)^+$ requires 1025.3703].

[Ir(cod)(L48c)]BAr_F: Yield: 35 mg (24%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 106.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.53-1.60 (m, 1H, CH_2, cod), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.73-2.09 (m, 6H, CH_2, cod), 1.80 (s, 6H, CH_3), 1.81 (s, 9H, ^{t}Bu), 2.29-2.32 (m, 1H, CH_2, cod), 3.01 (m, 1H, CH_2), 3.14 (m, 1H, CH=, cod), 3.26 (m, 1H, CH_2, cod), 4.46 (m, 1H, CH=, cod), 4.86 (m, 1H, CH=, cod), 4.96 (m, 1H, CH=, cod), 5.14 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 8.3 Hz), 5.39 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.8 Hz), 5.55 (m, 1H, CH-OP), 6.41-9.09 (m, 26H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.4 (CH_3), 16.6 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 26.5 (CH_2, cod), 29.8 (CH_2, cod), 31.6 (CH_3, ^{t}Bu), 32.7 (CH_3, ^{t}Bu), 32.9 (CH_2, cod), 34.6 (CH_2, cod), 34.9 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 37.6 (CH_2-O), 53.5 (CH-S), 66.7 (CH=, cod), 78.5 (CH=, cod), 84.1 (CH-OP), 102.2 (b, CH=, cod), 106.6 (b, CH=, cod), 117.4-144.7 (aromatic carbons), 161.1 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 51.9 Hz). MS HR-ESI [found 1025.3706, $C_{55}H_{61}IrO_3PS$ $(M)^+$r equires 1025.3703].

[Ir(cod)(L48d)]BAr_F: Yield: 75 mg (60%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 115.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.43-1.54 (m, 2H, CH_2, cod), 1.78-1.89 (m, 2H, CH_2, cod), 1.97-2.04 (m, 2H, CH_2, cod), 2.21-2.32 (m, 2H, CH_2, cod), 3.09 (m, 1H, CH_2), 3.25 (m, 1H, CH_2), 3.36 (m, 1H, CH=, cod), 3.52 (m, 2H, CH=, cod), 4.79 (m, 1H, CH=, cod), 5.17 (m, 1H, CH-OP), 5.25 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 8.7 Hz), 5.49 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.8 Hz), 6.61-9.04 (m, 34H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 27.4 (CH_2, cod), 30.3 (CH_2, cod), 31.2 (CH_2, cod), 32.8 (CH_2, cod), 38.3 (CH_2-O), 54.2 (CH-S), 70.6 (CH=, cod), 74.1 (CH=, cod), 83.2 (CH-OP), 97.8 (d, CH=, cod, $J_{C\text{-}P}$= 10.6 Hz), 99.9 (d, CH=, cod, $J_{C\text{-}P}$= 12.4 Hz), 117.4-161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.9 Hz). MS HR-ESI [found 827.2087, $C_{43}H_{39}IrOPS$ $(M)^+$ requires 827.2083].

[Ir(cod)(L48e)]BAr_F: Yield: 55 mg (43%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 119.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.40-1.52 (m, 2H, CH_2, cod), 1.64-1.76 (m, 1H, CH_2, cod), 1.79-2.04 (m, 3H, CH_2, cod), 2.07-2.16 (m, 1H, CH_2, cod), 2.25 (s, 3H, CH_3, *o*-Tol), 2.31-2.44 (m, 2H, CH_2, cod), 2.97 (m, 1H, CH=, cod), 2.99 (m, 1H, CH_2), 3.11 (m, 1H, CH_2), 3.13 (m, 1H, CH=, cod), 3.24 (s, 3H, CH_3, *o*-Tol), 3.42 (m, 1H, CH=, cod), 4.49 (m, 1H, CH-OP), 5.07 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.8 Hz), 5.19 (m, 1H, CH=, cod), 5.51 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 9.0 Hz), 6.49-9.49 (m, 32H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 21.8 (CH_3, *o*-Tol), 22.1 (CH_3, *o*-Tol), 26.3 (CH_2, cod), 29.9 (CH_2, cod), 31.4 (CH_2, cod), 34.1 (CH_2, cod), 38.3 (CH_2-O), 53.4 (CH-S), 67.8 (CH=, cod), 77.2 (CH=, cod), 81.3 (CH-OP), 97.9 (d, CH=, cod, $J_{C\text{-}P}$= 9.9 Hz), 98.4 (d, CH=, cod, $J_{C\text{-}P}$= 12.4

Hz), 117.4-142.9 (aromatic carbons), 161.66 (q, C-B, BAr_F, $^1J_{C-B}$= 50.0 Hz). MS HR-ESI [found 855.2399, $C_{45}H_{43}IrOPS$ $(M)^+$ requires 855.2396].

3.10.4.6. General procedure for the hydrogenation of olefins S1-S33

The alkene (0.5 mmol) and Ir complex (2 mol %) were dissolved in the corresponding solvent CH_2Cl_2 (2 mL) and placed in a high-pressure autoclave. The autoclave was purged 4 times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short plug of celite. The enantiomeric excess was determined by chiral GC or chiral HPLC and conversions were determined by ^{1}H NMR (for hydrogenation products from **S1**-**S3**, **S12-S13**, **S16**, **S21**, **S23** and **S25**-**S33** see previous Section 3.1.4.5 and for hydrogenation products from **S4**-**S10**, **S14**-**S15**, **S17**-**S19**, **S22** and **S24** see previous Section 3.2.4.6).

3.10.4.7. General procedure for the hydrogenation of cyclic β-enamides S34-S41

The enamide (0.25 mmol) and the corresponding catalyst precursor [Ir(cod)(**L**)]BAr_F (1 mol%) were dissolved in in the corresponding solvent CH_2Cl_2 (1 mL) and placed in a high-pressure autoclave, which was purged four times with hydrogen. It was then pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short celite plug. Conversions were determined by ^{1}H NMR and enantiomeric excesses by HPLC (for hydrogenation products from **S34**-**S40** see previous Section 3.2.4.7).

3.10.5. Acknowledgments

We all acknowledge MINECO for INTECAT network CTQ2016-81293-REDC/AEI. The URV members gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P) and European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Award to M.D.). The ICIQ members gratefully acknowledge financial support from CERCA Programme/Generalitat de Catalunya, the Spanish Ministry of Economy and Competitiveness (CTQ2015-69136-R, CTQ2017-87792-R, AEI/MINECO/FEDER, UE, and Severo Ochoa Excellence Accreditation 2014-2018, SEV-2013-2019), and DEC Generalitat de Catalunya (Grant No. 2014SGR827). The CELLEX Foundation is also acknowledged for financing the High Throughput Experimentation (HTE) laboratory.

3.10.6. References

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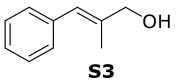
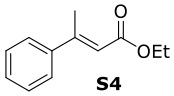
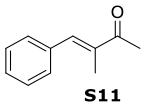
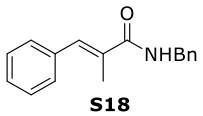
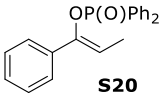
3.10.7. Supporting Information

3.10.7.1. Table SI.1. Full set of results for the asymmetric hydrogenation of trisubstituted olefins S3-S20[a]

	 **S3**		 **S4**		 **S11**	
Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b,d]	% ee[c]
L41a	100	7 (*S*)	100	20 (*S*)	100	11 (*R*)
L41b	100	24 (*R*)	100	7 (*S*)	100	7 (*R*)
L41c	100	17 (*S*)	100	25 (*S*)	100	11 (*R*)
L41d	100	50 (*S*)	100	30 (*S*)	100	48 (*S*)
L41e	100	70 (*S*)	100	11 (*S*)	100	33 (*S*)
L41f	22	25 (*R*)	35	64 (*R*)	35	20 (*S*)
L42b	100	30 (*R*)	100	11 (*S*)	100	12 (*R*)
L43b	100	21 (*R*)	100	13 (*S*)	100	21 (*R*)
L43e	100	63 (*S*)	100	86 (*S*)	100	83 (*S*)
L44b	100	11 (*R*)	100	21 (*S*)	100	34 (*R*)
L45b	100	5 (*R*)	100	22 (*S*)	100	36 (*R*)
L45c	100	65 (*S*)	100	43 (*S*)	100	62 (*S*)
L45d	100	78 (*S*)	100	77 (*S*)	100	35 (*S*)
L45e	100	63 (*S*)	100	84 (*S*)	100	70 (*S*)
L46b	100	9 (*R*)	100	19 (*S*)	100	33 (*R*)
L47b	100	8 (*R*)	100	20 (*S*)	100	36 (*R*)
L48b	100	12 (*R*)	100	26 (*S*)	100	38 (*R*)
L48c	100	64 (*S*)	100	49 (*S*)	100	68 (*S*)
L48d	100	79 (*S*)	79	90 (*S*)	100	63 (*S*)
L48e	100	77 (*S*)	87	94 (*S*)	100	81 (*S*)

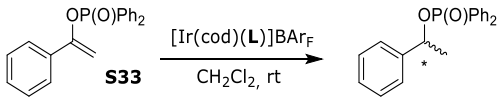
[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor at 100 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by HPLC; [d] Reaction carried out for 18 h.

3.10.7.1. Table SI.1. Full set of results for the asymmetric hydrogenation of trisubstituted olefins S3-S20 (Continuation)[a]

	 **S18**		 **S20**	
Ligand	% Conv[b,d]	% ee[c]	% Conv[b]	% ee[c]
L41a	100	35 (*R*)	-	-
L41b	100	37 (*R*)	-	-
L41c	87	63 (*R*)	-	-
L41d	100	30 (*R*)	-	-
L41e	100	29 (*R*)	-	-
L41f	23	22 (*R*)	-	-
L42b	100	16 (*R*)	-	-
L43b	100	20 (*R*)	-	-
L43e	100	79 (*S*)	-	-
L44b	100	29 (*R*)	-	-
L45b	100	34 (*R*)	-	-
L45c	48	20 (*S*)	-	-
L45d	100	30 (*R*)	100	41 (*S*)
L45e	100	73 (*R*)	100	88 (*S*)
L46b	100	31 (*R*)	-	-
L47b	100	30 (*R*)	-	-
L48b	100	34 (*R*)	-	-
L48c	100	65 (*S*)	100	87 (*S*)
L48d	100	69 (*S*)	100	27 (*R*)
L48e	100	84 (*S*)	100	92 (*S*)

[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor at 100 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by HPLC; [d] Reaction carried out for 18 h.

3.10.7.2. Table SI.2. Full set of results for the asymmetric hydrogenation of 1,1-disubstituted olefin S33[a]



Ligand	% Conv[b,D]	% ee[c]
L41a	100	0
L41b	100	11 (*R*)
L41c	100	10 (*R*)
L41d	100	33 (*S*)
L41e	100	3 (*R*)
L41f	84	97 (*S*)
L42b	100	10 (*R*)
L43b	100	13 (*R*)
L43e	100	93 (*S*)
L44b	100	21 (*R*)
L45b	100	25 (*R*)
L45c	100	25 (*S*)
L45d	100	12 (*S*)
L45e	100	5 (*R*)
L46b	100	20 (*R*)
L47b	100	24 (*R*)
L48b	100	51 (*S*)
L48c	100	2 (*S*)
L48d	100	50 (*S*)
L48e	100	46 (*S*)

[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor at 1 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by HPLC.

UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull

3.11. The application of phosphite/phosphinite-thioether ligands to enantioselective Ir-catalyzed hydrogenation of unfunctionalized olefins

Biosca, M.; Caldentey, X.; Rodriguez, C.; Pericàs, M. A.; Pàmies, O.; Diéguez, M. *Preliminary results.*

In collaboration with the group of Prof. M. A. Pericàs (ICIQ, Tarragona).

Abstract: A phosphite/phosphinite-thioether ligand family was successfully synthesized in only four steps from commercially available (*R*,*R*)-hydrobenzoin. The synthetic strategy used allow us to study the effect of the thioether substituent and the electronic and steric nature of the different types of P-donor groups. By carefully selecting the ligand parameters, we have been able to achieve high enantioselectivities in the asymmetric hydrogenation of a range of *E*-trisubstituted and 1,1'-disubstituted olefins, including examples with poorly coordinative neighboring polar groups (ee's up to 99%). Promising enantioselectivities were also achieved in the asymmetric hydrogenation of more challenging tetrasubstituted olefins (ee's up to 77%).

3.11.1. Introduction

Metal-catalyzed asymmetric reactions have become one of the most powerful tools for the production of enantiomerically pure products. The growing demand of these chiral compounds have stimulated the research in this field. The success in these catalytic processes largely depends on the selection of the appropriate catalyst structure. For this reason, the search of new chiral ligands is essential for the development of new catalytic systems which provide successful results in asymmetric catalysis.[1]

Due to its high efficiency, atom economy and operational simplicity, asymmetric hydrogenation has become one of the most reliable catalytic methods for preparing optically active compounds.[1] For the hydrogenation of functionalized olefins with Rh- and Ru-catalysts a large number of ligands have been developed and successfully applied. However, the efficiency of these catalysts relies in the chelating ability of the substrate which is key in transferring the chiral information from the catalyst to the product.[1-2] Thus, Rh- and Ru-catalysts are not able to successfully hydrogenate olefins without a good coordinating group close to C=C bond. A breakthrough in this field come when Pfaltz developed a new class of hydrogenation Ir-catalysts with chiral phosphine-oxazoline PHOX ligands.[3] Since then, most of the research has been devoted to develop new chiral P,N-ligands.[4] Despite the success of some of these ligands, the range of substrates efficiently hydrogenated was limited.[5] Our group have shown that the

introduction of biaryl phosphite moieties in these P,N-ligands increases the range of substrates that could be successfully hydrogenated.[6] However, more research is needed to find more versatile ligand systems due to there are still important substrate classes whose hydrogenation is still not solved.

More recently, research has focused in the possibility of changing the nature of the N-donor atom in these heterodonor ligands. The application of chiral P,thioether-ligands in this process has proven to be a good choice.[7] Nevertheless, the development of new P,S-ligands to fully demonstrate their possibilities in this process is still needed.

In this context, herein we reported the application of a new P,S-ligand library **L49**-**L50a**-**e** (Figure 3.11.1), with a simple ligand backbone, in Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins. The modular ligands design of these phosphite/phosphinite-thioether ligands allowed us to study the effect of the thioether group (ligands **L49**-**L50**), the type of the P-donor group (phosphite vs phosphinite) as well as the effect of different configurations at the phosphite moiety (**a**-**b**) and different substituents at the phosphinite group (**c**-**e**).

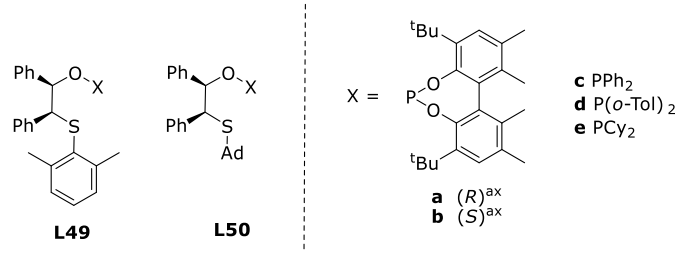


Figure 3.11.1. Phosphite/phosphinite-thioether ligands **L49**-**L50a**-**e**.

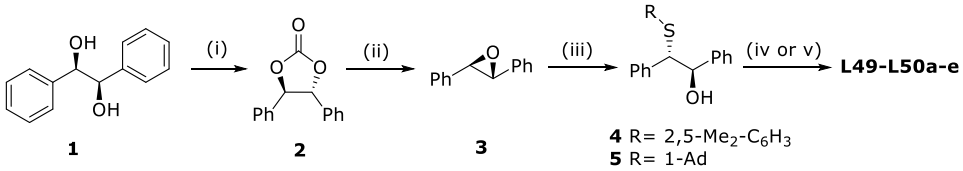
3.11.2. Results and Discussion

3.11.2.1. Synthesis of ligands

The synthesis of new phosphite/phosphinite-thioether ligands **L49**-**L50a**-**e** is showed in Scheme 3.11.1. Ligands **L49**-**L50a**-**e** can be easily prepared in four steps from commercially available (*R*,*R*)-hydrobenzoin **1**. First, a transesterification with dimethyl carbonate of compound **1** yields the cyclic carbonate **2** (step i).[8] Then, LiCl catalyzes the stereoselective nucleophilic opening of carbonate **2** to give epoxide **3** with loss of CO_2 (step ii).[8] Next, the regio- and stereospecific ring opening of **3** with the corresponding thiol using sodium hydroxide in a mixture of DMF/water was carried out (step iii). Finally, the coupling of the corresponding hydroxyl-thioether **4**-**5** with the desired phosphorochloridite ($ClP(OR)_2$; $(OR)_2$= **a**-**b**; step iv) or chlorophosphine ($ClPR_2$, R= **c**-**e**, step v) gave access to phosphite/phosphinite-thioether ligands **L49**-**L50a-e**.

Ligands **L49**-**L50a**-**e** were isolated in good yields as white solids (phosphite-thioether ligands **L49**-**L50a**-**b** and phosphinite-thioether **L49**-**L50e**) or colorless oils

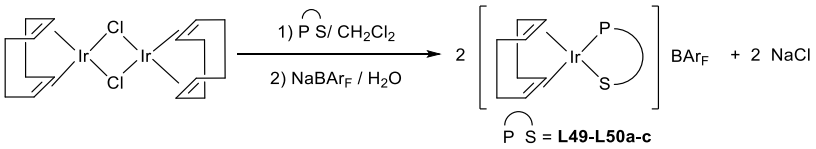
(phosphinite-thioether ligands **L49**-**L50c**-**d**). All ligands were characterized by $^{31}P\{^{1}H\}$, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy and HRMS-ESI. All data were in agreement with assigned structures. The spectra assignments were supported by the information obtained from ^{1}H-^{1}H and ^{1}H-^{13}C correlation measurements. The $^{31}P\{^{1}H\}$, ^{1}H, and $^{13}C\{^{1}H\}$ NMR spectra showed the expected pattern for the *C1*-ligands.



Scheme 3.11.1. Synthesis of new phosphite/phosphinite-thioether ligands **L49**-**L50a**-**e**; (i) NaOH cat., dimethyl carbonate, 90 ºC; (ii) LiCl cat., DMF, 70 ºC, 7 h; (ii) RSH, NaOH, DMF/ H_2O, 55 ºC; (iv) $ClP(OR)_2$ (OR_2=**a**-**b**), pyridine, DMAP cat., toluene, 80 °C, 16 h; (v) $ClPR_2$ (R=**c**-**e**), NEt_3, DMAP cat., toluene, 20 min.

3.11.2.2. Synthesis of Ir-catalyst precursors

Catalyst precursors [Ir(**L49**-**L50a**-**e**)(cod)]BAr_F were prepared by treating 0.5 equivalent of [Ir(μ-Cl)(cod)]$_2$ with an equimolar amount of the appropriate P,S-ligand (**L49**-**L50a**-**e**) in dichloromethane at 40 ºC for 1 h. The Cl^-/BAr_F^- counterion exchange was then performed by reaction with sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate ($NaBAr_F$; 1 equiv) in water (Scheme 3.11.2). The catalyst precursors were obtained in pure form as air-stable orange solids.



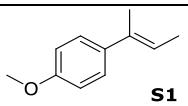
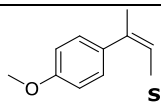
Scheme 3.11.2. Synthesis of [Ir(cod)(P-S)]BAr_F (P-S = **L49**-**L50a**-**e**).

The HRMS-ESI spectra show the heaviest ions at m/z which correspond to the loss of the BAr_F anion from the molecular species. The complexes were also characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments, made using ^{1}H–^{1}H and ^{13}C–^{1}H correlation measurements, were as expected for these *C1*-symmetric iridium complexes. It should be noted that for complex containing ligand **L49c** and **L50e**, two species in solution are present. The 2D DOSY $^{31}P\{^{1}H\}$ NMR experiments showed that these two species have the same diffusion coefficient, which indicates that they must be isomers. This behavior could be due to the presence of different conformations of the 6-memberred chelate ring, to the presence of a diastereomeric mixture from the different coordination of the thioether to Ir (note that the S atom becomes a stereogenic center upon coordination), or to both.

3.11.2.3. Asymmetric hydrogenation of olefins trisubstituted olefins

The potential of phosphite/phosphinite-thioether ligands (**L49**-**L50a**-**e**) has been first investigated in the hydrogenation of model substrates *E*-2-(4-methoxyphenyl)-2-butene **S1** and *Z*-2-(4-methoxyphenyl)-2-butene **S2**. Substrates **S1** and **S2** were chosen as a models because the enantioselectivity is highly dependent on the substrate geometry.[5] The results are shown in Table 3.11.1. They indicated that the enantioselectivity is affected by the thioether substituent and the nature of the P-donor group as well as its substituents and configurations. In general, enantioselectivities are better for ligands containing a phosphinite group rather than a phosphite moiety (e.g. entries 8-10 vs 6 and 7). However, the effects of the rest of ligand parameters are highly dependent on the olefin geometry. Thus, for **S1**, the highest enantioselectivity (up to 93% ee, entry 4) was achieved using **L49d** (with a 2,6-dimethylphenyl thioether group and di-*ortho*-tolyl phosphinite moiety), while Ir-**L50e** (with an adamantyl thioether group and a dicyclohexyl phosphinite moiety) provided the highest ee's in the reduction of **S2** (ee's up to 57%, entry 10).

Table 3.11.1. Ir-catalyzed hydrogenation of **S1** and **S2** using **L49**-**L50a**-**e**.[a]

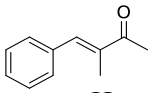
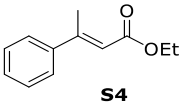
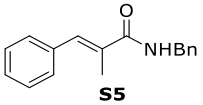
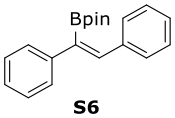
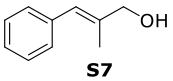
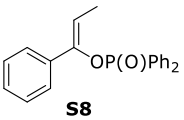
		 **S1**		 **S2**	
Entry	Ligand	% Conv[b]	%ee[c]	% Conv[b]	% ee[c]
1	**L49a**	100	35 (*R*)	100	46 (*R*)
2	**L49b**	100	11 (*S*)	100	17 (*R*)
3	**L49c**	100	45 (*S*)	100	33 (*R*)
4	**L49d**	100	93 (*S*)	100	17 (*R*)
5	**L49e**	100	50 (*S*)	100	56 (*R*)
6	**L50a**	100	2 (*S*)	100	2 (*R*)
7	**L50b**	100	34 (*S*)	100	21 (*S*)
8	**L50c**	100	48 (*S*)	100	30 (*R*)
9	**L50d**	100	34 (*S*)	100	17 (*R*)
10	**L50e**	100	65 (*S*)	100	57 (*R*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (50 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^1H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by GC analysis.

To further study the scope of [Ir(**L49**-**L50a**-**e**)(cod)]BAr_F catalyst precursors, we chose several representative trisubstituted substrates with poorly coordinative neighboring polar groups. The results are summarized in Table 3.11.2 (for a complete series of results, see Table SI-1 in Supporting Information at the end of this chapter).

We found that to obtain the highest enantioselectivities, the ligand parameters must be carefully selected.

Table 3.11.2. Selected results for the asymmetric hydrogenation of **S3-S9** using [Ir(cod)(**L49**-**L50a**-**e**)]BAr_F catalyst precursors.[a]

Entry	Ligand	Substrate	% Conv[b]	% ee[c]
1	**L49e**	 **S3**	100	98 (*S*)
2	**L49e**	 **S4**	100	96 (*S*)
3[d]	**L49e**	 **S5**	100	92 (*R*)
4[d]	**L50c**	 **S6**	100	64 (-)
5	**L49c**	 **S7**	100	76 (*S*)
6	**L50b**	 **S8**	100	96 (*S*)
7	**L50a**	 **S9**	100	99 (*S*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (50 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^1H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by HPLC analysis. [d] Reaction carried out for 18 h.

We were pleased to find out that the hydrogenation of α,β-unsaturated enone **S3**, ester **S4** and amide **S5** follow a similar catalytic behavior as in the reduction of **S1**. High enantioselectivities were therefore obtained with Ir/**L49e** catalytic system (ee's up to 98%, entries 1-3). Nevertheless, moderate enantioselectivities were obtained in the hydrogenation of alkenyl boronic ester **S6** and allylic alcohol **S7**. The reduction of alkenyl boronic ester **S6** follow a similar trend as substrate **S2** (ee's up to 64% and 76%, respectively; entries 4 and 5).

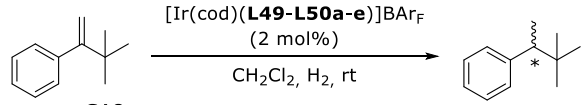
Interestingly, for enol phosphinate **S8** and α,β-unsaturated lactone **S9** the use of ligands with a biaryl phosphite group instead of phosphinite moiety had a positive effect

on enantioselectivity. It should be pointed out that the configuration of the biaryl phosphite moiety must be appropriate selected to maximize the ee's for each substrate. Thus, excellent enantioselectivities (ee's up to 99%) were achieved using Ir/**L50b** and Ir/**L50a** catalytic systems, respectively.

3.11.2.4. Asymmetric hydrogenation of disubstituted olefins

Next, we screened the phosphite/phosphinite-thioether ligands **L49**-**L50a**-**e** in the hydrogenation of more challenging 1,1'-disubstituted olefins. The control of asymmetric induction in this class of substrates is more difficult than in trisubstituted olefins. This is because of the catalyst has the added difficulty of controlling not only the face selectivity coordination (only two substituents compared with the three of trisubstituted olefins), but also the isomerization of the olefins to form the more stable *E*-trisubstituted substrates, which are hydrogenated to form the opposite enantiomer.[5e,5h]

Table 3.11.3. Ir-catalyzed hydrogenation of **S10** using **L49**-**L50a**-**e**.[a]



S10

Entry	Ligand	% Conv[b]	%ee[c]
1	**L49a**	100	93 (*S*)
2	**L49b**	100	88 (*R*)
3	**L49c**	100	92 (*R*)
4	**L49d**	100	97 (*R*)
5	**L49e**	100	80 (R)
6	**L50a**	100	55 (*S*)
7	**L50b**	100	60 (*R*)
8	**L50c**	100	80 (*R*)
9	**L50d**	100	78 (R)
10	**L50e**	100	92 (R)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (1 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^1H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by GC analysis.

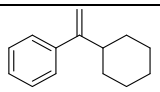
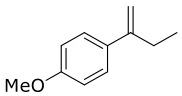
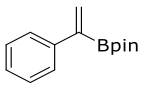
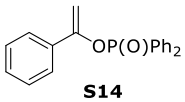
In a first set of experiments, we studied the reduction of disubstituted substrate **S10**. The results, which are found in Table 3.11.3, indicated that the enantioselectivity is again highly affected by the substituent on the thioether moiety, the nature of the P-donor group and the configuration/substituents of the phosphorus group. In general, the use of ligands **L49**, with a 2,6-dimethylphenyl thioether group, led to better

enantioselectivities than the use of ligands **L50** with an adamantyl thioether moiety (i.e. entry 1 vs 6). Moreover, albeit the use of phosphite based ligands offers the possibility to achieve both enantiomers of the hydrogenated product in high ee's (up to 92% ee) by simply varying the configuration of the biaryl phosphite group (e.g. entries 1 and 2), the highest enantioselectivity was achieved using the catalytic system modified with phosphinite thioether ligand **L49d** (ee's up to 97%, entry 4).

Encouraged by the satisfactory results in the hydrogenation of substrate **S10**, we subsequently tested ligands **L49**-**L50a**-**e** in the hydrogenation of other disubstituted substrates (Table 3.11.4, for a complete series of results, see Table SI-2 in Supporting Information at the end of this chapter). Comparing the results obtained with **S10** with those obtained with substrates **S11** and **S12**, we can conclude that the catalyst could not control the competing isomerization pathway. The highest enantioselectivities in the reduction of **S11** and **S12** were obtained with [Ir(cod)(**L49e**)]BAr_F catalyst precursor (ee's up to 53% and 60%, respectively; entries 1 and 2).

The reduction of the disubstituted alkenyl boronic ester **S13** and enol phosphinate **S14** follow the same catalytic performance than their related trisubstituted counterparts **S6** and **S8**, respectively. While the hydrogenation of **S13** proceeds with moderate enantioselectivities (77% ee, entry 3), high enantioselectivity (96% ee) was achieved in the reduction of enolphosphinate **S14** using Ir/**L50b** catalytic system (entry 4).

Table 3.11.4. Selected results for the asymmetric hydrogenation of **S11-S14** using [Ir(cod)(**L49**-**L50a**-**e**)]BAr_F catalyst precursors.[a]

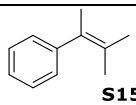
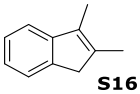
Entry	Ligand	Substrate	% Conv[b]	% ee[c]
1	**L49e**	 **S11**	100	53 (*R*)
2	**L49e**	 **S12**	100	60 (*R*)
3	**L49a**	 **S13**	100	77 (*R*)
4	**L50b**	 **S14**	100	96 (*S*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (1 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^1H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by GC or HPLC analysis.

3.11.2.5. Asymmetric hydrogenation of tetrasubstituted olefins

Finally, we turned our attention in the hydrogenation of tetrasubstituted olefins. As previously mentioned, the hydrogenation of this class of substrates is still a challenge. We evaluated [Ir(**L49**-**L50a**-**e**)] catalysts precursors in the hydrogenation of two types of tetrasubstituted olefins, acyclic (3-methylbut-2-en-2-yl)benzene **S15** and cyclic 2,3-dimethyl-1*H*-indene **S16**. The results found in Table 3.11.5 showed that enantioselectivities are again highly affected by all the ligands parameters. Interestingly, the hydrogenation of both substrates follow a similar trend than for *Z*-trisubstituted substrate **S2**. The best enantioselectivities were therefore obtained using [Ir(cod)(**L50e**)]BAr_F catalyst precursor (ee's up to 77% and 64%, respectively; entry 10).

Table 3.11.5. Ir-catalyzed hydrogenation of **S15** and **S16** using **L49**-**L50a**-**e**.[a]

		 **S15**		 **S16**	
Entry	Ligand	% Conv[b]	%ee[c]	% Conv[b]	% ee[c]
1	**L49a**	100	63 (*R*)	100	41 (*R,R*)
2	**L49b**	100	4 (*S*)	100	0
3	**L49c**	100	22 (*S*)	100	34 (*R,R*)
4	**L49d**	100	41 (*S*)	100	32 (*R,R*)
5	**L49e**	100	53 (*S*)	100	35 (*R,R*)
6	**L50a**	100	23 (*R*)	100	10 (*S,S*)
7	**L50b**	100	12 (S)	100	15 (*R,R*)
8	**L50c**	100	11 (*S*)	100	48 (*R,R*)
9	**L50d**	100	10 (*S*)	100	35 (*R,R*)
10	**L50e**	100	77 (*S*)	100	64 (*R,R*)

[a] Reactions conditions: Substrate (0.5 mmol), Ir-catalyst precursor (2 mol%), H_2 (50 bar), CH_2Cl_2 (2 mL), rt; [b] Conversion measured by ^{1}H NMR spectroscopic analysis after 4 h; [c] Enantiomeric excesses determined by GC analysis.

3.11.3. Conclusions

A phosphite/phosphinite-thioether ligand family was successfully synthesized in only four steps from commercially available (*R*,*R*)-hydrobenzoin. The synthetic strategy used allow us to study the effect of the thioether substituent and the electronic and steric nature of the different types of P-donor groups. Both groups have been found to be highly important for the enantioselectivity of the process. Nevertheless, to achieve high enantioselectivities, the ligand parameters have to be correctly selected for each

particular substrate. We have been able to achieve high enantioselectivities in the asymmetric hydrogenation of a range of *E*-trisubstituted and 1,1'-disubstituted olefins, including examples with poorly coordinative neighboring polar groups (ee's up to 99%). Promising enantioselectivities were also achieved in the asymmetric hydrogenation of more challenging tetrasubstituted olefins (ee's up to 77%).

3.11.4. Experimental Section

3.11.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[9] Enantiopure (+)-(*R*,*R*)-stilbene oxide **3**[8] were prepared as previously reported. Substrates **S1**-**S2**,[10] **S3**,[11] **S4**,[12] **S5**,[13] **S7**,[14] **S8**,[15] **S9**,[16] **S10**,[17] **S11**,[18] **S12**,[19] **S14**[15] and **S15**-**S16**[20] were prepared following the reported procedures and **S6** and **S13** were commercially available. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC.

3.11.4.2. General procedure for the preparation of thioether-alcohols 4-5

A solution of (2*R*,3*R*)-2,3-diphenyloxirane (588.7 mg, 3 mmol) in DMF (3.3 mL/mmol of stilbene oxide) is treated with the corresponding thiol (6 mmol). Then, a solution of NaOH (240.0 mg, 6 mmol) in water (0.4 mL/mmol of stilbene oxide) is added dropwise. The reaction mixture is capped and stirred at 55 ºC until the epoxide is consumed according to TLC analysis (*ca*. 60-120 min). After this, the mixture is cooled to room temperature, diluted with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers are dried over $MgSO_4$ and concentrated to give a residue that is purified by flash chromatography on silica gel (gradient from cyclohexane/EtOAc = 100:0 to cyclohexane/EtOAc = 80:20) to give the desired thioether-alcohol **4** and **5** as white solids.

(1*R*, 2*S*)-2-((2,6-dimethylphenyl)thio)-1,2-diphenylethan-1-ol (4): Yield: 903 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.30 (s, 6H, CH_3-Ar), 2.49 (d, 1H, OH, *J*= 2.9 Hz), 4.05 (d, 1H, CH-S, *J*= 6.4 Hz), 5.01 (dd, 1H, CH-O, *J*= 6.4 Hz, *J*= 2.9 Hz), 6.93-7.42 (m, 13H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 21.8, 61.0, 75.9, 76.7, 77.0, 77.3, 126.7, 127.5, 127.9, 128.0, 128.1, 128.2, 128.4, 128.9, 132.2, 138.2, 140.9, 143.4.

(1*R*, 2*S*)-2-((adamantan-1-yl)thio)-1,2-diphenylethan-1-ol (5): Yield: 1.04 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.60-1.87 (m, 12H), 1.93-2.05 (m, 2H), 2.88 (d, 1H, *J*= 5.9 Hz), 4.29 (d, 1H, CH-S, *J*= 5.5 Hz), 4.99 (dd, CH-O, *J*= 5.7 Hz, *J*= 5.5 Hz), 7.00-7.11 (m, 2H, CH=), 7.13-7.31 (m, 8H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 29.7, 36.1, 43.9, 46.4, 52.9, 76.7, 77.0, 77.3, 126.8, 127.0, 127.5, 127.6, 128.0, 129.1, 140.7, 140.9.

3.11.4.3. General procedure for the preparation of phosphite-thioether ligands L49-L50a-b

The corresponding phosphorochloridite (0.55 mmol) produced *in situ* was dissolved in toluene (3 mL), and pyridine (0.15 mL, 1.8 mmol) was added. The corresponding thioether-hydroxyl compound (0.5 mmol) was azeotropically dried with toluene (3 x 2 mL) and then dissolved in toluene (3 mL) to which pyridine (0.15 mL, 1.8 mmol) and DMAP (6.7 mg, 0.05 mmol) were added. The alcohol solution was transferred slowly to a solution of phosphorochloridite. The reaction mixture was stirred at 80 ºC overnight, after which the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in silica (toluene/NEt_3 = 100/1) to produce the corresponding ligand as a white solid.

L49a: Yield: 210 mg (58%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.40 (s, 18H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.25 (s, 6H, CH_3-ArS), 4.23 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 6.3 Hz), 5.48 (dd, 1H, CH-OP, $^3J_{H\text{-}P}$= 8.9 Hz, $^3J_{H\text{-}H}$= 6.3 Hz), 6.81-6.91 (m, 7H, CH=), 7.06-7.15 (m, 4H, CH=), 7.38-7.40 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.0 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 21.7 (CH_3-ArS), 31.1 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.2 Hz), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.5 (C, ^{t}Bu), 61.2 (CH-S), 80.0 (CH-OP), 126.4-146.5 (aromatic carbons). MS HR-ESI [found 717.3531, $C_{46}H_{54}O_3PS$ $(M+H)^+$ requires 717.3526].

L49b: Yield: 240 mg (67%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 133.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.21 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.43 (s, 6H, CH_3-ArS), 4.65 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 4.7 Hz), 5.19 (dd, 1H, CH-OP, $^3J_{H\text{-}P}$= 9.6 Hz, $^3J_{H\text{-}H}$= 4.7 Hz), 6.87-6.96 (m, 7H, CH=), 7.04-7.11 (m, 4H, CH=), 7.15-7.17 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.0 (CH_3), 16.2 (CH_3), 19.8 (CH_3), 20.0 (CH_3), 22.5 (CH_3-ArS), 30.9 (CH_3, ^{t}Bu), 31.0 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.3 Hz), 31.0 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 62.7 (CH-S), 81.1 (CH-OP), 125.3-145.8 (aromatic carbons). MS HR-ESI [found 717.3533, $C_{46}H_{54}O_3PS$ $(M+H)^+$ requires 717.3526].

L50a: Yield: 320 mg (86%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 139.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.37-1.42 (m, 6H, CH_2, Ad), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3,

^{t}Bu), 1.61 (s, 3H, CH_3), 1.62-1.64 (m, 2H, CH_2, Ad), 1.65-1.69 (m, 4H, CH_2, CH, Ad), 1.71 (s, 3H, CH_3), 1.73-1.76 (m, 2H, CH_2, Ad), 1.77-1.79 (m, 1H, CH_2, Ad), 1.99 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 4.47 (d, 1H, CH-S, $^3J_{H-H=}$ 4.5 Hz), 5.32 (dd, 1H, CH-OP, $^3J_{H-P}$= 9.8 Hz, $^3J_{H-H}$= 4.5 Hz), 6.88-7.00 (m, 5H, CH=), 7.05-7.07 (m, 1H, CH=), 7.08-7.12 (m, 3H, CH=), 7.14-7.16 (m, 2H, CH=), 7.22 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.1 (CH_3), 16.4 (CH_3), 20.1 (CH_3), 20.2 (CH_3), 21.1 (C, Ad), 29.7 (CH, Ad), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.0 Hz), 31.7 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 36.2 (CH_2, Ad), 43.9 (CH_2, Ad), 45.8 (CH_2, Ad), 51.8 (CH-S), 81.0 (d, CH-OP, $^2J_{C-P}$= 5.7 Hz), 125.3-145.7 (aromatic carbons). MS HR-ESI [found 747.4002, $C_{48}H_{60}O_3PS$ $(M+H)^+$ requires 747.3995].

L50b: Yield: 340 mg (95%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 131.5 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.16 (s, 9H, CH_3, ^{t}Bu), 1.41-1.50 (m, 5H, CH_2, Ad), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.74-1.78 (m, 5H, CH_2, CH, Ad), 1.80-1.82 (m, 2H, CH_2, Ad), 1.88 (s, 3H, CH_3), 1.90-1.92 (m, 2H, CH_2, Ad), 1.93-1.95 (m, 1H, CH_2, Ad), 1.97 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 4.89 (d, 1H, CH-S, $^3J_{H-H=}$ 3.4 Hz), 5.15 (dd, 1H, CH-OP, $^3J_{H-P}$= 10.5 Hz, $^3J_{H-H}$= 3.4 Hz), 6.88-7.00 (m, 5H, CH=), 6.76 (s, 1H, CH=), 6.79-6.82 (m, 2H, CH=), 6.91-7.02 (m, 6H, CH=), 7.06-7.11 (m, 1H, CH=), 7.27-7.30 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.0 (CH_3), 16.3 (CH_3), 19.7 (CH_3), 20.2 (CH_3), 21.1 (C, Ad), 29.7 (CH, Ad), 30.9 (CH_3, ^{t}Bu), 31.4 (d, CH_3, ^{t}Bu, J_{C-P}= 5.2 Hz), 34.3 (C, ^{t}Bu), 34.5 (C, ^{t}Bu), 36.1 (CH_2, Ad), 43.9 (CH_2, Ad), 45.2 (CH_2, Ad), 52.0 (CH-S), 81.6 (d, CH-OP, $^2J_{C-P}$= 5.9 Hz), 125.2-146.2 (aromatic carbons). MS HR-ESI [found 747.3999, $C_{48}H_{60}O_3PS$ $(M+H)^+$ requires 747.3995].

3.11.4.4. General procedure for the preparation of phosphinite-thioether ligands L49-L50c-e

The corresponding thioether-hydroxyl compound (0.5 mmol) and DMAP (6.7 mg, 0.055 mmol) were dissolved in toluene (1 mL), and triethylamine was added (0.09 mL, 0.65 mmol), followed by the addition of the corresponding chlorophosphine (0.55 mmol) via syringe. The reaction was stirred for 20 min at rt. The solvent was removed *in vacuo*, and the product was purified by flash chromatography on alumina (toluene/NEt_3= 100/1) to produce the corresponding ligand as an oil (**L49**-**L50c**-**d**) or a solid (**L49**-**L50e**).

L49c: Yield: 90 mg (35%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 114.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 2.13 (s, 6H, CH_3-ArS), 4.22 (d, 1H, CH-S, $^3J_{H-H}$= 7.9 Hz), 5.46 (pt, 1H, CH-OP, J= 8.1 Hz), 6.71-6.82 (m, 3H, CH=), 6.89-7.06 (m, 11H, CH=), 7.10-7.14 (m, 3H, CH=), 7.20-7.23 (m, 4H, CH=), 7.28-7.31 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 21.8 (CH_3-ArS), 61.0 (d, CH-S, $^3J_{C-P}$= 6.9 Hz), 85.7 (d, CH-OP, $^2J_{C-P}$= 21.7 Hz), 126.6-143-4 (aromatic carbons).

L49d: Yield: 228 mg (83%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 96.8 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 2.02 (s, 3H, CH_3, *o*-Tol), 2.03 (s, 3H, CH_3, *o*-Tol), 2.10 (s, 6H, CH_3-ArS), 4.17 (d, 1H, CH-S, $^{3}J_{H-H}$= 7.8 Hz), 5.37 (pt, 1H, CH-OP, *J*= 7.6 Hz), 6.71-7.01 (m, 16H, CH=), 7.11-7.15 (m, 3H, CH=), 7.36-7.40 (m, 1H, CH=), 7.45-7.48 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 19.9 (d, CH_3, *o*-Tol, $^{3}J_{C-P}$= 4.8 Hz), 20.1 (d, CH_3, *o*-Tol, $^{3}J_{C-P}$= 6.4 Hz), 21.7 (CH_3-ArS), 61.4 (d, CH-S, $^{3}J_{C-P}$= 6.4 Hz), 85.5 (d, CH-OP, $^{2}J_{C-P}$= 23.5 Hz), 125.3-143.4 (aromatic carbons).

L49e: Yield: 240 mg (88%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 153.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.87-1.18 (m, 10H, CH_2, Cy), 1.36-1.52 (m, 2H, CH, Cy), 1.60-1.68 (m, 10H, CH_2, Cy), 2.23 (s, 6H, CH_3-ArS), 4.27 (d, 1H, CH-S, $^{3}J_{H-H}$= 8.0 Hz), 5.28 (pt, 1H, CH-OP, *J*= 8.0 Hz), 6.79-6.86 (m, 3H, CH=), 6.97-7.05 (m, 3H, CH=), 7.11-7.26 (m, 5H, CH=), 7.42 (d, 2H, CH=, $^{3}J_{H-H}$= 6.9 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 21.8 (CH_3-ArS), 26.4-28.1 (CH_2, Cy), 38.2 (CH, Cy), 38.4 (CH, Cy), 60.8 (CH-S), 87.1 (d, CH-OP, $^{2}J_{C-P}$= 20.5 Hz), 126.8-143.3 (aromatic carbons).

L50c: Yield: 230 mg (84%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 112.0 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.33-1.40 (m, 6H, CH_2, Ad), 1.60-1.71 (m, 9H, CH_2, CH, Ad), 4.40 (d, 1H, CH-S, $^{3}J_{H-H}$= 6.8 Hz), 5.28 (pt, 1H, CH-OP, *J*= 7.6 Hz), 6.92-7.15 (m, 12H, CH=), 7.19-7.22 (m, 2H, CH=), 7.37-7.43 (m, 6H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 21.1 (C, Ad), 30.6 (CH, Ad), 36.0 (CH_2, Ad), 43.7 (CH_2, Ad), 45.9 (CH_2, Ad), 52.5 (CH-S), 86.6 (d, CH-OP, $^{2}J_{C-P}$= 20.8 Hz), 125.3-142.8 (aromatic carbons).

L50d: Yield: 256 mg (89%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 96.3 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.25-1.34 (m, 6H, CH_2, Ad), 1.50-1.55 (m, 3H, CH, Ad), 1.60-1.65 (m, 6H, CH_2, Ad), 2.03 (s, 3H, CH_3, *o*-Tol), 2.11 (s, 3H, CH_3, *o*-Tol), 4.29 (d, 1H, CH-S, $^{3}J_{H-H}$= 7.2 Hz), 5.16 (pt, 1H, CH-OP, *J*= 7.2 Hz), 6.74-7.12 (m, 16H, CH=), 7.38 (d, 2H, CH=, $^{3}J_{H-H}$= 7.0 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 20.0 (CH_3, *o*-Tol), 20.2 (CH_3, *o*-Tol), 29.6 (CH, Ad), 36.0 (CH_2, Ad), 43.6 (CH_2, Ad), 45.9 (C, Ad), 52.6 (d, CH-S, $^{3}J_{C-P}$= 7.0 Hz), 86.8 (d, CH-OP, $^{2}J_{C-P}$= 22.8 Hz), 125.5-143.0 (aromatic carbons).

L50e: Yield: 242 mg (86%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 149.8 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.01-1.94 (m, 37H, CH and CH_2, Cy and Ad), 4.54 (d, 1H, CH-S, $^{3}J_{H-H}$= 7.0 Hz), 5.16 (pt, 1H, CH-OP, *J*= 7.6 Hz), 7.18-7.24 (m, 2H, CH=), 7.26-7.32 (m, 4H, CH=), 7.43 (d, 2H, CH=, $^{3}J_{H-H}$= 7.8 Hz), 7.61 (d, 2H, CH=, $^{3}J_{H-H}$= 7.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 26.6-28.3 (CH_2, Cy), 29.8 (CH, Ad), 36.2 (CH_2, Ad), 38.3 (d, CH, Cy, $^{1}J_{C-P}$= 21.0 Hz), 38.7 (d, CH, Cy, $^{1}J_{C-P}$= 19.0 Hz), 43.9 (CH_2, Ad), 45.9 (C, Ad), 52.6 (d, CH-S, $^{3}J_{C-P}$= 6.0 Hz), 87.9 (d, CH-OP, $^{2}J_{C-P}$= 20.1 Hz), 126.7-143.4 (aromatic carbons).

3.11.4.5. General procedure for the preparation of [Ir(cod)(L49-L50a-e)]BAr_F

The corresponding ligand (0.074 mmol) was dissolved in CH_2Cl_2 (5 mL) and [Ir(μ-Cl)(cod)]$_2$ (25.0 mg, 0.037 mmol) was added. The reaction mixture was heated to reflux at 40 °C for 1 h. After 5 min at rt, $NaBAr_F$ (77.2 mg, 0.080 mmol) and water (5 mL) were added and the reaction mixture was stirred vigorously for 30 min at rt. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ filtered through a plug of Celite and the solvent was evaporated to give the product as an orange solid.

[Ir(cod)(L49a)]BAr_F: Yield: 127 mg (91%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 97.5 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.04 (s, 9H, CH_3, ^{t}Bu), 1.75 (s, 9H, CH_3, ^{t}Bu), 1.78 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.90-2.08 (m, 4H, CH_2, cod), 2.04 (s, 3H, CH_3), 2.14-2.20 (m, 3H, CH_2, cod), 2.23 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.35-2.40 (m, 1H, CH_2, cod), 2.98 (m, 1H, CH=, cod), 3.06 (s, 3H, CH_3), 4.13 (m, 2H, CH-S, CH=, cod), 4.61 (m, 1H, CH=, cod), 4.93 (m, 1H, CH=, cod), 6.51 (d, 1H, CH-OP, $^3J_{C\text{-}P}$= 10.6 Hz), 6.86-7.72 (m, 27H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.3 (CH_3), 16.4 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 22.3 (CH_3), 22.7 (CH_3), 27.3 (CH_2, cod), 29.9 (CH_2, cod), 31.2 (CH_3, ^{t}Bu), 31.9 (CH_2, cod), 32.5 (CH_3, ^{t}Bu), 33.8 (CH_2, cod), 34.7 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 66.5 (CH-S), 67.8 (CH=, cod), 77.2 (CH=, cod), 84.9 (d, CH-OP, $^2J_{C\text{-}P}$= 10.1 Hz), 104.5 (d, CH=, cod, $J_{C\text{-}P}$= 13.3 Hz), 105.3 (d, CH=, cod, $J_{C\text{-}P}$= 16.0 Hz), 117.4-144.4 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.9 Hz). MS HR-ESI [found 1017.4018, $C_{86}H_{77}BF_{24}IrO_3PS$ (M-BAr_F)$^+$ requires 1017.4021].

[Ir(cod)(L49b)]BAr_F: Yield: 125 mg (90%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 92.4 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.60 (s, 3H, CH_3), 1.64 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 9H, CH_3, ^{t}Bu), 1.72-1.79 (m, 2H, CH_2, cod), 1.81 (s, 3H, CH_3), 1.84-1.94 (m, 3H, CH_2, cod), 2.04 (s, 3H, CH_3), 2.07-2.18 (m, 2H, CH_2, cod), 2.20 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.33-2.36 (m, 1H, CH_2, cod), 2.88 (s, 4H, CH_3, CH=, cod), 4.15 (d, 1H, CH-S, $^3J_{H\text{-}H}$= 3.8 Hz), 4.43 (m, 1H, CH=, cod), 4.53 (m, 1H, CH=, cod), 4.66 (m, 1H, CH=, cod), 6.36 (dd, 1H, CH-OP, $^3J_{C\text{-}P}$= 12.9 Hz, $^3J_{H\text{-}H}$= 3.8 Hz), 6.71-7.72 (m, 27H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.5 (CH_3), 16.6 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 22.2 (CH_3), 23.0 (CH_3), 27.3 (CH_2, cod), 29.3 (CH_2, cod), 31.6 (CH_2, cod), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_2, cod), 32.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 59.7 (CH-S), 65.6 (CH=, cod), 76.3 (CH=, cod), 81.6 (CH-OP), 102.6 (d, CH=, cod, $J_{C\text{-}P}$= 14.8 Hz), 105.6 (d, CH=, cod, $J_{C\text{-}P}$= 15.3 Hz), 117.3-144.1 (aromatic carbons), 161.6 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 50.0 Hz). MS HR-ESI [found 1017.4019, $C_{86}H_{77}BF_{24}IrO_3PS$ (M-BAr_F)$^+$ requires 1017.4021].

[Ir(cod)(L49c)]BAr_F: This compound was further purified using neutral silica and a mixture of dichloromethane and hexane (3:1) as eluent. Yield: 70 mg (56%). Major isomer (74%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 109.7 (s). ^{1}H NMR (400 MHz, $CDCl_3$):

δ= 1.90-1.98 (m, 2H, CH_2, cod), 2.09 (s, 3H, CH_3-ArS), 2.16-2.38 (m, 4H, CH_2, cod), 2.96-3.07 (m, CH_2, cod), 3.47 (m, 1H, CH=, cod), 3.60 (m, 1H, CH=, cod), 4.11 (m, 2H, CH=, cod, CH-S), 4.77 (m, 1H, CH=, cod), 6.22 (dd, 1H, CH-OP, $^3J_{H-P}$= 11.4 Hz, $^3J_{H-H}$= 2.4 Hz), 6.58-8.01 (m, 35H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 22.3 (CH_3-ArS), 27.8 (CH_2, cod), 30.6 (CH_2, cod), 31.0 (CH_2, cod), 33.7 (CH_2, cod), 63.3 (CH-S), 69.7 (CH=, cod), 73.6 (CH=, cod), 86.9 (CH-OP), 98.9 (d, CH=, cod, J_{C-P}= 9.9 Hz), 99.8 (d, CH=, cod, J_{C-P}= 12.9 Hz), 117.5-154.6 (aromatic carbons), 167.8 (q, C-B, BAr_F, J_{C-B}= 49.8 Hz). Minor isomer (26%): ^{31}P NMR (161.9 MHz, C_6D_6): δ= 97.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.76-1.97 (m, 2H, CH_2, cod), 2.30-2.36 (m, 2H, CH_2, cod), 2.94-2.96 (m, 1H, CH_2, cod), 3.03 (s, 3H, CH_3-ArS), 3.10-3.13 (m, 2H, CH_2, cod), 3.50 (m, 1H, CH_2, cod), 3.68 (m, 1H, CH-S), 3.83 (m, 1H, CH=), 4.68 (m, 1H, CH=, cod), 3.58 (m, 1H, CH=, cod), 5.18 (d, 1H, CH-OP, $^3J_{C-P}$= 11.3 Hz), 5.20 (m, 1H, CH=, cod), 6.68-7.90 (m, 35H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 12.9 (CH_2, cod), 23.2 (CH_3-ArS), 25.5 (CH_2, cod), 28.4 (CH_2, cod), 36.5 (CH_2, cod), 60.2 (CH-S), 79.9 (CH-OP), 82.6 (CH=, cod), 92.7 (CH=, cod), 97.3 (d, CH=, cod, J_{C-P}= 15.2 Hz), 104.1 (d, CH=, cod, J_{C-P}= 10.2 Hz), 117.5-154.6 (aromatic carbons), 167.8 (q, C-B, BAr_F, J_{C-B}= 49.8 Hz). MS HR-ESI [found 819.2399, $C_{74}H_{55}BF_{24}IrOPS$ $(M\text{-}BAr_F)^+$ requires 819.2401].

[Ir(cod)(L49d)]BAr_F: This compound was further purified using neutral silica and a mixture of dichloromethane and hexane (3:1) as eluent. Yield: 52 mg (42%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 109.3 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.82-2.08 (m, 3H, CH_2, cod), 2.12 (s, 3H, CH_3), 2.13-2.19 (m, 2H, CH_2, cod), 2.20 (s, 3H, CH_3), 2.29-2.37 (m, 3H, CH_2, cod), 2.52 (s, 3H, CH_3), 3.05 (m, 1H, CH=, cod), 3.08 (s, 3H, CH_3), 3.31 (m, 1H, CH=, cod), 4.12 (m, 1H, CH=, cod), 4.27 (b, 1H, CH-S), 4.75 (m, 1H, CH=, cod), 6.43 (d, 1H, CH-OP, $^3J_{C-P}$= 9.2 Hz), 6.16-9.07 (m, 33H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 22.2 (CH_3), 22.7 (CH_3), 22.8 (CH_3), 27.8 (CH_2, cod), 30.7 (CH_2, cod), 30.9 (CH_2, cod), 33.8 (CH_2, cod), 65.8 (CH-S), 69.6 (CH=, cod), 75.6 (CH=, cod), 89.8 (CH-OP), 98.4 (b, CH=, cod), 98.5 (b, CH=, cod), 117.4-143.8 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz). MS HR-ESI [found 847.2711, $C_{76}H_{59}BF_{24}IrOPS$ $(M\text{-}BAr_F)^+$ requires 847.2714].

[Ir(cod)(L49e)]BAr_F: This compound was further purified using neutral silica and a mixture of dichloromethane and hexane (3:1) as eluent. Yield: 53 mg (43%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 132.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.90-2.48 (m, CH_2, 18H, cod and Cy), 1.72-1.74 (m, 1H, CH, Cy), 1.99 (s, 3H, CH_3-ArS), 2.43-2.45 (m, 1H, CH, Cy), 3.00 (s, 3H, CH_3-ArS), 3.65 (m, 1H, CH=, cod), 3.83 (m, 1H, CH=, cod), 4.13 (d, 1H, CH-S, $^3J_{H-H}$= 3.3 Hz), 4.28 (m, 1H, CH=, cod), 4.68 (m, 1H, CH=, cod), 5.84 (dd, 1H, CH-OP, $^3J_{H-P}$= 12.1 Hz, $^3J_{H-H}$= 3.3 Hz), 6.90-7.79 (m, 25H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 22.1 (CH_3-ArS), 22.5 (CH_3-ArS), 25.6 (CH_2, cod and Cy), 29.3-31.4 (CH_2, cod and Cy), 35.4 (CH_2, cod), 40.9 (d, CH, Cy, $^1J_{C-P}$= 23.0 Hz), 41.3 (d, CH, Cy, $^1J_{C-P}$= 39.4 Hz), 61.9 (CH-S), 65.4 (CH=, cod), 73.1 (CH=, cod), 86.9 (CH-OP), 95.4

(d, CH=, cod, $J_{C\text{-}P}$= 13.6 Hz), 96.5 (d, CH=, cod, $J_{C\text{-}P}$= 8.2 Hz), 117.4-143.0 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.8 Hz). MS HR-ESI [found 831.3336, $C_{74}H_{67}BF_{24}IrOPS$ $(M\text{-}BAr_F)^+$ requires 831.3340].

[Ir(cod)(L50a)]BAr_F: Yield: 124 mg (88%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 100.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.91 (s, 9H, CH_3, ^{t}Bu), 1.57-1.68 (m, 8H, CH_2, Ad, cod), 1.75 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 1.79 (s, 9H, CH_3, ^{t}Bu), 1.89-1.99 (m, 8H, CH_2, Ad, cod), 2.06-2.10 (m, 3H, CH, Ad), 2.11-2.14 (m, 2H, CH_2, cod), 2.20 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.35-2.40 (m, 2H, CH_2, cod), 3.38 (m, 1H, CH=, cod), 4.36 (m, 1H, CH=, cod), 4.54 (m, 1H, CH-S), 6.13 (m, 1H, CH=, cod), 6.25 (m, 1H, CH=, cod), 6.30 (d, 1H, CH-OP, $^3J_{C\text{-}P}$= 11.9 Hz), 6.64-7.73 (m, 24H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.3 (CH_3), 16.4 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 28.1 (CH_2, cod), 30.2 (CH_2, cod), 30.6 (CH_3, ^{t}Bu), 30.9 (CH_2, cod), 31.0 (CH_3, ^{t}Bu), 32.5 (CH_2, Ad), 33.8 (CH_2, cod), 34.6 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.2 (CH, Ad), 43.4 (CH_2, Ad), 56.8 (CH-S), 65.5 (CH=, cod), 67.1 (C, Ad), 72.3 (CH=, cod), 85.7 (d, CH-OP, $^2J_{C\text{-}P}$= 12.1 Hz), 97.5 (d, CH=, cod, $J_{C\text{-}P}$= 14.2 Hz), 100.9 (d, CH=, cod, $J_{C\text{-}P}$= 14.9 Hz), 117.4-144.5 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.8 Hz). MS HR-ESI [found 1047.4488, $C_{88}H_{83}BF_{24}IrO_3PS$ $(M\text{-}BAr_F)^+$ requires 1047.4491].

[Ir(cod)(L50b)]BAr_F: Yield: 131 mg (93%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 95.2 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.31 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.67-1.87 (m, 6H, CH_2, Ad), 1.69 (s, 9H, CH_3, ^{t}Bu), 1.75 (s, 3H, CH_3), 2.00-2.21 (m, 6H, CH_2, Ad), 2.06-2.16 (m, 4H, CH_2, cod), 2.15 (s, 3H, CH_3), 2.20-2.24 (m, 3H, CH, Ad), 2.25-2.32 (m, 3H, CH_2, cod), 2.29 (s, 3H, CH_3), 2.48-2.51 (m, 1H, CH_2, cod), 3.54 (m, 1H, CH=, cod), 4.68 (m, 1H, CH=, cod), 4.72 (m, 1H, CH-S), 5.50 (m, 1H, CH=, cod), 5.81 (m, 1H, CH=, cod), 5.96 (d, 1H, CH-OP, J= 8.4 Hz), 6.69-7.73 (m, 24H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 16.3 (CH_3), 16.5 (CH_3), 20.2 (CH_3), 20.3 (CH_3), 22.6 (CH_2, cod), 27.0 (CH_2, cod), 29.8 (CH_2, cod), 30.7 (CH, Ad), 31.6 (CH_2, cod), 31.9 (CH_3, ^{t}Bu), 32.6 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.3 (CH_2, Ad), 43.4 (CH_2, Ad), 48.5 (CH-S), 65.5 (C, Ad), 67.0 (CH=, cod), 74.0 (CH=, cod), 82.6 (CH-OP), 100.2 (d, CH=, cod, $J_{C\text{-}P}$= 17.2 Hz), 105.3 (d, CH=, cod, $J_{C\text{-}P}$= 14.1 Hz), 117.4-144.3 (aromatic carbons), 161.7 (q, C-B, BAr_F, $^1J_{C\text{-}B}$= 49.8 Hz). MS HR-ESI [found 1047.4489, $C_{88}H_{83}BF_{24}IrO_3PS$ $(M\text{-}BAr_F)^+$ requires 1047.4491].

[Ir(cod)(L50c)]BAr_F: This compound was further purified using neutral silica and a mixture of dichloromethane and hexane (3:1) as eluent. Yield: 80 mg (63%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 102.0 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.64-1.76 (m, 6H, CH_2, Ad), 1.72-1.79 (m, 2H, CH_2, cod), 2.03-2.17 (m, 9H, CH_2 and CH), 2.16-2.26 (m, 4H, CH_2, cod), 2.40-2.46 (m, 2H, CH_2, cod), 2.61 (m, 1H, CH=, cod), 3.26 (m, 1H, CH=, cod), 3.79 (m, 1H, CH=, cod), 4.56 (m, 1H, CH-S), 5.50 (m, 2H, CH=, cod), 5.60 (d, 1H, CH-OP, J= 8.5 Hz), 6.88-7.90 (m, 32H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 28.0 (CH_2, cod), 30.2 (CH_2, cod), 30.8 (CH, Ad), 31.3 (CH_2, cod), 34.2 (CH_2, cod), 35.2

(CH_2, Ad), 45.1 (CH_2, Ad), 47.9 (CH-S), 64.9 (C, Ad), 68.4 (CH=, cod), 74.2 (CH=, cod), 81.9 (CH-OP), 97.8 (d, CH=, cod, J_{C-P}= 11.8 Hz), 104.2 (d, CH=, cod, J_{C-P}= 12.4 Hz), 117.5-137.9 (aromatic carbons), 161.8 (q, C-B, BAr_F, J_{C-B}= 49.8 Hz) . MS HR-ESI [found 849.2867, $C_{76}H_{61}BF_{24}IrOPS$ $(M\text{-}BAr_F)^+$ requires 849.2871].

[Ir(cod)(L50d)]BAr_F: This compound was further purified using neutral silica and a mixture of dichloromethane and hexane (3:1) as eluent. Yield: 45 mg (36%). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 111.1 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 1.63 (s, 3H, CH_3, *o*-Tol), 1.65-1.72 (m, 6H, CH_2, Ad), 1.66-2.07 (m, 3H, CH_2, cod), 1.87-2.02 (m, 6H, CH_2, Ad), 2.08-2.12 (m, 3H, CH, Ad), 2.22-2.66 (m, 5H, CH_2, cod), 2.86 (s, 3H, CH_3, *o*-Tol), 2.89 (m, 1H, CH=, cod), 3.80 (m, 1H, CH=, cod), 4.32 (CH-S), 5.08 (m, CH=, cod), 5.50 (d, 1H, CH-OP, $^3J_{C-P}$= 9.9 Hz), 5.65 (m, 1H, CH=, cod), 6.04-8.77 (m, 30H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 20.7 (CH_3, *o*-Tol), 23.3 (CH_3, *o*-Tol), 26.3 (CH_2, cod), 28.8 (CH_2, cod), 30.7 (CH, Ad), 33.2 (CH_2, cod), 35.2 (CH_2, Ad), 35.8 (CH_2, cod), 44.2 (CH_2, Ad), 48.0 (CH-S), 64.4 (C, Ad), 71.3 (CH=, cod), 73.4 (CH=, cod), 83.2 (CH-OP), 95.0 (d, CH=, cod, J_{C-P}= 13.0 Hz), 104.5 (d, CH=, cod, J_{C-P}= 12.4 Hz), 117.4-143.2 (aromatic carbons), 161.2 (q, C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz). MS HR-ESI [found 877.3180, $C_{78}H_{65}BF_{24}IrOPS$ $(M\text{-}BAr_F)^+$ requires 877.3184].

[Ir(cod)(L50e)]BAr_F: This compound was further purified using neutral silica and a mixture of dichloromethane and hexane (3:1) as eluent. Yield: 40 mg (32%). Major isomer (54%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 128.7 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 1.12-3.43 (m, 45H, CH_2 and CH, cod, Ad, Cy), 3.79 (m, CH=, cod), 4.53 (m, 1H, CH-S), 4.69 (m, 1H, CH=, cod), 5.63 (m, 1H, CH=, cod), 5.87 (m, 1H, CH=, cod), 6.01 (d, 1H, CH-OP, J_{C-P}= 7.5 Hz), 6.64-7.70 (m, 22H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 11.4-43.9 (CH_2 and CH, cod, Ad, Cy), 58.2 (CH-S), 64.4 (C-Ad), 68.4 (CH=, cod), 83.7 (CH=, cod), 87.0 (CH-OP), 90.1 (d, CH=, cod, J_{C-P}= 11.6 Hz), 106.4 (d, CH=, cod, J_{C-P}= 9.1 Hz), 117.4-145.7 (aromatic carbons), 161.7 (C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz). Minor isomer (46%): ^{31}P NMR (161.9 MHz, $CDCl_3$): δ= 88.0 (s). ^1H NMR (400 MHz, $CDCl_3$): δ= 1.12-3.43 (m, 45H, CH_2 and CH, cod, Ad, Cy), 3.73 (m, CH=, cod), 4.37 (m, 1H, CH-S), 4.69 (m, 1H, CH=, cod), 5.25 (m, 1H, CH=, cod), 5.49 (d, 1H, CH-OP, J_{C-P}= 10.1 Hz), 5.70 (m, 1H, CH=, cod), 6.64-7.70 (m, 22H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 11.4-43.9 (CH_2 and CH, cod, Ad, Cy), 52.8 (CH-S), 60.2 (C-Ad), 66.6 (CH=, cod), 83.2 (CH=, cod), 86.8 (CH-OP), 89.9 (d, CH=, cod, J_{C-P}= 13.1 Hz), 93.0 (d, CH=, cod, J_{C-P}= 9.9 Hz), 117.4-145.7 (aromatic carbons), 161.7 (C-B, BAr_F, $^1J_{C-B}$= 49.8 Hz). MS HR-ESI [found 861.3807, $C_{76}H_{73}BF_{24}IrOPS$ $(M\text{-}BAr_F)^+$ requires 861.3810].

3.6.4.6. General procedure for the asymmetric hydrogenation

The alkene (0.5 mmol) and Ir complex (2 mol%) were dissolved in CH_2Cl_2 (2 mL) and placed in a high-pressure autoclave. The autoclave was purged 4 times with

hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized, and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short plug of Celite. The enantiomeric excess was determined by chiral GC or chiral HPLC and conversions were determined by ^1H NMR (for hydrogenation products from **S1**-**S3**, **S6**-**S8** and **S10**-**S14** see previous Section 3.1.4.5 and for hydrogenation products from **S4**-**S5** and **S9** see previous Section 3.2.4.6).

3.11.5. Acknowledgements

We all acknowledge MINECO for INTECAT network CTQ2016-81293-REDC/AEI. The URV members gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P) and European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Award to M.D.). The ICIQ members gratefully acknowledge financial support from CERCA Programme/Generalitat de Catalunya, the Spanish Ministry of Economy and Competitiveness (CTQ2015-69136-R, CTQ2017-87792-R, AEI/MINECO/FEDER, UE, and Severo Ochoa Excellence Accreditation 2014-2018, SEV-2013-2019), and DEC Generalitat de Catalunya (Grant No. 2014SGR827). The CELLEX Foundation is also acknowledged for financing the High Throughput Experimentation (HTE) laboratory.

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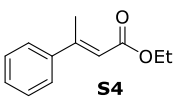
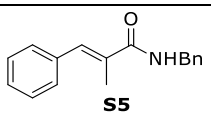
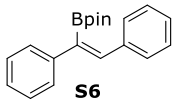
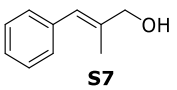
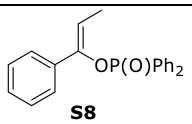
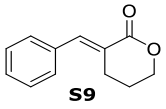
3.11.7. Supporting Information

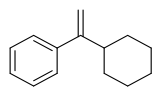
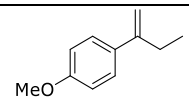
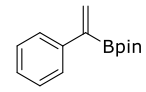
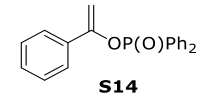
3.11.7.1. Table SI.1. Full set of results for the asymmetric hydrogenation of trisubstituted olefins S3-S9[a]

	 **S3**		 **S4**		 **S5**		 **S6**	
Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
L49a	100	4 (*R*)	100	5 (*R*)	100	20 (*R*)	100	15 (-)
L49b	100	62 (*S*)	100	44 (*S*)	100	52 (*S*)	100	12 (+)
L49c	100	81 (*S*)	100	85 (*S*)	100	74 (*R*)	100	51 (-)
L49d	100	85 (*S*)	100	94 (*S*)	100	89 (*R*)	100	-
L49e	100	98 (*S*)	100	96 (*S*)	100	92 (*R*)	100	-
L50a	100	45 (*R*)	100	2 (*S*)	100	16 (*R*)	100	33 (+)
L50b	100	88 (*R*)	100	30 (*S*)	100	48 (*R*)	100	56 (-)
L50c	100	87 (*S*)	100	61 (*S*)	100	80 (*R*)	100	64 (-)
L50d	100	84 (*S*)	100	47 (*S*)	100	81 (*R*)	100	-
L50e	100	80 (*S*)	100	89 (*S*)	100	90 (*R*)	100	-

	 **S7**		 **S8**		 **S9**	
Ligand	% Conv[b]	% ee[c]	% Conv[b,D]	% ee[c]	% Conv[b]	% ee[c]
L49a	100	2 (*R*)	100	1 (*S*)	100	3 (*R*)
L49b	100	62 (*S*)	100	24 (*S*)	100	26 (*S*)
L49c	100	76 (*S*)	100	40 (*S*)	100	85 (*S*)
L49d	100	73 (*S*)	100	37 (*S*)	100	84 (*S*)
L49e	100	44 (*S*)	100	4 (*S*)	100	72 (*S*)
L50a	100	15 (*S*)	100	12 (*S*)	100	99 (*S*)
L50b	100	4 (*S*)	100	96 (*S*)	100	56 (*S*)
L50c	100	31 (*S*)	100	16 (*S*)	100	90 (*S*)
L50d	100	16 (*S*)	100	50 (*S*)	100	75 (*S*)
L50e	100	64 (*S*)	100	21 (*S*)	100	67 (*S*)

[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor at 50 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by HPLC; [d] Reaction carried out for 18 h.

3.11.7.2. Table SI.2. Full set of results for the asymmetric hydrogenation of disubstituted olefins S11-S14[a]

	 **S11**		 **S12**		 **S13**		 **S14**	
Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
L49a	100	41 (*S*)	100	2 (*S*)	100	77 (*R*)	100	5 (*S*)
L49b	100	42 (*R*)	100	30 (*R*)	100	32 (*R*)	100	40 (*S*)
L49c	100	43 (*R*)	100	44 (*R*)	100	71 (*R*)	100	81 (*S*)
L49d	100	24 (*R*)	100	53 (*R*)	100	76 (*R*)	100	87 (*S*)
L49e	100	53 (*R*)	100	60 (*R*)	100	12 (*R*)	100	69 (*S*)
L50a	100	35 (*R*)	100	2 (*R*)	100	17 (*S*)	100	2 (*S*)
L50b	100	2 (*S*)	100	13 (*R*)	100	48 (*R*)	100	96 (*S*)
L50c	100	11 (*R*)	100	20 (*R*)	100	51 (*R*)	100	85 (*S*)
L50d	100	52 (*R*)	100	21 (*R*)	100	43 (*R*)	100	69 (*S*)
L50e	100	24 (*R*)	100	15 (*R*)	100	21 (*R*)	100	79 (*S*)

[a] Reactions carried out at room temperature using 0.5 mmol of substrate and 2 mol% of Ir-catalyst precursor at 1 bar of H_2 with dichloromethane (2 mL) as solvent; [b] Conversion measured by ^{1}H-NMR after 4 h; [c] Enantiomeric excess determined by GC or HPLC;

3.12. Rh-catalyzed asymmetric hydrogenation of functionalized olefins using P*-stereogenic *N*-phosphine-phosphite ligands

Biosca, M.; Riera, A.; Verdaguer, X.; Pàmies, O.; Diéguez, M. *Preliminary results.*

In collaboration with the group of Prof. A. Riera (University of Barcelona).

Abstract: A modular P*-stereogenic *N*-phosphine-phosphite ligand library has been easily prepared from commercially available (1*R*,2*S*)-(-)-ephedrine and (1*S*,2*R*)-(-)-*cis*-amino-2-indanol and applied in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins. The enantioselectivities are highly dependent on the ligand parameters and the substrate structure. By carefully selecting the ligand parameters for each particular substrate, moderate-to-excellent enantioselectivities have been achieved in the reduction of several types of functionalized alkenes, including examples of more challenging β-dehydroamino acid derivatives and β-enamides (ee's ranging from 60% to >99%).

3.12.1. Introduction

Because of its high efficiency, operational simplicity and perfect atom economy, asymmetric metal-catalyzed hydrogenation is nowadays one of the most widely used and reliable catalytic methods for the preparation of optically active compounds.[1] Over many years the scope of this reaction has gradually extended in terms of reactant structure and catalysts efficiency. In this field, Rh- and Ru-catalysts containing chiral diphosphine and diphosphinite ligands plays a dominant role in the reduction of functionalized alkenes.[1-2] Despite the early success of the P*-stereogenic diphosphine ligand DIPAMP,[3] widely used in the industrial production of L-DOPA (a drug used to treat Parkinson's disease),[4] most of the diphosphine ligands have been designed by introducing the chirality at the ligand backbone rather than in the P-moieties. The main reason for this is the difficulty in the preparation of phosphines bearing the chirality on the phosphorus atom. Nevertheless, with the development of new methodologies to obtain this chirality on the phosphine moiety, some P*-stereogenic phosphine ligands have been developed and successfully applied in this process (e.g. (*R*,*R*)-QuinoxP*,[5] (*S*)-TCFP[6] and MaxPHOS[7]; Figure 3.12.1).

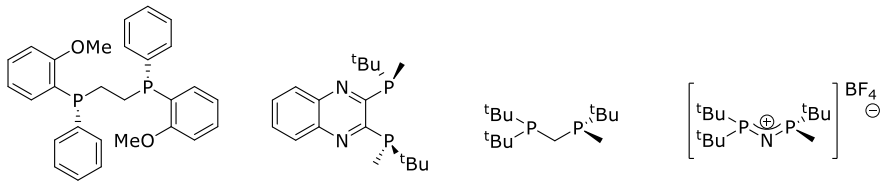


Figure 3.12.1. P*-stereogenic diphosphine ligands.

The use of heterodonor ligands has also proved to be highly successful due to the presence of two coordinating functionalities with different nature, which facilitates the transfer of the chiral information from the catalyst to the hydrogenated product. Among the heterodonor ligands, mixed P,P'-ligands have been successfully applied in the Rh-catalyzed asymmetric hydrogenation of a broad range of functionalized substrates.[2d,8,9] Among them, ligands combining a phosphine group with a more π-acceptor phosphorus moiety (i.e. phosphite or phosphoroamidite) have demonstrated their potential in this process. In this context, several groups made a significant contribution in terms of substrate scope with the development of several phosphine-phosphite/phosphoroamidite ligands.[2d,8] Nevertheless, for this latter class of ligands the introduction of a P*-stereogenic phosphine moiety on the ligand design has been overlooked. To best of our knowledge, there is only one report on the use of heterodonor P*-stereogenic *N*-phosphine-phosphite ligands.[9] In this report, Kamer *et al.* showed the application of a series of resin-bound P*-stereogenic *N*-phosphine-phosphite ligands in the hydrogenation of a limited range of α-dehydroamino acids with only moderate-to-good enantioselectivities (ee's up to 87%). Therefore, more research is needed to study the possibilities offered by *N*-phosphine-phosphite ligands as a new class of ligands for this process.

For this purpose, in this section we reported the synthesis of a new family of P*-stereogenic *N*-phosphine-phosphite ligands (**L51**-**L54a**-**c**; Figure 3.12.2) and their application in the Rh-catalyzed asymmetric hydrogenation of several types of functionalized olefins. This new ligand library allows us to systematically study the effect of: (a) the substituents in the P*-stereogenic *N*-phosphine group (**L51**-**L52**), (b) the configuration of the biaryl phosphite moiety (**a**-**c**) and (c) the rigidity of the ligand backbone (**L51-L52** vs **L54**). In addition, for comparative purpose we also synthetized ligands **L53b**-**c** without chirality on the *N*-phosphine moiety.

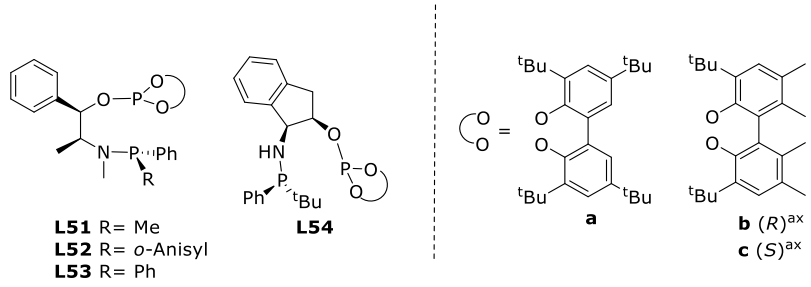


Figure 3.12.2. The new P*-stereogenic *N*-phosphine-phosphite ligand library **L51**-**L54a**-**c**.

3.12.2. Results and Discussion

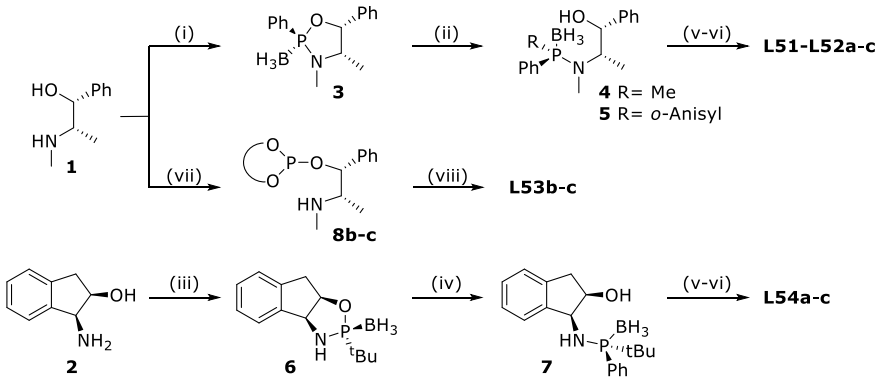
3.12.2.1. Synthesis of ligands

The synthetic routes for the synthesis of P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**L54a**-**c** are showed in Scheme 3.12.1. They have been easily prepared from commercially available (1*R*,2*S*)-(-)-ephedrine (**1**) and (1*S*,2*R*)-(-)-*cis*-amino-2-indanol (**2**).

The synthesis of ligands **L51**-**L52a**-**c** started with the condensation of bis(diethylamino)phenyl phosphine and (1*R*,2*S*)-(-)-ephedrine **1** followed by *in situ* protection of the P-atom to obtain the key intermediate borane-protected oxazaphospholidine **3** (step i).[10] Then, ring opening of the compound **3** with methyl-lithium or *ortho*-anisyl-lithium reagent resulted in exclusive cleavage of the P-O bond to give the desired hydroxyl compounds **4** and **5** (step ii).[10] The ring cleavage of compound **3** proceeded with retention of the configuration at the phosphorus atom. Similarly, for the synthesis of ligands **L54**, the protected *N*-phosphine-hydroxyl compound **7** was prepared from **2** by reaction with chloro-*tert*-butyl(diethylamino)-phosphine (step iii), followed by ring opening of the *tert*-butyl-oxazaphospholidine **6** with phenyl magnesium bromide (step iv).[11] In this case, this latter reaction takes place with inversion of configuration at the phosphorus center to achieve the desired borane-protected phosphine-hydroxyl compound **7**. The last steps for the synthesis of ligands **L51**-**L52a-c** and **L54a**-**c** were common for all of them. They consisted in the coupling of the corresponding *N*-phosphine-hydroxyl compounds **4**, **5** and **7** with the desired *in situ* formed phosphorochloridite ($ClP(OR)_2$; $(OR)_2$= **a**-**c**; step v), followed by the subsequent deprotection of the borane-protected phosphine (step vi).

Ligands **L53b**-**c** were efficiently obtained by coupling the (1*R*,2*S*)-(-)-ephedrine compound **1** with the desired phosphorochloridite ($ClP(OR)_2$; $(OR)_2$= **b**-**c**; step vii) to form amino-phosphites **8** and the subsequent reaction of these intermediates with chlorodiphenylphosphine (step viii).

All ligands were obtained as white solids after purification on neutral silica or alumina under argon atmosphere. They were characterized by $^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy and HRMS-ESI. All data were in agreement with assigned structures. The spectra assignments were supported by the information obtained from ^1H-^1H and ^1H-^{13}C correlation measurements. The ^1H and ^{13}C NMR spectra were as expected for these C_1 ligands.



Scheme 3.12.1. Synthetic route for the synthesis of P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**L54a**-**c**: (i) One pot procedure: a) **1**, $P(NEt_2)_2Ph$, toluene, reflux, 16 h; b) $BH_3(CH_3)_2S$ (2 M in toluene), rt, 12 h; (ii) *o*-AnLi or MeLi, THF, -78 ºC, 30 min-16 h; (iii) One pot procedure: a) **2**, $ClP(NEt_2)^tBu$, THF, reflux, 8 h; b) $BH_3(CH_3)_2S$, 0 ºC, 30 min; (iv) PhMgBr, toluene, reflux, 2 h; (v) $ClP(OR)_2$; $(OR)_2$= **a**-**c**, NEt_3 or NEt_3/DMAP cat., toluene, 80 ºC, 16 h; (vi) $NHEt_2$, reflux, 16 h; (vii) $ClP(OR)_2$; $(OR)_2$= **b**-**c**, NEt_3/DMAP cat., toluene, rt, 4 h; (viii) NEt_3, THF, $ClPPh_2$, 55 ºC, 16 h.

3.12.2. Asymmetric hydrogenation of functionalized olefins

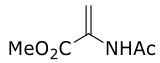
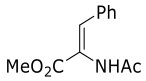
3.12.2.1. Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives

In a first step of experiments we evaluated P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**L54a**-**c** in the Rh-catalyzed hydrogenation of benchmark α-dehydroamino acid derivatives, methyl 2-acetamidoacrylate **S1** and methyl 2-acetamidocinnmate **S2**. The results, which are summarized in Table 3.12.1, indicated that enantioselectivities are highly affected by the substituents on the *N*-phosphine moiety, the configuration of the biaryl phosphite group and the rigidity of the ligand backbone.

The results using ligands **L51a**-**c**, with a flexible ephedrine-backbone, indicated that the ephedrine ligand backbone is not able to control the tropoisomerism of the biaryl phosphite moiety **a** upon coordination to the rhodium (entry 1 vs 2 and 3). They also indicated that there is a cooperative effect between all stereogenic centers that results in a matched combination for ligand **L51c**, containing an enantiopure (*S*)-biaryl phosphite moiety (ee's up to 85%, entry 3).

The results using ligands **L51-L53** indicated that enantioselectivity is affected by the nature of the substituents at the P*-stereogenic *N*-phosphine group and the presence of the P*-stereogenic moiety. The use of ligands with a diaryl *N*-phosphine group (ligands **L52** and **L53**) provided higher enantioselectivities than with **L51** (entries 5 and 7 vs 3). Nevertheless, the presence of the P*-stereogenic unit is crucial to maximize enantioselectivities (up to ≥99% ee for both substrates, entry 5).

Table 3.12.1. Asymmetric hydrogenation of α-dehydroamino acid derivatives **S1** and **S2** using Rh/**L51**-**L54a**-**c** catalysts precursors.[a]

		 **S1**		 **S2**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L51a**	100	61 (*R*)	100	61 (*R*)
2	**L51b**	100	66 (*R*)	100	64 (*R*)
3	**L51c**	100	85 (*R*)	100	80 (*R*)
4	**L52b**	100	40 (*R*)	100	37 (*R*)
5	**L52c**	100	99 (*R*)	100	>99 (*R*)
6	**L53b**	100	50 (*S*)	100	52 (*S*)
7	**L53c**	100	94 (*R*)	100	96 (*R*)
8	**L54a**	100	96 (*S*)	100	94 (*S*)
9	**L54b**	100	>99 (*S*)	100	99 (*S*)
10	**L54c**	100	78 (*R*)	100	75 (*R*)

[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), substrate (0.25 mmol), THF (2 mL), H_2 (25 bar), 20 h at rt; [b] Conversions determined by GC; [c] Enantiomeric excesses determined by GC.

On the other hand, the results using *N*-phosphine-phosphite ligands **L54a**-**c** indicated that the introduction of more rigid backbone has a positive effect on the enantioselectivity (entries 8-10) and that, in contrast with previous ligands tested, the best results were obtained with ligand that contain an (*R*)-biaryl phosphite group (ee's up to 99%, entry 9). These better results can be also attributed to the presence of bulky *tert*-butyl substituent on the P*-stereogenic *N*-phosphine moiety. Interestingly, the results obtained with ligand **L54a** with the inexpensive tropoisomeric biphenyl phosphite group **a** were also satisfactory (entry 8). Therefore, this more rigid ligand backbone is able to control the tropoisomerism of the biaryl phosphite moiety **a**, which upon coordination preferentially adopts an (*R*)-configuration.

In summary, enantioselectivities up to >99% ee were achieved for both substrates, **S1** and **S2**. In addition, by carefully selecting the ligand parameters both enantiomers of the hydrogenated product could be obtained in excellent enantioselectivities (entries 5 and 9).

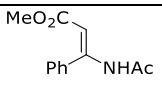
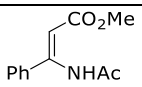
3.12.2.2. Rh-catalyzed hydrogenation of β-dehydroamino acid derivatives

Encouraged by the high enantioselectivities obtained in the hydrogenation of α-dehydroamino acid derivatives, we next tested *N*-phosphine-phosphite ligands **L51**-**L54a**-**c** in the reduction of more challenging β-dehydroamino acid derivatives. The hydrogenation of such substrates lead to important structures present in several

biologically active products (i.e. β-peptides, β-lactam antibiotics,…).[12] The hydrogenation of this class of substrates is highly dependent on the olefin geometry, being the *Z*-isomers more difficult to be efficiently hydrogenated than the *E*-olefins.[13] Having that in mind, we chose *E*-methyl 3-acetamido-3-phenylacrylate (**S3**) and *Z*-methyl 3-acetamido-3-phenylacrylate (**S4**) as model substrates to study the possibilities that the new catalytic systems offers.

The results, which are found in Table 3.12.2, indicated that again enantioselectivities are highly affected by the substituents on the *N*-phosphine moiety, the configuration of the biaryl phosphite group as well as by the rigidity of the ligand backbone. However, their effect not only followed a different trend to that observed for α-dehydroamino acids but also depended on the olefin geometry. Thus, while for substrate **S3** (with *E*-geometry) the use of ligand **L52c**, with an *ortho*-anisyl substituent at the P*-stereogenic *N*-phosphine group, provided the best enantioselectivity (60% ee, entry 5), the use of ligand **L51c**, with methyl substituent at the P*-stereogenic *N*-phosphine moiety, afforded the best ee's for substrate **S4** (with *Z*-geometry; 80% ee, entry 3).

Table 3.12.2. Asymmetric hydrogenation of β-dehydroamino acid derivatives **S3** and **S4** using Rh/**L51**-**L54a**-**c** catalysts precursors.

		 **S3**		 **S4**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L51a**	100	14 (*R*)	100	31 (*R*)
2	**L51b**	100	3 (*S*)	100	21 (*S*)
3	**L51c**	100	22 (*R*)	100	80 (*R*)
4	**L52b**	100	3 (*R*)	100	8 (*S*)
5	**L52c**	100	60 (*R*)	100	20 (*S*)
6	**L53b**	100	25 (*R*)	100	15 (*S*)
7	**L53c**	100	16 (*R*)	100	1 (*S*)
8	**L54a**	100	40 (*S*)	100	35 (*S*)
9	**L54b**	100	33 (*S*)	100	64 (*S*)
10	**L54c**	100	25 (*S*)	100	11 (*S*)

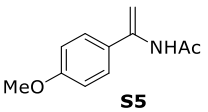
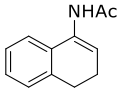
[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), substrate (0.25 mmol), THF (2 mL), H_2 (25 bar), 20 h at rt; [b] Conversions determined by GC; [c] Enantiomeric excesses determined by GC.

3.12.2.3. Rh-catalyzed hydrogenation of enamides

Subsequently, we turned our attention to the hydrogenation of enamides. The hydrogenation of enamides give rise to optically active secondary amines, which are useful frameworks for the synthesis of fine chemicals.[14] Most of the research in this area has been focused in the hydrogenation of α-enamides. For the purpose of comparison,

we therefore chose *N*-(1-(4-methoxyphenyl)vinyl)acetamide **S5** and *N*-(3,4-dihydronaphthalen-1-yl)acetamide **S6** as model substrates. The results, which are found in Table 3.12.3, again indicated that the ligand parameters have to be carefully selected for each substrate to obtain the highest enantioselectivities.

Table 3.12.3. Asymmetric hydrogenation of α-enamides **S5** and **S6** using Rh/**L51**-**L54a**-**c** catalysts precursors.

		 **S5**		 **S6**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L51a**	100	80 (*S*)	100	35 (*R*)
2	**L51b**	100	96 (*R*)	100	53 (*S*)
3	**L51c**	100	96 (*S*)	100	74 (*R*)
4	**L52b**	100	64 (*S*)	100	5 (*S*)
5	**L52c**	100	84 (*S*)	100	95 (*R*)
6	**L53b**	100	7 (*R*)	100	2 (*R*)
7	**L53c**	100	88 (*S*)	100	93 (*R*)
8	**L54a**	100	89 (*R*)	100	11 (*R*)
9	**L54b**	100	95 (*R*)	100	9 (*R*)
10	**L54c**	100	55 (*S*)	100	2 (*R*)

[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), substrate (0.25 mmol), THF (2 mL), H_2 (25 bar), 20 h at rt; [b] Conversions determined by ^1H NMR; [c] Enantiomeric excesses determined by HPLC.

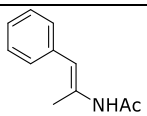
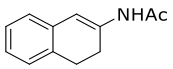
For substrate **S5**, the best enantioselectivities were obtained with **L51b**-**c** that contain a methyl substituent. Remarkably, with ligands **L51** the sense of enantioselectivity is mainly controlled by the biaryl phosphite moiety. Both enantiomers of the hydrogenated product were therefore accessible by simply varying the configuration of the biaryl phosphite moiety (ee's up to 96%, entries 2 and 3). In contrast, for substrate **S6**, the presence of an *ortho*-anisyl substituent on the P*-stereogenic *N*-phosphine moiety has a positive effect on enantioselectivity. Thus, enantioselectivity up to 95% ee was obtained using ligand **L52c** (entry 5). However, with ligands **L52**, there is a cooperative effect between stereocenters, resulting in a mismatching effect with ligand **L52b**.

The effect of the rigidity of the ligand backbone on enantioselectivity is also highly dependent on the substrate used. Thus, while in the reduction of substrate **S5**, high enantioselectivity was also attained using ligand **L54b** (entry 9); for substrate **S6**, the use of ligands **L54**, with a more rigid ligand backbone, had a negative effect on ee's (entries 9 and 10 vs 5 and 6).

Encouraged by the high enantioselectivities achieved in the hydrogenation of α-enamides, we finally moved to study the effectiveness of ligands **L51**-**L54a**-**b** in the Rh-catalyzed hydrogenation of more challenging β-enamides. As previously mentioned, the hydrogenation of β-enamides has been less studied than the α-enamides, albeit their hydrogenation give rise to important building blocks (e.g. 2-aminotetralines and 2-aminochromanes).[15] *E*-*N*-(1-phenylprop-1-en-2-yl)acetamide (**S7**) and *N*-(3,4-dihydronaphthalen-2-yl)acetamide **S8** were chosen as models. The results are shown in Table 3.12.4. Again, the effect of the ligand parameters on enantioselectivity is different for this substrate class.

The reduction of **S7** follows the same trend than the hydrogenation of cyclic α-enamide **S6**, therefore the best enantioselectivity was obtained with ligand **L52c** (60% ee, entry 5). However, in this case the enantioselectivity obtained was only moderate. Interestingly, in the hydrogenation of **S8**, the results indicated that the chirality at the P*-stereogenic *N*-phosphine group is not required to maximize ee's. Promising enantioselectivity (up to 80% ee) was therefore achieved using *N*-phosphine-phosphite ligand **L53c**.

Table 3.12.4. Asymmetric hydrogenation of β-enamides **S7** and **S8** using Rh/**L51**-**L54a**-**c** catalysts precursors.

		 **S7**		 **S8**	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[b]	% ee[c]
1	**L51a**	100	14 (*R*)	100	58 (*R*)
2	**L51b**	100	3 (*S*)	100	7 (*R*)
3	**L51c**	100	22 (*R*)	100	55 (*R*)
4	**L52b**	100	3 (*R*)	100	17 (*S*)
5	**L52c**	100	60 (*R*)	100	44 (*R*)
6	**L53b**	100	25 (*R*)	100	9 (*S*)
7	**L53c**	100	16 (*R*)	100	80 (*R*)
8	**L54a**	100	40 (*S*)	100	17 (*S*)
9	**L54b**	100	33 (*S*)	100	9 (*S*)
10	**L54c**	100	25 (*S*)	100	10 (*S*)

[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), substrate (0.25 mmol), THF (2 mL), H_2 (25 bar), 20 h at rt.[b] Conversions determined by ^1H NMR. [c] Enantiomeric excesses determined by HPLC.

3.12.3. Conclusions

We reported the synthesis and application of a new family of P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**L54a**-**c** in the Rh-catalyzed asymmetric hydrogenation of functionalized alkenes. These ligands allow the study of the effect of several factors (the rigidity of the ligand backbone, the substituents at the P*-stereogenic *N*-phosphine group and the configuration of the biaryl phosphite moiety). All the ligand parameters play a crucial role in the enantioselectivity. By suitable tuning the ligand parameters, we have been able to achieve moderate-to-high enantioselectivities in the hydrogenation of a variety of functionalized substrates (ee's ranging from 60% to >99%).

3.12.4. Experimental Section

3.12.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.[16] ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H, ^{13}C, and ^{31}P assignments were made on the basis of ^{1}H-^{1}H gCOSY, and ^{1}H-^{13}C gHSQC. Compounds **4**-**5**[10] and **7**[11] were prepared as previously described. Substrate **S1**was commercially available and **S2**,[17] **S3**-**S4**,[18] **S5**,[19] **S6**,[20] **S7**[21] and **S8**[22] were prepared following the reported procedures.

3.12.4.2. General procedure for the preparation of *N*-phosphine-phosphite ligands L51a-c and L54a-c

To a solution of *in situ* generated phosphorochloridite (1.1 mmol) in dry toluene (6 mL), triethylamine (0.27 mL, 2.0 mmol) was added. Then, this solution was placed in a 0 ºC bath. After 2 min at that temperature, a solution of the corresponding hydroxyl compound **4** or **7** (1.0 mmol) and triethylamine (0.27 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at 0 °C. The mixture was left to warm to 80 ºC and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral silica and dry toluene/hexane (1:1) as eluent system (1% NEt_3)) to afford the corresponding borane-protected *N*-phosphine-phosphite compound as white solids.

L51a·BH_3**:** Yield: 367 mg (60%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 149.4 (bs, P-O), 68.7 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.14 (pt, 6H, CH_3-CH, CH_3-P, J= 8.6 Hz), 1.22 (s, 9H, CH_3, ^{t}Bu), 1.27 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 18H, CH_3, ^{t}Bu), 1.98 (d, 3H, CH_3-N, $^3J_{H\text{-}P}$= 8.2 Hz), 4.39-4.48 (m, 1H, CH-N), 5.54-5.58 (m, 1H, CH-O), 6.83-6.88 (m, 2H, CH=), 6.96-2.15 (m, 7H, CH=), 7.25 (s, 1H, CH=), 7.30 (s, 1H, CH=), 7.52-7.57 (m, 3H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 10.8 (d, CH_3-P, $J_{C\text{-}P}$= 39.1 Hz), 13.4 (CH_3-CH), 28.4 (CH_3-N), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.2 (d, C, ^{t}Bu, $J_{C\text{-}P}$= 8.1 Hz), 35.2 (C, ^{t}Bu), 57.8 (CH-N), 81.2 (CH-O), 124.0-146.4 (aromatic carbons).

L51b·BH_3**:** Yield: 114 mg (22%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 143.4 (s, P-O), 68.4 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.01 (d, 3H, CH_3-P, $^2J_{H\text{-}P}$= 6.8 Hz), 1.08 (d, 3H, CH_3-CH, $^3J_{H\text{-}H}$= 8.8 Hz), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.84 (d, 3H, CH_3-N, $^3J_{H\text{-}P}$= 8.2 Hz), 2.00 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 4.34-4.43 (m, CH-N), 5.36 (dd, CH-O, $^3J_{H\text{-}P}$= 8.7 Hz, $^3J_{H\text{-}H}$= 6.6Hz), 6.85-6.92 (m, 2H, CH=), 6.98-7.05 (m, 3H, CH=), 7.10-7.19 (m, 5H, CH=), 7.60-7.63 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 11.0 (d, CH_3-P, $^1J_{C\text{-}P}$= 38.8 Hz), 13.4 (CH_3-CH), 16.1 (CH_3), 16.5 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 28.0 (d, CH_3-N, $^2J_{C\text{-}P}$= 3.0 Hz), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 57.9 (CH-N, $^2J_{C\text{-}P}$= 10.1 Hz), 81.1 (CH-O), 127.9-145.4 (aromatic carbons).

L51c·BH_3**:** Yield: 87 mg (16%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 140.9 (s, P-O), 68.2 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.10 (d, 3H, CH_3-P, $^2J_{H\text{-}P}$= 8.7 Hz), 1.16 (d, 3H, CH_3-CH, $^3J_{H\text{-}H}$= 6.5 Hz), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.13 (d, 3H, CH_3-N, $^3J_{H\text{-}P}$= 8.2 Hz), 4.37-4.39 (m, CH-N), 5.37 (dd, CH-O, $^3J_{H\text{-}P}$= 8.7 Hz, $^3J_{H\text{-}H}$= 6.6 Hz), 6.90-6.92 (m, 3H, CH=), 6.95-7.04 (m, 5H, CH=), 7.11 (s, 2H, CH=), 7.17-7.21 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 11.0 (d, CH_3-P, $^1J_{C\text{-}P}$= 38.8 Hz), 13.4 (CH_3-CH), 16.1 (CH_3), 16.5 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 28.0 (d, CH_3-N, $^2J_{C\text{-}P}$= 3.0 Hz), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 57.9 (CH-N, $^2J_{C\text{-}P}$= 10.1 Hz), 81.1 (CH-O), 127.9-145.4 (aromatic carbons).

L54a·BH_3**:** Yield: 113 mg (59%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 146.5 (bs, P-O), 71.8 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.96 (d, 9H, CH_3, ^{t}Bu-P, $^3J_{H\text{-}P}$= 13.9 Hz), 1.15 (s, 9H, ^{t}Bu), 1.20 (s, 9H, ^{t}Bu), 1.24 (s, 9H, ^{t}Bu), 1.45 (s, 9H, ^{t}Bu), 2.24-2.29 (m, 1H, CH_2), 2.98-3.01 (m, 1H, CH_2), 3.38-3.43 (m, 1H, NH), 4.33-4.38 (m, 1H, CH-O), 4.96-5.03 (m, 1H, CH-N), 6.85-6.88 (m, 1H, CH=), 6.96-7.17 (m, 5H, CH=), 7.26-7.33 (m, 2H, CH=), 7.45-7.77 (m, 5H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 24.3 (CH_3, ^{t}Bu-P), 29.6-31.3 (CH_3, ^{t}Bu), 34.1-35.3 (C, ^{t}Bu), 37.5 (d, CH_2, $^3J_{C\text{-}P}$= 15.3 Hz), 61.1 (CH-N), 80.4 (CH-O), 122.9-150.1 (aromatic carbons).

L54b·BH_3**:** Yield: 53 mg (15%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 139.4 (s, P-O), 71.9 (bs, P-N). ^1H NMR (400 MHz, C_6D_6): δ = 1.02 (d, 9H, CH_3, ^{t}Bu-P, $^3J_{H-P}$= 13.9 Hz), 1.13 (s, 9H, ^{t}Bu), 1.47 (s, 9H, ^{t}Bu), 1.60 (s, CH_3), 1.64 (s, CH_3), 1.96 (s, CH_3), 2.00 (s, CH_3), 2.20-2.25 (m, 1H, CH_2), 2.93 (d, 1H, CH_2, $^1J_{H-H}$= 16.9 Hz), 3.64 (dd, 1H, NH, $^2J_{H-P}$= 10.8 Hz, $^3J_{H-H}$= 3.5 Hz), 4.09 (dt, 1H, CH-O, $^2J_{H-P}$= 9.7 Hz, $^3J_{H-H}$= 4.8 Hz), 4.85-4.91 (m, 1H, CH-N), 6.86 (d, 1H, CH=, $^3J_{H-H}$= 7.4 Hz), 7.05-7.30 (m, 7H, CH=), 7.53-7.57 (m, 2H, CH=), 7.80 (d, 1H, CH=, $^3J_{H-H}$= 7.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 24.3 (CH_3, ^{t}Bu-P), 30.3 (C, ^{t}Bu-P), 30.9 (d, CH_3, ^{t}Bu, J_{C-P}= 5.2 Hz), 31.4 (CH_3, ^{t}Bu), 33.9 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 37.7 (d, CH_2, $^3J_{C-P}$= 16.5 Hz), 60.9 (CH-N), 80.1 (CH-O), 124.4-145.7 (aromatic carbons).

L54c·BH_3**:** Yield: 42 mg (12%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 141.5 (s, P-O), 71.7 (bs, P-N). ^1H NMR (400 MHz, C_6D_6): δ = 1.01 (d, 9H, CH_3, ^{t}Bu-P, $^3J_{H-P}$= 14.0 Hz), 1.11 (s, 9H, ^{t}Bu), 1.48 (s, 9H, ^{t}Bu), 1.62 (s, CH_3), 1.73 (s, CH_3), 1.84 (s, CH_3), 2.04 (s, CH_3), 2.25-2.29 (m, 1H, CH_2), 2.93-2.98 (m, 1H, CH_2), 3.20-3.24 (m, 1H, NH), 4.33-4.47 (m, 1H, CH-O), 5.07-5.11 (m, 1H, CH-N), 6.89 (d, 1H, CH=, $^3J_{H-H}$= 7.4 Hz), 6.99-7.17 (m, 6H, CH=), 7.23 (s, 1H, CH=), 7.63-7.68 (m, 2H, CH=), 7.76 (d, 1H, CH=, $^3J_{H-H}$= 7.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 16.2 (CH_3), 16.7 (CH_3), 19.9 (CH_3), 20.1 (CH_3), 24.6 (CH_3, ^{t}Bu-P), 30.5 (C, ^{t}Bu-P), 31.1 (CH_3, ^{t}Bu), 31.6 (d, CH_3, ^{t}Bu, J_{C-P}= 5.5 Hz), 34.4 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 37.5 (d, CH_2, $^3J_{C-P}$= 10.1 Hz), 61.0 (CH-N), 78.3 (CH-O), 124.6-145.1 (aromatic carbons).

For deprotection, the borane-adduct (0.68 mmol) was dissolved in dry and deoxygenated diethylamine (20 mL) and heated to 55 ºC for 16 h. After this time, the mixture was evaporated to dryness and the residue was purified by flash chromatography (under argon, using neutral alumina and dry and deoxygenated toluene/hexane (1:1) as eluent system (1% NEt_3)) to afford the corresponding ligands **L51a-c** and **L54a**-**c** as white solids.

L51a: Yield: 221 mg (75%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 147.8 (bs, P-O), 49.4 (s, P-N). ^1H NMR (400 MHz, C_6D_6): δ = 1.13 (d, 3H, CH_3-P, $^2J_{H-P}$= 8.4 Hz), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.34 (d, 3H, CH_3-CH, $^3J_{H-H}$= 6.6 Hz), 2.10 (d, 3H, CH_3-N, $^3J_{H-P}$= 8.0 Hz), 3.73-3.83 (m, 1H, CH-N), 5.41 (pt, 1H, CH-O, J= 8.4 Hz), 6.83-6.86 (m, 1H, CH=), 6.98-7.14 (m, 7H, CH=), 7.29 (s, 2H, CH=), 7.35-7.37 (m, 2H, CH=), 7.54-7.56 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 12.2 (d, CH_3-P, $^1J_{C-P}$= 21.7 Hz), 16.3 (d, CH_3-CH, $^3J_{C-P}$= 6.5 Hz), 30.5 (d, CH_3-N, $^2J_{C-P}$= 8.2 Hz), 31.0 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 34.3 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 64.7 (d, CH-N, $^3J_{C-P}$= 38.1 Hz), 80.6 (CH-O), 123.9-146.5 (aromatic carbons). MS HR-ESI [found 726.4236, $C_{45}H_{61}NO_3P_2$ $(M+H)^+$ requires 726.4205].

L51b: Yield: 74 mg (60%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 143.0 (s, P-O), 51.2 (s, P-N). ^1H NMR (400 MHz, C_6D_6): δ = 1.03 (d, 3H, CH_3-P, $^1J_{H-P}$= 6.3 Hz), 1.21 (d, CH_3-CH,

$^3J_{H-H}$= 6.7 Hz), 1.53 (s, CH_3, 9H, ^{t}Bu), 1.54 (s, CH_3, 9H, ^{t}Bu), 1.65 (s, CH_3), 1.74 (CH_3), 1.95 (d, CH_3-N, $^2J_{H-P}$= 3.5 Hz), 2.00 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 3.74-3.84 (m, 1H, CH-N), 5.23 (pt, CH-O, J= 8.9 Hz), 6.70-6.73 (m, 2H, CH=), 6.96-6.99 (m, 3H, CH=), 7.04-7.08 (m, 1H, CH=), 7.10-7.16 (m, 3H, CH=), 7.24 (s, 1H, CH=), 7.47-7.50 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 12.2 (d, CH_3-P, $^1J_{C-P}$= 22.2 Hz), 16.2 (CH_3), 16.4 (d, CH_3-CH, $^3J_{C-P}$= 4.7 Hz), 16.5 (CH_3), 20.0 (CH_3), 29.6 (d, CH_3-N, $^2J_{C-P}$= 8.9 Hz), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.6 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 64.8 (CH-N, $^2J_{C-P}$= 37.0 Hz), 80.7 (CH-O), 126.8-145.5 (aromatic carbons). MS HR-ESI [found 670.3576, $C_{41}H_{53}NO_3P_2$ $(M+H)^+$ requires 670.3579].

L51c: Yield: 60 mg (67%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 140.6 (s, P-O), 49.0 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.11 (d, 3H, CH_3-P, $^1J_{H-P}$= 6.5 Hz), 1.40 (d, CH_3-CH, $^3J_{H-H}$= 6.7 Hz), 1.43 (s, CH_3, 9H, ^{t}Bu), 1.57 (s, CH_3, 9H, ^{t}Bu), 1.63 (s, CH_3), 1.99 (CH_3), 2.06 (s, 3H, CH_3), 2.09 (d, CH_3-N, $^2J_{H-P}$= 3.6 Hz), 3.69-3.80 (m, 1H, CH-N), 5.33 (pt, CH-O, J= 7.7 Hz), 6.80-6.83 (m, 2H, CH=), 6.94-7.15 (m, 10H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 12.3 (d, CH_3-P, $^1J_{C-P}$= 21.4 Hz), 16.2 (CH_3), 16.3 (CH_3), 16.6 (d, CH_3-CH, $^3J_{C-P}$= 7.2 Hz), 20.0 (CH_3), 20.1 (CH_3), 30.8 (d, CH_3-N, $^2J_{C-P}$= 8.0 Hz), 31.0 (d, CH_3, ^{t}Bu, J_{C-P}= 5.2 Hz), 31.5 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 64.8 (CH-N), 80.2 (CH-O), 125.4-145.6 (aromatic carbons). MS HR-ESI [found 670.3578, $C_{41}H_{53}NO_3P_2$ $(M+H)^+$ requires 670.3579].

L54a: Yield: 65 mg (58%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 145.6 (s, P-O), 56.4 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.99 (d, 9H, CH_3, ^{t}Bu-P, $^3J_{H-P}$= 12.3 Hz), 1.20 (s, 9H, ^{t}Bu), 1.26 (s, 9H, ^{t}Bu), 1.31 (s, 9H, ^{t}Bu), 1.43 (s, 9H, ^{t}Bu), 2.41-2.46 (m, 1H, CH_2), 2.90-3.01 (m, 2H, CH_2, NH), 4.46-4.56 (m, 2H, CH-N, CH-O), 6.86-6.90 (m, 1H, CH=), 7.00-7.176 (m, 5H, CH=), 7.29-7.34 (m, 2H, CH=), 7.47-7.51 (m, 3H, CH=), 7.59-7.65 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 26.1 (d, CH_3, ^{t}Bu-P, $^1J_{C-P}$= 14.7 Hz), 30.9 (CH_3, ^{t}Bu), 31.0 (C, ^{t}Bu-P), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.3 (d, C, ^{t}Bu, J_{C-P}= 7.4 Hz), 34.3 (d, C, ^{t}Bu, J_{C-P}= 13.7 Hz), 37.6 (d, CH_2, $^3J_{C-P}$= 10.4 Hz), 66.4 (CH-N), 80.0 (CH-O), 123.9-146.5 (aromatic carbons). MS HR-ESI [found 752.4361, $C_{47}H_{63}NO_3P_2$ $(M+H)^+$ requires 752.4356].

L54b: Yield: 29 mg (56%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 139.0 (s, P-O), 58.9 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.04 (d, 9H, CH_3, ^{t}Bu-P, $^3J_{H-P}$= 12.2 Hz), 1.29 (s, 9H, ^{t}Bu), 1.44 (s, 9H, ^{t}Bu), 1.63 (s, CH_3), 1.69 (s, CH_3), 1.98 (s, CH_3), 2.06 (s, CH_3), 2.36-2.41 (m, 1H, CH_2), 2.83 (d, 1H, CH_2, $^1J_{H-H}$= 16.8 Hz), 3.00-3.15 (m, 1H, NH), 4.35-4.44 (m, 2H, CH-O, CH-N), 6.84 (d, 1H, CH=, $^3J_{H-H}$= 7.4 Hz), 7.94-7.25 (m, 7H, CH=), 7.42-7.46 (m, 2H, CH=), 7.64 (d, 1H, CH=, $^3J_{H-H}$= 7.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 26.0 (d, CH_3, ^{t}Bu-P, $^1J_{C-P}$= 14.6 Hz), 29.8 (C, ^{t}Bu-P), 31.1 (d, CH_3, ^{t}Bu, J_{C-P}= 5.2 Hz), 31.3 (CH_3, ^{t}Bu), 34.2 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 37.8 (d, CH_2, $^3J_{C-P}$= 10.4 Hz), 66.4 (d, CH-N, $^2J_{C-P}$= 27.6 Hz), 80.5 (CH-O), 124.9-145.6

(aromatic carbons). MS HR-ESI [found 696.3733, $C_{43}H_{55}NO_3P_2$ $(M+H)^+$ requires 696.3730].

L54c: Yield: 23 mg (62%). ^{31}P NMR (161.9 MHz, C_6D_6): $\delta =$ 142.2 (s, P-O), 56.8 (s, P-N). ^1H NMR (400 MHz, C_6D_6): $\delta =$ 1.01 (d, 9H, CH_3, ^{t}Bu-P, $^3J_{H-P}$= 14.0 Hz), 1.11 (s, 9H, ^{t}Bu), 1.48 (s, 9H, ^{t}Bu), 1.62 (s, CH_3), 1.73 (s, CH_3), 1.84 (s, CH_3), 2.04 (s, CH_3), 2.25-2.29 (m, 1H, CH_2), 2.93-2.98 (m, 1H, CH_2), 3.20-3.24 (m, 1H, NH), 4.33-4.47 (m, 1H, CH-O), 5.07-5.11 (m, 1H, CH-N), 6.89 (d, 1H, CH=, $^3J_{H-H}$= 7.4 Hz), 6.99-7.17 (m, 6H, CH=), 7.23 (s, 1H, CH=), 7.63-7.68 (m, 2H, CH=), 7.76 (d, 1H, CH=, $^3J_{H-H}$= 7.4 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): $\delta =$ 16.4 (CH_3), 16.8 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 26.3 (d, CH_3, ^{t}Bu-P, $^2J_{C-P}$= 14.6 Hz), 30.9 (d, C, ^{t}Bu-P, $^1J_{C-P}$= 3.4 Hz), 31.3 (CH_3, ^{t}Bu), 31.6 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 37.4 (d, CH_2, $^3J_{C-P}$= 9.5 Hz), 65.9 (d, CH-N, $^2J_{C-P}$= 30.3 Hz), 78.6 (CH-O), 124.7-145.4 (aromatic carbons). MS HR-ESI [found 696.3734, $C_{43}H_{55}NO_3P_2$ $(M+H)^+$ requires 696.3730].

3.12.4.3. General procedure for the preparation of *N*-phosphine-phosphite ligands L52b-c

To a solution of *in situ* generated phosphorochloridite (1.1 mmol) in dry toluene (6 mL), triethylamine (0.27 mL, 2.0 mmol) and DMAP (6.7 mg, 0.055 mmol) was added. Then, this solution was placed in a 0 ºC bath. After 2 min at that temperature, a solution of the corresponding hydroxyl compound **5** (393.3 mg, 1.0 mmol), triethylamine (0.27 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at 0 °C. The mixture was left to warm to 80 ºC and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral silica and dry toluene as eluent system (1% NEt_3)) to afford the corresponding deprotected *N*-phosphine-phosphite compound **L52b**-**c** as white solids.

L52b: Yield: 175 mg (45%). ^{31}P NMR (161.9 MHz, C_6D_6): $\delta =$ 143.4 (s, P-O), 56.1 (s, P-N). ^1H NMR (400 MHz, C_6D_6): $\delta =$ 1.34 (d, 3H, CH_3-N, $^3J_{H-H}$= 6.6 Hz), 1.52 (s, 18H, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.07 (d, CH_3-N, $^3J_{H-P}$= 2.7 Hz), 3.09 (s, 3H, CH_3-O), 3.94-4.09 (m, 1H, CH-N), 5.35 (pt, 1H, CH-OP, J= 8.8 Hz), 6.44 (dd, 1H, CH=, $^3J_{H-H}$= 8.3 Hz, $^4J_{H-H}$= 4.1 Hz), 6.74 (t, 1H, CH=, $^3J_{H-H}$= 7.4 Hz), 6.83-6.87 (m, 2H, CH=), 6.91-7.05 (m, 4H, CH=), 7.06-7.20 (m, 6H, CH=), 7.49 (d, 2H, $^3J_{H-H}$= 6.9 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): $\delta =$ 15.7 (d, CH_3-CH, $^3J_{C-P}$= 4.2 Hz), 16.2 (CH_3), 16.6 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 21.1 (CH_3-N), 31.1 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.6 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 54.4 (CH_3-O), 65.5 (d, CH-N, $^2J_{C-P}$= 41.8 Hz), 81.3 (dd, CH-O, $^2J_{C-P}$= 10.7 Hz, $^3J_{C-P}$= 6.6 Hz), 110.2-160.8 (aromatic carbons). MS HR-ESI [found 762.3841, $C_{47}H_{57}NO_4P_2$ $(M+H)^+$ requires 762.3836].

L52c: Yield: 160 mg (41%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 140.1 (s, P-O), 54.4 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.42 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 12H, CH_3, ^{t}Bu, CH_3-CH), 1.62 (s, 6H, CH_3), 1.99 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.26 (d, 3H, CH_3-N, $^3J_{H-P}$= 2.6 Hz), 3.11 (s, 3H, CH_3-O), 3.83-4.03 (m, 1H, CH-N), 5.49 (pt, 1H, CH-O, J= 7.7 Hz), 6.42-6.52 (m, 1H, CH=), 6.79 (t, 1H, CH=, $^3J_{H-H}$= 7.4 Hz), 6.90-7.01 (m, 9H, CH=), 7.07-7.14 (m, CH=, 5H). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 16.0 (d, CH_3-CH, $^3J_{C-P}$= 5.3 Hz), 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.1 (d, CH_3, ^{t}Bu, J_{C-P}= 5.1 Hz), 31.4 (C, ^{t}Bu), 32.7 (d, CH_3-N, $^2J_{C-P}$= 9.5 Hz), 34.4 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 54.4 (CH_3-O), 65.3 (dd, CH-N, $^2J_{C-P}$= 39.7 Hz, $^3J_{C-P}$= 5.0 Hz), 80.9 (dd, CH-O, $^2J_{C-P}$= 9.9 Hz, $^3J_{C-P}$= 5.3 Hz), 110.1-160.8 (aromatic carbons). MS HR-ESI [found 762.3840, $C_{47}H_{57}NO_4P_2$ $(M+H)^+$ requires 762.3836].

3.12.4.4. General procedure for the preparation of compounds 8b-c

To a solution of *in situ* generated phosphorochloridite (0.55 mmol) in dry toluene (3 mL), triethylamine (0.14 mL, 1.0 mmol) was added. Then, this solution was placed in a 0 ºC bath. After 2 min at that temperature, a solution of the corresponding hydroxyl compound **1** (82.0 mg, 0.5 mmol), DMAP (6.7 mg, 0.055 mmol) and triethylamine (0.14 mL, 1.0 mmol) in toluene (3 mL) was added dropwise at 0 °C. The mixture was left to warm to rt and stirred for 4 h at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography on alumina (toluene/NEt_3= 100/1) to produce the corresponding to afford the corresponding amino-phosphite compound **8b**-**c** as white solids.

8b: Yield: 60 mg (22%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 142.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.71 (d, 3H, CH_3-CH, $^3J_{H-H}$= 6.5 Hz), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.17 (s, 3H, CH_3-N), 2.54-2.60 (m, 1H, CH-N), 5.23 (dd, 1H, CH-O, $^3J_{H-P}$= 7.7 Hz, $^3J_{H-H}$= 3.1 Hz), 7.01-7.03 (m, 1H, CH=), 7.07-7.11 (m, 2H, CH=), 7.17-7.20 (m, 3H, CH=), 7.22 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 14.2 (CH_3-CH), 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.8 (d, CH_3, ^{t}Bu, J_{C-P}= 4.8 Hz), 31.3 (CH_3, ^{t}Bu), 33.5 (CH_3-N), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 61.1 (CH-N), 77.8 (d, CH-O, $^2J_{C-P}$= 8.7 Hz), 127.1-146.4 (aromatic carbons).

8c: Yield: 87 mg (32%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 141.7 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.86 (d, CH_3-CH, $^3J_{H-H}$= 6.5 Hz), 1.33 (s, 9H, ^{t}Bu), 1.56 (s, 9H, ^{t}Bu), 1.65 (s, 6H, CH_3), 1.99 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.19 (s, 3H, CH_3-N), 2.86-2.99 (m, 1H, CH-N), 5.22 (dd, 1H, CH-O, $^3J_{C-P}$= 8.9 Hz, $^3J_{H-H}$= 3.9 Hz), 6.96-7.22 (m, 7H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 15.1 (CH_3-CH), 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 30.9 (d, CH_3, ^{t}Bu, J_{C-P}= 5.2 Hz), 31.5 (CH_3, ^{t}Bu), 33.8 (CH_3-N), 34.2 (C, ^{t}Bu), 34.7 (C, ^{t}Bu),

59.8 (d, CH-N, $^3J_{C-P}$= 6.0 Hz), 80.3 (d, CH-O, $^2J_{C-P}$= 11.2 Hz), 125.3-145.8 (aromatic carbons).

3.12.4.5. General procedure for the preparation of *N*-phosphine-phosphite ligands L53b-c

The corresponding amino-phosphite compound **8b**-**c** (273.8 mg, 0.5 mmol) was dissolved in THF (4 ml), and triethylamine was added (0.09 mL, 0.65 mmol) at rt, followed by the addition of chlorodiphenylphosphine (0.1 mL, 0.55 mmol) via syringe. The reaction was stirred overnight at 55 ºC. The solvent was removed *in vacuo*, and the product was purified by flash chromatography on alumina (dry and deoxygenated toluene/NEt_3= 100/1) to produce the corresponding ligand as white solid.

L53b: Yield: 48 mg (70%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 143.3 (s, P-O), 64.5 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.23 (d, 3H, CH_3-CH, $^3J_{H-H}$= 6.7 Hz), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.66 (CH_3), 1.75 (CH_3), 2.00 (CH_3), 2.02 (d, 3H, CH_3-N, $^3J_{H-P}$= 2.9 Hz), 2.05 (s, 3H, CH_3), 3.93-4.02 (m, 1H, CH-N), 5.35 (pt, 1H, CH-O, *J*= 7.3 Hz), 6.84-6.89 (m, 1H, CH=), 6.91-7.03 (m, 5H, CH=), 7.05-7.12 (m, 6H, CH=), 7.17-7.22 (m, 3H, CH=), 7.45-7.49 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 16.1 (d, CH_3-CH, $^3J_{C-P}$= 4.4 Hz), 16.2 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 21.1 (CH_3-N), 31.3 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.6 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 65.6 (d, CH-N, $^2J_{C-P}$= 39.6 Hz), 81.1 (dd, CH-O, $^2J_{C-P}$= 11.0 Hz, $^3J_{C-P}$= 7.5 Hz), 125.3-145.4 (aromatic carbons). MS HR-ESI [found 732.3733, $C_{46}H_{55}NO_3P_2$ $(M+H)^+$ requires 732.3730].

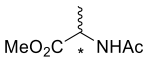
L53c: Yield: 70 mg (60%). ^{31}P NMR (161.9 MHz, C_6D_6): δ = 140.1 (s, P-O), 63.3 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.42 (d, 3H, CH_3-CH, $^3J_{H-H}$= 7.5 Hz), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.16 (d, 3H, CH_3-N, $^3J_{H-P}$= 2.9 Hz), 3.88-3.97 (m, 1H, CH-N), 5.43 (pt, 1H, CH-O, *J*= 7.8 Hz), 6.90-7.12 (m, 15H, CH=), 7.19-7.24 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 16.2 (CH_3), 16.3 (CH_3), 16.4 (d, CH_3-CH, $^3J_{C-P}$= 6.3 Hz), 20.0 (CH_3), 20.1 (CH_3), 31.1 (d, CH_3, ^{t}Bu, J_{C-P}= 5.2 Hz), 31.4 (C, ^{t}Bu), 32.1 (d, CH_3-N, $^2J_{C-P}$= 10.0 Hz), 34.4 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 65.4 (dd, CH-N, $^2J_{C-P}$= 37.8 Hz, $^3J_{C-P}$= 5.8 Hz), 80.7 (dd, CH-O, $^2J_{C-P}$= 10.6 Hz, $^3J_{C-P}$= 5.6 Hz), 125.3-145.7 (aromatic carbons). MS HR-ESI [found 732.3732, $C_{46}H_{55}NO_3P_2$ $(M+H)^+$ requires 732.3730].

3.12.4.6. General procedure for the asymmetric hydrogenation

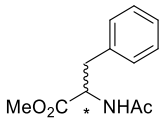
In a typical run, $[Rh(cod)_2]BF_4$ (1.0 mg, 0.0025 mmol), the corresponding ligand (0.0025 mmol) and the desired substrate (0.25 mmol) were dissolved in THF (2 mL). The reaction mixture was then placed in the autoclave and the autoclave was purged four times with hydrogen gas. Then, it was pressurized to the desired pressure. After

the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (2 mL) and filtered through a short celite plug. For hydrogenation products of substrates **S1**-**S4** conversions and enantiomeric excesses were determined by chiral GC, while for hydrogenation products of substrates **S5**-**S8**, conversions were measured by ^{1}H-NMR and enantiomeric excesses were determined by chiral HPLC (for hydrogenation product of **S8** see previous Section 3.2.4.7).

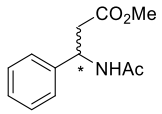
Methyl acetylalaninate.[23] Enantiomeric excess determined by GC using a L-Chirasil-Val column (100 kPa H_2, Isotherm at 100 C). t_R 4.8 min (*R*); t_R 5.7 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.38 (d, 3H, *J*= 7.1 Hz), 2.00 (s, 3H), 3.74 (s, 3H), 4.58 (p, 1H, *J*= 7.3 Hz), 6.02 (s, 1H).



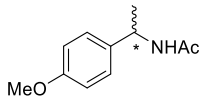
Methyl acetylphenylalaninate.[23] Enantiomeric excess determined by GC using a L-Chirasil-Val column (150 kPa H_2, Isotherm at 150 C). t_R 8.7 min (*R*); t_R 9.8 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.96 (s, 3H), 3.09 (m, 2H), 3.70 (s, 3H), 4.86 (q, 1H, *J*= 5.9 Hz), 5.97 (d, 1H, *J*= 6.5 Hz), 7.06 (d, 2H, *J*= 7.1 Hz), 7.18-7.30 (m, 3H).



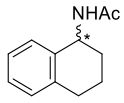
Methyl 3-acetamido-3-phenylpropanoate.[24] Enantiomeric excess determined by GC using a L-Chirasil-Val column (150 kPa H_2, Isotherm at 150 C). t_R 15.6 min (*S*); t_R 16.3 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 2.01 (s, 3H), 2.83 (dd, 1H, *J*= 15.8 Hz, *J*= 6.0 Hz), 2.93 (dd, 1H, *J*= 15.8 Hz, *J*= 5.9 Hz), 3.61 (s, 3H), 5.43 (dt, 1H, *J*= 8.4 Hz, *J*= 6.0 Hz), 6.67 (d, 1H, *J*= 5.9 Hz), 7.26-7.35 (m, 5H).



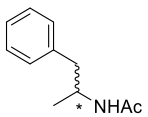
N-(1-(4-Methoxyphenyl)ethyl)acetamide.[25] Enantiomeric excess determined by HPLC using Chiralcel AD (hexane/2-propanol=95/5, 1 mL/min, 220 nm). t_R = 16.9 min (*S*); t_R 21.3 min (*R*). ^{1}H-NMR ($CDCl_3$), δ: 1.46 (d, 3H, *J*= 6.9 Hz), 1.96 (s, 3H), 3.79 (s, 3H), 5.03-5.13 (m, 1H), 5.65 (bs, 1H), 6.87 (d, 2H, *J*= 8.7 Hz), 7.24 (d, 2H, *J*= 8.7 Hz).



N-(1,2,3,4-Tetrahydronaphthalen-1-yl)acetamide.[25] Enantiomeric excess determined by HPLC using Chiralcel OD-H (hexane/2-propanol=90/10, 0.5 mL/min, 220 nm). t_R = 20.8 min (*S*); t_R 26.6 min (*R*). ^{1}H-NMR ($CDCl_3$), δ: 1.73-1.89 (m, 3H), 1.95-2.09 (m, 4H), 2.68-2.89 (m, 2H), 5.08-5.23 (m, 1H), 5.69 (br s, 1H), 7.05-7.22 (m, 4H).



N-(1-Phenylpropan-2-yl)acetamide.[26] Enantiomeric excess determined by HPLC using Chiralcel OD-H (hexane/2-propanol=90/10, 1 mL/min, 220 nm). t_R = 7.9 min (*S*); t_R 8.4 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.09 (d, 3H, *J*= 6.4 Hz), 1.91 (s, 3H), 2.69(dd, 1H, *J*= 13.6 Hz, *J*= 7.2 Hz), 2.82 (dd, 1H, *J*=13.6 Hz, *J*= 5.6 Hz), 4.21-4.27 (m, 1H), 5.44 (bs, 1H), 7.15-7.30 (m, 5H).



3.12.5. Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P), European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D.).

3.12.6. References

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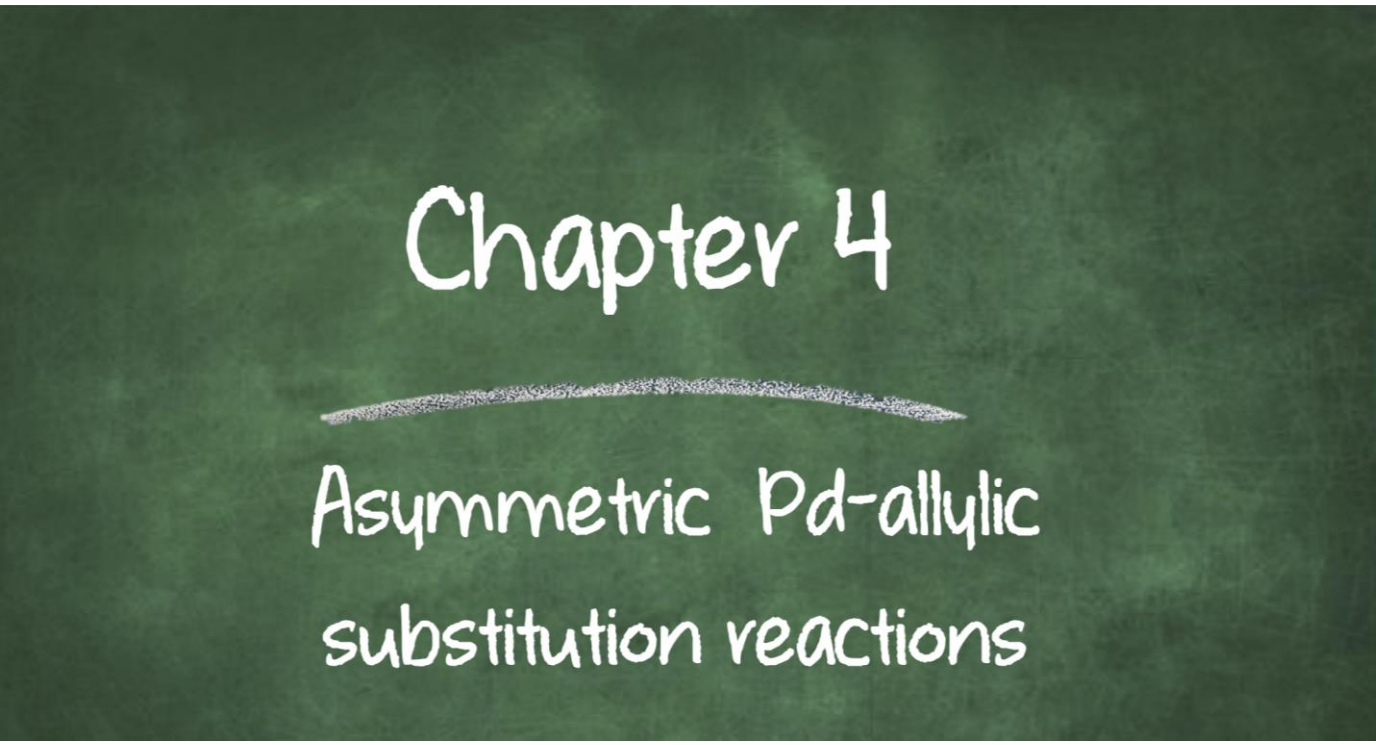

Chapter 4
Asymmetric Pd-allylic
substitution reactions

UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull

4.1. Conformational preferences of a tropos biphenyl phosphinooxazoline – a ligand with wide substrate scope

Bellini, R.*; Magre, M.*; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M.; Moberg, C. *ACS Catal*. **2016**, *6*, 1701. *Both authors contributed equally to this study.

In collaboration with the group of Prof. C. Moberg (KTH, Stockholm) and Prof. P.-O. Norrby (AstraZeneca, Sweden).

Abstract: Excellent enantioselectivities are observed in palladium-catalyzed allylic substitutions of a wide range of substrate types and nucleophiles using a bidentate ligand composed of oxazoline and chirally flexible biaryl phosphite elements. This unusually wide substrate scope is shown by experimental and theoretical studies of its η^3-allyl and η^2-olefin complexes not to be a result of configurational interconversion of the biaryl unit, since the ligand in all reactions adopts (S_a,S)-configuration when coordinated to palladium, but rather the ability of the ligand to adapt the size of the substrate-binding pocket to the reacting substrate. This ability also serves as an explanation to its excellent performance in other types of catalytic processes.

4.1.1. Introduction

Enantioselective metal-catalyzed synthetic processes are ubiquitous for the construction of nonracemic chiral organic compounds.[1] The stereodirecting power of a catalyst usually relies on the choice of chiral ligand bound to the metal. Ligands with broad substrate scope are desirable in order to limit time-consuming ligand design and preparation. The identification of privileged ligands[2] useful for a wide range of substrates and for different types of reactions is therefore an important issue.

Conformationally flexible ligands are viable candidates for the design of catalysts with wide substrate scope. Mikami *et al*.[3] have demonstrated that stereochemically dynamic, tropos[3d,4] ligands are capable of adapting their sense of chirality to a proximal chiral motif bound to the same metal center, and consequently to be able to replace rigid analogues with either absolute configuration. In a similar manner, adaptable ligand systems composed of a stereochemically flexible part covalently bound to a group with a rigid stereogenic element have been successfully employed in asymmetric catalysis.[5] In order to further exploit self-adaptable ligands in asymmetric catalysis, studies of their conformational preferences under different reaction conditions are desirable.

We have previously studied the conformational behavior of phosphepine and azepine ligands, such as **1** and **2** (Figure 4.1.1a).[6] By using palladium-catalyzed asymmetric allylic alkylation as an illustrative model process to probe the conformational issues, we found that the conformation of these flexible ligands may be influenced not only by

structural units present in the catalyst, but also by the substrate undergoing reaction. In this particular catalytic process different ligands are usually required for different types of substrates in order to obtain products with high enantiopurity.[7] By using bisazepine ligands with two flexible biaryl moities, we were able to demonstrate that in palladium olefin complexes **3** and **4**, aimed to mimic the product olefin complexes from reaction of bulky linear ("broad") and small cyclic ("narrow") substrates, respectively, (*R**,*R**) (C_2) configuration was preferred in the complex containing the *trans* olefin, whereas (*R**,*S**) (C_s) was preferred in the complex with the *cis* olefin (Figure 4.1.1b).[8] In contrast, (*R**,*S**) configuration of the ligand was observed in η^3-allyl palladium complexes derived from *E*-1,3-diphenyl-2-propenyl acetate as well as from 3-cyclohexenyl acetate (not shown).

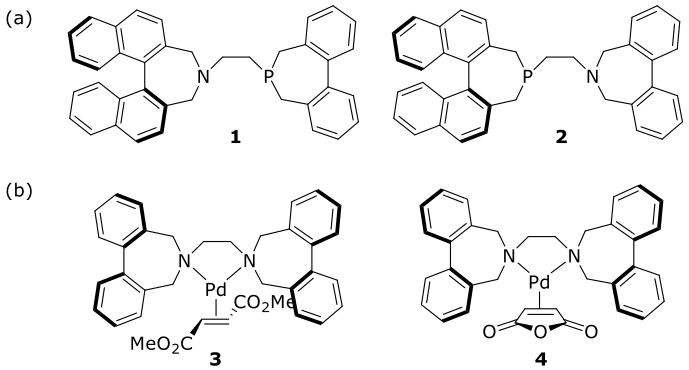


Figure 4.1.1. (a) Conformationally flexible phosphephine and azepine ligands **1** and **2**; (b) Palladium olefin complexes **3** and **4**.

Although tropoisomerization in azepine derivatives occurs while the ligand is coordinated to the metal center,[9] conformational change in ligands **1** and **2** was slow compared to nucleophilic attack, and the flexible ligands therefore behaved essentially as a mixture of the analogous rigid ligands, and thus proved to be less general than desired.

Ligands that tolerate a wide range of substrates are indeed rare. In this context, some of us were able to show that substrate versatility in Pd-catalyzed allylic substitutions can benefit from the introduction of a conformationally flexible biaryl phosphite element.[10] Thus, phosphite-oxazoline (*S*)-**L3a** (Figure 4.1.2) constitutes one of the few examples of ligands that have provided high ee's in the Pd-catalyzed allylic alkylation of both the hindered model compound *rac*-*E*-1,3-diphenyl-2-propenyl acetate (**S1**) and unhindered cyclic substrate *rac*-3-cyclohexenyl acetate (**S2**).[11] This ligand has also been successfully applied in enantioselective palladium-catalyzed Heck reactions,[12] rhodium-catalyzed hydrosilylation of ketones,[13] and iridium-catalyzed hydroboration of 1,1'-disubstituted olefins.[14] Since the barrier to inversion in phosphite ligands is known to be lower than that in phosphepine and azepine ligands,[15] we assumed that the broad

substrate tolerance of (*S*)-**L3a** may originate in its ability to adapt the conformation to the substrate undergoing reaction. In order to test if this was the case, we decided to study the conformational preferences of ligand (*S*)-**L3a** in palladium complexes with relevance for asymmetric allylic alkylation. To this aim, we needed access to rigid analogues of (*S*)-**L3a**. For this reason, (S_a,*S*)-**L3f** and (R_a,*S*)-**L3g** were prepared (Figure 4.1.2), their behavior in the catalytic reactions investigated, and the structures of the corresponding olefin complexes studied by NMR spectroscopy and DFT calculations.

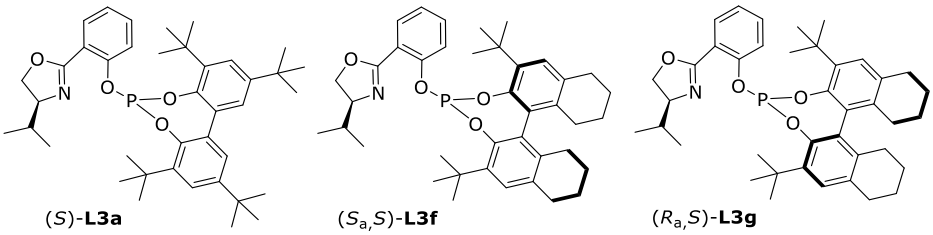


Figure 4.1.2. Phosphite-oxazoline ligands (*S*)-**L3a**, (S_a,*S*)-**L3f** and (R_a,*S*)-**L3g**.

We have also extended the previous work on dimethyl malonate and benzylamine to other C-nucleophiles and to O-nucleophiles, among which are the rarely studied α-substituted malonates, β-diketones, alkyl alcohols, silanols, and fluorobis(phenylsulfonyl)methane, and to alkylations of other substrates, thereby further underlining the versatility of ligand **L3a**.

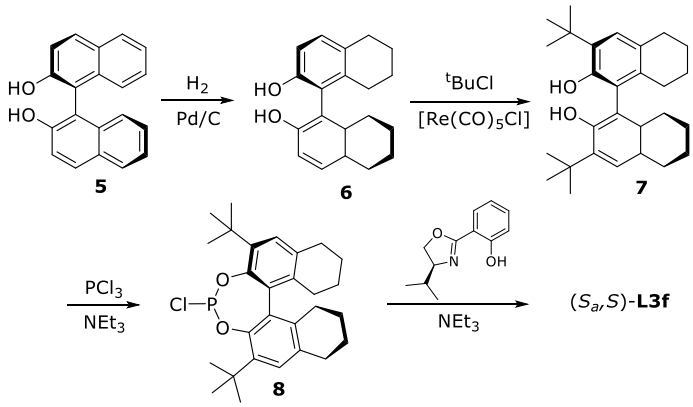
4.1.2. Results

4.1.2.1. Synthesis of ligands

Ligand (S_a,*S*)-**L3f** was prepared starting from (*S*)-binol (**5**), as shown in Scheme 4.1.1. Catalytic hydrogenation following a published procedure gave (*S*)-**6**,[16] which was reacted with *tert*-butyl chloride in the presence of chloropentacarbonylrhenium(I)[17] to yield (*S*)-**7**. Reaction with phosphorus trichloride gave compound (*S*)-**8**. Condensation of chlorophosphite (*S*)-**8** with (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol[18] afforded in good yield the final product (S_a,*S*)-**L3f**. Ligand (R_a,*S*)-**L3g** was prepared analogously starting from (*R*)-binol. The flexible ligand (*S*)-**L3a** was prepared as previously described.[11]

The rigid ligands gave rise to single signals in the ^{31}P NMR spectra, (S_a,*S*)-**L3f** at 127.9 ppm and (R_a,*S*)-**L3g** at 129.3 ppm. A single ^{31}P resonance was also observed from compound (*S*)-**L3a**, at 136.6 ppm. Interestingly, upon gradual cooling this signal first broadened and at around −20 °C split into two signals originating from the (S_a) and (R_a) conformers, as a result of tropoisomerization being slow on the NMR time scale. The original spectrum, containing a single ^{31}P resonance, was restored by warming the

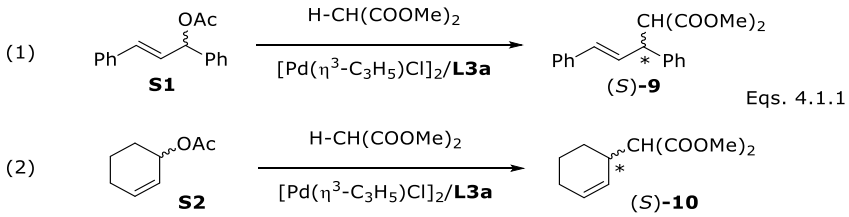
sample to 25 °C. In the ^{1}H NMR spectrum several signals were split upon cooling (see Supporting Information at the end of this chapter).



Scheme 4.1.1. Preparation of ligand (S_a,*S*)-**L3f**.

4.1.2.2. Catalytic reactions

Palladium-catalyzed allylic alkylations of *rac*-*E*-1,3-diphenyl-2-propenyl acetate (**S1**) and *rac*-3-cyclohexenyl acetate (**S2**), with dimethyl malonate as nucleophile and $[Pd(\eta^3\text{-}C_3H_3)Cl]_2$ as palladium source were studied employing the three ligands (Scheme 4.1.2, Eqs 4.1.1; Table 4.1.1). In reactions with **S1** as substrate, use of the catalyst containing flexible ligand (*S*)-**L3a** resulted in full conversion to the product (**9**) with (*S*) absolute configuration with >99% ee within 10 minutes (Table 4.1.1, entry 1). Whereas use of (S_a,*S*)-**L3f** also gave essentially enantiopure product with (*S*) absolute configuration (entry 2), a catalyst containing (R_a,*S*)-**L3g** gave the opposite product enantiomer with merely 20% ee (entry 3). By employing a mixture of (S_a,*S*)-**L3f** and (R_a,*S*)-**L3g**, the (*S*)-enantiomer was obtained with 90% ee (entry 4). This demonstrates that the catalyst containing the former ligand forms a considerably more reactive catalyst. These experiments also demonstrate that the flexible ligand thus behaved essentially in the same way as ligand (S_a,*S*)-**L3f**.

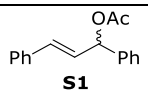


Eqs. 4.1.1

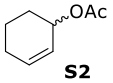
Scheme 4.1.2. Allylic alkylations of *rac*-*E*-1,3-diphenyl-2-propenyl acetate (**S1**) and *rac*-3-cyclohexenyl acetate (**S2**).

Also with **S2** as substrate the flexible ligand (*S*)-**L3a** gave the same product enantiomer, (*S*)-**10**, as (S_a,*S*)-**L3f** (Table 4.1.1, entries 1 and 2), but with somewhat lower selectivity (94% as compared to 99% ee). Reaction in the presence of ligand (R_a,*S*)-**L3g** resulted in the formation of the opposite enantiomer with lower enantioselectivity also in reactions with this substrate, although the difference was considerably smaller than for **S1** (entry 3). The higher reactivity of (S_a,*S*)-**L3f** was again shown from the results of an experiment where a mixture of the two rigid ligands was used (entry 4). The absolute configurations of the products obtained demonstrate that the binaphthyl part of the ligand is mainly responsible for chirality transfer, and that the conformation of (*S*)-**L3a** in the selectivity-determining complex resembles that of (S_a,*S*)-**L3f**.

Table 4.1.1. Palladium-catalyzed allylic alkylation of **S1** and **S2** with ligands (*S*)-**L3a**, (S_a,*S*)-**L3f** and (R_a,*S*)-**L3g**.[a]



S1



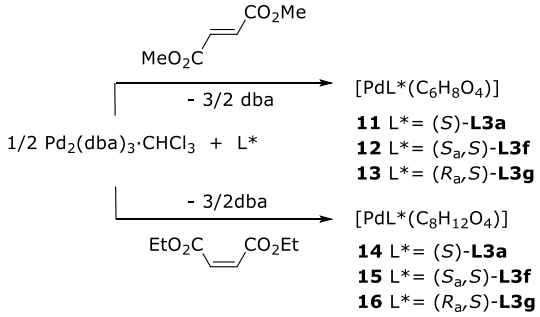
S2

Entry	Ligand	% Conv[b]	%ee[c]	% Conv[b]	% ee[c]
1	(*S*)-**L3a**	100	>99 (*S*)	100	94 (*S*)
2	(S_a,*S*)-**L3f**	100	>99 (*S*)	100	99 (*S*)
3	(R_a,*S*)-**L3g**	100	20 (*R*)	100	92 (*R*)
4	(S_a,*S*)-**L3g** + (R_a,*S*)-**L3f**	100	90 (*S*)	100	68 (*S*)

[a] 0.5 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, rt; [b] Measured by ^1H NMR after 10 min; [c] Determined by HPLC; [d] Determined by GC after 30 min; [e] Determined by GC.

4.1.2.3. Preparation and NMR studies of palladium olefin complexes

Nucleophilic attack on the allyl group in palladium-catalyzed allylic alkylations has been argued to occur via a late, i.e. product-like, transition state, and the stereochemistry accordingly governed by formation of the most stable olefin complex.[19] With the aim of gaining a deeper insight into the conformation of flexible ligand (*S*)-**L3a** in the selectivity-determining step, palladium(0) olefin complexes with the three ligands were prepared in order to mimic the product olefin complexes from allylic alkylations. Dimethyl fumarate and diethyl maleate were selected as olefins in order to form complexes with sufficient stability to allow isolation and studies by NMR spectroscopy. The complexes were obtained by stirring equimolar amounts of ligand and olefin with one equivalent of $Pd_2(dba)_3CHCl_3$ in deuterated dichloromethane (Scheme 4.1.3). Complex formation with dimethyl fumarate was achieved within 30 minutes at ambient temperature, whereas 16 hours were required to obtain the desired complexes from diethyl maleate.



Scheme 4.1.3. Preparation of Pd(0)-olefin complexes **11**–**16**.

As a result of the symmetry of the olefins employed, a maximum of two olefin complexes can form with each ligand, those from dimethyl fumarate depicted as **A** and **B** in Figure 4.1.3, and those from diethyl maleate as **C** and **D**. Attempts were first made to determine the configuration of flexible ligand (*S*)-**L3a** in complexes with the two types of olefins by comparison of the spectra of **11** and **14** with those of the complexes with rigid ligands, i.e. **12**–**13** and **15**–**16**, respectively.

The ^{31}P as well as ^{1}H NMR spectra of the complexes containing rigid ligands (**12**–**13** and **15**–**16**) suggested that essentially single isomers were obtained in each case. For instance, the proton coupled ^{31}P NMR spectrum of complex **12**, containing (S_a,*S*)-**L3f** and dimethyl fumarate, showed a doublet of doublet at δ 152.6 (J_{PH} = 15.9 and 4.7 Hz), along with a small signal at 151.7 (ratio ca 50:1), while the fumarate complex with (R_a,*S*)-**L3g** (**13**) showed a doublet of doublet at δ 154.0 (J_{PH} = 15.1 and 5.5 Hz) and a minor signal at 145.6 ppm (ratio ca 12:1), as well as a signal at 151.1, probably originating from a complex with dba. Diethyl maleate complex **15** showed a ^{31}P NMR signal at 153.2 ppm, which slowly replaced an initially observed signal at 149.3 ppm and that of **16** a signal at 155.1 (minor signal at 147.7 ppm and a signal at 152.5 ppm originating from a complex with dba). In the ^{31}P NMR spectra of complexes **11** and **14**, with the flexible ligand (*S*)-**L3a**, signals at 153.6 and 155.8 ppm, respectively, were observed together with minor signals (155.7 in **11** and at 156.6 ppm in **14**) originating from minor isomers (ratio ca 11:1 in both cases). No separation of signals in the ^{31}P or ^{1}H NMR spectra occurred upon cooling to –70 °C, thus demonstrating that the spectra observed at ambient temperature are not a result of rapid equilibration of isomers (see Supporting Information at the end of this chapter). Characteristic ^{1}H and ^{31}P signals are shown in Table 4.1.2.

Although the NMR spectra of the three complexes **11**–**13** have many features in common (Table 4.1.2 and Supporting Information), that of **11**, with flexible ligand (*S*)-**L3a**, resembles more that of the complex with rigid ligand (S_a,*S*)-**L3f** than that with (R_a,*S*)-**L3g**, as judged by the chemical shifts and coupling constants of the oxazoline

ring protons (see Supporting Information) and the olefinic protons as well as by the chemical shift difference of the *tert*-butyl protons *ortho* to the phosphite function ($\Delta\delta$ ppm ca 0.2 ppm in **11** and **12** and 0.01 ppm in **13**), which is influenced by the proximity of the coordinated olefin and thereby by the conformation of the ligand. These spectral features suggest that the ligand in complex **11** adopts (S_a,*S*)-configuration. Complete assignment of the ^{1}H NMR spectrum of **15** was hampered due to overlapping signals, but due to the similarity of the spectra **14** and **15**, in particular the chemical shifts of the oxazoline ring protons (see Supporting Information) and the *tert*-butyl protons *ortho* to the phosphite moiety, it was assumed that **14** and **15** have the same absolute configuration. Although the NMR study thus suggests that the flexible ligand adopts (S_a,*S*)-configuration in complexes with both types of olefins, the spectra do not allow definite conclusions about the configuration of the flexible ligand in the two complexes. For this reason DFT calculations were performed (see below).

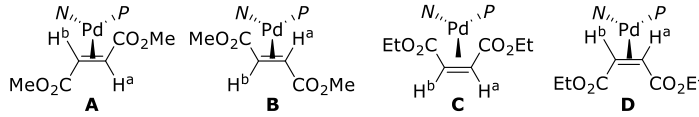


Figure 4.1.3. Possible isomers of palladium(0) olefin complexes.

Table 4.1.2. Characteristic NMR data for olefin protons H^a and H^b for complexes **11**–**16**.

Cmpd	δ H^a (ppm)	δ H^b (ppm)	δ P (ppm)	$J_{H^aH^b}$ (Hz)	J_{H^aP} (Hz)	J_{H^bP} (Hz)	δMe_{ligand} (ppm)	δMe_{olefin} (ppm)	$\delta^t Bu$ (ppm)
11	3.72	3.57	153.6	10.2	4.6	15	0.94, 1.01	3.42, 2.93	1.10, 1.3
12	3.72	3.55	152.6	10	4.7	16	0.88, 1.01	3.07, 3.41	1.07, 1.32
13	3.86	3.51	154.0	10	5.5	15	0.69, 0.95	2.97, 3.37	1.26, 1.29
14	3.76	3.42	155.8	10	5.1	12	0.93, 1.04	0.65, 1.04	1.10, 1.3
15[a]			153.2				0.90, 1.04	0.83, 1.03	1.08, 1.31
16	3.88	3.49	155.1	10	5.5	15	0.72, 1.00	0.78, 1.38	1.28, 1.29

[a] Assignments hampered due to overlapping signals.

Knowing that the catalyst with (S_a,*S*)-**L3f** leads to the (*S*) product enantiomer and that with (R_a,*S*)-**L3g** to the opposite enantiomer, each olefin was expected to coordinate with different faces to palladium in complexes with the two ligands. Nucleophilic attack *trans* to phosphorus rather than *trans* to nitrogen is expected as a result of the stronger *trans* influence of phosphorus.[20] Due to the analogy of the product olefin complexes and

our model complexes, those containing the (S_a,*S*)-**L3f** ligand were thus expected to be **A** and **C**, and those with the diastereomeric (R_a,*S*)-**L3g** ligand, **B** and **D** (Figure 4.1.3). However, NOESY experiments of the three palladium fumarate complexes **11**–**13** showed NOE interactions between the olefinic proton located *trans* to the phosphite moiety (H^b) and the proton of the isopropyl oxazoline substituent (Figure 4.1.4). This suggests that, in contrast to expectations, all fumarate complexes coordinate as in **A**, regardless of the configuration of the biaryl phosphite moiety.

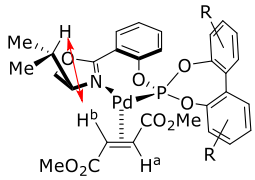


Figure 4.1.4. Relevant NOE contacts of Pd-complexes **11**–**13**.

4.1.2.4. Theoretical studies

In order to determine the configuration of the flexible ligand in reactions with the two substrates as well as whether the olefins coordinate via the same face in complexes with the two rigid ligands although products with different absolute configuration were obtained, DFT calculations were performed. The relative stabilities of the product olefin complexes were initially calculated, using the olefin complexes obtained from nucleophilic addition of dimethyl malonate to allyl complexes derived from the two substrates (Figures 4.1.5 and 4.1.6).

In agreement with the results of the NMR study, it was found that complexes containing product olefins with (*S*) absolute configuration were more stable than those with (*R*)-configuration for both ligands and for both olefins (Figures 4.1.5 and 4.1.6); large energy differences were indeed found for the two complexes (S_a,*S*)-*S* (**A**) and (S_a,*S*)-*R* (**B**) with linear olefin **9** (Figure 4.1.5a) as well as for (R_a,*S*)-*S* (**C**) and (R_a,*S*)-*R* (**D**), containing cyclic olefin **10** (Figure 4.1.6a).

A smaller energy difference between the two olefin complexes (R_a,*S*)-*S* (**A**) and (R_a,*S*)-*R* (**B**) was observed, although the configuration of the product **9** predicted by the calculations is opposite to that observed experimentally (Figure 4.1.5b). The opposite isomer is also predicted for reaction with 3-cyclohexenyl acetate using (R_a,*S*)-**L3g** (Figure 4.1.6b). The explanation for the formation of products with opposite absolute configuration from catalytic reactions using complexes containing (S_a,*S*)-**L3f** and (R_a,*S*)-**L3g** should therefore be sought in the relative stabilities of the transition states leading to the different products. Transition state (TS) calculations were therefore performed. In order to simplify the calculations, NH_3 was used as the nucleophile.

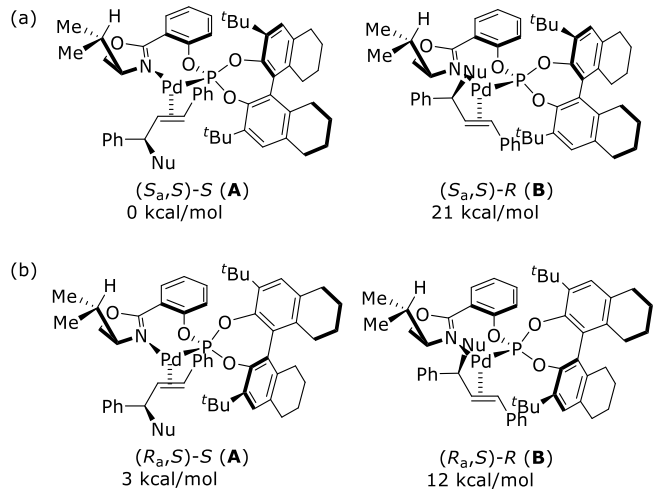


Figure 4.1.5. Calculated relative energies for palladium complexes **A** and **B** containing olefin **9** using ligands (a) (*S*a,*S*)-**L3f** and (b) (*R*a,*S*)-**L3g**. For use of **A** and **B**, compare Figure 4.1.3.

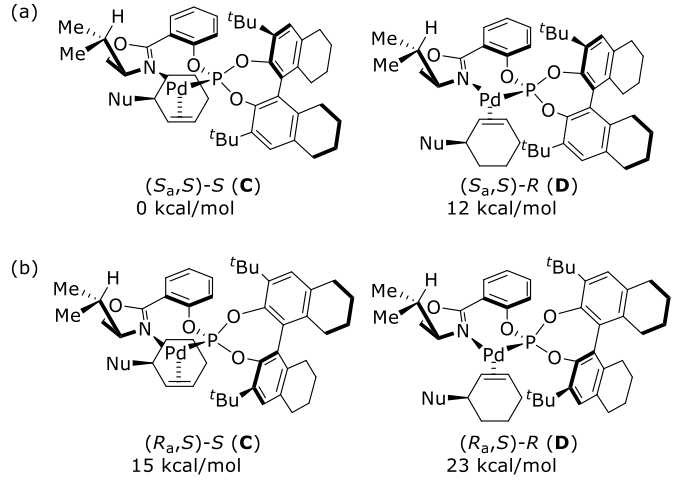


Figure 4.1.6. Calculated relative energies for palladium complexes **C** and **D** containing olefin **10** using ligands (a) (*S*a,*S*)-**L3g** and (b) (*R*a,*S*)-**L3f**. For use of **C** and **D**, compare Figure 4.1.3.

Neglecting *anti/anti* and *anti/syn* complexes, which constitute minor isomers, two *syn/syn* Pd-η^3-allyl, *exo* and *endo*, complexes derived from 1,3-diphenyl-2-propenyl acetate are possible from each ligand, as illustrated for (*S*a,*S*)-**L3g**, (*R*a,*S*)-**L3f**, and (*S*)-**L3a** in Figure 4.1.7. Assuming that nucleophilic attack on the allyl complex to form the product olefin complex proceeds by a least-motion reaction path,[21] allyl complexes (*S*a,*S*)-*exo* and (*R*a,*S*)-*endo* are those which lead to the observed products, with (*S*)- and (*R*)-configuration, respectively.

The calculated energies of the transition states leading to the observed product and the enantiomers are shown in Table 4.1.3. A larger energy difference was found between

the two TSs leading to opposite enantiomers in reactions with ligand (S_a,*S*)-**L3g** as compared to those with (R_a,*S*)-**L3f**, which is in accordance with the experimental results (>99% (*S*) vs 20% (*R*); Table 4.1.1, entries 2 vs 3). In addition, the TSs for (R_a,*S*)-**L3g** are higher in energy than the most stable TS for (S_a,*S*)-**L3f**, which fully accounts for the lower reactivity observed for the Pd/(R_a,*S*)-**L3g** catalytic system. The high ee's observed in reactions using (*S*)-**L3a** as ligand are also reflected in the energy difference calculated for the *endo* and *exo* structures with this ligand.

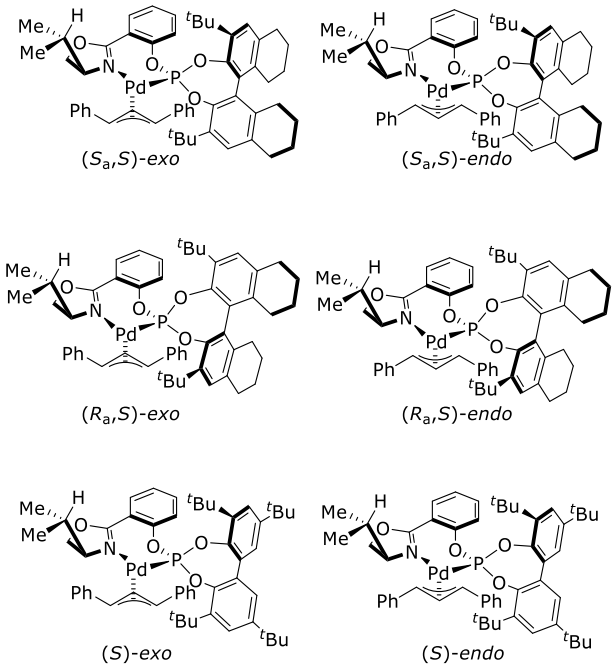


Figure 4.1.7. Pd-η^3-allyl *exo* and *endo* complexes from 1,3-diphenyl-2-propenyl acetate (**S1**).

Table 4.1.3. Calculated relative energies (in kcal/mol) for the TSs from *exo* and *endo* Pd-η^3-allyl intermediates, using **S1** and **S2** and NH_3 as nucleophile.

	S1		**S2**	
Ligand	*exo*	*endo*	*exo*	*endo*
(S_a,*S*)-**L3f**	0	4	2	0
(R_a,*S*)-**L3g**	2.6[a]	2.5[a]	2.2[b]	2.8[b]
(*S*)-**L3a**	0	4.3	1	0

[a] Energies relative to that of *exo*-(S_a,*S*)-**L3f**; [b] Energies relative to that of *endo*-(S_a,*S*)-**L3f**.

Analogous calculations were performed for complexes from 3-cyclohexenyl acetate (Figure 4.1.8). The calculated TS energy differences between the *exo* and *endo* complexes (Table 4.1.3) are in agreement with the high enantiomeric excesses observed using (S_a,*S*)-**L3f** as ligand, and also with the observation of opposite enantiomers of alkylated product **10** using the two diastereoisomeric ligands (S_a,*S*)-**L3f**

and (R_a,*S*)-**L3g** (99% (*S*) using (S_a,*S*)-**L3f** vs 92% (*R*) for (R_a,*S*)-**L3g**; Table 4.1.1, entries 2 vs 3). Again, the energy of the TS for the reaction catalyzed by (R_a,*S*)-**L3g** is higher than that of the reaction catalyzed by (S_a,*S*)-**L3g**, which is in agreement with the higher reactivity observed for Pd/(S_a,*S*)-**L3g** compared to Pd/(R_a,*S*)-**L3f** catalyst.

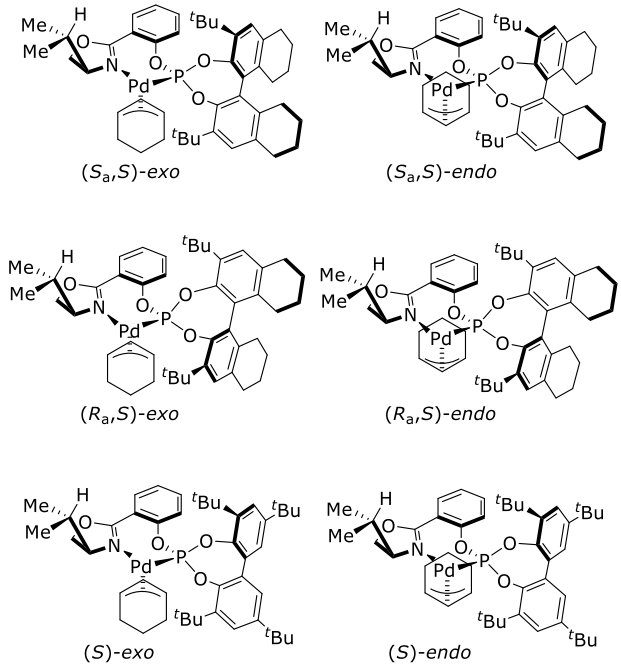


Figure 4.1.8. Pd-η^3-allyl *exo* and *endo* complexes from 3-cyclohexenyl acetate (**S2**).

The conclusion of the calculations is thus that in the reaction of *E*-1,3-diphenyl-2-propenyl acetate with (S_a,*S*)-**L3f** the TS leading to the product with (*S*)-configuration, which is the product observed experimentally, is lowest in energy, and the olefin complex of this product is that which is most stable. In contrast, for (R_a,*S*)-**L3g**, the TS leading to the product with (*R*)-configuration, which is the product observed experimentally, is lowest in energy, whereas the olefin complex of the product with (*S*) configuration is lowest in energy.

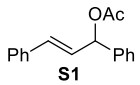
In the reaction of 3-cyclohexenyl acetate with (S_a,*S*,)-**L3f**, the TS leading to the product with (*S*)-configuration, which is the product observed experimentally, is lowest in energy, and the olefin complex of this product is that which is most stable. In contrast, for (R_a,*S*)-**L3g***,* the TS leading to the product with (*R)*-configuration, which is the product observed experimentally, is lowest in energy, whereas the olefin complex of the product with (*S*)-configuration is lowest in energy. Thus, in reactions with both types of substrates where (R_a,*S*)-**L3g** is used as ligand, the lowest energy transition state complexes lead to product olefin complexes which are higher in energy than those from olefins with opposite absolute configuration. The calculations thus provide an

explanation why the model olefins coordinate to palladium via the same face in complexes with the two rigid ligands, although they lead to products with opposite absolute configuration in the catalytic reactions.

4.1.2.5. Other substrates and nucleophiles. Scope and limitations

To further study the behavior of ligand (*S*)-**L3a** and its rigid analogues (S_a,*S*)-**L3f** and (R_a,*S*)-**L3g**, and to investigate whether the similar behavior of the two best ligands (*S*)-**L3a** and (S_a,*S*)-**L3f** is general, we extended the previous work to O-nucleophiles and C-nucleophiles other than dimethyl malonate as well as to the alkylation of other substrates (Tables 4.1.4–4.1.8).

Table 4.1.4. Pd-catalyzed allylic substitution of disubstituted linear substrates using ligand (*S*)-**L3a**.[a]

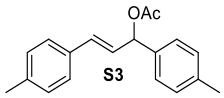
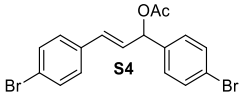
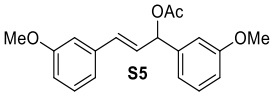
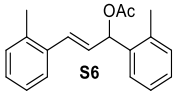
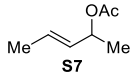
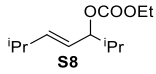
Entry	Substrate	H-Nu	Product	% Conv[b] (%Yield)	% ee[c]
1	 **S1**	H-CH(CO_2Me)$_2$	**9**	100 (94)	>99 (*S*)
2	**S1**	H-CH(CO_2Et)$_2$	**17**	100 (93)	>99 (*S*)
3	**S1**	H-CH(CO_2Bn)$_2$	**18**	100 (95)	>99 (*S*)
4	**S1**	H-CMe(CO_2Me)$_2$	**19**	96 (91)	99 (*R*)
5	**S1**	H-Callyl(CO_2Me)$_2$	**20**	100 (92)	>99 (*R*)
6	**S1**	H-Cbutenyl(CO_2Et)$_2$	**21**	100 (89)	>99 (*R*)
7	**S1**	H-Cpentenyl(CO_2Et)$_2$	**22**	100 (93)	93 (*R*)
8	**S1**	H-Cpropargyl(CO_2Me)$_2$	**23**	100 (91)	>99 (*R*)
9	**S1**	H-CH($COMe$)$_2$	**24**	100 (89)	98 (*S*)
10[d]	**S1**	H-CF(SO_2Ph)	**25**	100 (76)	99 (*R*)
11[d]	**S1**	H-OCH_2Ph	**26**	76 (69)	33 (*R*)
12[d]	**S1**	H-OCH_2(*p*-Me-C_6H_4)	**27**	82 (76)	25 (-)
13[d]	**S1**	H-OCH_2(*p*-CF_3-C_6H_4)	**28**	100 (93)	97 (-)
14[d]	**S1**	H-OCH_2(*m*-Me-C_6H_4)	**29**	75 (69)	37 (-)
15[d]	**S1**	H-Oallyl	**30**	89 (81)	32 (-)
16[d]	**S1**	H-Opropargyl	**31**	75 (70)	40 (*R*)
17[d]	**S1**	H-OSi(Me)$_2$Ph	**32**	94 (79)	98 (*R*)[e]
18[d]	**S1**	H-OSiPh_3	**33**	100 (91)	99 (*R*)[e]

[a] 0.5 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, rt; [b] % Conversion measured after 10 min. Isolated yield shown in parenthesis; [c] Enantiomeric excesses determined by chiral HPLC or GC; [d] Conversions and yields measured after 18 h; [e] Measured after desilylation to the corresponding alcohol.

Table 4.1.4 shows the results of the use of Pd/(*S*)-**L3a** in the allylic substitution of several symmetrically disubstituted linear substrates, with different steric and electronic properties using a wide range of C- and O-nucleophiles. We initially considered the allylic substitution of substrate **S1** (Table 4.1.4, entries 1–18). We were pleased to note that Pd/(*S*)-**L3a** is very tolerant to variation of the steric properties of the ester moiety and the substituents of the malonate nucleophiles (entries 2–8). A broad range of malonates provided products **17**–**23** in high yields and with excellent enantioselectivities, comparable to those obtained with dimetyl malonate (ee's up to >99%). Of particular interest are the high enantioselectivities achieved with allyl-, butenyl-, pentenyl- and propargyl-substituted malonates, whose products are key intermediates in the synthesis of more complex chiral products.[22] The addition of acetylacetone (compound **24**) also proceeded with similar high enantioselectivities (ee's up to 98%, entry 9). Interestingly, we could also reach ee's up to 99% and high yield in the allylic fluorobis(phenylsulfonyl)-methylation of **S1** using Pd/(*S*)-**L3a** (compound **25**, entry 10). The efficient allylic substitution with this type of nucleophile opens up a path for obtaining highly appealing chiral monofluoromethylated compounds, which are attracting significant attention in the field of medicinal chemistry.[23] Despite this, only one catalytic system has previously been successfully applied, although it resulted in lower enantioselectivity (ee's up to 96%) than the present system and also required lower temperature (0 ºC) than our Pd/(*S*)-**L3a** catalyst.[24]

We then considered the allylic substitution of **S1** using several O-nucleophiles (entries 11–18). The asymmetric Pd-catalyzed allylic etherification has recently attracted the attention of many researchers because the resulting chiral ethers and related derivatives are important intermediates in the synthesis of biologically active compounds.[25] Despite its importance, few successful examples exist and most of them use phenols as O-nucleophiles,[26] aliphatic ethers[27] and silanols[27d] being much less studied. The application of Pd/(*S*)-**L3a** to several aliphatic alcohols provided the desired products in excellent yields. For benzylic alcohols, the enantioselectivity was affected by the electronic nature of the nucleophile. The best enantioselectivity (97% ee, entry 13) was achieved with an electron-withdrawing group in the *para* position of the aryl group. Even more interesting are the almost perfect enantioselectivities (ee's up to 99%) and high yields achieved in the etherification of **S1** with silanols (entries 17–18). The results surpass those of the only Pd/CycloN_2P_2-Phos catalytic type system that has provided high enantioselectivities (up to 94% ee)[27d] so far. Therefore Pd/(*S*)-**L3a** can be used for preparing chiral silyl ethers that can be easily transformed into high-value compounds such as chiral aromatic allylic alcohols.

Table 4.1.5. Pd-catalyzed allylic substitution of disubstituted linear substrates using ligand (*S*)-**L3a**.[a]

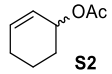
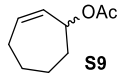
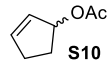
Entry	Substrate	H-Nu	Product	% Conv[b] (%Yield)	% ee[c]
1	 **S3**	H-CH(CO_2Me)$_2$	**34**	100 (93)	99 (*S*)
2	**S3**	H-Callyl(CO_2Et)$_2$	**35**	100 (91)	99 (*R*)
3	**S3**	H-Cbutenyl(CO_2Et)$_2$	**36**	100 (92)	94 (*R*)[e]
4	 **S4**	H-CH(CO_2Me)$_2$	**37**	100 (89)	99 (*S*)
5	 **S5**	H-CH(CO_2Me)$_2$	**38**	100 (91)	99 (*S*)
6	 **S6**	H-CH(CO_2Me)$_2$	**39**	100 (90)	99 (*S*)
7[f]	 **S7**	H-CH(CO_2Me)$_2$	**40**	100 (89)	93 (*S*)
8[f]	**S7**	H-CH(CO_2Bn)$_2$	**41**	100 (91)	82 (*S*)
9[f]	**S7**	H-CH(COMe)$_2$	**42**	100 (90)	85 (*S*)
10[f]	**S7**	H-CMe(CO_2Me)$_2$	**43**	100 (86)	80 (*S*)
11[f]	**S7**	H-Callyl(CO_2Me)$_2$	**44**	100 (89)	90 (*S*)
12[f]	**S7**	H-Cbutenyl(CO_2Et)$_2$	**45**	100 (90)	87 (*S*)
13[f]	**S7**	H-Cpropargyl(CO_2Me)$_2$	**46**	100 (87)	72 (*S*)
14[d]	 **S8**	H-CH(CO_2Me)$_2$	**47**	100 (92)	>95 (*S*)[g]

[a] 0.5 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, rt; [b] % Conversion measured after 10 min. Isolated yield shown in parenthesis; [c] Enantiomeric excesses determined by chiral HPLC or GC; [d] Conversions and yields measured after 18 h; [e] Measured after transformation to the corresponding RCM-adduct; [f] Reactions carried out at 0 ºC for 18 h; [g] ee measured by ^{1}H NMR using [Eu(hfc)$_3$].

The scope of Pd/(*S*)-**L3a** was further investigated by using other symmetrical linear substrates with steric and electronic requirements (**S3**–**S8**) different from those of **S1**. The Pd/(*S*)-**L3a** catalytic system can also be used for the alkylation of substrates **S3**–**S6**, with different substituents in the aryl groups, with various carbon nucleophiles with excellent enantioselectivities and yields, comparable to those of **S1** (Table 4.1.5, entries 1–6). We also found that the biaryl-phosphite group in Pd/(*S*)-**L3a** can adapt its chiral pocket and successfully catalyze the alkylation of **S7** (entries 7–13). This substrate is

less sterically demanding and therefore enantioselectivities tend to be lower than with model substrate **S1**. The present results are among the best in the literature for this substrate,[7] even using highly appealing nucleophiles such as α-substituted with methyl, allyl and butenyl groups, for which only very few catalytic systems have provided high enantioselectivities.[22] Interestingly, Pd/(*S*)-**L3a** can also successfully be used for the alkylation of **S8** (ee's up to >95%, entry 14). This substrate is more sterically demanding and it usually reacts with inferior catalytic performance than **S1** and **S3**–**S4**.

Table 4.1.6. Pd-catalyzed allylic substitution of cyclic substrates using ligand (S_a,*S*)-**L3g**.[a]

Entry	Substrate	H-Nu	Product	% Conv[b] (% yield)	% ee[c]
1	 **S2**	H-CH(CO_2Me)$_2$	**10**	100 (92)	99 (*S*)
2	**S2**	H-CH(CO_2Et)$_2$	**48**	100 (93)	>99 (*S*)
3	**S2**	H-CH(CO_2Bn)$_2$	**49**	100 (90)	97 (*S*)
4	**S2**	H-CMe(CO_2Me)$_2$	**50**	100 (89)	99 (+)
5	**S2**	H-Callyl(CO_2Me)$_2$	**51**	100 (91)	>99 (-)
6	**S2**	H-Cpropargyl(CO_2Me)$_2$	**52**	100 (88)	92 (*S*)
7	**S2**	H-CH(COMe)$_2$	**53**	100 (93)	99 (-)
8	 **S9**	H-CH(CO_2Me)$_2$	**54**	100 (92)	>99 (*S*)
9	**S9**	H-Cpropargyl(CO_2Me)$_2$	**55**	69 (65)	>99 (*S*)
10	 **S10**	H-CH(CO_2Me)$_2$	**56**	100 (86)	>95 (-)[d]
11	**S10**	H-Cpropargyl(CO_2Me)$_2$	**57**	100 (87)	96 (*S*)

[a] 0.5 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 1.1 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, rt; [b] % Conversion measured after 30 min. Isolated yield shown in parenthesis; [c] Enantiomeric excesses determined by chiral HPLC or GC; [d] Enantiomeric excess measured by ^{1}H NMR using [Eu(hfc)$_3$].

We then focused our attention on the allylic substitution of cyclic substrate **S2** with more challenging nucleophiles than dimethyl malonate and on the alkylation of other cyclic substrates with different ring sizes (**S9** and **S10**). Table 4.1.6 shows that a wide range of C-nucleophiles, including the less studied α-substituted malonates and acetylacetone, can efficiently react with **S2** to provide the corresponding compounds (**48**–**53**) with high yields and enantioselectivities (ee's up to >99%), comparable to those obtained with dimethyl malonate (**10**). The exception was propargyl-substituted malonate, which led to somewhat lower enantioselectivity (compound **52**, ee's up to 92%), but still good for this challenging C-nucleophile. Remarkably, Pd/(S_a,*S*)-**L3f** also efficiently catalyzes the alkylation of cyclic substrates **S9** and **S10** (Table 4.1.6, entries 8–11, compounds **54**–**57**). Excellent-to-high enantioselectivities (ee's between 96%

and >99%) were obtained in both cases, even with **S10**, which usually provides products with much lower enantioselectivities than cyclic **S2**.[7]

We next studied if the rigid analogues of (*S*)-**L3a** (ligands (S_a,*S*)-**L3f** and (R_a,*S*)-**L3g**) follow the same trend in the allylic substitution of unsymmetrical monosubstituted substrates **S11** and **S12** (Eqs 4.1.2) as in reactions with disubstituted substrates. The challenge in these substrates is that both the enantioselectivity and regioselectivity need to be controlled, and most palladium catalysts favor the formation of the usually undesired achiral linear product. [7,28,29] In our previous work we found that alkylation of **S11** and **S12** catalyzed by Pd/(*S*)-**L3a** proceeded with regio- and enantioselectivities comparable to those of the best ones reported.[11] As observed with the previously studied linear disubstituted substrates, Pd/(S_a*S*)-**L3f** gave the best results and provided the desired branched isomers (compounds **58** and **60**), with enantioselectivities that were as high as those obtained with Pd/(*S*)-**L3a**, as major products (Table 4.1.7).

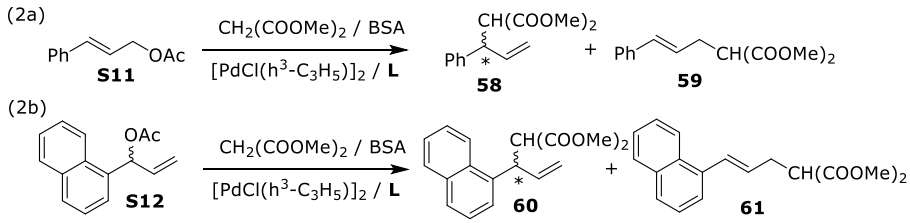


Table 4.1.7. Pd-catalyzed allylic substitution of monosubstituted substrates **S11** and **S12**.[a]

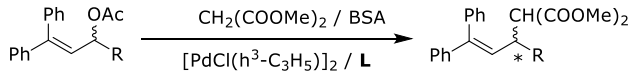
Entry	Substrate	Ligand	% Conv[b] (%yield)	% branched[c]	% ee[d]
1	**S11**	(*S*)-**L3a**	100 (91)	68	86 (*S*)
2	**S11**	(S_a,*S*)-**L3f**	100 (90)	65	85 (*S*)
3	**S11**	(R_a,*S*)-**L3g**	100 (90)	15	42 (*R*)
4	**S11**	(S_a,*S*)-**L3f**+(R_a,*S*)-**L3g**	100 (91)	50	79 (*S*)
5	**S12**	(*S*)-**L3a**	100 (92)	>99	92 (*S*)
6	**S12**	(S_a,*S*)-**L3f**	100 (89)	95	90 (*S*)
7	**S12**	(R_a,*S*)-**L3g**	100 (90)	40	41 (*R*)
8	**S12**	(S_a,*S*)-**L3f**+(R_a,*S*)-**L3g**	100 (91)	70	61 (*S*)

[a] 1 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 2.2 mol % ligand, benzene as solvent, BSA/KOAc as base, 0 °C; [b] % Conversion measured after 2 h. Isolated yield shown in parenthesis; [c] Regioselectivity measured by ^{1}H NMR; [d] Enantiomeric excesses determined by chiral HPLC.

Finally, the good performance of Pd/(*S*)-**L3a** and Pd/(S_a,*S*)-**L3f** also extended to the allylic substitution of unsymmetrical 1,3,3,-trisubstituted allylic substrates (**S13**–**S14**, Table 4.1.8). These reactions have a large interest because the substitution products can easily be transformed into chiral acid derivatives and lactones.[30] These substrates have been less studied and less successfully alkylated than disubstituted substrates because they are more sterically demanding than model substrate **S1**.[31] The results

shown in Table 4.1.8 show the same trend as for the allylic substitution of **S1**. The Pd-catalysts containing ligands (*S*)-**L3a** and (*S*$_a$,*S*)-**L3f** provided the best enantioselectivities (ee's up to >99% for both substrates). Again, the flexibility conferred by the biaryl phosphite moiety was enough to adequately control the size of the chiral pocket in order to achieve enantioselectivities comparable to the best one reported.[31] In line with the literature results, and as observed for **S8**, the activities were lower than in the alkylation reaction of **S1**.

Table 4.1.8. Pd-catalyzed allylic substitution of trisubstituted substrates **S13** and **S14**.[a]



S13 R= Ph
S14 R= Me

62 R= Ph
63 R= Me

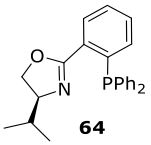
Entry	Substrate	Ligand	% Conv[b] (%yield)	% ee[c]
1	**S13**	(*S*)-**L3a**	87 (84)	>99 (*R*)
2	**S13**	(*S*$_a$,*S*)-**L3f**	84 (79)	99 (*R*)
3	**S13**	(*R*$_a$,*S*)-**L3g**	65 (62)	41 (*S*)
4	**S14**	(*S*)-**L3a**	98 (95)	>99 (*R*)
5	**S14**	(*S*$_a$,*S*)-**L3f**	95 (90)	99 (*R*)
6	**S14**	(*R*$_a$,*S*)-**L3g**	71 (65)	24 (*S*)

[a] 2 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 4.4 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, rt; [b] % Conversion measured after 24 h. Isolated yield shown in parenthesis; [c] Enantiomeric excesses determined by chiral HPLC.

4.1.3. Discussion

High enantiocontrol is achieved in a variety of processes employing metal complexes with phosphinooxazoline, PHOX, ligands (**64**) as catalysts,[32] and for this reason phosphinooxazolines are classified as privileged ligands.[2] In a variety of catalytic processes phosphite ligand (*S*)-**L3a** has properties similar to those of phosphine ligands **64**.[33] However, whereas (4*S*)-2-(2'-diphenylphosphino)phenyl-4-isopropyl-4,5-dihydrooxazole (**64**, R = ^{i}Pr; Figure 4.1.9) gives excellent results in asymmetric allylic alkylations with *rac*-*E*-1,3-diphenyl-2-propenyl as substrate (98% ee), modest to good results are obtained with 1,3-dialkyl-2-propenyl substrates, and racemic product with the 3-cyclohexenyl derivatives. In contrast, **L3a** provides excellent results with all these types of substrates. The chiral PHOX ligands interact with the substrate mainly at its wings. As a consequence, allylic systems with bulky substituents show high *exo*:*endo* ratios and high enantioselectivities, whereas narrow systems give low selectivity.[33] In contrast, ligands (*S*)-**L3a** and (*S*$_{a,}$*S*)-**L3f** are more flexible and can accommodate a wider range of substrates, thereby yielding excellent enantioselectivities for both "broad" and "narrow" substrates. In fact, by replacing the phosphine moiety by a biaryl phosphite in the PHOX ligand, we were able to identify unprecedented catalytic systems

(Pd/(*S*)-**L3a** and Pd/(*S*$_a$,*S*)-**L3f**) that with high enantiocontrol generate C-C, C-N, and C-O bonds for a number of hindered and unhindered mono-, di- and tri-substituted substrates using a wide range of C, N and O-nucleophiles.



64

Figure 4.1.9. Phosphino-oxazoline ligand **64**.

The enantioselectivity of the catalytic reactions is reflected by the energy difference between the *exo* and *endo* like transition states, provided that nucleophilic attack occurs only *trans* to phosphorus. In the reaction of *E*-1,3-diphenyl-2-propenyl acetate (**S1**) in the presence of (*S*$_a$,*S*)-**L3f** (with NH_3 as nucleophile) this difference was calculated to 4 kcal/mol, in good agreement with the selectivity observed experimentally (>99% ee). The selectivity observed experimentally in reaction with the cyclic substrate **S2** was slightly lower, 99% ee, well corresponding to the computed energy difference between the two transition states, 2 kcal/mol. For reactions of the two substrates in the presence of PHOX ligand **64** (R = ^{i}Pr; Figure 4.1.9) the corresponding values were calculated to 2.2 and 0 kcal/mol, respectively, thus reflecting the somewhat lower selectivity obtained from **S1** as compared to that obtained using (*S*$_a$,*S*)-**L3f** , and the formation of racemic product from **S2**.[21]

Contrary to expectations, the absolute configuration of the products could not be entirely predicted from the structure of the most stable olefin complex, implying that at least for reactions employing (*R*$_a$,*S*)-**L3g** as ligand, the transition states resemble the palladium allyl complexes rather than the olefin complexes. For (*S*)-**L3a** and (*S*$_a$,*S*)-**L3f** exo complexes are more stable than *endo* complexes, in analogy to complexes with PHOX ligands, whereas for (*R*$_a$,*S*)-**L3g** the *endo* complex has slightly higher stability than the *exo* complex.

While the previously studied semiflexible ligands **1** and **2** (Figure 4.1.1) adopt different configurations in product olefin complexes obtained in reactions with the two types of substrates, (*S*)-**L3a** prefers a (*S*$_a$,*S*)-configuration with both "broad" and "narrow" substrates. The ability of this ligand to adapt the size of the substrate-binding pocket to the reacting substrate is therefore a result of the high flexibility of the biaryl phosphite group.

4.1.4. Conclusions

Contrary to previously studied flexible ligands, (*S*)-**L3a** adopts (*S*$_a$,*S*)-configuration in complexes mimicking product olefin complexes obtained in palladium catalyzed allylic alkylations of both "broad" and "narrow" allylic substrates. Although the olefins

coordinate with the same face to palladium in diastereomeric rigid ligands with (S_a,*S*)- and (R_a,*S*)-configuration, products with opposite absolute configuration are obtained. The explanation is found in the different energies of the transition state complexes.

The origin of the exceptionally broad substrate scope of the ligand as well as its ability to control the stereochemistry in a variety of catalytic processes is connected to its defined stereochemical structure combined with the high flexibility of the tropos unit. The unique ability of the ligand to modify its chiral pocket would justify its addition to the family of privileged ligands.

4.1.5. Experimental Section

4.1.5.1. General considerations

Unless stated otherwise, reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques. NMR spectra (^{1}H, ^{13}C, and ^{31}P) were measured on Bruker DRX 400 MHz and Bruker DRX 500 MHz instruments; $CDCl_3$ was used as a solvent, if not further specified. With exception of the compounds given below, all reagents were purchased from commercial suppliers and used without further purification. The following compounds were synthesized according to published procedures: (*S*)-5,6,7,8,5,6,7,8-octahydro-(1,1'-binaphtalene)-2,2'-diol (*S*)-**6**,[16] (*R*)-5,6,7,8,5,6,7,8-octahydro-(1,1'-binaphtalene)-2,2'-diol (*R*)-**6**,[16] and (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol.[18] Racemic substrates **S1**–**S14**,[34] diethyl 2-(3-butenyl)malonate[35] and diethyl 2-(4-penten-1-yl)malonate[36] were prepared as previously reported.

4.1.5.2. Computational details

The geometries of all intermediates were optimized using the Gaussian 09 program,[37] employing the B3LYP[38] density functional and the LANL2DZ[39] basis set for iridium and the 6-31G* basis set for all other elements.[40] Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[41] The complexes were treated with charge +1 and in the single state. No symmetry constraints were applied. The energies were further refined by performing single point calculations using the above mentioned parameters, with the exception that the 6-311+G**[42] basis set was used for all elements except iridium, and by applying dispersion correction using DFT-D3[43] model. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + (E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*}) + E_{DFT\text{-}D3}$.

4.1.5.3. Procedures for the synthesis of L3a, L3f-g

Synthesis compound (*S*)-7.[17] In a Schlenk were placed (*S*)-**6** (1.0 g, 3.4 mmol), *tert*-butyl chloride (9.2 mL, 85 mmol), and chloropentacarbonylrhenium(I) (10 mol %). The reaction mixture was heated at reflux for 18 h under stream of nitrogen. The mixture was cooled to room temperature and concentrated. The residue was purified by flash chromatography (silica gel, hexane/CH_2Cl_2 3:1) to afford (*S*)-**8** (1.34 g, yield 97%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.33 (s, 18H), 1.59 (m, 4H), 1.65 (m, 4H), 2.02 (m, 2H), 2.11 (m, 2H), 2.66 (m, 4H), 4.78 (s, 2H), 6.99 (s, 2H). ^{13}C NMR (126 MHz): δ= 23.2 (CH_2), 26.8 (CH_2), 29.5 (CH_2), 29.6 (CH_3), 34.5 (CH), 119.5 (C), 128.3 (C), 129.1 (C), 133.8 (C), 134.5 (C), 150.1 (C).

Synthesis of compound (*S*)-8.[44] In a flame-dried Schlenk, distilled PCl_3 (0.21 mL, 2.46 mmol) and Et_3N (0.70 mL, 4.92 mmol) were dissolved in dry toluene (22 mL). The solution was cooled to -78 °C and a solution of (*S*)-**7** (500 mg, 1.23 mmol) and DMAP (10 mol %) in toluene (3 mL) was added dropwise over 10 min. The mixture was left to warm to room temperature overnight. After this time the formation of product was checked by ^{31}P NMR. The solvent and the residual PCl_3 were removed under vacuum. The resulting solid was used for the next step without any further purification.

Synthesis compound (*S$_a$*,*S*)-L3f. To a solution of compound (*S*)-**8** in dry toluene (7 mL) in a flame-dried Schlenk, a solution of (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol (252.4 mg, 1.23 mmol), Et_3N (0.51 mL, 3.69 mmol), and DMAP (10 mol %) in toluene (3 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered over a pad of celite and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (silica gel, hexane/Et_2O 10:1 to 3:1) and then crystallized from hexane/Et_2O 5:1 to afford (*S$_a$*,*S*)-**L3f** (75 mg, 10% over two steps) as white crystals. ^{31}P NMR (202 MHz): δ= 129.0. ^{1}H NMR (500 MHz, CD_2Cl_2): δ= 0.86 (dd, *J* = 10.0, 6.8 Hz, 3H), 0.97 (dd, *J* = 10.0, 6.7 Hz, 3H), 1.21 (d, *J* = 10.1 Hz, 9H), 1.40 (d, *J* = 10.1 Hz, 9H), 1.57 (m, 4H), 1.46 (m, 1H), 1.71 (m, 4H), 1.94 – 1.77 (m, 2H), 2.25 (m, 2H), 2.67 (m, 2H), 2.84 – 2.74 (m, 2H), 3.95 (dd, *J* = 18.1, 8.3 Hz, 1H), 4.02 (dd, *J* = 17.1, 7.7 Hz, 1H), 4.29 (dd, *J* = 17.8, 9.6 Hz, 1H), 6.92 (s, 1H), 5.58 (m, 1H), 6.98 (m, 1H), 6.93 (s, 1H), 7.12 (d, *J* = 10.1 Hz, 1H), 7.64 (m, 1H). ^{13}C NMR (126 MHz): δ= 18.8 (CH_3), 19.3 (CH_3), 23.35 (CH_2), 23.38 (CH_2), 23.5 (CH_2), 23.6 (CH_2), 27.4 (CH_2), 27.7 (CH_2), 29.9 (CH_2), 30.7 (CH_2), 31.2 (CH_3), 33.6 (CH_2), 34.7 (CH), 34.9 (CH), 70.2 (CH_2), 73.5 (CH_2), 123.7 (C), 124.1 (CH), 127.6 (CH), 127.8 (CH), 130.2 (CH), 131.5 (C), 133.0 (CH), 133.6 (CH), 135.5 (CH), 135.7 (CH), 138.3 (CH), 138.8 (C), 145.4 (C), 151.0 (C), 151.7 (C), 160.9 (CH). MS HR-ESI [found 662.3377, $C_{40}H_{50}NO_4P$ $(M\text{-}Na)^+$ requires 662.3375].

Synthesis compound (*R*)-7.[17] In a Schlenk were placed (*R*)-**7** (1.0 g, 3.4 mmol), *tert*-butyl chloride (9.2 mL, 85 mmol), and chloropentacarbonylrhenium(I) (10 mol %). The reaction mixture was heated at reflux for 18 h under a stream of nitrogen. The mixture was cooled to room temperature and concentrated. The residue was purified by flash chromatography (silica gel, hexane/CH_2Cl_2 3:1) to afford (*R*)-**7** (1.0 g, yield 72 %) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (s, 18H), 1.59 (m, 4H), 1.65 (m, 4H), 2.02 (m, 2H), 2.11 (m, 2H), 2.66 (m, 4H), 4.78 (s, 2H), 6.99 (s, 2H). ^{13}C NMR (126 MHz): δ= 23.2 (CH_2), 26.8 (CH_2), 29.5 (CH_2), 29.6 (CH_3), 34.5 (CH), 119.5 (C), 128.3 (C), 129.1 (C), 133.8 (C), 134.5 (C), 150.1 (C).

Synthesis compound (*R*)-8.[44] In a flame-dried Schlenk, distilled PCl_3 (0.21 mL, 2.46 mmol) and Et_3N (0.70 mL, 4.92 mmol) were dissolved in dry toluene (22 mL). The solution was cooled to –78 °C and a solution of (*R*)-**8** (500 mg, 1.23 mmol) and DMAP (10 mol %) in toluene (3 mL) was added dropwise over 10 min. The mixture was left warming to room temperature overnight. After this time the formation of product was checked by ^{31}P NMR. The solvent and the residual PCl_3 were removed under vacuum. The resulting solid was used for the next step without any further purification.

Synthesis compound (R_a,*S*)-L3g. To a solution of compound (*R*)-**9** in dry toluene (7 mL) in a flame-dried Schlenk, a solution of the (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol (252.4 mg, 1.23 mmol), Et_3N (0.51 mL, 3.69 mmol), and DMAP (10 mol %) in toluene (3 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered over a pad of celite and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (silica gel, hexane/Et_2O 10:1) to afford (R_a,*S*)-**L3g** (69 mg, 9% over two steps) as a white foam. ^{31}P NMR (162 MHz): δ= 129.33. ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.82 (d, *J* = 8.0 Hz, 3H), 0.96 (d, *J* = 8.0 Hz, 3H), 1.21 (m, 10H), 1.34 (m, 1H), 1.38 (m, 9H), 1.47 (s, 2H), 1.66 (m, 8H), 1.92 (m, 2H), 2.30 (m, 2H), 2.70 (m, 2H), 2.77 (m, 2H), 3.94 (m, 2H), 4.28 (m, 1H), 6.12 (m, 1H), 6.98 (m, 2H), 7.09 (m, 1H), 7.71 (m, 1H). ^{13}C NMR (101 MHz): δ= 18.7 (CH_3), 19.6 (CH_3), 23.35 (CH_2), 23.38 (CH_2), 23.47 (CH_2), 23.48 (CH_2), 23.51 (CH_2), 27.9 (CH_2), 30.2 (CH_2), 31.3 (CH_2), 31.5 (CH_3), 33.6 (CH_2), 35.05 (CH), 35.07 (CH), 70.7 (CH_2), 73.6 (CH_2), 121.7 (C), 124.2 (CH), 127.8 (CH), 128.1 (CH), 130.0 (CH), 131.8 (C), 133.2 (CH), 133.9 (CH), 135.5 (CH), 135.4 (CH), 138.6 (CH), 139.0 (C), 144.9 (C), 145.3 (C), 150.8 (C), 161.7 (CH). MS HR-ESI [found 662.3379, $C_{40}H_{50}NO_4P$ $(M\text{-}Na)^+$ requires 662.3375].

4.1.5.4. General procedure for the preparation of the Pd(0)-olefin complexes for NMR studies

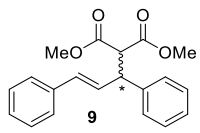
A solution of ligand (0.015 mmol)**,** olefin (dimethyl fumarate or diethyl maleate) (0.015 mmol), and [$Pd_2(dba)_3{\cdot}CHCl_3$] (0.0075 mmol) in CD_2Cl_2 (15 mM) was stirred for 30 min when dimethyl fumarate was used, and for 16 h when diethyl maleate was used.

After this time the mixture was transferred into a 5 mm NMR tube and the spectra were recorded. For NMR data, see Table 4.1.2 and Supporting Information.

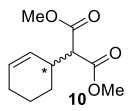
4.1.5.5. Typical procedure for the allylic alkylation of linear (S1, S3–S8 and S11–S12) and cyclic (S2, S9 and S10) substrates

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand **L3** (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), nucleophile (1.5 mmol), *N,O*-bis(trimethylsilyl)-acetamide (1.5 mmol) and f KOAc (3 mg, 0.03 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For compounds **9**, **17**–**25**, **34**–**39**, **41**, **44**–**46**, **48**–**51**, **55**, **58**, **60** and **62**–**63**, the solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC. For compounds **10**, **40**, **42**–**43**, **52**–**54** and **57**, conversion and enantiomeric excesses were determined by GC. For compounds **47** and **56**, conversions were measured by ^{1}H NMR and ees were determined by ^{1}H NMR using $[Eu(hfc)_3]$.

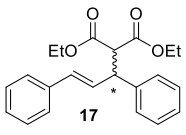
Dimethyl 2-(1,3-diphenylallyl)malonate (9).[45, 31b] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min). t_R 32.8 min (*R*); t_R 38.6 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 3.52 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.95 (d, 1H, CH, *J*=10.9 Hz), 4.26 (m, 1H, CH), 6.34 (dd, 1H, CH=, *J*=16.0 Hz, *J*=8.4 Hz), 6.48 (d, 1H, CH=, *J*=16.0 Hz), 7.1-7.4 (m, 10H, CH=).



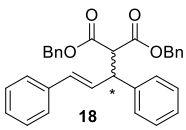
Dimethyl 2-(1,3-cyclohexanylallyl)malonate (10).[31b] Enantiomeric excess determined by GC using Chiralsil-Dex CB column (77 kPa H_2, Isotherm at 110 ºC). t_R 20.1 min (*S*); t_R 20.5 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.36 (m, 1H, CH_2), 1.56 (m, 1H, CH_2), 1.70 (m, 1H, CH_2), 1.76 (m, 1H, CH_2), 1.99 (m, 2H, CH_2), 3.29 (d, 1H, CH, *J*=9.6 Hz), 3.73 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 5.22 (m, 1H, CH=), 5.79 (m, 1H, CH=).



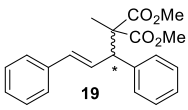
Diethyl 2-(1,3-diphenylallyl)malonate (17).[46] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min). t_R 17.5 min (*R*); t_R 20.0 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.01 (t, 6H, CH_3, *J*=6.8 Hz), 3.92 (d, 1H, CH, *J*=11.2 Hz), 4.19 (q, 4H, CH_2, *J*=7.2 Hz), 4.23 (m, 1H, CH), 6.34 (dd, 1H, CH=, *J*=20 Hz, *J*=10 Hz), 6.41 (d, 1H, CH=,*J*=18 Hz), 7.1-7.4 (m, 10H, CH=).



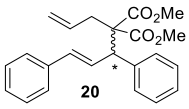
Dibenzyl 2-(1,3-diphenylallyl)malonate (18).[46] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (95% hexane/2-propanol, flow 1 mL/min). t_R 94.0 min (*R*); t_R 107.3 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 4.03 (d, 1H, CH, *J*=9.6 Hz), 4.29 (t, 1H, CH, *J*=10 Hz), 4.92 (s, 2H, CH_2), 5.09 (s, 2H, CH_2), 6.28 (dd, 1H, CH=, *J*=24 Hz, *J*=8.4 Hz), 6.40 (d, 1H, CH=, *J*=17 Hz), 7.0-7.4 (m, 20H, CH=).



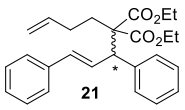
Dimethyl 2-(1,3-diphenylallyl)-2-methylmalonate (19).[31b] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (90% hexane/2-propanol, flow 1 mL/min, λ= 254 nm). t_R 9.9 min (*S*); t_R 12.5 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.48 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 4.29 (d, 1H, CH, *J*=8.8 Hz), 6.46 (d, 1H, CH=, *J*=16 Hz), 6.68 (dd, 1H, CH=, *J*=16 Hz, *J*=8.8 Hz), 7.1-7.4 (m, 10H, CH=).



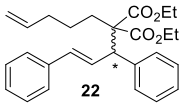
Dimethyl 2-allyl-2-(1,3-diphenylallyl)malonate (20).[47] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 19.4 min (*S*); t_R 26.1 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 2.48 (dd, 1H, CH_2, *J*=14 Hz, *J*=8.8 Hz), 2.67 (dd, 1H, CH_2, *J*=14 Hz, *J*=8 Hz), 3.66 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 4.20(d, 1H, CH, *J*=8.8 Hz), 5.06 (m, 2H, CH_2=), 5.77 (m, 1H, CH=), 6.40 (d, 1H, CH=, *J*=15.6 Hz), 6.77 (dd, 1H, CH=, *J*=16.4 Hz, *J*=8.4 Hz), 7.2-7.4 (m, 10H, CH=).



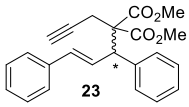
Diethyl 2-(but-3-en-1-yl)-2-(1,3-diphenylallyl)malonate (21). Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (87% hexane/2-propanol, flow 0.15 mL/min, λ= 254 nm). t_R 29.9 min (*S*); t_R 34.2 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.22 (m, 6H, CH_3), 1.97 (m, 2H, CH_2), 2.08 (m, 2H, CH_2), 3.98 (m, 2H, CH_2), 4.17 (m, 3H, CH_2), 4.89 (m, 2H, CH_2=), 5.68 (m, 1H, CH=), 6.32 (d, 1H, CH=, *J*=16.0 Hz), 6.76 (dd, 1H, CH=, *J*=16.0 Hz, *J*=9.2 Hz), 7.1-7.4 (m, 10H, CH=).



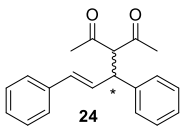
Diethyl 2-(1,3-diphenylallyl)-2-(pent-4-en-1-yl)malonate (22). Enantiomeric excess determined by HPLC using Chiralcel IA column (99% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 12.3 min (*S*); t_R 14.4 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.20 (t, 3H, CH_3, *J*=6.4 Hz), 1.26 (t, 3H, CH_3, *J*=6.4 Hz), 1.31 (m, 1H, CH_2), 1.45 (m, 1H, CH_2), 1.74 (m, 1H, CH_2), 1.86 (m, 1H, CH_2), 1.96 (m, 2H, CH_2), 4.18 (m, 5H, CH_2-O, CH), 4.94 (m, 2H, CH_2=), 5.72 (m, 1H, CH=), 6.36 (d, 1H, CH=, *J*=15.6 Hz), 6.78 (dd, 1H, CH=, *J*=15.6 Hz, *J*=8.8 Hz), 7.1-7.4 (m, 10H, CH=).



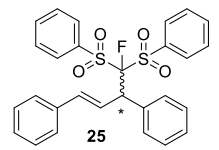
Dimethyl 2-(1,3-diphenylallyl)-2-(prop-2-yn-1-yl)malonate (23). Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (90% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 19.5 min (*S*); t_R 41.7 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 2.13 (m, 1H, CH), 2.64 (dd, 1H, CH_2, *J*=17.2 Hz, *J*=2.4 Hz), 2.82 (dd, 1H, CH_2, *J*=14.2 Hz, *J*=2.8 Hz), 3.71 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 4.45 (d, 1H, CH, *J*=8.4 Hz), 6.46 (d, 1H, d, CH=, *J*=15.6 Hz,), 6.79 (dd, 1H, CH=, *J*=8.4 Hz, *J*=8.4 Hz), 7.31 (m, 10H, CH=).



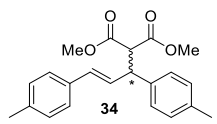
(1,3-Diphenylallyl)pentane-2,4-dienone (24).[47, 48] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (98% hexane/2-propanol, flow 1 mL/min). t_R 53.1 min (*R*); t_R 56.9 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.93 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.34 (m, 2H, CH), 6.20 (dm, 1H, CH=, *J*=15.6 Hz), 6.44 (d, 1H, CH=, *J*=15.6 Hz), 7.1-7.4 (m, 10H, CH=).



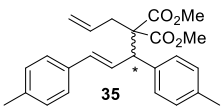
(1-Fluoro-2,4-diphenylbut-3-ene-1,1-diyldisulfonyl)dibenzene (25). [24] Enantiomeric excess determined by HPLC using Chiralcel AD column (90% hexane/2-propanol, flow 1 mL/min). t_R 25.0 min (*S*); t_R 26.2 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 5.10 (m, 1H, CH), 6.32 (m, 1H, CH=), 6.62 (dd, 1H, CH=, *J*=15.6 Hz, *J*=4.0 Hz), 7.10-7.50 (m, 20H, CH=).



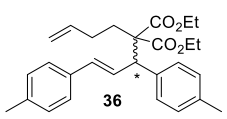
Dimethyl 2-(1,3-di-p-tolylallyl)malonate (34).[50] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (95% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 12.4 min (*S*); t_R 13.3 min (*R*).^{1}H NMR ($CDCl_3$), δ: 2.32 (s, 6H, CH_3), 3.52 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.21 (m, 1H, CH), 6.14 (dd, 1H, CH=, *J*=16.4 Hz, *J*=10 Hz), 6.43 (d, 1H, CH=, *J*=16.4 Hz), 7.10-7.30 (m, 8H, CH=).



Dimethyl 2-allyl-2-(1,3-di-p-tolylallyl)malonate (35).[51] Enantiomeric excess determined by HPLC using Chiralcel IA column (98% hexane/2-propanol, flow 0.2 mL/min, λ= 254 nm). t_R 40.8 min (*S*); t_R 44.0 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 2.47 (s, 6H, CH_3), 2.64 (dd, 1H, CH_2, *J*=14.4 Hz, *J*=8.4 Hz), 2.80 (dd, 1H, CH_2, *J*=14.4 Hz, *J*=6.4 Hz), 3.81 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 5.19 (m, 2H, CH_2=), 5.94 (m, 1H, CH=), 6.50 (d, 1H, CH=, *J*=15.6 Hz), 6.84 (dd, 1H, CH=, *J*=15.6 Hz, *J*=8.8 Hz), 7.25 (m, 6H, CH=), 7.40 (d, 2H, *J*=8.0 Hz).

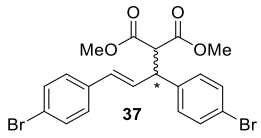


Diethyl 2-(but-3-en-1-yl)-2-(1,3-di-p-tolylallyl)malonate (36).[51] Enantiomeric excess determined by HPLC using Chiralcel IA column (98% hexane/2-propanol, flow 0.2 mL/min, λ= 254 nm). t_R 39.9 min (*S*); t_R 46.6 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.37 (t, 3H, CH_3, *J*=7.2 Hz), 1.43 (t, 3H, CH_3, *J*=7.2 Hz), 1.94 (m, 1H, CH_2), 2.09 (m,

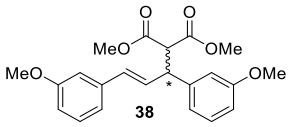


2H, CH_2), 2.25 (m, 1H, CH_2), 2.46 (s, 6H, CH_3), 4.32 (m, 5H, CH, CH_2), 5.06 (m, 1H, CH_2=), 5.18 (m, 1H, CH_2=), 5.86 (m, 1H, CH=), 6.49 (d, 1H, CH=, *J*=12.0 Hz), 6.86 (dd, 1H, CH=, *J*=12.0 Hz, *J*=9.2 Hz), 7.24 (m, 6H, CH=), 7.38 (d, 2H, *J*=8.0 Hz).

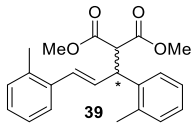
Dimethyl 2-(1,3-di-p-bromophenylallyl)malonate (37).[51] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 34.4 min (*R*); t_R 49.8 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 3.54 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 3.92 (m, 1H, CH), 4.23 (m, 1H, CH), 6.30 (dd, 1H, CH=, *J*=15.6 Hz, *J*=8.4 Hz), 6.44 (d, 1H, CH=, *J*=15.6 Hz), 7.10-7.48 (m, 8H, CH=).



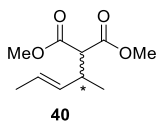
Dimethyl 2-(1,3-di-m-methoxyphenylallyl)malonate (38).[51] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 29.9 min (*R*); t_R 40.5 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 2.29 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 4.08 (d, 1H, CH, *J*=11.6 Hz), 4.58 (m, 1H, CH), 6.03 (dd, 1H, CH=, *J*=15.6 Hz, *J*=8.4 Hz), 6.68 (d, 1H, CH=, *J*=15.6 Hz), 7.10-7.35 (m, 8H, CH=).



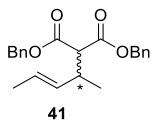
Dimethyl 2-(1,3-di-o-tolylallyl)malonate (39).[51] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 13.2 min (*R*); t_R 18.8 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 3.54 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.96 (d, 1H, CH, *J*=10.8 Hz), 4.24 (m, 1H, CH), 6.31 (dd, 1H, CH=, *J*=16.0 Hz, *J*=8.8 Hz), 6.48 (d, 1H, CH=, *J*=16 Hz), 6.76 (m, 2H, CH=), 6.85 (m, 2H, CH=), 6.90 (m, 2H, CH=), 7.23 (m, 2H, CH=).



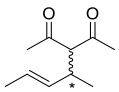
Dimethyl 2-(1,3-dimethylallyl)malonate (40).[31b] Enantiomeric excess determined by GC using Chiralsil-Dex CB column (90 kPa H_2, Isotherm at 65 ºC). t_R 38.6 min (*R*); t_R 39.5 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.03 (d, 3H, CH_3, *J*=6.4 Hz), 1.62 (d, 3H, CH_3, *J*=6.4Hz), 2.88 (m, 1H, CH), 3.25 (d, 1H, CH_3, *J*=9.0 Hz), 3.68 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 5.31 (dd, 1H, CH=,*J*=15.2 Hz, *J*=8 Hz), 5.50 (m, 1H, CH=).



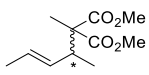
Dibenzyl 2-(1,3-dimethylallyl)malonate (41).[52] Enantiomeric excess determined by HPLC using Chiralcel IA column (98% hexane/2-propanol, flow 0.5 mL/min). t_R 21.9 min (+); t_R 23.4 min (-). ^{1}H NMR ($CDCl_3$), δ: 1.02 (d, 3H, CH_3, *J*=6.4 Hz), 1.53 (d, 3H, CH_3, *J*=6.4 Hz), 2.90 (m, 1H, CH), 3.32 (d, 1H, CH_3, *J*=6.8 Hz), 5.02 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 5.32 (m, 1H, CH=), 5.44 (m, 1H, CH=), 7.2-7.4 (m, 10H, CH=).



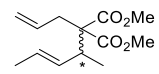
(1,3-Dimethylallyl)pentane-2,4-dienone (42).[22a] Enantiomeric excess determined by GC using Chiradex B-DM column (100 kPa H_2, Isotherm at 60 ºC). t_R 37.2 min (-); t_R 38.0 min (+). ^{1}H NMR ($CDCl_3$), δ: 0.95 (d, 3H, CH_3, *J*=6.4 Hz), 1.61 (d, 3H, CH_3, *J*=5.2 Hz), 2.10 (s, 2H, CH_2), 2.19 (s, 2H, CH_2), 2.97 (m, 1H, CH), 3.54 (d, 1H, CH, *J*=10.4 Hz), 5.19 (dd, 1H, CH=,*J*=15.2 Hz, *J*=10.4 Hz), 5.48 (m, 1H, CH=).


42

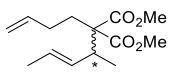
Dimethyl 2-(1,3-dimethylallyl)-2-methylmalonate (43).[53] Enantiomeric excess determined by GC using Chiralsil-Dex CB column (90 kPa H_2, Isotherm at 60 ºC). t_R 69.6 min (-); t_R 71.1 min (+). ^{1}H NMR ($CDCl_3$), δ: 1.01 (d, 3H, CH_3, *J*=8 Hz), 1.32 (s, 3H, CH_3), 1.62 (d, 3H, CH_3, *J*=8 Hz), 2.92 (m, 1H, CH), 3.67 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 5.31 (dd, 1H, CH=,*J*=16 Hz, *J*=8 Hz), 5.47 (m, 1H, CH=).


43

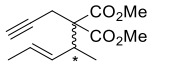
Dimethyl 2-allyl-2-(1,3-dimethylallyl)malonate (44).[22a] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (99.5% hexane/2-propanol, flow 0.5 mL/min). t_R 10.3 min (+); t_R 10.9 min (-). ^{1}H NMR ($CDCl_3$), δ: 1.06 (d, 3H, CH_3, *J*=6.4 Hz), 1.64 (d, 3H, CH_3, *J*=6.8 Hz), 2.59 (m, 2H, CH_2), 2.77 (m, 1H, CH), 3.68 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 5.03 (m, 2H, CH_2=), 5.33 (dd, 1H, CH=, *J*=16.4 Hz, *J*=8.8 Hz), 5.48 (m, 1H, CH=), 5.76 (m, 1H, CH=).


44

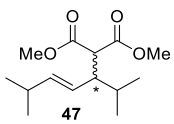
Diethyl 2-(but-3-en-1-yl)-2-(1,3-dimethylallyl)malonate (45).[22a] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (99.5% hexane/2-propanol, flow 0.15 mL/min, λ= 254 nm). t_R 35.3 min (*S*); t_R 37.1 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.02 (d, 3H, CH_3, *J*=6.8 Hz), 1.22 (m, 6H, CH_3), 1.61 (d, 3H, CH_3, *J*=6.4 Hz), 1.86 (m, 2H, CH_2), 1.94 (m, 1H, CH_2), 2.01 (m, 1H, CH_2), 2.75 (m, 1H, CH), 4.14 (m, 4H, CH_2), 4.90 (m, 2H, CH_2=), 5.31 (m, 1H, CH=), 5.45 (m, 1H, CH=), 5.71 (m, 1H, CH=).


45

Dimethyl 2-(1,3-dimethylallyl)-2-(prop-2-yn-1-yl)malonate (46).[54] Enantiomeric excess determined by HPLC using Chiralcel IC column (98% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 13.5 min (*S*); t_R 15.1 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.09 (d, 3H, CH_3, *J*=6.4 Hz), 1.62 (d, 3H, CH_3, *J*=6.4 Hz), 1.98 (m, 1H, CH), 2.74 (m, 2H, CH_2), 2.98 (m, 1H, CH), 3.70 (m, 3H, CH_3), 3.72 (m, 3H, CH_3), 5.25 (m, 1H, CH=), 5.53 (m, 1H, CH=).

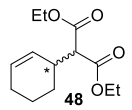

46

Dimethyl 2-(1,3-diisopropylallyl)malonate (47).[31b] Enantiomeric excess determined by ^{1}H-NMR using [Eu(hfc)$_3$] in C_6D_6. ^{1}H NMR ($CDCl_3$), δ: 0.81 (d, 3H, CH_3, *J*=6.8 Hz), 0.87 (d, 3H, CH_3, *J*=6.8 Hz), 0.93 (d, 3H, CH_3, *J*=6.8 Hz), 0.95 (d, 3H, CH_3, *J*=6.8 Hz), 1.69 (m, 1H, CH), 2.25 (m, 1H, CH), 2.58 (m, 1H, CH), 3.51 (d, 1H, CH, *J*=10.0 Hz),


47

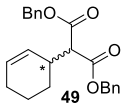
3.66 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 5.23 (dd, 1H, CH=, *J*=15.2 Hz, *J*=10.0 Hz), 5.44 (dd, 1H, CH=, *J*=15.2 Hz, *J*=6.8 Hz).

Diethyl 2-(1,3-cyclohexanylallyl)malonate (48).[22a] Enantiomeric excess determined by HPLC using Chiralpak IC column (98% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 22.4 min (+); t_R 23.5 min (-). ^{1}H NMR ($CDCl_3$), δ: 1.24 (m, 6H, CH_3), 1.36 (m, 1H, CH_2), 1.50 (m, 1H, CH_2), 1.70 (m, 2H, CH_2), 1.96 (m, 2H, CH_2), 2.87 (m, 1H, CH), 3.20 (d, 1H, CH, *J*=9.6 Hz), 4.17 (m, 4H, CH_2), 5.50 (m, 1H, CH=), 5.72 (m, 1H, CH=).



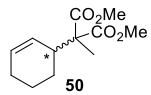
48

Dibenzyl 2-(1,3-cyclohexanylallyl)malonate (49).[22a, 55] Enantiomeric excess determined by HPLC using Chiralpak IA column (90% hexane/2-propanol, flow 0.5 mL/min, λ= 226 nm). t_R 15.1 min (-); t_R 16.3 min (+). ^{1}H NMR ($CDCl_3$), δ: 1.41 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 1.95 (m, 2H, CH_2), 2.96 (m, 1H, CH), 3.40 (d, 1H, CH, *J*=9.6 Hz), 5.15 (s, 4H, CH_2), 5.55 (m, 1H, CH=), 5.75 (m, 1H, CH=), 7.2-7.4 (m, 10H, CH=).



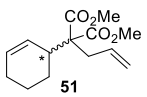
49

Dimethyl 2-(1,3-cyclohexanylallyl)-2-methylmalonate (50). [22a, 56] Enantiomeric excess determined by HPLC using Chiralpak IC column (99.5% hexane/2-propanol, flow 0.5 mL/min, λ= 226 nm). t_R 36.4 min (-); t_R 39.8 min (+). ^{1}H NMR ($CDCl_3$), δ: 1.29 (s, 3H, CH_3), 1.51 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 1.92 (m, 2H, CH_2), 2.99 (m, 1H, CH), 3.68 (s, 6H, CH_3), 5.43 (m, 1H, CH=), 5.74 (m, 1H, CH=).



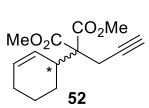
50

Dimethyl 2-allyl-2-(1,3-cyclohexanylallyl)malonate (51). [22a]**¡Error! Marcador no definido.** Enantiomeric excess determined by HPLC using Chiralpak IC column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 226 nm). t_R 15.3 min (-); t_R 17.0 min (+). ^{1}H NMR ($CDCl_3$), δ: 1.49 (m, 2H, CH_2), 1.77 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.86 (m, 1H, CH), 3.65 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 5.06 (m, 2H, CH_2=), 5.71 (m, 3H, CH=).



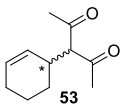
51

Dimethyl 2-propargyl-2-(1,3-cyclohexanylallyl)malonate (52).[22b] Enantiomeric excess determined by GC using Chiraldex β-DM column (90 kPa H_2, 110 ºC, 40 min- 5 ºC/min- 150 ºC). t_R 50.0 min (*S*); t_R 51.2 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.33 (m, 2H, CH_2), 1.52 (m, 1H), 1.77 (m, 2H, CH_2), 1.92 (m, 1H, CH_2), 2.00 (m, 1H, CH), 3.03 (m, 2H, CH_2), 3.09 (m, 1H, CH), 3.68 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 5.67 (m, 1H, CH=), 5.74 (m, 1H, CH=).



52

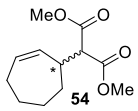
(1,3-cyclohexanylallyl)pentane-2,4-dienone (53).[22a] Enantiomeric excess determined by GC using Chiralsil-Dex CB column (77 kPa H_2, Isotherm at 100 ºC). t_R 21.6 min (-); t_R 22.4 min (+). ^{1}H NMR ($CDCl_3$), δ: 1.48 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.91 (m, 2H, CH_2),2.09 (s, 3H, CH_3),2.12



53

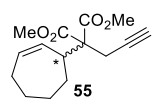
(s, 3H, CH_3), 2.94 (m, 1H, CH), 3.54 (d, 1H, CH, *J*=10.8 Hz), 5.30 (m, 1H, CH=), 5.70 (m, 1H, CH=).

Dimethyl 2-(1,3-cycloheptanylallyl)malonate (54).[31b] Enantiomeric excess determined by GC using Chiralsil-Dex CB column (90 kPa H_2, Isotherm at 110 ºC). t_R 28.8 min (*S*); t_R 29.7 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.33 (m, 1H, CH_2), 1.95 (m, 3H, CH_2), 2.17 (m, 1H, CH_2), 3.05 (m, 1H, CH_2), 3.49 (d, 1H, CH, *J*=8.4 Hz), 3.73 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 5.60 (m, 1H, CH=), 5.84 (m, 1H, CH=).



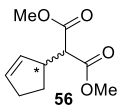
54

Dimethyl 2-propargyl-2-(1,3-cycloheptanylallyl)malonate (55).[22b] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (98% hexane/2-propanol, flow 0.5 mL/min, λ= 226 nm). t_R 11.3 min (*R*); t_R 12.0 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.24 (m, 3H), 1.70 (m, 2H, CH_2), 1.83 (m, 1H, CH_2), 2.03 (m, 2H, CH_2, CH), 2.16 (m, 2H, CH_2), 2.84 (m, 2H, CH_2), 3.18 (m, 1H, CH), 3.74 (s, 6H, CH_3), 5.66 (m, 1H, CH=), 5.84 (m, 1H, CH=).



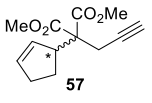
55

Dimethyl 2-(1,3-cyclopentanylallyl)malonate (56).[31b] Enantiomeric excess determined by ^{1}H NMR using [Eu(hfc)$_3$] in C_6D_6. ^{1}H NMR ($CDCl_3$), δ: 1.61 (m, 1H, CH_2), 2.15 (m, 1H, CH_2), 2.35 (m, 2H, CH_2), 3.30 (d, 1H, CH, *J*=9.6 Hz), 3.39 (m, 1H, CH), 3.71 (s, 6H, CH_3), 5.65 (m, 1H, CH=), 5.84 (m, 1H, CH=).



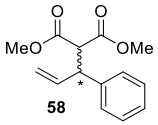
56

Dimethyl 2-propargyl-2-(1,3-cyclopentanylallyl)malonate (57).[22b] Enantiomeric excess determined by GC using Chiraldex β-DM column (90 kPa H_2, Isotherm at 110 ºC). t_R 29.9 min (*R*); t_R 30.9 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.70 (m, 1H, CH_2), 2.07 (m, 2H, CH_2, CH), 2.24 (m, 2H, CH_2), 2.31 (m, 2H, CH_2), 3.61 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 5.74 (m, 1H, CH=), 5.79 (m, 1H, CH=).



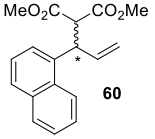
57

Dimethyl 2-(1-phenylallyl)malonate (58).[57] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (87% hexane/2-propanol, flow 0.7 mL/min, λ= 220 nm). t_R 23.2 min (*S*); t_R 25.0 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 3.39 (m, 3H), 3.65 (m, 3H), 3.79 (d, 1H, CH, *J*=10.8 Hz), 4.03 (dd, 1H, CH=, *J*=10.8 Hz, *J*=8.4 Hz), 5.01 (d, 1H, CH=, *J*=10 Hz), 5.04 (d, 1H, CH=, *J*=16.8 Hz), 5.92 (m, 1H, CH=), 7.1-7.3 (m, 5H, CH=).



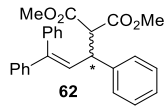
58

Dimethyl 2-(1-(naphthalen-1-yl)allyl)malonate (60).[57] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (87% hexane/2-propanol, flow 0.7 mL/min, λ= 220 nm). t_R 20.1 min (*S*); t_R 28.9 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 3.38 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 4.15 (d, 1H, CH, *J*=10 Hz), 5.03 (dd, 1H, CH, *J*=10.0 Hz, *J*=8.4 Hz), 5.09 (d, 1H, CH=, *J*=10.0 Hz), 5.16 (m, 1H, CH=), 6.08 (m, 1H, CH=), 7.3-8.2 (m, 7H, CH=).



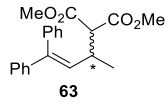
60

Dimethyl 2-(1,1,3-triphenylallyl)malonate (62).[31b] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 13.9 min (*S*); t_R 17.4 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 3.45 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.90 (d, 1H, CH, *J*=10 Hz), 4.22 (m, 1H, CH=), 6.35 (d, 1H, CH, *J*=10 Hz), 7.1-7.4 (m, 15H, CH=).



62

Dimethyl 2-(1,1-diphenylbut-2-en-1-yl)malonate (63).[31b] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 11.1 min (*S*); t_R 14.7 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 0.86 (d, 3H, CH_3, *J*=6.4 Hz), 3.12 (m, 1H, CH), 3.30 (d, 3H, CH, *J*=10 Hz), 3.60 (s, 3H, CH_3), 3.61 (s, 3H, CH_3), 6.01 (d, 1H, CH, *J*=10.4 Hz), 7.2-7.5 (m, 10H, CH=).

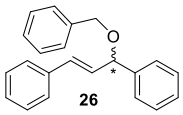


63

4.1.5.6. Typical procedure for the allylic etherification and silylation of substrate S1

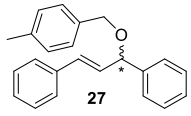
A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand **L3** (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 min, Cs_2CO_3 (122 mg, 0.375 mmol) and the corresponding alkyl alcohol or silanol (0.375 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversion was measured by ^{1}H NMR. HPLC was used to determine enantiomeric excesses of substrates **26**–**33**.

1,3-Diphenyl-3-(benzyloxy)-1-propene (26).[27c] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (98% hexane/2-propanol, flow 0.75 mL/min). t_R 18.2 min (*S*); t_R 21.5 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 4.64 (m, 2H, CH_2), 5.08 (d, 1H, CH, *J*=6.8 Hz), 6.41 (dd, 1H, CH=, *J*=16.0 Hz, *J*=7.2 Hz), 6.68 (d, 1H, CH=, *J*=16.0 Hz), 7.1-7.5 (m, 15H, CH=).



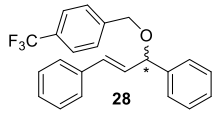
26

1,3-Diphenyl-3-(4-methylbenzyloxy)-1-propene (27).[27c] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (98% hexane/2-propanol, flow 0.75 mL/min). t_R 16.8 min (+); t_R 24.1 min (-). ^{1}H NMR ($CDCl_3$), δ: 2.44 (s, 3H, CH_3), 4.63 (m, 2H, CH_2), 5.08 (d, 1H, CH, *J*=7.2 Hz), 6.43 (dd, 1H, CH=, *J*=16.4 Hz, *J*=7.6 Hz), 6.70 (d, 1H, CH=, *J*=16.0 Hz), 7.1-7.5 (m, 14H, CH=).



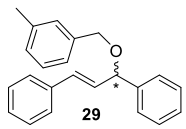
27

1,3-Diphenyl-3-(4-trifluoromethylbenzyloxy)-1-propene (28).[27c] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (96% hexane/2-propanol, flow 0.75 mL/min). t_R 20.8 min (+); t_R 25.2 min (-). ^{1}H NMR ($CDCl_3$), δ: 4.67 (m, 2H, CH_2), 5.06 (d, 1H, CH, *J*=7.6 Hz), 6.39 (dd, 1H, CH=, *J*=16.4 Hz, *J*=7.2 Hz), 6.70 (d, 1H, CH=, *J*=16.0 Hz), 7.1-7.7 (m, 14H, CH=).



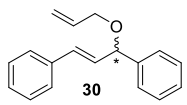
28

1,3-Diphenyl-3-(3-methylbenzyloxy)-1-propene (29).[27c] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (96% hexane/2-propanol, flow 0.75 mL/min). t_R 17.8 min (+); t_R 22.6 min (-). ^{1}H NMR ($CDCl_3$), δ: 2.44 (s, 3H, CH_3), 4.62 (m, 2H, CH_2), 5.09 (d, 1H, CH, *J*=7.2 Hz), 6.42 (dd, 1H, CH=, *J*=16.4 Hz, *J*=7.2 Hz), 6.71 (d, 1H, CH=, *J*=16.0 Hz), 7.2-7.5 (m, 14H, CH=).



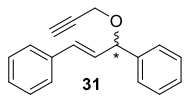
29

1,3-Diphenyl-(E)-3-(allyloxy)-1-propene (30).[27c] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (99.75% hexane/2-propanol, flow 0.25 mL/min). t_R 35.2 min (+); t_R 38.7 min (-). ^{1}H NMR ($CDCl_3$), δ: 4.04 (m, 2H, CH_2), 5.01 (d, 1H, CH, *J*=6.8 Hz), 5.22 (d, 1H, CH_2=, *J*=10.4 Hz), 5.34 (dd, 1H, CH_2=, *J*=17.2 Hz, *J*=2.0 Hz), 6.01 (m, 1H, CH=), 6.33 (dd, 1H, CH=, *J*=16.0 Hz, *J*=7.2 Hz), 6.65 (d, 1H, CH=, *J*=16.4 Hz), 7.2-7.5 (m, 10H, CH=).



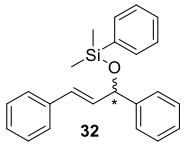
30

(3-(Prop-2-yn-1-yloxy)prop-1-ene-1,3-diyl)dibenzene (31).[49] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (90% hexane/2-propanol, flow 0.5 mL/min). t_R 25.5 min (*S*); t_R 44.0 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 2.44 (t, 1H, CH, *J*=2.4 Hz), 4.18 (m, 2H), 5.20 (d, 1H, CH, *J*=6.8 Hz), 6.28 (dd, 1H, CH=, *J*=6.8 Hz, *J* = 16.0 Hz), 6.65 (d, 1H, CH=, *J*=16.0 Hz), 7.2-7.4 (m, 10H).



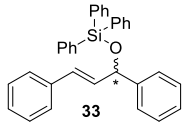
31

((1,3-Diphenylallyl)oxy)dimethyl(phenyl)silane (32).[27d] Enantiomeric excess determined by HPLC using Chiralcel OD-H column after desilylation using TBAF (87% hexane/2-propanol, flow 0.5 mL/min). t_R 20.4 min (*S*); t_R 28.1 min (*R*).^{1}H NMR ($CDCl_3$), δ: 0.51 (s, 3H, CH_3), 0.54 (s, 3H, CH_3), 5.46 (d, 1H, CH, *J*=6.4 Hz), 6.40 (dd, 1H, CH=, *J*=15.4 Hz, *J*=6.4 Hz), 6.65 (d, 1H, CH=, *J*=16.0 Hz), 7.3-7.7 (m, 15H, CH=).



32

((1,3-Diphenylallyl)oxy)triphenylsilane (33).[27d] Enantiomeric excess determined by HPLC using Chiralcel OD-H column after desilylation using TBAF (87% hexane/2-propanol, flow 0.5 mL/min). t_R 20.4 min (*S*); t_R 28.1 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 5.54 (d, 1H, CH, *J*=6.4 Hz), 6.32 (dd, 1H, CH=, *J*=16.0 Hz, *J*=6.4 Hz), 6.43 (d, 1H, CH=, *J*=16.0 Hz), 7.3-7.7 (m, 25H, CH=).



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4.1.6. Acknowledgements

Financial support from the Swedish Research Council (Grant 621-2012-3391), the Spanish Government (CTQ2013-40568P), the Catalan Government (2014SGR670), and the ICREA Foundation (ICREA Academia awards to M. Diéguez and O. Pàmies) is gratefully acknowledged.

4.1.7. References

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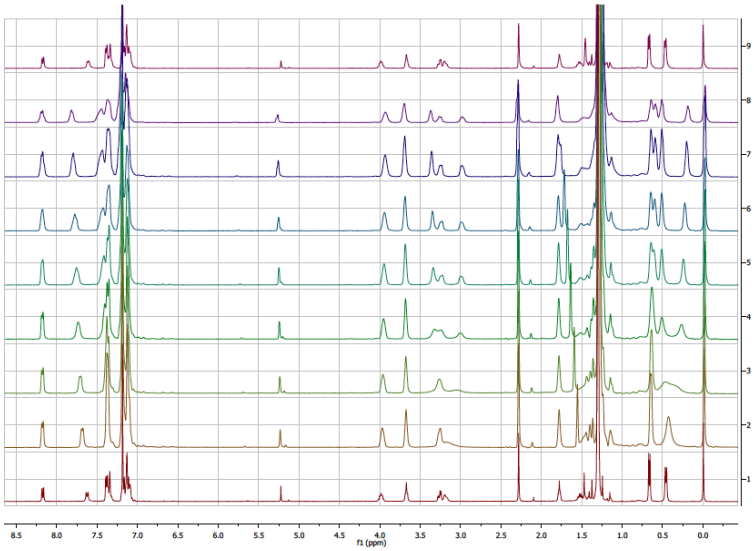
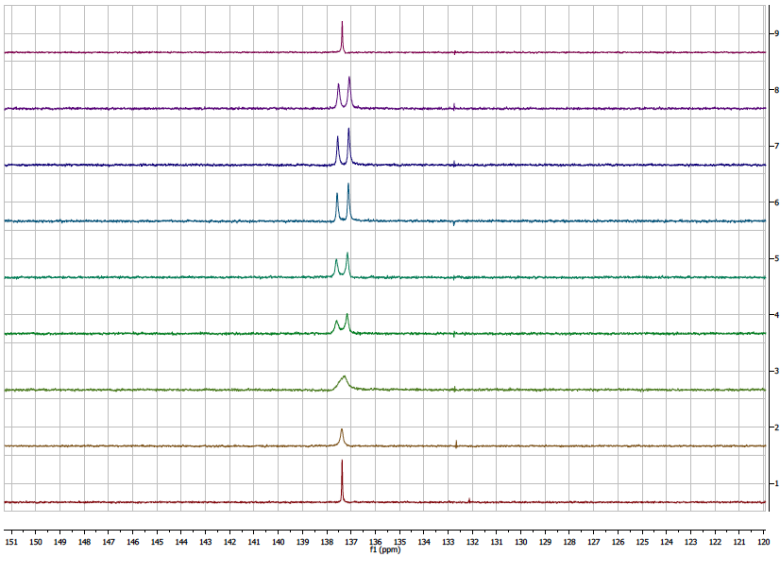
4.1.8. Supporting Information

4.1.8.1. Low temperature NMR spectra of ligand (*S*)-L3a

The low temperature NMR experiment was conducted varying the temperature from 25 °C to -70 °C and then back to 25 °C. **^{1}H NMR of ligand (*S*)-L3a:** Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.

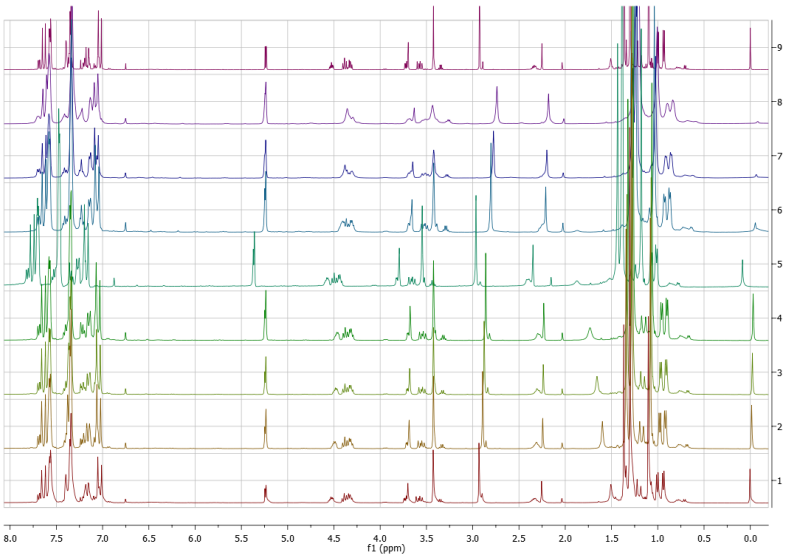


^{31}P{^{1}H} NMR of ligand (*S*)-L3a: Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.



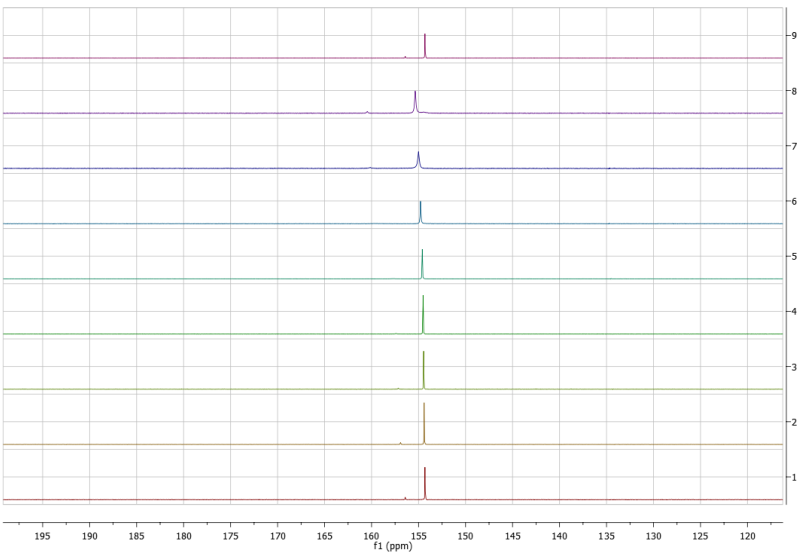
4.1.8.2. Low temperature NMR spectra of [Pd((*S*)-L3a)($C_6H_8O_4$)] complex (11)

The low temperature NMR experiment was conducted varying the temperature from 25 °C to -70 °C and then back to 25 °C. **^{1}H NMR:** Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.



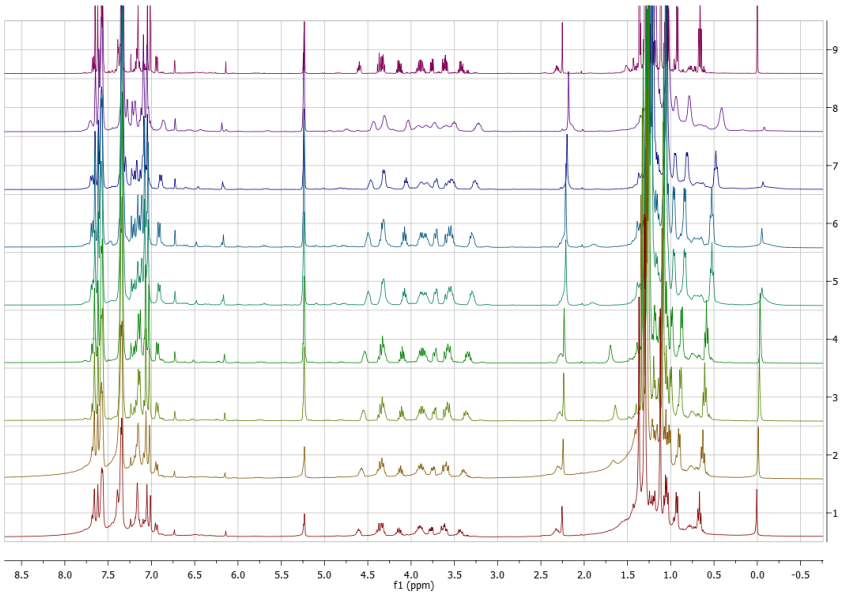
^{31}P{^{1}H} NMR:

Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.

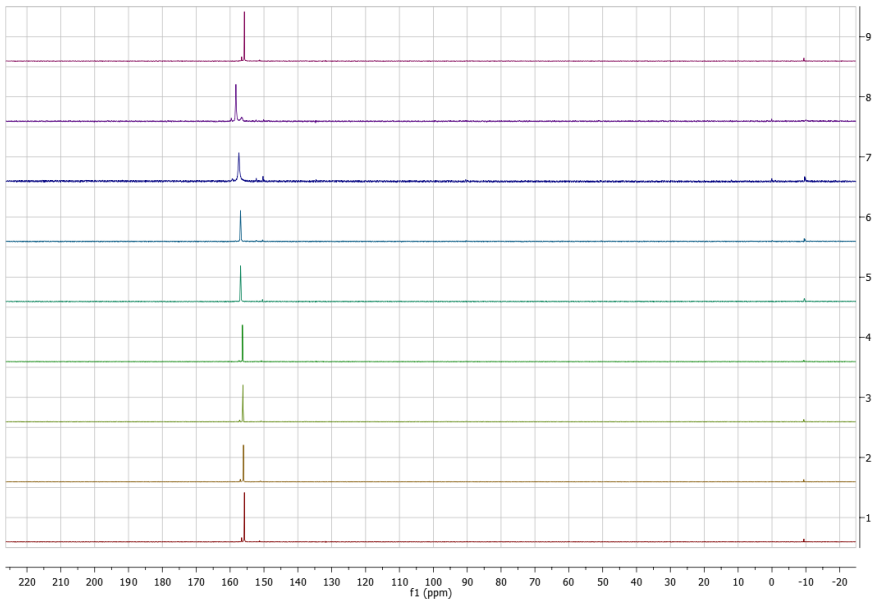


4.1.8.2. Low temperature NMR spectra of [Pd((*S*)-L3a)($C_8H_{14}O_4$)] complex (14)

The low temperature NMR experiment was conducted varying the temperature from 25 °C to -70 °C and then back to 25 °C. **^{1}H NMR:** Spectra: 1 = 25 °C, 2 = 0 °C, 3 = -10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.



^{31}P-{^{1}H} NMR: Spectra: 1 = 25 °C, 2 = 0 °C, 3 = - 10 °C, 4 = - 20 °C, 5 = - 30 °C, 6 = - 40 °C, 7 = - 50 °C, 8 = - 70 °C, 9 = 25 °C.



UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull

4.2. Tailor-made ligands for highly active and enantioselective Pd-catalyzed allylic substitution reactions. Ligands with an exceptionally wide substrate and nucleophile scope

Biosca, M.; Saltó, J.; Magre, M.; Pàmies, O.; Diéguez, M. *Manuscript in preparation.*

Abstract: A library of phosphite-oxazoline PHOX-based ligands containing an alkyl backbone chain has been successfully applied to the Pd-catalyzed allylic substitution reactions. By carefully selecting the ligand components (i.e. substituents at both oxazoline and alkyl backbone chain, as well as the biaryl phosphite group), high activities (TOF > 8000 mol substrate·(mol Pd·h)$^{-1}$) and excellent enantioselectivities have been achieved for hindered and unhindered substrates with a wide range of C-, N- and O-nucleophiles (ee's up to 99%). In addition, the allylic alkylation of monosubstituted substrates also proceeded with a good catalytic performance, achieving good levels of regioselectivities and high enantioselectivities (regio's up to 80% towards the branched product and ee's up to 98%). Moreover, DFT calculations and NMR studies of the key Pd-intermediates allowed us to better understand the origin of the excellent enantioselectivities observed experimentally.

4.2.1. Introduction

Many pharmaceutical, fragrance and crop protection industries rely on enantiomerically pure compounds. The discovery of synthetic routes for their preparation is a recurrent research in chemistry[1] and the Pd-catalyzed asymmetric allylic substitution has been shown to be one of the most powerful approaches. Among its advantages one can point out the mild reaction conditions, the high functional group tolerance and the versatility of the alkene functionality for further functionalization.[1-2] Its main constraint is still that asymmetric induction is highly dependent on the steric demands of the substrate.[2] Most of the best-performing ligands rarely tolerate a broad range of substrates since each type of substrate requires a particular ligand to optimize enantiopurity. In addition, the range of nucleophiles needs to be further expanded to reach more complex chiral compounds. Our group early found that diphosphite and phosphite-phosphoroamidite ligands favor substrate versatility.[3] The adaptability of biaryl phosphite/phosphoroamidite groups enables the catalyst to appropriately fit its chiral pocket to accommodate substrates with different steric requirements. In addition, the π-acceptor capacity of the phosphite/phosphoroamidite moieties has an extremely positive effect on activities, providing higher TOF than the most commonly used diphosphine ligands.[3-4] Encouraged by the excellent enantioselectivities achieved with heterodonor ligands in this process we then moved our efforts to the development of heterodonor ligands containing a biaryl phosphite moiety. In this respect, our group

took one of the most successful ligand families developed for this process, the phosphine-oxazoline PHOX ligand **1** (Figure 4.2.1) and replaced the phosphine moiety with a simple and inexpensive biaryl phosphite group (**L3a**, Figure 4.2.1), which were previously presented in Section 4.1. Whereas Pd-PHOX catalyst **1** gave excellent results with the model *rac*-*E*-1,3-diphenyl-2-propenyl substrate, modest to good results with 1,3-dialkyl-2-propenyl substrates and racemic results for cyclic substrates,[5] the Pd/phosphite-oxazoline analogue **L3** was very successful in all of them (see Section 4.1).[4c,d] **L3** turned to be an unprecedented catalytic system to generate C−C and C−O bonds with high enantiocontrol for a number of hindered and unhindered di- and trisubstituted substrates using a wide range of C- and O-nucleophiles, affording excellent reaction rates (TOF's up to >2400 mol·(mol·h)$^{-1}$. NMR and DFT studies confirmed that the broad substrate scope of this ligand is due to the ability of the ligand to adapt the size of the substrate-binding pocket to the reacting substrate. This ability also explains its excellent performance in other types of catalytic processes.[4d] We also confirmed that the biaryl phosphite moiety facilitated the allylic substitution of challenging monosubstituted substrates. Regioselectivity towards the desired branched isomer in this substrate class increased thanks to the π-acceptor ability of the phosphite moiety, which decreased the electron density of the most substituted allylic terminal carbon atom via the trans influence, thus favoring the nucleophilic attack at this carbon atom. Despite the wide scope of ligands **L3**, there still room of improvement both in terms of substrate and nucleophile scope. Thus, for instance, the catalytic efficiency disclosed for non-symmetrical substrates (e.g. monosubstituted substrates **S14**-**S20**) has to be further enhanced and the nucleophile scope has to be expanded to cover a wide range of aliphatic amines and alcohols. The enantioselectivity in Pd-**L3** catalytic systems using aliphatic alcohols as nucleophiles depends to a large extent on the type of alcohol and slight modifications in its electronic properties lead to important differences in enantioselectivity. The highest enantioselectivity was only obtained if the benzylic alcohol contained an electron-deficient *para*-CF_3 substituent (ee's up to 97%), and the selectivity diminished dramatically if the substituent was more electron rich.

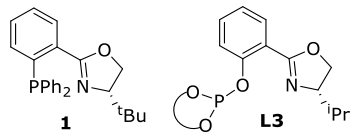


Figure 4.2.1. PHOX-based ligands.

To continue the improvement of Pd-catalysts with readily available ligands, we replaced the *ortho*-phenylene tether in privileged ligands **L3** by an alkyl backbone chain (**L10**-**L16a**-**e**; Figure 4.2.1). With this simple modification, we have extended the number of ligand parameters than can been modified to maximize the catalyst performance. Therefore, in addition to studying different substituents and configurations

in the oxazoline and phosphite groups we also studied the effect of a new stereogenic center in the alkyl backbone chain and the effect of varying the substituents in the alkyl backbone chain. We also showed that these new Pd/**L10**-**L16a**-**e** catalytic systems can be used in the synthesis of chiral carbo– and heterocyclic compounds using straightforward sequences allylic substitution/cycloisomerization or allylic substitution/Pauson-Khand reactions. Finally, we used DFT calculations and the study of the key Pd-π-allyl intermediates to explain the origin of enantioselectivity.

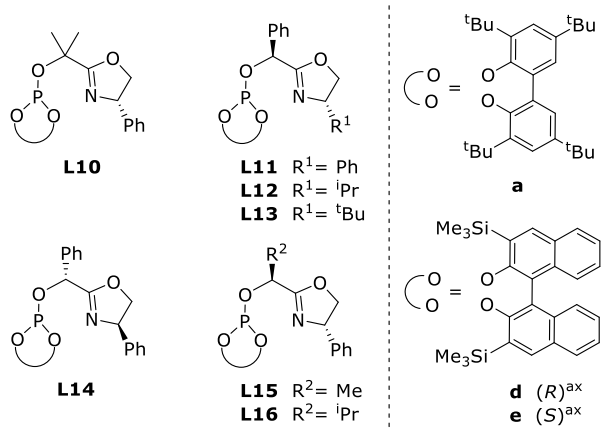


Figure 4.2.2. Phosphite-oxazoline ligands **L10**-**L16a**-**e**.

4.2.2. Results and Discussion

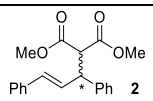
4.2.2.1. Allylic substitution of disubstituted substrates S1-S2 using dimethyl malonate as nucleophile

The effectiveness of the novel phosphite-oxazoline ligands **L10**-**L16a**-**e** was first studied in the Pd-allylic alkylation of two model substrates with different steric properties, *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** and *rac*-3-acetoxycyclohexene **S2**. For comparison we used the same optimal reaction conditions found in our previous study with related Pd/PHOX-based phosphite-oxazoline catalysts (Pd/**L3**). The reactions were therefore performed at room temperature, using 0.5 mol% of *in situ* generated catalyst, from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the corresponding ligand, using dimethyl malonate as nucleophile. It should be noted, that the enantioselectivity for cyclic **S2** is more difficult to control than for **S1** due to the presence of less bulky *anti* substituents.[2] However, by carefully selecting the ligand components, we have been able to identify two particular ligands, **L10e** and **L15e**, that performs exceptionally well for both substrate types, with enantioselectivities up to 99% ee and TOF's up to 8640 mol substrate·(mol Pd·h)$^{-1}$. The results (Table 4.2.1) indicated that enantioselectivities are affected by the substituents at both the oxazoline and at the alkyl backbone chain as well as by the biaryl phosphite groups. However, the effect of these parameters on

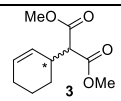
enantioselectivity is different for both substrates. While for substrate **S1** the best enantioselectivities were achieved with ligands **L15a** and **L15e** (ee's up to 99%), for substrate **S2** ligand **L10e** provided the best selectivity (ee's up to 99%).

The results with ligands **L10a**,**d**-**e**, with an achiral alkyl backbone chain (entries 1-3), indicated that the ligand backbone is only able to control the tropoisomerization of the biphenyl phosphite moiety (**a**) for substrate **S1**. While high enantioselectivities are achieved with ligands **L10a** and **L10e** for substrate **S1** (96% ee, entries 1 and 3), the use of ligand **L10e** with an enantiopure (*S*)-biaryl phosphite group is necessary to maximize enantioselectivities for substrate **S2** (99% ee, entry 3 vs 1 and 2). The same behavior is found with ligands **L11**-**L16** that differ from **L10** in that they contain a substituent at the alkyl backbone chain that generates a new chiral center.

Table 4.2.1. Asymmetric Pd-catalyzed allylic alkylation of substrates **S1** and **S2** using phosphite-oxazoline ligands **L10**-**L16a**-**e**.[a]



2



3

Entry	Ligand	% Conv[b]	% ee[c]	% Conv[d]	% ee[e]
1	**L10a**	100	96 (*S*)	100	60 (*S*)
2	**L10d**	100	86 (*S*)	100	78 (*R*)
3	**L10e**	100	96 (*S*)	100	99 (*S*)
4	**L11a**	100	93 (*S*)	100	40 (*S*)
5	**L11d**	100	40 (*S*)	100	74 (*R*)
6	**L11e**	100	90 (*S*)	100	90 (*S*)
7	**L12a**	100	92 (*S*)	100	7 (*S*)
8	**L13a**	100	73 (*S*)	100	4 (*S*)
9	**L14a**	100	90 (*R*)	100	20 (*R*)
10	**L14d**	100	94 (*R*)	100	81 (*R*)
11	**L14e**	100	55 (*R*)	100	77 (*S*)
12	**L15a**	100	97 (*S*)	100	44 (*S*)
13	**L15d**	100	89 (*S*)	100	65 (*R*)
14	**L15e**	100	99 (*S*)	100	96 (*S*)
15	**L16a**	100	84 (*S*)	100	33 (*S*)
16	**L16d**	100	91 (*S*)	100	60 (*R*)
17	**L16e**	100	90 (*S*)	100	97 (*S*)
18[f]	**L15e**	72	99 (*S*)	41	96 (*S*)

[a] Reaction conditions: 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch); [b] Conversion percentage determined by ^{1}H-NMR after 10 min; [c] Enantiomeric excesses determined by HPLC. Absolute configuration drawn in parentheses; [d] Conversion percentage determined by GC after 30 min; [e] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses; [f] Reactions carried for 5 min using 0.1 mol% of catalyst precursor.

The results with ligands **L11**-**L13a**, also indicated that enantioselectivities are dependent on the oxazoline substituent. In contrast to the phosphine-oxazoline PHOX ligands **1** the presence of bulky substituents has a negative effect on enantioselectivity (entries 7-8). Thus, the highest enantioselectivities for both substrates were achieved using ligand **L11e**, containing a phenyl oxazoline substituent (entry 4). This represents an important advantage over the traditional phosphine-oxazoline PHOX ligands **1** because enantiopure phenylglycinol (used for the synthesis of **L11**) is much cheaper than *tert*-leucinol used for the synthesis of PHOX ligands **1**.

The results comparing the use of diasteriomeric ligands **L11d-e** and **L14d-e** indicated that there is a cooperative effect between the configuration of the biaryl phosphite group and the configuration of the oxazoline substituent. This resulted in a matched combination for ligands **L11e** and **L14d** (entries 6 and 10). In addition, while for linear substrate **S1** the sense of enantioselectivity is controlled by the configuration of the oxazoline substituent (ligands **L11** provide the opposite enantiomer of alkylated products than ligands **L14**; entries 4-6 vs 9-11), for the cyclic substrate **S2** it is controlled by the configuration of the biaryl phosphite (ligands **L11d** and **L14d** provides the opposite enantiomers than ligands **L11e** and **L14e**). Both enantiomers of the products can be therefore obtained by simple selecting the correct combination of ligand parameters.

Finally, the effect of the substituent at the alkyl chain was studied using ligands **L10**, **L11**, **L15** and **L16**. The best enantioselectivities were achieved with ligands **L10** (for **S2**) and **L15** (for **S1**) containing two or one methyl group at the alkyl backbone chain, respectively.

In summary, the enantioselectivities with Pd/**L10e** and Pd/**L15a**,**e** are excellent and similar to the ones with previous Pd/PHOX-based phosphite-oxazoline catalysts (Pd/**L3**), which have recently emerged as one of the most successful catalysts designed for this process, with the added advantage that the activity is much higher (TOF's up to >8640 mol substrate·(mol Pd·h)$^{-1}$ for Pd/**L15e** vs >2400 mol substrate·(mol Pd·h)$^{-1}$ for previous Pd/**L** catalysts). In addition, the phosphite-oxazoline ligands that provided the best selectivities contained the Ph substituent in the oxazoline moiety instead of the expensive ^{t}Bu substituent found in the PHOX phosphine-oxazoline **1**.

4.2.2.2. Substrate and nucleophile scope

4.2.2.2.1. Allylic substitution of other disubstituted linear and cyclic substrates with other nucleophiles. Scope and limitations

We further studied the performance of **L10**-**L16a**-**e** in the allylic substitution of other linear and cyclic disubstituted substrates with different electronic and steric properties. The range of nucleophiles was also extended with special attention to the more

challenging and appealing from a synthetic point of view, such as several functionalized malonates, β-diketones, 2-cyanoacetates, amines, pyrroles and alkyl alcohols.

In a first set of experiments we used the Pd-catalyzed allylic substitution of **S1** to study the nucleophile scope using ligand **L15e**, which had provided the best results in the allylic alkylation of **S1** with dimethyl malonate. The results, which are shown in Figure 4.2.3, indicated that a wide range C-, N- and O-nucleophiles could be efficiently used for this transformation. Numerous malonates, including those substituted with allyl-, butenyl-, pentenyl- and propargyl-groups, reacted with **S1** to provide the alkylated products **4**-**10** in excellent yields and enantioselectivities (ee's ≥99%). These results are important because the resulting products (**4**-**10**) are crucial intermediates for preparing more complex chiral compounds (see section 4.2.2.2.3 below). The use of malononitrile (compound **11**) and acetylacetone (compound **13**) also afforded the desired alkylated products in excellent enantioselectivities (>99% ee). Similarly to previous reports, the use of isopropyl cyanoacetate (compound **12**) as nucleophile resulted in the formation of two diastereoisomers,[6] albeit both diastereoisomers were obtained in almost perfect enantiopurity (ee's up to 99%).

The scope was then extended to the use of pyrroles as nucleophiles (Figure 4.2.3, compounds **14** and **15**). Only two studies have reported the successful use of pyrroles in this reaction, however one of these reports required low temperature (-20 °C) to achieved high ee.[7] The difficulty of this reaction is more evident if we consider that, even two of the most successful ligands developed for this process (Trost diphosphine and PHOX **1**), did not work with pyrroles. We were pleased to see that we could reach ee's up to 99% and high yield working at room temperature. These are important results because pyrroles are present in many relevant compounds with biological and synthetic applications.[8]

The reaction also worked well when the nucleophiles were amines. The use of a broad range of primary and secondary amines (aryl-, alkyl-, allyl- and propargyl-substituted amines) provided products **16**-**27** in high yields and enantioselectivities comparable to those achieved with C-nucleophiles. Therefore, several benzylic amines, including the addition of the furfurylamine, afforded the substitution products **16**-**19** in excellent enantioselectivity (>99% ee). Enantiocontrol was also excellent in the addition of alkyl primary amines (products **20**-**21**) and cyclic secondary amines (products **22**-**23**). Gratifyingly, Pd/**L15e** was also successfully applied in the addition of sulfonamide and aromatic amines (products **24** and **25**, ee up to >99%). Finally, enantioselectivities up to 98% with high yields were also found using allyl- and propargyl-substituted amines (compounds **26** and **27**, respectively).

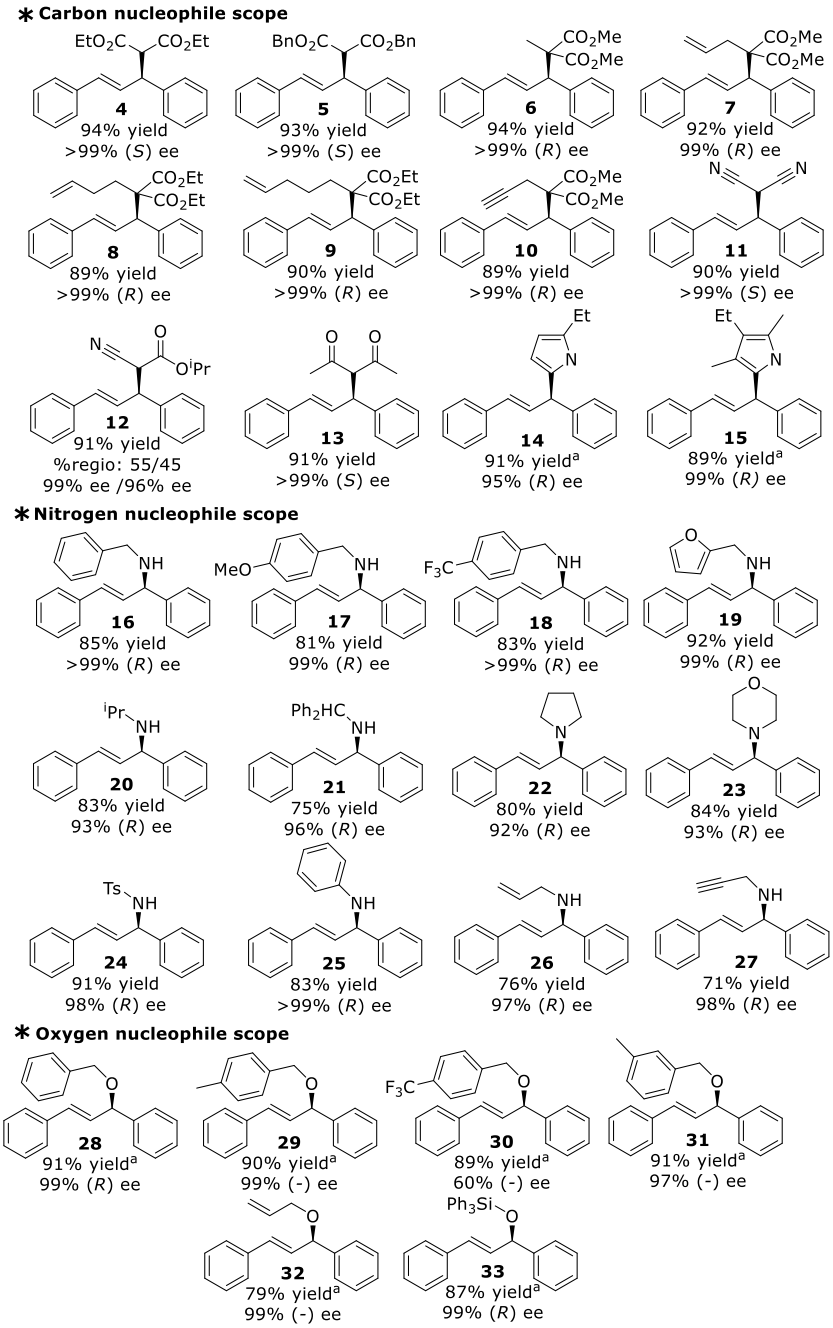
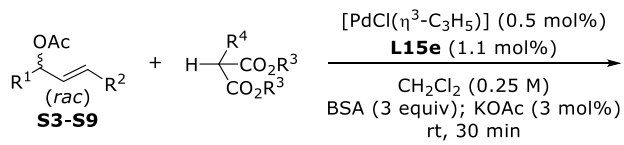


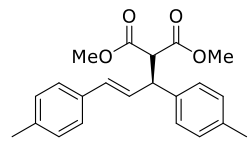
Figure 4.2.3. Allylic substitution of **S1** with C-, N- and O-nucleophiles using Pd-**L15e** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after 2 h. [a] Reactions carried out using 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand, and Cs_2CO_3 (3 equiv). Full conversions were achieved after 18 h.

The excellent enantioselectivity also extends to the addition of several O-nucleophiles (Figure 4.2.3, compounds **28**-**33**) with a catalytic performance as high as those obtained with dimethyl malonate. Aliphatic alcohols are another relevant set of nucleophiles because the resulting chiral ethers are found in biologically active targets.[9,10] Despite the addition of aliphatic alcohols is currently studied by many groups, few successful examples have been accounted. In addition, the enantioselectivity is influenced by the type of aliphatic alcohol and its value can vary largely by modification of its electronic properties. In this respect, for previous phosphite-oxazoline PHOX systems **L3** the highest enantioselectivity was only obtained if the benzylic alcohol contained an electron-deficient *para*-CF_3 substituent (ee's up to 97%), and the selectivity diminished dramatically if the substituent was more electron rich. Improving these previous results, with Pd/**L15e** catalyst high enantioselectivities were achieved in the substitution of a broad range of benzylic alcohols with different steric and electronic properties of the aryl group (compounds **28**-**31**, ee's up to 99%). The only exception was compound **30** containing an electron-deficient *para*-CF_3 substituent that led to lower enantioselectivity. Also excellent enantioselectivities (up to 99% ee) were achieved to the addition of much less studied allylic alcohol (compound **32**) and the triphenylsilanol (compound **33**).[11]

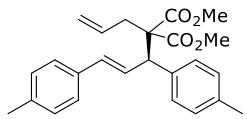
We then study other symmetrical disubstituted linear substrates **S3**-**S8** (Table 4.2.2) with electronic and steric requirements different from those of **S1** using Pd/**L15e** catalytic system. The results, which are collected in Table 4.2.2, indicated that Pd/**L15e** can also be used for the alkylation of substrates **S3**–**S6**, with different substituents in the aryl groups, even with highly appealing nucleophiles such as malonates substituted with allyl, pentenyl and propargyl groups, with yields and enantioselectivities comparable to those of **S1** (compounds **34**-**40**, ee's ≥99%). Interestingly, Pd/**L15e** can also successfully adapt its chiral pocket in the alkylation of the much less sterically demanding substrate **S7** (compounds **41** and **42**), even using propargyl malonate as nucleophile for which only very few catalytic systems have provided high enantioselectivity. These results are among the best reported in the literature for this challenging unhindered substrate and comparable of those achieved using phosphite-oxazoline PHOX-ligands **L3**. A remarkable enantioselectivity was still achieved in the Pd-catalyzed allylic alkylation of **S8**, a much more sterically demanding substrate than **S1**, that typically gives rise to the corresponding substitution products in much lower enantioselectivities.

Table 4.2.2. Allylic substitution of **S3-S9** with C-nucleophiles using Pd-**L15e** catalytic system.[a]

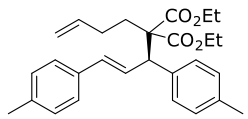




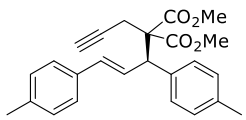
34
91% yield
>99% (*S*) ee



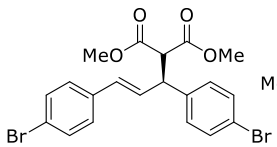
35
92% yield
>99% (*R*) ee



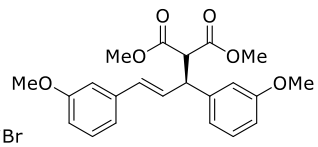
36
88% yield
>99% (*R*) ee



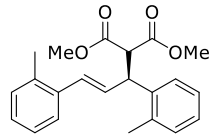
37
90% yield
99% (*R*) ee



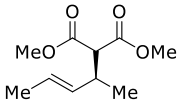
38
89% yield
>99% (*S*) ee



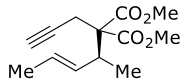
39
86% yield
>99% (*S*) ee



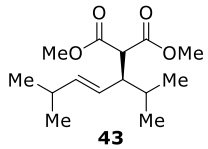
40
87% yield
>99% (*S*) ee



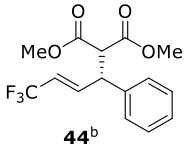
41
86% yield
82% (*S*) ee



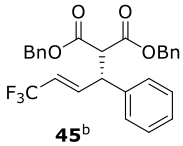
42
87% yield
83% (*S*) ee



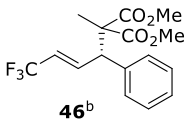
43
86% yield
>95% (*S*) ee



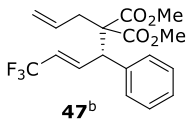
44[b]
72% yield
76% (*R*) ee



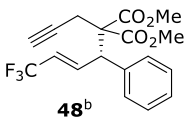
45[b]
62% yield
78% (*R*) ee



46[b]
43% yield
80% (*R*) ee



47[b]
47% yield
77% (*R*) ee



48[b]
46 % yield
73% (*R*) ee

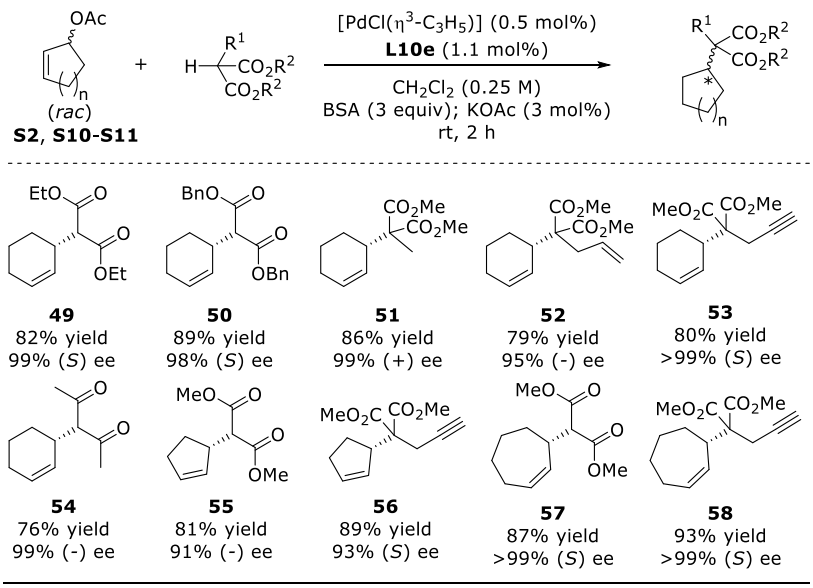
[a] Reaction conditions: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc, rt. Full conversions were achieved after 2 h (except for reactions using substrates **S6** and **S7** that were run for 12 h); [b] Complete regioselectivity towards the nucleophilic attack at carbon next to the aryl group was obtained.

Next, we focused our attention in the allylic allylation of a more challenging class of substrates - the unsymmetrical 1,3-disubstituted ones. The allylic substitution of such substrates has been much less developed than the symmetrical ones, because a mixture of regioisomers can be reached.[2] Among all the unsymmetrical disubstituted linear substrates, we focused on the use of CF_3-group-substituted substrate **S9**. The asymmetric allylic substitution of such substrates has been overlooked,[12] albeit its

substitution products give rise to interesting compounds that can be used in the medicinal and agrochemical fields.[13] We were pleased to see that promising enantioselectivities up to 80% ee were achieved using the *rac*-**S9** and different C-nucleophiles (compounds **44**-**48**). The result obtained using propargyl malonate as nucleophile (compound **48**) is also interesting due to this alkylated product is a relevant intermediate in the synthesis of more complex frameworks (see section 4.2.2.2.3 below).

Encouraged by the previous results, we then turned our attention to the allylic substitution of a more challenging class of substrates – the cyclic ones. A number of cyclic substrates with different ring sizes (**S2**, **S10** and **S11**) were tested using ligand **L10e** which had provided the best results in the allylic alkylation of model cyclic substrate **S2** with dimethyl malonate (see Table 4.2.1 above). The results, which are shown in Table 4.2.3, indicated that high yields and excellent enantioselectivities (ee's from 95% to >99%) could be achieved in the allylic alkylation of **S2** using a wide range of C-nucleophiles, including the less studied α-functionalized malonates and acetylacetone (compounds **49**-**54**).

Table 4.2.3. Asymmetric Pd-catalyzed allylic alkylation of substrates **S2**, **S10** and **S11** with C-nucleophiles using Pd/**L10e** catalytic system.[a]

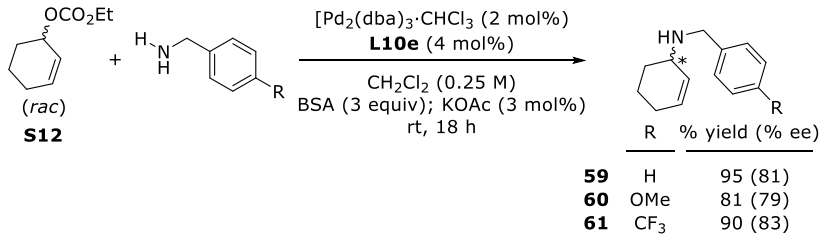


[a] Reaction conditions: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc, rt. Full conversions were achieved after 2 h.

Pd/**L10e** is also able to efficiently catalyze the alkylation of cyclic substrates **S10** and **S11** (compounds **55**-**58**; ee's up to >99%). High enantioselectivities were therefore obtained in both cases, even with **S10**, which usually provides products with much lower

enantioselectivities than cyclic **S2**. These results are among the best in the literature for these substrates, even with synthetically useful nucleophiles other than dimethyl malonate (see section 4.2.2.2.3 below), for which only Pd/**L3** catalytic systems have provided such high enantioselectivities.

The satisfactory results obtained with C-nucleophiles led us to turn our attention to asymmetric allylic amination of this class of substrates with different benzylic amines (Scheme 4.2.1). Compared to amination reactions involving benchmark linear substrate **S1**, cyclic substrates have proven to be a more challenging issue.[4b,14] Thus, the allylic amination of cyclic substrates has been less studied and in general provide low enantioselectivities. Pd-**L10e** catalytic system also proved to be well suited for the allylic amination of this substrate class albeit the enantioselectivities obtained were somewhat lower than those obtained with C-nucleophiles. The results indicated that enantioselectivity is not affected by the electronic nature of the group at the *para*-position of the aromatic ring.



Scheme 4.2.1. Pd-catalyzed allylic aminations of cyclic substrate **S12** using ligand **L10e**.

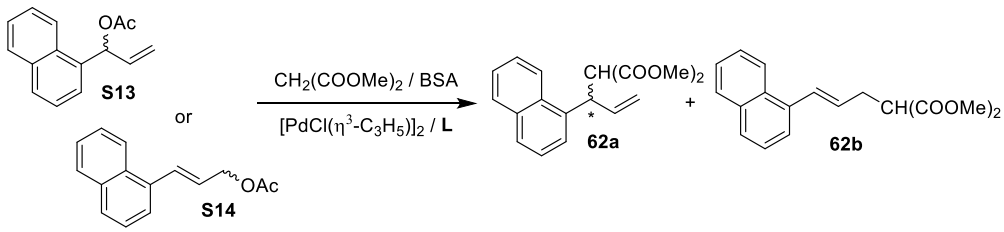
4.2.2.2.2. Allylic substitution of monosubstituted substrates S13-S21

Finally, we investigated whether the high catalytic performance achieved in the allylic substitution of disubstituted substrates could be retained for the notoriously difficult monosubstituted ones. The challenge in these substrates is that both enantioselectivity and regioselectivity need to be controlled. Most Pd-catalysts favor the formation of the undesired achiral linear product. The development of highly regio- and enantioselective Pd-catalysts is therefore still an important issue.[15] In our previous study with Pd/**L3** we obtained excellent regioselectivities, comparable to the best values reported, and high enantioselectivities (ee's up to 92%).

Initially, we explored the allylic alkylation of **S13** to study the effect of the ligand parameters (**L10**-**L16a**-**e**) on the catalytic performance. We use the same optimal reaction conditions found in our previous study with related Pd/PHOX-based phosphite-oxazoline catalysts (Pd/**L3**). The results are collected in Table 4.2.4. Regioselectivity was found to hardly depend on the ligand structure. High regioselectivities (up to 80%) towards the desired branched products were achieved. Concerning enantioselectivities, while the effect of the configuration/substituents at both the oxazoline and the biaryl phosphite groups is similar to the effect in the alkylation of **S1**, the effect of the

substituent at the alkyl backbone chain is different. Therefore, enantioselectivities were better with ligand **L16e**, containing an isopropyl group at the alkyl backbone chain (ee's up to 98%; entry 12). As for substrate **S1**, the sense of enantioselectivity is dictated by the configuration of the oxazoline substituent (entries 4-6 vs 7-9) and there is cooperative effect between the configurations of the biaryl phosphite group and oxazoline substituent, that results again in a matched combination for ligands containing either an (*S*)-configurated biaryl phosphite group and oxazoline substituent (i.e ligand **L11e**; entry 6) or (*R*)-configurated phosphite and oxazoline moieties (i.e. ligand **L14d**; entry 7). It should be pointed out that both matched combinations led to opposite enantiomers of the substitution products.

Table 4.2.4. Selected results for the regio- and enantioselective Pd-catalyzed allylic substitution of monosubstituted substrate **S13**-**S14**.[a]



Entry	Ligand	% Conv[b] (%yield)	% branched[c]	% ee[d]
1	**L10a**	100 (88)	55	60 (*S*)
2	**L10d**	100 (89)	55	34 (*S*)
3	**L10e**	100 (88)	60	84 (*S*)
4	**L11a**	100 (91)	50	59 (*S*)
5	**L11d**	100 (89)	65	30 (*S*)
6	**L11e**	100 (90)	50	88 (*S*)
7	**L14a**	100 (89)	55	43 (*R*)
8	**L14d**	100 (88)	65	84 (*R*)
9	**L14e**	100 (91)	40	42 (*R*)
10	**L15e**	100 (90)	40	89 (*S*)
11	**L16e**	100 (88)	65	94 (*S*)
12[e]	**L16e**	100 (91)	80	98 (*S*)
13[e,f]	**L16e**	100 (92)	80	98 (*S*)

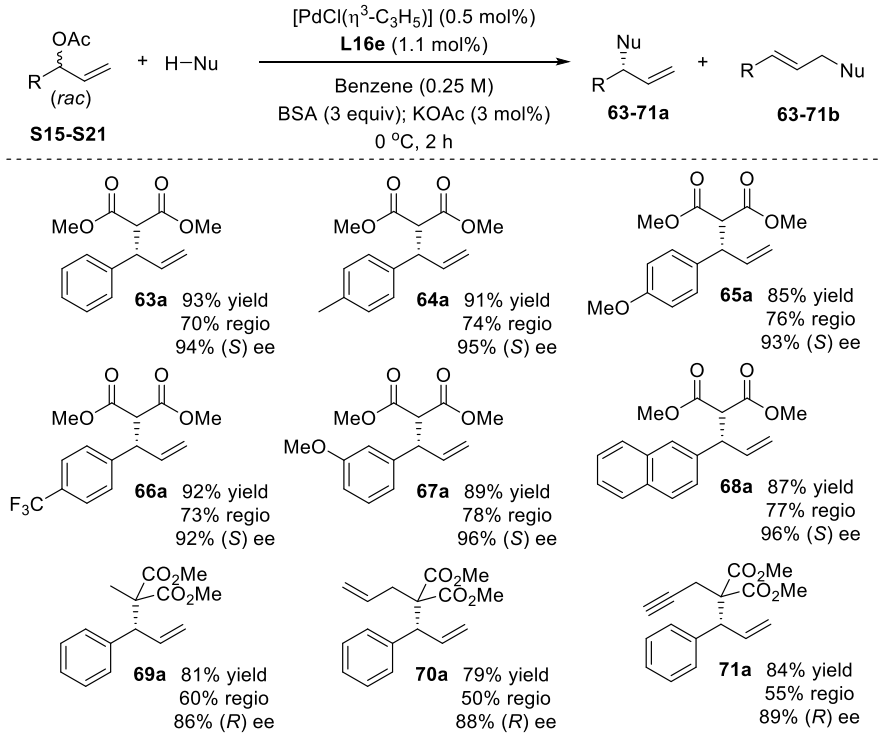
[a] Reaction conditions: 1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2.2 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base; [b] % Conversion measured after 30 min. Isolated yield shown in parenthesis; [c] Regioselectivity measured by ^1H NMR; [d] Enantiomeric excesses determined by chiral HPLC; [e] Reaction carried out in benzene at 0 °C for 2 h; [f] Reaction carried out using 1-(1-naphthyl)-3-acetoxyprop-1-ene **S14**.

Next, we carried out the allylic alkylation of monosubstituted substrate **S14** in order to see if the regiochemical information of the substrate is transferred to the product

(entry 13).[16] No memory effect was observed since independently of the substrate employed the level of regioselectivity is maintained (entry 12 vs 13).

With the optimal ligand, the Pd-catalyzed allylic substitution of several monosubstituted substrates with different steric and electronic properties using dimethyl malonate as nucleophile was studied. The results, presented in Table 4.2.5, showed that enantioselectivities were only slightly affected by the type or the substitution pattern of the substituent of the aryl group. Therefore, high enantioselectivities and promising regioselectivities were obtained in substrates bearing either an electron-donating group or electron-withdrawing group on the aromatic ring (**63a**-**68a**). The good performance in terms of regioselectivity was not retained with the use of other C-nucleophiles, however the asymmetric induction was maintained (**69a**-**71a**).

Table 4.2.5. Results for the regio- and enantioselective Pd-catalyzed allylic substitution of monosubstituted substrates **S15-S21** with ligand **L16e**.[a]

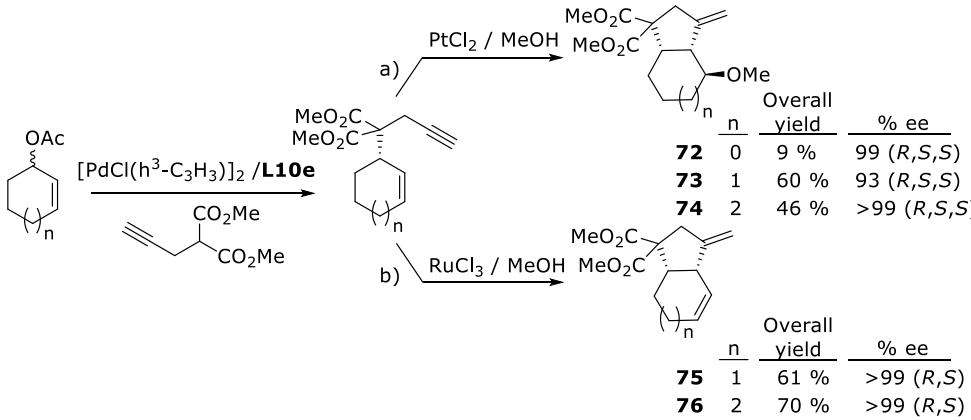


[a] Reaction conditions: 1 mol % $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2.2 mol % ligand, CH_2Cl_2 as solvent, BSA/KOAc as base. Regioselectivity measured by ^1H NMR and enantiomeric excesses determined by chiral HPLC.

4.2.2.2.3. Synthetic applications of the allylic substitution products

Compounds **2**, **44**, **53**, **56**, **58** and **63a** obtained through the Pd-catalyzed allylic substitution using nucleophiles with a propargyl group, are good starting points for the preparation of more complex chiral molecules. In this sense, we prepared a range of chiral carbobicycles (**72**-**76**) and bicyclopentenones (**77**-**80**) with multiple stereocentres from the enantioenriched allylic substitution products. These compounds have been synthesized by tandem reactions involving allylic substitution of the appropriate substrates followed by either 1,6-enyne cyclization (Scheme 4.2.2) or Pauson−Khand enyne cyclization (Scheme 4.2.3).

With the first sequence of reactions several carbocycles were prepared (Scheme 4.2.2). The cyclization of propargylated derivatives **53**, **56** and **58**, which differ only in the size of the cycloalkane ring, was carried out using two different methodologies. Depending on the catalyst employed, the bicycle formed is different. While with the use of $PtCl_2$/MeOH leads to the formation of bicycles with insertion of methanol in the double bond (Scheme 4.2.2a),[17] the use of $RuCl_3$/MeOH give rise to the formation of the bicycle with the double bond intact (Scheme 4.2.2b)[18]. All bicycles were obtained in good yields, except for the most sterically constrained compound **72**, and high enantioselectivities thus, the ee value of the first asymmetric allylic alkylation reaction was maintained during the second cyclization reaction.

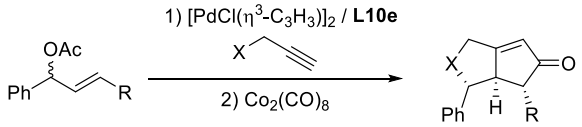


	n	Overall yield	% ee
72	0	9 %	99 (*R*,*S*,*S*)
73	1	60 %	93 (*R*,*S*,*S*)
74	2	46 %	>99 (*R*,*S*,*S*)

	n	Overall yield	% ee
75	1	61 %	>99 (*R*,*S*)
76	2	70 %	>99 (*R*,*S*)

Scheme 4.2.2. Preparation of chiral carbobicycles compounds **72**-**76**.

The second tandem reaction, which consist in the allylic alkylation/Pauson-Khand reaction, allows us to synthetize three different bicyclopentenones in good yields (**77**-**79**, Scheme 4.2.3). The enantiomeric purity of the product depends upon the optical purity of the propargylated product, which was obtained by the Pd-catalyzed allylic substitution reaction. This methodology was not affected by the substituents of the substrate employed (**77-79**).



	R	X	Overall yield	% ee
77	Ph	$CH(CO_2Me)_2$	62 %	99 (*R*,*R*,*S*)
78	CF_3	$CH(CO_2Me)_2$	28 %	73 (*R*,*R*,*R*)
79	H	$CH(CO_2Me)_2$	41 %	89 (*R*,*S*)

Scheme 4.2.3. Preparation of chiral bicyclopentenone compounds **77**-**79**.

4.2.2.3. Origin of enantioselectivity

4.2.2.3.1. DFT-computational studies

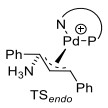
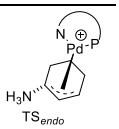
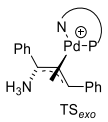
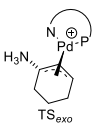
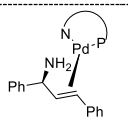
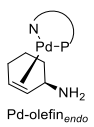
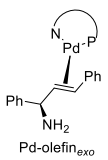
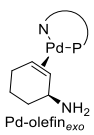
Initially, we performed a DFT computational study of the key intermediates and transition states involved in the enantiocontrol of the Pd-catalyzed allylic substitution of hindered substrate **S1** and the unhindered substrate **S2** with ligands **L10d**, **L10e** and **L15e**. We chosen these ligands to evaluate the observed effect on enantioselectivity of varying the configuration of the biaryl phosphite moiety (ligands **L10d** and **L10e**) as well as the effect of having a chiral center in the alkyl backbone chain (ligand **L15e**). Previous reported mechanistic studies, have found that enantioselectivity is controlled in the nucleophilic attack, but transition state (TS) for this step can be either early or late. In an early TS, enantioselectivity is mainly governed by the relative electrophilicity of the allylic carbon atoms, with an allyl terminus *trans* to a P atom being more reactive than one *trans* to the oxazoline group.[19] For the late TS the enantioselectivity is controlled by the formation of the most stable Pd-olefin complex.[20] Reported studies have found that to accelerate DFT calculations ammonia can be used instead of dimethyl malonate as a good model nucleophile.[21] Note that using ammonia results in the inversion of the CIP descriptor in the 1,3-diphenylallyl case, due to the change in priority of the groups, although the sense of stereoselectivity is maintained.

We therefore calculated the relative stability of the transition states TS_{endo} and TS_{exo}, using NH_3 as nucleophile and the Pd-olefin intermediates (Pd-$olefin_{endo}$ and Pd-$olefin_{exo}$), with ligands **L10d**, **L10e** and **L15e**. Only the two *syn*/*syn* allyl complexes were calculated, neglecting the contribution of other allylic species of higher energy (*anti*/*anti* and *syn*/*anti*). Of all TSs and Pd-olefins calculated for ligands **L10d**, **L10e** and **L15e**, Table 4.2.6 collect the most stables (the full set of calculated TSs and Pd-olefins can be found in the Supporting Information). The energy differences of the calculated TSs using **S1** and **S2** agree with the catalytic results. Thus, for instance, they correctly identify Pd/**L10e** and Pd/**L15e** catalytic systems as the most enantioselective. In addition, the energy difference between the TSs using **S1** with **L10d** ($\Delta G^{\#}$= 11.2 $kJmol^{-1}$) is lower than that of **L10e** ($\Delta G^{\#}$= 21 $kJmol^{-1}$) which is in good agreement with the higher

enantioselectivities achieved using **L10e** than **L10d** (Table 4.2.1, 96% (*S*) ee for **L10e** vs. 86% (*S*) ee for **L10d**). Furthermore, the TS calculations using **S2** as substrate correctly predicts the formation of the opposite product enantiomers when **L10d** and **L10e** are applied, and again correctly identify Pd/**L10e** and Pd/**L15e** catalytic systems as the most enantioselective.

Finally, the calculated energies of the Pd-olefin intermediates do not correlate well with the experimental results. Thus, for instance, the calculated results with **S1** ($\Delta G^{\#} \geq 30$ kJmol^{-1}) indicated that all three ligands should provide excellent levels of enantioselectivity (ee_{calc}>99.9% (S)). In addition, for **S2**, although the energy difference between the Pd-olefin intermediates correctly predicts the formation of opposite enantiomers of the substitution products when using ligands **L10d** and **L10e**; the calculated energy differences between Pd-olefin complexes containing **L10d** are higher than that of intermediates containing **L10e**, which wrongly predicts much higher enantioselectivities when using Pd-**L10d**.

Table 4.2.6. Calculated energies for the TSs and Pd-π-olefin complexes using **S1** and **S2** and NH_3 as nucleophile.[a]

Structure	**L10d**	**L10e**	**L15e**	Structure	**L10d**	**L10e**	**L15e**
 TS_{endo}	16.6[b]	21	14.2	 TS_{endo}	5[c]	0	0
 TS_{exo}	5.4[b]	0	0	 TS_{exo}	4[c]	15.6	13.6
 Pd-olefin$_{endo}$	36.6[d]	33.2	30.0	 Pd-olefin$_{endo}$	4.4	6.2[e]	0
 Pd-olefin$_{exo}$	5.1[d]	0	0	 Pd-olefin$_{exo}$	0	8.2[e]	6.1

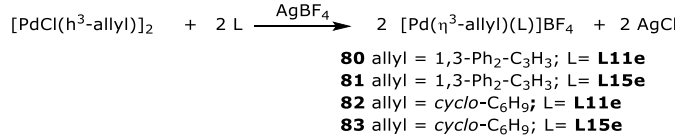
[a] Relative energies in kJ/mol; [b] Energies relative to that of TS_{exo}-**L10e**, [c] Energies relative to that of TS_{endo}-**L10e**; [d] Energies relative to that of Pd-olefin$_{exo}$-**L10e**; [e] Energies relative to that of Pd-olefin$_{exo}$-**L10d**.

In summary, DFT calculations indicate that enantiocontrol is determined during the nucleophilic attack. Consequently, elucidation of the structure of the Pd-allyl

intermediates and their reactivity toward the nucleophile are therefore crucial to understand their catalytic behavior.

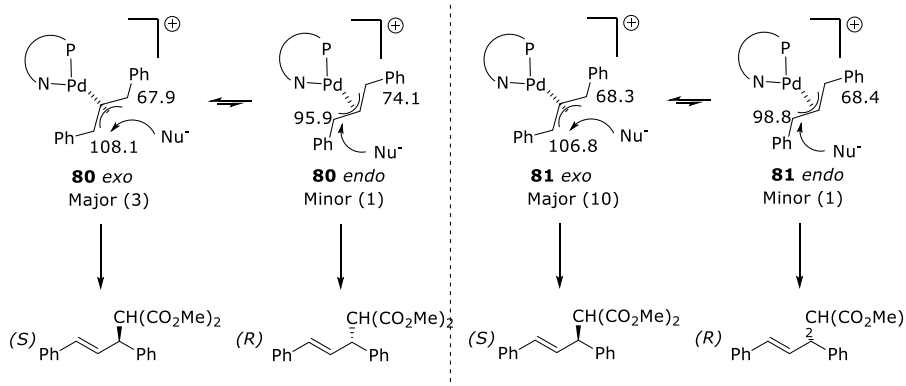
4.2.2.3.2. Preparation and NMR study of Pd-allyl intermediates

To provide further insight into how ligand parameters affect catalytic performance, we studied the Pd-π-allyl compounds **80**-**83** [Pd(η^3-allyl)(L)]BF_4 (L= **L11e** and **L15e**). Ligands **L11e** and **L15e** have been chosen to study the effect of different substituents in the alkyl backbone chain. These ionic palladium complexes, which contain 1,3-diphenyl or cyclohexenyl allyl groups, were prepared using the previously reported method from the corresponding Pd-allyl dimer and the appropriate ligand in the presence of silver tetrafluoroborate (Scheme 4.2.4).[22] The complexes were characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments were based on information from ^1H-^1H, ^{31}P-^1H and ^{13}C-^1H correlation measurements in combination with ^1H-^1H NOESY experiments. Unfortunately, we were unable to obtain crystal of sufficient quality to perform X-ray diffraction measurements.



Scheme 4.2.4. Preparation of [Pd(η^3-allyl)(L)]BF_4 complexes **80**-**83**.

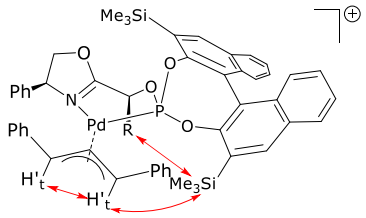
The VT-NMR study (30 ºC to -80 ºC) of Pd-1,3-diphenyl allyl intermediates **80** and **81**, showed a 3:1 and a 10:1 mixture of two isomers in equilibrium (Scheme 4.2.5).



Scheme 4.2.5. Diastereoisomer Pd-allyl intermediates for **S1** with ligands **L11e** (isomers **80**) and **L15e** (intermediates **81**). The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

Both isomers were unambiguously assigned by NMR to the two *syn*/*syn* Pd-η^3-*exo* and *endo* isomer. In both isomers, the NOE indicated interactions between the two

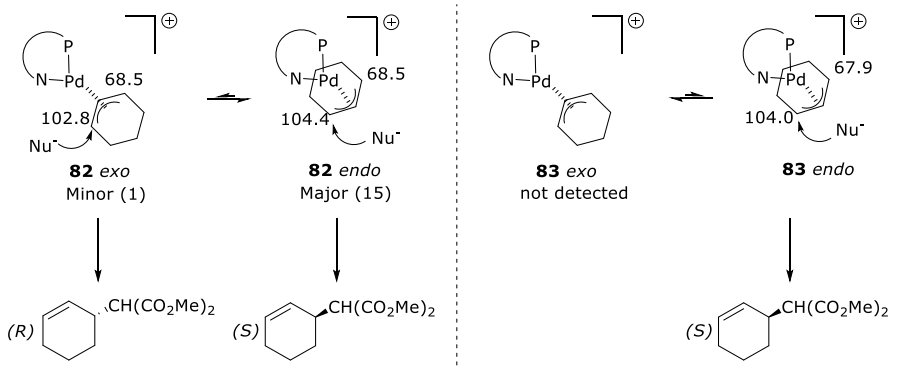
terminal protons of the allyl group, which clearly indicates a *syn*/*syn* disposition (Figure 4.2.4). Moreover, there is a NOE interaction between the terminal allyl proton *trans* to the oxazoline with the TMS group that shows a NOE interaction with the substituent at the alkyl backbone chain (Figure 4.2.4). These interactions can be explained by assuming a *syn*/*syn exo* disposition for the major isomer. The carbon chemical shifts of compounds **80** and **81** indicate that the most electrophilic allylic terminal carbon is located *trans* to the phosphite moiety in the major isomer ($\Delta\delta(^{13}C) \approx 12.4$ ppm for **80** and $\Delta\delta(^{13}C) \approx 8$ ppm for **81**). This indicates that not only the major isomers react faster than the minor isomers but also that the relative reaction rate is higher for intermediate **80** than for **81**. The latter has been verified by studying the reactivity of the Pd-1,3-diphenyl allyl intermediates **80** and **81** with sodium malonate at low temperature by *in situ* NMR. Our results showed that while the major isomer of **80** reacts 8 times faster than the minor isomer, the relative reaction rate of **81** is of 6. Thus, although the use of Pd/**L11e**, with a phenyl substituent at the alkyl backbone chain, does not effectively control the population of Pd-allyl intermediates, it exerts a high electronic differentiation, which is key for achieving enantioselectivities as high as 90% ee (Table 4.2.1). Gratifyingly, the use of Pd/**L15e**, with a methyl alkyl substituent at the alkyl backbone chain, effectively controls both the population and the relative electrophilicity of the allylic carbons in the Pd-allyl intermediates.



80 R= Ph
81 R= Me

Figure 4.2.4. Relevant NOE contacts from the NOESY experiments for the major isomers of [Pd(η^3-1,3-diphenylallyl)(L)]BF_4 **80** and **81**.

The VT-NMR study (30 °C to -80 °C) of Pd-1,3-cyclohexenyl allyl intermediate **82** show a 15:1 mixture of two isomers in equilibrium, while for intermediate **83** only one isomer has been isomer (Scheme 4.2.6).



Scheme 4.2.6. Diastereoisomer Pd-allyl intermediates for **S2** with ligands **L11e** (isomers **82**) and **L15e** (intermediates **83**). The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

The major isomers of intermediates **82** and **83** shows NOE interactions between the central allyl proton with the TMS group that shows a NOE interaction with the substituent at the alkyl backbone chain (Figure 4.2.5). These interactions can be explained by assuming an *endo* disposition for the major isomers. The carbon NMR chemical shifts indicated again that the most electrophilic allylic terminus carbon is *trans* to the phosphite moiety. For intermediate **82**, the fact that the electrophilicity of the allylic terminal carbon atom *trans* to the phosphite is rather similar in both *endo* and *exo* isomers ($\Delta\delta(^{13}C) \approx 1.6$ ppm) suggests that both isomers react at a similar rate. So, the enantioselectivity is mainly affected by the population of the *endo* and *exo* isomers. The much higher enantioselectivity obtained using Pd/**L15e** can therefore be attributed to the fact that only the *endo* isomer is detected.

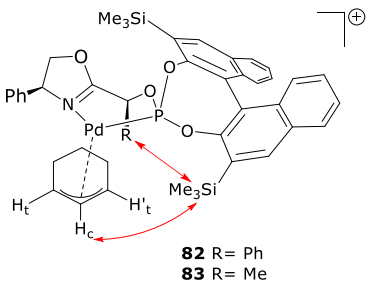


Figure 4.2.5. Relevant NOE contacts from the NOESY experiments for the major isomers of [Pd(η^3-1,3-cyclohexenylallyl)(L)]BF_4 **82** and **83**.

4.2.3. Conclusions

We report a new generation of phosphite-oxazoline PHOX-based ligand library for the Pd-catalyzed allylic substitution of several substrate and nucleophile types. These ligands allow us to study the influence of a second stereocenter on the ligand backbone,

the substituents/configurations on the oxazoline group as well as the variation of the biaryl phosphite group, which showed to be crucial in terms of enantioselectivity. By suitable tuning the ligand parameters we have been able to achieve high activities (TOF > 8000 mol substrate·(mol Pd·h)$^{-1}$) and excellent enantioselectivities (ee's up to >99%) for a range of hindered and unhindered substrates using a wide range of C, N- and O-nucleophiles. The highest enantioselectivities were achieved using ligands **L10e** and **L15e** (ee's up to 99%) containing two or one methyl group at the alkyl backbone chain, respectively. Moreover, good levels of regio- and excellent enantioselectivities were achieved in the allylic alkylation of monosubstituted substrates (regio's up to 80% towards the branched product and ee's up to 98%). In addition, the enantiopure alkylated products were used for the preparation of more complex chiral molecules without loss of enantioselectivity through cycloisomerization or Pauson-Khand reactions.

The DFT studies of Pd-olefin intermediates do not correlate well with the experimental results, thus the calculations agree that the reaction proceeds via an early transition state. The enantioselectivities can be therefore explained by both the population of the Pd-η^3-allyl intermediates and the relative electrophilicity of the allylic carbon atoms (as demonstrated by the NMR study of the Pd-allyl intermediates).

4.2.4. Experimental Section

4.2.4.1. General Considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C{^{1}H}) or H_3PO_4 (^{31}P{^{1}H}) as internal standard. Phosphite-oxazoline ligands were prepared as previously described in Section 3.3. Substrates **S1**-**S13**[23] and **S15**-**S21**[24] were prepared following reported procedures and **S14** was commercially available.

4.2.4.2. Computational details

The geometries of all intermediates were optimized using the Gaussian 09 program,[25] employing the B3LYP[26] density functional and the LANL2DZ[27] basis set for palladium and the 6-31G* basis set for all other elements.[28] Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[29] The complexes were treated with charge +1 and in the single state. No symmetry constraints were applied. The energies were further refined by performing single point calculations using the above mentioned parameters, with the exception that the 6-311+G**[30] basis set was used for all elements except iridium for which SDD basis

set was employed. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + (E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*})$.

4.2.4.3. General procedure for the preparation of [Pd(η^3-allyl)(P-N)]BF_4 complexes 80-83

The corresponding ligand (0.05 mmol) and the complex [Pd(μ-Cl)(η^3-1,3-allyl)]$_2$ (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.05 mmol) was added after 30 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over celite under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated as pale-yellow solids by adding hexane.

[Pd(η^3-1,3-diphenylallyl)(L11e)]BF_4 (80): Major isomer (75%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 139.1 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.30 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 4.38 (m, 1H, CH_2), 4.47 (m, 1H, CH= *trans* to N), 5.01 (m, 2H, CH_2, CH-N), 5.96 (m, 1H, CHc=), 6.15 (m, 2H, CH-O, CH= *trans* to P), 7.10-8.21 (m, 30H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.1 (CH_3, $SiMe_3$), 0.6 (CH_3, $SiMe_3$), 67.7 (CH-N), 67.9 (d, CH= *trans* to N, $J_{C\text{-}P}$= 10.7 Hz), 76.3 (CH-OP), 78.0 (CH_2), 108.1 (d, CH= *trans* to P, $J_{C\text{-}P}$= 29.8 Hz), 112.6 (d, CHc=, $J_{C\text{-}P}$= 9.9 Hz), 120.0-150.0 (aromatic carbons), 169.5 (C=N). Minor isomer (25%): ^{31}P NMR (161.9 MHz, CD_2Cl2): δ = 140.2 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.20 (s, 9H, CH_3, $SiMe_3$), 0.39 (s, 9H, CH_3, $SiMe_3$), 4.35 (m, 1H, CH_2), 4.74 (m, 1H, CH-N), 5.01 (m, 1H, CH_2), 5.23 (m, 1H, CH= *trans* to N), 5.27 (m, 1H, CH= *trans* to P), 5.60 (m, 1H, CHc=), 6.15 (m, 1H, CH-OP), 7.1-8.2 (m, 25H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.5 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), 68.9 (CH-N), 74.1 (d, CH= *trans* to N, $J_{C\text{-}P}$= 10.7 Hz), 75.9 (CH-OP), 77.6 (CH_2), 95.9 (d, CH= *trans* to P, $J_{C\text{-}P}$= 42 Hz), 109.2 (d, CHc=, $J_{C\text{-}P}$= 13.0 Hz), 120.0-150.0 (aromatic carbons), 170.2 (C=N).

[Pd(η^3-1,3-diphenylallyl)(L15e)]BF_4 (81): Major isomer (91%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 140.3 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.46 (s, 9H, CH_3, $SiMe_3$), 0.74 (s, 9H, CH_3, $SiMe_3$), 1.96 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 4.33 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 8.8 Hz, $^3J_{H\text{-}H}$= 4.8 Hz), 4.51 (m, 1H, CH= *trans* to N), 4.88 (m, 1H, CH-N), 5.00 (m, 1H, CH_2), 5.12 (m, 1H, CH-OP), 6.02 (m, 2H, CHc=, CH= *trans* to P), 6.3-8.4 (m, 25H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.1 (CH_3, $SiMe_3$), 0.8 (CH_3, $SiMe_3$), 22.6 (b, CH_3), 67.3 (CH-N), 68.3 (d, CH= *trans* to N, $J_{C\text{-}P}$= 9.9 Hz), 71.5 (CH-OP), 78.2 (CH_2), 106.8 (d, CH= *trans* to P, $J_{C\text{-}P}$= 30.4 Hz), 112.2 (d, CHc=, $J_{C\text{-}P}$= 9.8 Hz), 121.0-150.0 (aromatic carbons), 172.1 (C=N). Minor isomer (9%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 142.9 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.41 (s, 9H, CH_3, $SiMe_3$), 0.62 (s, 9H, CH_3, $SiMe_3$), 1.75 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 4.39 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 8.8 Hz, $^3J_{H\text{-}H}$= 4.4 Hz), 4.53 (m, 1H, CH= *trans* to N), 4.71 (m, 1H, CH_2), 4.88 (m, 1H, CH-N), 5.12 (m, 1H, CH-OP), 5.98 (m, 1H, CH= *trans* to P), 6.09 (m, 1H, CHc=), 6.3-8.4 (m, 25H, CH=). ^{13}C (100.6

MHz, CD_2Cl_2): δ= 0.1 (CH_3, $SiMe_3$), 0.3 (CH_3, $SiMe_3$), 22.4 (b, CH_3), 68.1 (CH-N), 68.4 (d, CH= *trans* to N, J_{C-P}= 9.2 Hz), 70.9 (CH-OP), 78.0 (CH_2), 98.8 (d, CH= *trans* to P, J_{C-P}= 32.4 Hz), 112.7 (d, CHc=, J_{C-P}= 9.2 Hz), 121.0-150.0 (aromatic carbons), 172.3 (C=N).

[Pd(η³-1,3-cyclohexenyl)(L11e)]BF_4 (82): Major isomer (95%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 143.3 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.10 (m, 1H, CH_2), 0.61 (s, 9H, CH_3, $SiMe_3$), 0.81 (m, 1H, CH_2), 0.89 (s, 9H, CH_3, $SiMe_3$), 1.0-1.3 (m, 4H, CH_2), 4.05 (b, 1H, CH= *trans* to N), 4.53 (dd, 1H, CH_2, $^2J_{H-H}$= 9.6 Hz, $^3J_{H-H}$= 7.2 Hz), 5.18 (m, 1H, CH_2),5.33 (m, 1H, CHc=), 5.95 (m, 2H, CH-N, CH= *trans* to P), 6.36 (d, 1H, CH-OP, J_{C-P}= 26.0 Hz), 7.10 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz) , 7.11-7.30 (m, 2H, CH=), 7.42-7.60 (m, 14H, CH=), 8.02 (d, 2H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.24 (s, 1H, CH=).^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.4 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 19.9 (CH_2), 27.0 (b, CH_2), 68.5 (d, CH= *trans* to N, J_{C-P}= 9.1 Hz), 74.5 (CH-OP), 76.4 (CH-N), 78.2 (CH_2), 104.4 (d, CH= *trans* to P, J_{C-P}= 39.5 Hz), 111.6 (d, CHc=, J_{C-P}= 10.7 Hz), 122.7-151.0 (aromatic carbons), 169.4 (C=N). Minor isomer (5%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 139.5 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.10 (m, 1H, CH_2), 0.42 (s, 9H, CH_3, $SiMe_3$), 0.81 (m, 1H, CH_2), 0.89 (s, 9H, CH_3, $SiMe_3$), 1.0-1.3 (m, 4H, CH_2), 3.94 (b, 1H, CH= *trans* to N), 4.42 (m, 1H, CH_2), 5.21 (m, 1H, CH_2), 5.33 (m, 1H, CHc=), 5.89 (m, 1H, CH= *trans* to P), 6.06 (m, 1H, CH-N), 6.34 (d, 1H, CH-OP, J_{C-P}= 21.0 Hz), 7.0-8.2 (m, 20H, CH=).

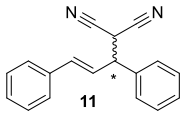
[Pd(η³-1,3-cyclohexenyl)(L15e)]BF_4 (83): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ = 143.7 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.11 (m, 1H, CH_2), 0.47 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 0.68 (m, 1H, CH_2), 1.0-1.3 (m, 4H, CH_2), 1.89 (d, 1H, CH_3, $^3J_{H-H}$= 6.8 Hz), 4.04 (b, 1H, CH= *trans* to N), 4.51 (dd, 1H, CH_2, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 8 Hz), 5.15 (dd, 1H, CH_2, $^2J_{H-H}$= 9.2 Hz, $^3J_{H-H}$= 10.8 Hz), 5.33 (m, 1H, CHc=), 5.36 (q, 1H, CH, $^3J_{H-H}$= 6.8 Hz), 5.71 (dd, 1H, CH-N, $^3J_{H-H}$= 8.0 Hz, $^3J_{H-H}$= 10.8 Hz), 5.95 (m, 1H, CH= *trans* to P), 6.99 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.12 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.28 (m, 2H, CH=), 7.41-7.50 (m, 7H, CH=), 8.02 (t, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 8.23 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz).^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.1 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 19.5 (CH_2), 22.9 (d, CH_3, J_{C-P}= 4.5 Hz), 27.1 (b, CH_2), 67.9 (d, CH= *trans* to N, J_{C-P}= 9.2 Hz), 71.6 (CH-OP), 74.3 (CH-N), 78.2 (CH_2), 104.0 (d, CH= *trans* to P, J_{C-P}= 40 Hz), 111.7 (d, CHc=, J_{C-P}= 10.7 Hz), 121.0-151.0 (aromatic carbons), 171.8 (C=N).

4.2.4.4. Typical procedure for the allylic alkylation of linear (S1, S3-S8), cyclic (S2, S10-S11) and monosubstituted (S9, S13-S21)

A degassed solution of [PdCl(η³-C_3H_5)]$_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (1 mmol) in dichloromethane (1.5 mL), nucleophile (3 mmol), *N,O*-bis(trimethylsilyl)-acetamide (3 mmol) and KOAc (3 mg,

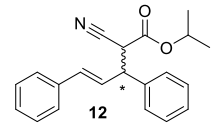
0.03 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For compounds **2**, **4**-**13**, **34**-**40**, **42**, **44**-**48**, **51**-**52**, **58** and **62**-**71** conversions were measured by ^1H NMR and enantiomeric excesses were determined by HPLC, while for compounds **3**, **41**, **49**-**50**, **53**-**54** and **56**-**57** conversion and enantiomeric excess were determined by GC. For compounds 43 and 55 conversions and enantiomeric excess were determined by ^1H NMR using [Eu(hfc)$_3$] (for more details for compounds **2**-**10**, **13**, **34**-**36**, **38**-**43**, **49**-**58** and **62a**-**63a**, see previous Section 4.1.5.5).

2-(1,3-Diphenylallyl)malononitrile (11).[31] Enantiomeric excess determined by HPLC using Chiralcel O*J*-H column (70% hexane/2-propanol, flow 1 mL/min). t_R 18.2 min (*R*); t_R 19.4 min (*S*). ^1H NMR ($CDCl_3$), δ: 4.07 (m, 2H, CH), 6.47 (dd, 1H, CH=, *J*= 15.6 Hz, *J*= 8 Hz), 6.70 (d, 1H, CH=, *J*= 15.6 Hz), 7.22-7.51 (m, 10H, CH=).



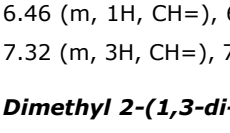
11

Isopropyl 2-cyano-3,5-diphenylpent-4-enoate (12).[6c] Enantiomeric excess determined by HPLC using Chiralcel IC column (99% hexane/2-propanol, flow 0.5 mL/min). Major diastereoisomer, t_R 51.0 (*major*) and t_R 53.1 min (*minor*). Minor diastereoisomer, t_R 58.2 (*minor*) and t_R 79.7 min (*major*). ^1H NMR ($CDCl_3$), δ: 1.14 (m, 6H, CH_3), 3.86 (dd, 1H, CH, *J*= 13.6 Hz, *J*= 8.0 Hz), 4.20 (m, 1H, CH), 4.98 (m, 1H, CH=), 6.46 (m, 1H, CH=), 6.58 (dd, 1H, CH=, *J*= 11.6 Hz, *J*= 16.0 Hz), 7.25 (m, 1H, CH=), 7.32 (m, 3H, CH=), 7.35 (m, 6H, CH=).



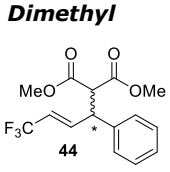
12

Dimethyl 2-(1,3-di-p-tolylallyl)-2-(prop-2-yn-1-yl)malonate (37). Enantiomeric excess determined by HPLC using Chiralcel OD-H column (98% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 18.6 min (*R*); t_R 23.4 min (*S*). ^1H NMR ($CDCl_3$), δ: 2.03 (t, 1H, CH≡, *J*= 2.6 Hz), 2.23 (s, 6H, 2xCH_3), 2.55 (dd, 1H, CH_2, *J*= 17.1 Hz, *J*= 2.6 Hz), 2.72 (dd, 1H, CH_2, *J*= 17.1 Hz, *J*= 2.6 Hz), 3.63 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 4.30 (d, 1H, CH, *J*= 8.5 Hz), 6.33 (d, 1H, CH=, *J*= 15.7 Hz), 6.62 (dd, 1H, CH=, *J*= 15.7 Hz, *J*= 8.5 Hz), 7.02 (m, 6H, CH=), 7.16 (m, 2H, CH=). ^{13}C NMR ($CDCl_3$), δ: 21.1 (CH_3), 21.2 (CH_3), 24.5 (CH_2), 51.7 (CH), 52.5 (CH_3), 52.6 (CH_3), 61.8 (C), 71.9 (CH≡), 79.5 (C≡), 126.3 (CH=), 127.8 (CH=), 129.1 (CH=), 129.1 (CH=), 129.1 (CH=), 132.2 (CH=), 134.7 (C=), 135.7 (C=), 137.0 (C=), 137.1 (C=), 169.7 (C=O), 169.8 (C=O).



37

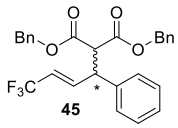
Dimethyl 2-(4,4,4-trifluoro-1-phenylbut-2-en-1-yl)malonate (44).[12a] Enantiomeric excess determined by HPLC using Lux-amylose-1 column (95% hexane/2-propanol, flow 1 mL/min, λ= 254 nm). t_R 10.6 min (*R*); t_R 12.1 min (*S*).^1H NMR ($CDCl_3$), δ: 3.52 (s, 3H, OMe), 3.75 (s,



44

3H, OMe), 3.89 (d, 1H, CH, *J*= 10.7 Hz), 4.21 (pt, 1H, CH, *J*= 9.5 Hz), 5.67 (m, 1H, CH=), 6.56 (m, 1H, CH=), 7.21 (m, 5H, CH=).

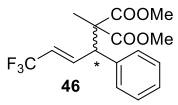
Dibenzyl 2-(4,4,4-trifluoro-1-phenylbut-2-en-1-yl)malonate (45).[12a]



45

Enantiomeric excess determined by HPLC using Lux-amylose-1 column (95% hexane/2-propanol, flow 1 mL/min, λ= 254 nm). t_R 15.7 min (*R*); t_R 18.6 min (*S*).^{1}H NMR ($CDCl_3$), δ: 3.87 (m, 1H, CH), 4.20 (m, 1H, CH), 4.82 (m, 2H, CH_2), 5.05 (m, 2H, CH_2), 5.52 (m, 1H, CH=), 6.45 (m, 1H, CH=), 6.96 (m, 2H, CH=), 7.08 (m, 2H, CH=), 7.22 (m, 11H, CH=).

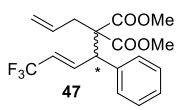
Dimethyl 2-methyl-2-(4,4,4-trifluoro-1-phenylbut-2-en-1-yl)malonate (46). [12a]



46

Enantiomeric excess determined by HPLC using Lux-amylose-1 column (95% hexane/2-propanol, flow 1 mL/min, λ= 254 nm). t_R 9.0 min (*R*); t_R 9.5 min (*S*).^{1}H NMR ($CDCl_3$), δ: 1.34 (s, 3H, CH_3), 3.58 (s, 3H, OMe), 3.67 (s, 3H, OMe), 4.11 (dt, 1H, CH, *J*= 7.9 Hz, *J*= 1.4 Hz), 5.53 (dqd, 1H, CH=, *J*= 15.7 Hz, *J*= 6.3 Hz, *J* = 1.4 Hz), 6.81 (ddq, 1H, CH=, *J* = 15.7 Hz, *J*= 7.9 Hz, *J*= 2.1 Hz), 7.10 (m, 2H, CH=), 7.26 (m, 3H, CH=).

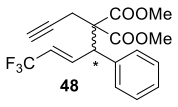
Dimethyl 2-allyl-2-(4,4,4-trifluoro-1-phenylbut-2-en-1-yl)malonate (47).



47

Enantiomeric excess determined by HPLC using Lux-amylose-1 column (95% hexane/2-propanol, flow 1 mL/min, λ= 254 nm). t_R 8.1 min (*R*); t_R 8.8 min (*S*).^{1}H NMR ($CDCl_3$), δ: 2.27 (dd, 1H, CH_2, *J*= 14.3 Hz, *J*= 8.1 Hz), 2.50 (dd, 1H, CH_2, *J*= 14.3 Hz, *J*= 6.5 Hz), 3.64 (s, 3H, OMe), 3.70 (s, 3H, OMe), 4.05 (dt, 1H, CH=, *J*= 6.9 Hz, *J*= 2.1 Hz), 4.95 (m, 2H, CH_2=), 5.37 (dqd, 1H, CH=, *J*= 15.8 Hz, *J*= 6.4 Hz, *J*= 1.6 Hz), 5.63 (dddd, 1H, CH=, *J*= 16.8 Hz, *J*= 10.2 Hz, *J*= 8.1 Hz, *J*= 6.5 Hz), 6.86 (ddq, 1H, CH=, *J*= 15.8 Hz, *J*= 6.4 Hz, *J*= 2.0 Hz), 7.96 (m, 2H, CH=), 7.23 (m, 3H, CH=). ^{13}C NMR ($CDCl_3$), δ: 38.9 (CH_2), 51.5 (CH), 52.3 (OMe), 52.5 (OMe), 62.2 (C), 119.3 (CH_2=), 119.9 (CH=), 128.1 (CH=), 128.8 (CH=), 129.3 (CH=), 132.4 (CH=), 140.4 (m, CH=), 170.1 (C=O), 170.3 (C=O).

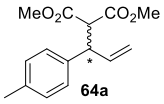
Dimethyl 2-(prop-2-yn-1-yl)-2-(4,4,4-trifluoro-1-phenylbut-2-en-1-yl)malonate (48).



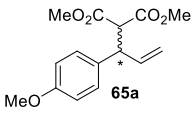
48

Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 254 nm). t_R 9.6 min (*R*); t_R 11.6 min (*S*).^{1}H NMR ($CDCl_3$), δ: 2.08 (t, 1H, CH≡, *J*= 2.7 Hz), 2.41 (dd, 1H, CH_2, *J*= 17.3 Hz, *J*= 2.7 Hz), 2.71 (dd, 1H, CH_2, *J*= 17.3 Hz, *J*= 2.7 Hz), 3.70 (s, 3H, OMe), 3.73 (s, 3H, OMe), 4.36 (m, 1H, CH), 5.46 (m, 1H, CH=), 6.97 (m, 1H, CH=), 7.10 (m, 2H, CH=), 7.28 (m, 3H, CH=). ^{13}C NMR ($CDCl_3$), δ: 24.2 (CH_2), 49.8 (CH), 52.7 (OMe), 53.0 (OMe), 60.7 (C), 72.83 (C≡), 78.5 (C≡), 120.4 (q, CH=, *J*= 33.5 Hz), 128.2 (CH), 128.8 (CH), 129.3 (C), 136.2 (C), 169.2 (C=O), 169.2 (C=O).

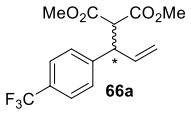
Dimethyl 2-(1-(p-tolyl)allyl)malonate (64a).[32] Enantiomeric excess determined by HPLC using Chiralpak OD-H column (90% hexane/2-propanol, flow 0.7 mL/min, λ= 220 nm). t_R 10.8 min (*R*); t_R 12.0 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 2.30 (s, 3 H), 3.51 (s, 3H), 3.73 (s, 3H), 4.07 (dd, 1H, *J*= 10.9 Hz, *J*= 8.2 Hz), 5.07 (d, 1H, *J*= 9.4 Hz), 5.11 (d, 1H, *J*= 17.0 Hz), 5.98 (ddd, 1H, *J*= 17.1 Hz, *J*= 9.4 Hz, *J*= 8.2 Hz), 7.10 (s, 4H).



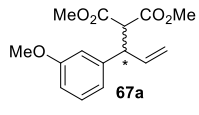
Dimethyl 2-(1-(4-methoxyphenyl)allyl)malonate (65a).[33] Enantiomeric excess determined by HPLC using Chiralpak OD-H column (90% hexane/2-propanol, flow 0.7 mL/min, λ= 220 nm). t_R 9.4 min (*R*); t_R 10.6 min (*S*).^{1}H NMR ($CDCl_3$), δ: 3.50 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 3.82 (d, 1H, *J*= 10.9 Hz), 4.06 (dd, 1H, *J*= 10.9 Hz, *J*= 8.3 Hz), 5.06 (d, 1H, *J*= 8.6 Hz), 5.09 (d, 1H, *J*= 15.4 Hz), 5.97 (ddd, 1H, *J*= 17.1 Hz, *J*= 10.1 Hz, *J*= 7.8 Hz), 6.85 (d, 2H, *J*= 8.6 Hz), 7.14 (d, 2H, *J*= 8.6 Hz).



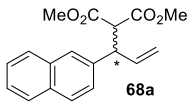
Dimethyl 2-(1-(4-(trifluoromethyl)phenyl)allyl)malonate (66a).[33] Enantiomeric excess determined by HPLC using Chiralpak OD-H column (99.5% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 34.5 min (*R*); t_R 35.4 min (*S*).^{1}H NMR ($CDCl_3$), δ: 3.53 (s, 3H), 3.76 (s, 3H), 3.90 (d, 1H, *J*= 11.1 Hz), 4.19 (dd, 1H, *J*= 10.9 Hz, *J*= 8.6 Hz), 5.12 (s, 1H), 5.16 (d, 1H, *J*= 7.6 Hz), 5.97 (ddd, 1H, *J*= 16.9 Hz, *J*= 10.1 Hz, *J*= 8.1 Hz), 7.36 (d, 2H, *J*= 8.3 Hz), 7.57 (d, 2H, *J*= 8.1 Hz).



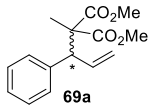
Dimethyl 2-(1-(3-methoxyphenyl)allyl)malonate (67a).[33] Enantiomeric excess determined by HPLC using Chiralpak OD-H column (99% hexane/2-propanol, flow 0.7 mL/min, λ= 220 nm). t_R 17.8 min (*R*); t_R 20.4 min (*S*).^{1}H NMR ($CDCl_3$), δ: 3.49 (s, 3H), 3.72 (s, 3H), 3.85 (s, 3H), 4.18 (d, 1H, *J*= 10.6 Hz), 4.33 (dd, 1H, *J*= 10.6 Hz, *J*= 8.6 Hz), 5.04 (dd, 1H, *J*= 10.1 Hz, *J*= 0.8 Hz), 5.12 (dt, 1H, *J*= 17.2 Hz, *J*= 1.3 Hz), 6.14 (ddd, 1H, *J*= 17.0 Hz, *J*= 10.1 Hz, *J*= 8.6 Hz), 6.89 (m, 2H), 7.16 (dd, 1H, *J*= 7.6 Hz, *J*= 1.5 Hz), 7.20 (td, 1H, *J*= 7.6 Hz, *J*= 1.8 Hz).



Dimethyl 2-(1-(naphthalen-2-yl)allyl)malonate (68a).[33] Enantiomeric excess determined by HPLC using Chiralpak OD-H column (97% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 15.98 min (*R*); t_R 17.2 min (*S*).^{1}H NMR ($CDCl_3$), δ: 3.77 (s, 3H), 3.46 (s, 3H), 4.01 (d, 1H, *J*= 11.1 Hz), 4.30 (dd, 1H, *J*= 9.6 Hz, *J*= 8.4 Hz), 5.04 (d, 1H, *J*= 10.1 Hz), 5.18 (d, 1H, *J*= 17.2 Hz), 6.08 (ddd, 1H, *J*= 17.2 Hz, *J*= 10.4 Hz, *J*= 8.1 Hz), 7.37 (dd, 1H, *J*= 8.6, *J*= 1.5 Hz), 7.47- 7.44 (m, 2H), 7.69 (s, 1H), 7.81–7.79 (m, 3H).

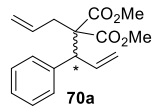


Dimethyl 2-methyl-2-(1-phenylallyl)malonate (69a).[34] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 19.3 min (*R*); t_R 22.1 min (*S*).^{1}H NMR ($CDCl_3$), δ: 1.44 (s, 3H, CH_3), 3.62 (s, 3H, OMe), 3.71 (s, 3H, OMe), 4.15 (d, 1H, CH, *J*= 8.7 Hz), 5.12 (m, 2H, CH=), 6.32 (ddd, 1H, CH=, *J*= 16.9 Hz, *J*= 10.2 Hz, *J*= 8.7 Hz), 7.18- 7.33 (m, 5H, CH=).



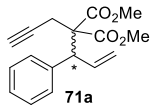
69a

Dimethyl 2-allyl-2-(1-phenylallyl)malonate (70a).[35] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 18.0 min (*R*); t_R 20.5 min (*S*).^{1}H NMR ($CDCl_3$), δ: 2.34 (dd, 1H, CH_2, *J*= 14.1 Hz, *J*= 8.2 Hz), 2.52 (ddt, 1H, CH_2, *J*= 14 Hz, *J*= 6.2 Hz, *J*= 1.2 Hz), 3.60 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.94 (d, 1H, CH, *J*= 8.5 Hz), 4.90 – 5.02 (m, 3H, CH=), 5.05 (ddd, 1H, CH=, *J*= 10.2 Hz, *J*= 1.6 Hz, *J*= 0.8 Hz), 5.73 (m, 1H, CH=), 6.32 (ddd, 1H, CH=, *J*= 17 Hz, *J*= 10.2 Hz, *J*= 8.5 Hz), 7.08 (m, 2H, CH=), 7.20 (m, 3H, CH=).



70a

Dimethyl 2-(1-phenylallyl)-2-(prop-2-yn-1-yl)malonate (71a).[36] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 12.8 min (*R*); t_R 14.6 min (*S*).^{1}H-NMR ($CDCl_3$), δ: 2.09 (t, 1H, CH≡, *J*= 2.6 Hz), 2.55 (dd, 1H, CH_2, *J* = 17.1 Hz, *J*= 2.6 Hz), 2.75 (dd, 1H, CH_2, *J*= 17.1 Hz, *J*= 2.6 Hz) , 3.72 (s, 3H, OMe), 3.76 (s, 3H, OMe), 4.25 (d, 1H, CH, *J*= 8.2 Hz), 5.15 (m, 2H, CH=), 6.42 (ddd, 1H, CH=, *J*= 17.2 Hz, *J*= 10 Hz, *J*= 8.2 Hz), 7.25 (m, 5H, CH=).

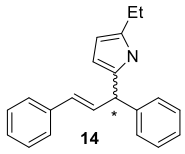


71a

4.2.4.5. Typical procedure for the allylic alkylation of disubstituted linear substrate S1 using pyrroles

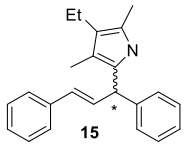
A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite/phosphinite-thioether (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), the corresponding pyrrole (0.4 mmol) and K_2CO_3 (110 mg, 0.8 mmol) were added. The reaction mixture was stirred at room temperature. After 18 h, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC.

2-(1,3-Diphenylallyl)-5-ethyl-1λ²-pyrrole (14).[7] Enantiometic excess determined by HPLC using Chiralpak AD-H column (99% hexane/2-propanol, flow 0.7 mL/min, λ= 254 nm) t_R 12.1 min; t_R 12.9 min. ^{1}H NMR ($CDCl_3$), δ: 1.19 (t, 3H, CH_3, *J*= 7.6 Hz), 2.55 (q, 2H, CH_2, *J*= 7.6 Hz), 4.81 (d, 1H, CH=, *J*= 7.6 Hz), 5.84 (m, 2H, CH=), 6.42 (d, 1H, CH=, *J*=15.6 Hz), 6.58 (dd, 1H, CH=, *J*= 15.6 Hz, *J*= 7.6 Hz), 7.37−7.18 (m, 10H, CH=), 7.53 (brs, 1H, NH).



14

2-(1,3-diphenylallyl)-4-ethyl-3,5-dimethyl-1λ²-pyrrole (15).[31] Enantiometic excess determined by HPLC using Chiralpak AD-H column (99,5% hexane/2-propanol, flow 0.7 mL/min, λ= 254 nm) t_R 17.8 min; t_R 19.7 min. ^{1}H NMR ($CDCl_3$) δ: 1.96 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 4.94 (d, 1H, CH=, *J*= 6.8 Hz), 5.73 (m, 1H, CH=), 6.31 (d, 1H, CH=, *J*= 15.6 Hz), 6.56 (dd, 1H, CH=, *J*= 15.6 Hz, *J*= 6.8 Hz), 7.37−7.18 (m, 11H, CH=).

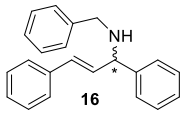


15

4.2.4.6. Typical procedure for the allylic amination of linear S1 and cyclic S12 substrates

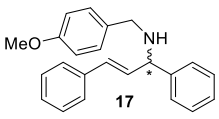
A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (0.5 mmol) in dichloromethane (1.5 mL), the corresponding amine (1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 2 hours, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC.

N-Benzyl-1,3-diphenylprop-2-en-1-amine (16).[37] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (99% hexane/2-propanol, flow 0.5 mL/min). t_R 22.4 min (*R*); t_R 26.2 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 3.77 (d, 1H, NH, *J*= 13.2 Hz), 3.80 (d, 1H, CH, *J*= 13.2 Hz), 4.41 (m, 2H, CH_2), 6.34 (dd, 1H, CH=, *J*= 16 Hz, *J*= 7.2 Hz), 6.57 (d, 1H, CH=, *J*= 16 Hz), 7.12-7.45 (m, 15H, CH=).



16

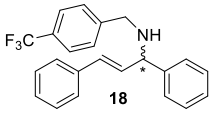
N-(4-Methoxybenzyl)-1,3-diphenylprop-2-en-1-amine (17).[10h] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (95% hexane/2-propanol, flow 0.5 mL/min). t_R 19.5 min (*R*); t_R 28.3 min (*S*).^{1}H-NMR ($CDCl_3$), δ: 3.73 (dd, 2H, CH_2, *J*= 16.9 Hz, *J*= 13.2 Hz), 3.81 (s, 3H, OCH_3), 4.39 (d, 1H, CH, *J*= 7.2 Hz), 6.36



17

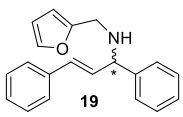
(dd, 1H, CH=, *J*= 15.8 Hz, *J*= 7.2 Hz), 6.58 (d, 1H, CH=, *J*= 15.8 Hz), 6.87 (m, 2H, CH=), 7.25 (m, 6H, CH=), 7.35 (m, 4H, CH=), 7.43 (m, 2H, CH=).

1,3-Diphenyl-N-(4-(trifluoromethyl)benzyl)prop-2-en-1-amine (18).[10h]

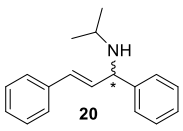


Enantio-meric excess determined by HPLC using Chiralcel OD-H column (95% hexane/2-propanol, flow 0.5 mL/min). t_R 15.9 min (*R*); t_R 17.9 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 3.86 (m, 2H, CH_2), 4.39 (d, 1H, CH, *J*= 7.6 Hz), 6.33 (dd, 1H, CH=, *J*= 15.9 Hz, *J*= 7.6 Hz), 6.59 (d, 1H, CH=, *J*= 15.9 Hz), 7.23 (m, 1H, CH=), 7.31 (m, 3H, CH=), 7.38 (m, 4H, CH=), 7.45 (m, 3H, CH=), 7.60 (m, 2H, CH=).

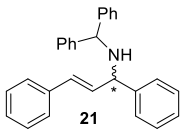
N-(Furan-2-ylmethyl)-1,3-diphenylprop-2-en-1-amine (19).[38] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (95% hexane/2-propanol, flow 0.5 mL/min). t_R 24.9 min (*S*); t_R 39.8 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 3.79 (s, 2H, CH_2), 4.39 (d, 1H, CH=, *J*= 7.6 Hz), 6.17 (dd, 1H, CH=, *J*= 3.1 Hz, *J*= 0.8 Hz), 6.30 (d, 1H, CH=, *J*= 7.6), 6.32 (m, 1H), 6.59 (d, 1H, CH=, *J*= 15.6 Hz), 7.30 (m, 11H, CH=).



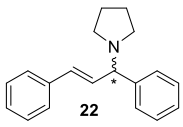
N-Isopropyl-1,3-diphenylprop-2-en-1-amine (20).[39] Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (99% hexane/2-propanol, flow 0.5 mL/min). t_R 22.4 min (*R*); t_R 26.2 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.07 (d, 3H, CH_3, *J*= 6.3 Hz), 1.10 (d, 3H, CH_3, *J*= 6.3 Hz), 1.61 (bs, 1H, NH), 2.81 (pt, 1H, CH, *J*= 6.3 Hz), 4.49 (d, 1H, CH, *J*= 7.4 Hz), 6.30 (dd, 1H, CH=, *J*= 16 Hz, *J*= 7.4 Hz), 6.52 (d, 1H, CH=, *J*= 16 Hz), 7.16-7.22 (m, 1H, CH=), 7.24-7.30 (m, 3H, CH=), 7.31-7.41 (m, 6H, CH=).



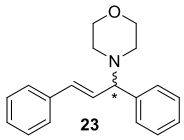
N-benzhydryl-1,3-diphenylprop-2-en-1-amine (21).[39] Enantiomeric excess determined by HPLC using Chiralcel AD-H column (99% hexane/2-propanol, flow 0.5 mL/min). t_R 12.1 min (*S*); t_R 14.5 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 4.30 (d, 1H, CH, *J*= 7.2 Hz), 4.89 (s, 1H, CH), 6.31 (dd, 1H, CH=, *J*= 15.8 Hz, *J*= 7.2 Hz), 6.51 (d, 1H, CH=, *J*= 15.8 Hz), 7.30 (m, 20H, CH=).



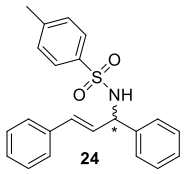
1-(1,3-Diphenylallyl)pyrrolidine (22).[40] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (99% hexane/2-propanol, flow 1 mL/min). t_R 4.4 min (*S*); t_R 4.9 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 1.80 (m, 4H, CH_2), 2.40 (m, 4H, CH_2), 3.76 (d, 1H, CH, *J*= 8.5 Hz), 6.42 (dd, 1H, CH=, *J*= 15.6 Hz, *J*= 8.5 Hz), 6.59 (d, 1H, CH=, *J*= 15.6 Hz), 7.25 (m, 8H, CH=), 7.42 (m, 2H, CH=).



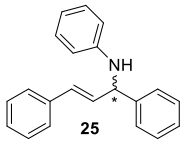
4-(1,3-Diphenylallyl)morpholine (23).[41] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (90% hexane/2-propanol, flow 1 mL/min). t_R 6.2 min (*S*); t_R 12.1 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 2.40 (m, 2H, CH_2), 3.72 (t, 4H, CH_2, *J*= 5.2 Hz), 3.80 (d, 1H, CH, *J*= 9.1 Hz), 6.29 (dd, 1H, CH=, *J*= 15.8 Hz, *J*= 9.1 Hz), 6.58 (d, 1H, CH=, *J*= 15.8 Hz), 7.30 (m, 8H, CH=), 7.41 (m, 2H, CH=).



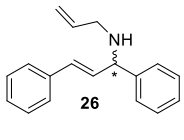
N-(1,3-Diphenylallyl)-4-methylbenzenesulfonamide (24).[41] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (90% hexane/2-propanol, flow 0.5 mL/min). t_R 35.9 min (*R*); t_R 47.5 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 2.32 (s, 3H, CH_3), 5.11 (td, 1H, CH, *J*= 7.3 Hz, *J*= 1.2 Hz), 5.21 (d, 1H, CH, *J*= 7.3 Hz), 6.08 (dd, 1H, CH=, *J*= 15.8 Hz, *J*= 6.8 Hz), 6.34 (dd, 1H, CH=, *J*= 15.8 Hz, *J*= 1.2 Hz), 7.20 (m, 12H, CH=), 7.65 (m, 2H, CH=).



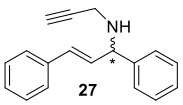
N-(1,3-Diphenylallyl)aniline (25).[10h] Enantiomeric excess determined by HPLC using Chiralcel AD-H column (95% hexane/2-propanol, flow 1 mL/min). t_R 9.5 min (*R*); t_R 12.0 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 5.14 (d, 1H, CH, *J*= 6.1 Hz), 6.45 (dd, 1H, CH, *J*= 15.9 Hz, *J*= 6.1 Hz), 6.69 (m, 3H, CH), 6.76 (tt, 1H, CH=, *J*= 7.5 Hz, *J*= 1.1 Hz), 7.20 (m, 2H, CH=), 7.27 (m, 1H, CH=), 7.34 (m, 3H, CH=), 7.41 (m, 4H, CH=), 7.48 (m, 2H, CH=).



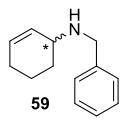
N-Allyl-1,3-diphenylprop-2-en-1-amine (26).[10h] Enantiomeric excess determined by HPLC using Chiralcel OD-H column (99% hexane/2-propanol, flow 1 mL/min). t_R 7.1 min (*S*); t_R 8.4 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 3.25 (m, 2H, CH_2), 4.43 (d, 1H, CH, *J*= 7.5 Hz), 5.14 (m, 1H, CH=), 5.21 (m, 1H, CH=), 5.96 (ddt, 1H, CH=, *J*= 17.1 Hz, *J*= 10.2 Hz, *J*= 6 Hz), 6.32 (dd, 1H, CH=, *J*= 15.8, *J*= 7.5 Hz), 6.60 (d, 1H, CH=, *J*= 15.8 Hz), 7.30 (m, 10H, CH=).



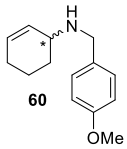
1,3-Diphenyl-N-(prop-2-yn-1-yl)prop-2-en-1-amine (27).[42] Enantiomeric excess determined by HPLC using Chiralcel AD-H column (95% hexane/2-propanol, flow 0.5 mL/min). t_R 19.6 min (*R*); t_R 21.9 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 2.28 (t, 1H, CH≡, *J*= 2.3 Hz), 3.43 (pdq, 2H, CH_2, *J*= 17.2 Hz, *J*= 2.3 Hz), 4.64 (d, 1H, CH, *J*= 7.7 Hz), 6.29 (dd, 1H, CH=, *J*= 15.8 Hz, *J*= 7.7 Hz), 6.67 (d, 1H, CH=, *J*= 15.8 Hz), 7.30 (m, 10H, CH=).



N-Benzylcyclohexanamine (59).[39] Enantiomeric excess determined by HPLC using Chiralpak OB-H column (95% hexane/2-propanol, flow 0.5 mL/min, λ= 226 nm). t_R 13.5 min (*R*); t_R 15.1 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.31 (b, 1H, NH), 1.52 (m, 2H, CH_2), 1.74 (m, 1H, CH_2), 1.96 (m, 3H, CH_2), 3.22 (m, 1H, CH), 3.85 (m, 2H, CH_2), 5.75 (m, 2H, CH=), 7.12-7.43 (m, 5H, CH=).

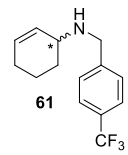


N-(4-Methoxybenzyl)cyclohexanamine (60). Enantiomeric excess determined by HPLC using Chiralpak OB-H column (95% hexane/2-propanol, flow 0.5 mL/min, λ= 226 nm). t_R 16.4 min (*R*); t_R 16.9 min (*S*). ^{1}H NMR ($CDCl_3$), δ: 1.50 (m, 2H, CH_2), 1.75 (m, 1H, CH_2), 1.93 (m, 3H, CH_2), 3.20 (m, 1H, CH), 3.77 (m, 5H, CH_2, OMe), 5.75 (m, 2H, CH=), 6.85 (m, 2H, CH=), 7.27 (m, 2H, CH=). ^{13}C NMR ($CDCl_3$), δ: 20.3 (CH_2), 25.3 (CH_2), 29.5 (CH_2), 50.4 (CH_2), 52.3 (CH), 55.3 (CH_3), 113.7 (CH=), 128.9 (CH=), 129.3 (CH=), 129.9 (CH=), 132.8 (C=), 158.6 (C=).



60

N-(4-(Trifluoromethyl)benzyl)cyclohexanamine (61). Enantiomeric excess determined by HPLC using Chiralpak OD-H column (98% hexane/2-propanol, flow 0.5 mL/min, λ= 226 nm). t_R 8.6 min (R); t_R 8.9 min (S). ^{1}H NMR ($CDCl_3$), δ: 1.53 (m, 2H, CH_2), 1.75 (m, 1H, CH_2), 1.96 (m, 3H, CH_2), 3.18 (m, 1H, CH), 3.91 (m, 2H, $ArCH_2$), 5.75 (m, 2H, CH=), 7.47 (m, 2H, CH=), 7.57 (m, 2H, CH=). ^{13}C NMR ($CDCl_3$), δ: 20.1 (CH_2), 25.3 (CH_2), 29.4 (CH_2), 50.4 (CH_2), 52.4 (CH), 125.2 (q, CH=, *J*= 3.8 Hz), 128.3 (CH=), 129.3 (C=), 129.6 (CH=), 145.0 (C=).



61

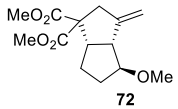
4.2.4.7. Typical procedure for the allylic etherification and silylation of linear substrate S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 minutes, Cs_2CO_3 (122 mg, 0.375 mmol) and the corresponding alcohol or silanol (0.375 mmol) were added. The reaction mixture was stirred at room temperature. After 18 h, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC (for more details for compounds **28**-**33** see previous Section 4.1.5.6).

4.2.4.8. Typical procedure for the preparation of bicyclic compounds 72-76

A mixture of the enyne (1 mmol) and $PdCl_2$ or $RuCl_3$ (0.05 mmol) was heated under refluxing conditions in the appropriate MeOH (5 mL). After being cooled to room temperature, the solvent was evaporated and the residue was chromatographed (hexane: EtOAc mixtures) to give the desired bicycle.

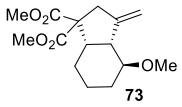
Dimethyl 4-methoxy-3-methylenehexahydropentalene-1,1(2H)-dicarboxylate



72

(72). Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (95% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 13.3 min; t_R 13.9 min.^{1}H NMR ($CDCl_3$), δ: 1.17 (m, 1H, CH_2), 1.62 (m, 1H, CH_2), 1.84 (m, 2H, CH_2), 2.69 (dq, 1H, CH_2, *J*= 16.7 Hz, *J*= 1.3 Hz), 3.05 (dq, 1H, CH_2, *J*= 16.7 Hz, *J*= 1.3 Hz), 3.13 (m, 1H, CH), 3.29 (m, 1H, CH), 3.34 (s, 3H, CH_3), 3.60 (m, 1H, CH), 3.69 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 4.93 (m, 1H, CH_2=), 4.98 (m, 1H, CH_2=). ^{13}C NMR ($CDCl_3$), δ: 26.1 (CH_2), 32.0 (CH_2), 39.4 (CH_2), 47.6 (CH), 52.5 (CH_3), 52.7 (CH_3), 54.1 (CH), 56.8 (CH), 62.9 (C), 90.1 (CH), 109.1 (CH_2=), 149.9 (C=), 170.6 (C=O), 172.0 (C=O).

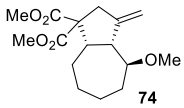
Dimethyl 4-methoxy-3-methyleneoctahydro-1H-indene-1,1-dicarboxylat



73

(73).[17] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (95% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 18.0 min; t_R 20.2 min.^{1}H NMR ($CDCl_3$), δ: 0.88 (m, 1H, CH_2), 1.31 (m, 1H, CH_2), 1.39 (m, 1H, CH_2), 1.41 (m, 1H, CH_2), 1.58 (m, 1H, CH_2), 1.74 (m, 1H, CH_2), 2.91 (m, 1H, CH_2), 2.92 (m, 1H, CH), 3.03 (bs, 1H, CH), 3.31 (m, 1H, CH_2), 3.36 (s, 3H, CH_3), 3.63 (dd, 1H, CH, *J*= 5.4 Hz, *J*= 2.8 Hz,), 3.71 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 4.79 (dd, 1H, CH_2=, *J*= 5 Hz, *J*= 2.6 Hz), 5.02 (dd, CH_2=, *J*= 5 Hz, *J*= 2.6 Hz).

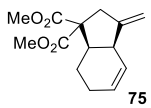
Dimethyl 4-methoxy-3-methyleneoctahydroazulene-1,1(2H)-dicarboxylat



74

(74). Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (95% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 11.3 min; t_R 12.7 min.^{1}H NMR ($CDCl_3$), δ: 1.11 (m, 1H, CH_2), 1.30 (m, 2H, CH_2), 1.58 (m, 1H, CH_2), 1.87 (m, 3H, CH_2), 2.92 (m, 3H, 2xCH, CH_2), 3.13 (m, 1H, CH_2), 3.19 (m, 2H, CH, CH_2), 3.32 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 4.97 (m, 1H, CH_2=), 5.14 (m, 1H, CH_2=). ^{13}C NMR ($CDCl_3$), δ: 27.2 (CH_2), 27.5 (CH_2), 30.0 (CH_2), 30.9 (CH_2), 38.5 (CH_2), 47.4 (CH), 52.4 (CH), 52.6 (CH_3), 52.9 (CH_3), 55.6 (CH), 64.1 (C), 86.4 (CH), 107.9 (CH_2=), 150.3 (C=), 170.4 (C=O), 171.7 (C=O).

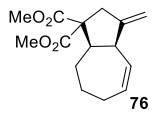
Dimethyl 3-methylene-2,3,3a,6,7,7a-hexahydro-1H-indene-1,1-di-carboxylate



75

(75).[18] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (95% hexane/2-propanol, flow 0.5 mL/min, λ= 210 nm). t_R 10.5 min; t_R 11.4 min. ^{1}H NMR ($CDCl_3$), δ: 1.13 (m, 1H, CH_2), 1.32 (m, 1H, CH_2), 2.03 (m, 2H, CH_2), 2.86 (m, 2H, CH, CH_2), 3.21 (m, 1H, CH), 3.32 (m, 1H, CH_2), 3.71 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.84 (m, 1H, CH_2=), 4.98 (m, 1H, CH_2=), 5.76 (m, 1H, CH=), 5.86 (m, 1H, CH=).

Dimethyl 3-methylene-3,3a,6,7,8,8a-hexahydroazulene-1,1(2H)-dicarboxylate (76).[18] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (95% hexane/2-propanol, flow 0.5 mL/min, λ= 210 nm). t_R 11.6 min; t_R 12.5 min. ^{1}H NMR ($CDCl_3$), δ: 1.27 (m, 1H, CH_2), 1.76 (m, 1H, CH_2), 2.23 (m, 5H, CH_2), 2.75 (m, 1H, CH_2), 3.11 (d, 1H, CH_2, *J*= 17.3 Hz), 3.25 (d, 1H, CH, *J*= 11.3 Hz), 3.62 (pt, 1H, CH, *J*= 7.4 Hz), 3.72 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 4.92 (m, 1H, CH_2=), 4.98 (m, 1H, CH_2=), 5.79 (m, 1H, CH=), 5.87 (m, 1H, CH=).

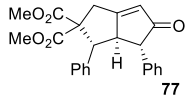


76

4.2.4.9. Typical procedure for the preparation of bicyclic compounds 77-79

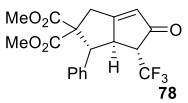
Under an atmosphere of argo n a solution of the enyne (1.0 mmol.) and $Co_2(CO)_8$ (1.05–1.1 mmol.) in dry CH_2Cl_2 (0.06M) was stirred at room temperature until TLC monitoring indicated full conversion. Then $Me_3NO{\cdot}2H_2O$ (3–10 mmol.) was added in one portion. Stirring was continued until TLC monitoring showed complete consumption of the cobalt-alkyne complex. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate).

Dimethyl -5-oxo-3,4-diphenyl-3,3a,4,5-tetrahydropentalene-2,2(1H) -dicarboxylate (77). Enantiomeric excess determined by HPLC using Chiralpak IA column (87% hexane/2-propanol, flow 0.7 mL/min, λ= 220 nm). t_R 16.4 min; t_R 25.0 min.^{1}H NMR ($CDCl_3$), δ: 3.12 (ddd, 1H, CH_2, *J*= 18.7 Hz, *J*= 2.3 Hz, *J*= 1.2 Hz), 3.17 (s, 3H, CH_3), 3.27 (d, 1H, CH, *J*= 3.3 Hz), 3.75 (pdt, 1H, CH, *J*= 12.9 Hz, *J*= 3.3 Hz, *J*= 1.3 Hz), 3.78 (s, 3H, CH_3), 3.84 (d, 1H, CH, *J*= 12.9 Hz), 3.86 (d, 1H, CH_2, *J*= 18.7 Hz), 6.11 (ptd, 1H, CH=, *J*= 2.3 Hz, *J*= 1.2 Hz), 6.85 (m, 2H, CH=), 7.08 – 7.22 (m, 8H, CH=). ^{13}C NMR ($CDCl_3$), δ: 36.7 (CH_2), 52.5 (CH_3), 53.0 (CH_3), 55.3 (CH), 56.9 (CH), 59.5 (CH), 65.6 (C), 125.1 (CH=), 126.9 (CH=), 127.7 (CH=), 128.0 (CH=), 128.3 (CH=), 128.5 (CH=), 128.6 (CH=), 135.8 (C=), 138.1 (C=), 170.6 (C=O), 171.2 (C=O), 181.9 (C=), 208.9 (C=O).



77

Dimethyl 5-oxo-3-phenyl-4-(trifluoromethyl)-3,3a,4,5-tetrahy-dropentalene-2,2(1H)-dicarboxylate (78). Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 39.5 min; t_R 53.5 min.^{1}H NMR ($CDCl_3$), δ: 2.80 (dq, 1H, CH, *J*= 9.8 Hz, *J*= 3.4 Hz), 3.07 (d, 1H, CH_2, *J*= 18.7 Hz), 3.20 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.73 (m, 2H, 2xCH), 3.84 (d, 1H, CH2, *J*= 18.7 Hz), 6.01 (m, 1H, CH=), 7.25 (m, 5H, CH=). ^{13}C NMR ($CDCl_3$), δ: 36.5 (CH_2), 49.5 (CH), 52.8 (CH_3), 53.2 (CH_3), 54.7 (CH), 54.9 (q, CH, *J*= 27.4 Hz), 65.5 (C), 125.5 (CH=), 128.2 (CH=), 128.2 (CH=), 128.7 (CH=), 135.2 (C=), 170.4 (C=O), 170.9 (C=O), 182.1 (C=O).



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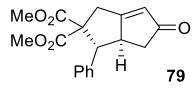
Dimethyl 5-oxo-3-phenyl-3,3a,4,5-tetrahydropentalene-2,2(1H)-di-carboxylate (79).[36] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (87% hexane/2-propanol, flow 0.5 mL/min, λ= 220 nm). t_R 24.6 min; t_R 29.2 min.^{1}H NMR ($CDCl_3$), δ: 2.04 (dd, 1H, CH_2, *J*= 18.6 Hz, *J*= 2.3 Hz), 2.54 (dd, 1H, CH_2, *J*= 18.1 Hz, *J*= 5.5 Hz), 3.05 (d, 1H, CH, *J*= 18.6 Hz), 3.15 (s, 3H, CH_3), 3.61 (m, 2H, CH_2), 3.74 (s, 3H, CH_3), 3.80 (d, 1H, CH, *J*= 18.6 Hz), 5.96 (s, 1H, CH=), 7.24 (m, 5H, CH=).



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4.2.5. Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P), European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D.).

4.2.6. References

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4.3. Asymmetric Pd-catalyzed allylic alkylation using hydrazone-phosphite ligands

Biosca, M.; Pàmies, O.; Diéguez, M. *Preliminary results.*

Abstract: New phosphite-hydrazone ligands have been synthetized and screened in the Pd-catalyzed allylic alkylation of the benchmark substrates (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**), (*rac*)-3-acetoxycylohexene (**S2**) and (*rac*)-1-(naphtalen-1-yl)allyl acetate (**S3**) using dimethyl malonate as nucleophile. Promising enantio-selectivities were only obtained for cyclic substrate **S2** (ee's up to 81%). Interestingly, the sense of enantioselectivity is mainly controlled by the configuration of the biaryl phosphite moiety; therefore, both enantiomers of the alkylated product could be obtained.

4.3.1. Introduction

Transition metal asymmetric catalysis is recognized as one of the most powerful approach to access a wide range of enantiomerically pure compounds because of its high selectivity and atom-economic nature. In this field, asymmetric Pd-catalyzed allylic substitution is one of the most studied strategies for the syntheses of chiral C-C and C-heteroatom bonds due to its high functional group tolerance and the mild reaction conditions employed.[1] The chiral ligands play a key role in controlling the enantioselectivities of products. In this sense, heterodonor ligands are among the most successful ligands for this process. The effectiveness of these ligands relies in the different electronic properties of the two coordinating functions. The different *trans* influences of the donor groups allows an efficient electronic differentiation between the two allylic carbon terminal atoms so that the nucleophilic attack takes place predominantly *trans* to the donor group with stronger *trans* influence.[1] Among these heterodonor ligands, phosphine/phosphinite-oxazoline ligands are the most studied. However, most of them rarely tolerate a broad range of substrates and nucleophiles.[1] Our group found that the introduction of π-acceptor biaryl phosphite moiety improve these limitations due to the flexibility of this moiety that allows the catalyst to adapt the chiral pocket to the steric demands of the substrate. In addition, in the allylic substitution of monosubstituted linear substrates, regioselectivity towards the desired branched isomer increased because of the π-acceptor ability of the phosphite moiety that together with the steric effect of the ligand favors the nucleophilic attack at this carbon atom.[2]

On the other hand, the research has also focused on the development of ligands containing more robust groups than oxazoline (e.g. amine,[3] pyridine,[4] thioether[5]). Several phosphine/phosphinite/phosphite-other N- and S-donor atoms have been

developed, however again most of them provide high substrate specificity and low nucleophile scope. Among them, imine-containing ligands are one of the most developed. However the study of this ligands was mainly centered on phosphine-imine ligands[6] and much less extended to their phosphinite/phosphite analogues[7]. Nevertheless, under certain conditions the imino group is prone to be easily hydrolyzed to the corresponding amine and carbonyl compound.[8] Hydrazones, on the other hand, are more stable and easy to handle compounds than imines.[9] Nevertheless, the use of hydrazone-based ligands has been much less explored. The first example was reported by Yamashita, Mino, *et al.* who applied phosphine-hydrazone ligands **1** (Figure 4.3.1) in the allylic alkylation of the model substrate with dimethyl, diethyl malonate and α-substituted malonates with high enantioselectivities (ee's up to 98%).[10] The same authors also successfully applied ferrocene-based ligands **2** (Figure 4.3.1) in the Pd-catalyzed asymmetric allylic alkylation and amination reactions with the benchmark substrate and using dimethyl malonate and benzylamine as nucleophiles (ee's up to 96% and 93%, respectively).[11] Later, Widhalm *et al.* applied phosphine-hydrazone ligands **3** (Figure 4.3.1) in the alkylation of the model substrate obtaining high enantioselectivities (up to 95% ee).[12] However, low enantioselectivities were obtained for cyclic and monosubstituted substrates.

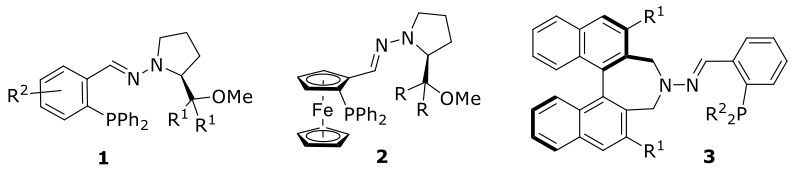


Figure 4.3.1. Phosphine-hydrazone ligands **1**-**3**.

To further evaluate the possibilities offered by this class of ligands, in this section we reported the synthesis and application of phosphite-hydrazone ligands **L55a**-**c** (Figure 4.3.2) in the Pd-catalyzed allylic alkylation of the benchmark substrates (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**), (*rac*)-3-acetoxycyclohexene (**S2**) and (*rac*)-1-(naphtalen-1-yl)allyl acetate (**S3**) using dimethyl malonate as nucleophile. These ligands will allow us to study the effect of the configuration of the biaryl phosphite moiety in the presence of hydrazone group.

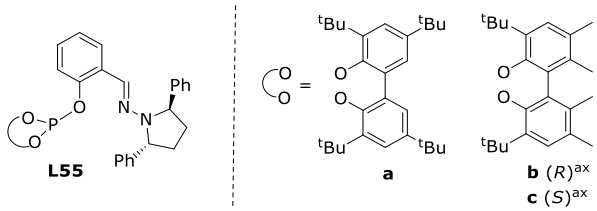


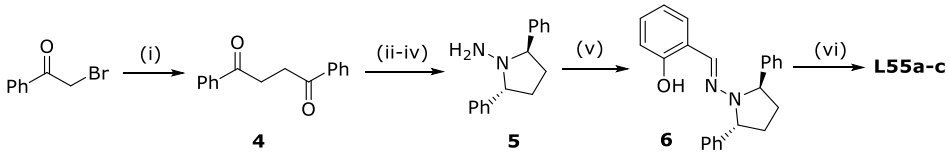
Figure 4.3.2. Phosphite-hydrazone ligands **L55a**-**c**.

4.3.2. Results and Discussions

4.3.2.1. Synthesis of ligands

The synthetic route for the synthesis of phosphite-hydrazone ligands **L55a**-**c** is showed in Scheme 4.3.1. Diketone **4** was obtained by the reaction of 2-bromo-1-phenylethanone with sodium hydroxymethanesulfinate.[13] Then, oxazaborolidine-catalyzed reduction,[14] mesylation[15] and subsequently reaction with hydrazine[15] give rise to hydrazine **5** which was coupled with salicylaldehyde to afford hydroxyl-hydrazone compound **6**. Treating compound **6** with one equivalent of the appropriate phosphorochloridite formed *in situ*[16] in the presence of triethylamine and catalytic amounts of DMAP provided direct access to the desired phosphite-hydrazone ligands **L55a**-**c**.

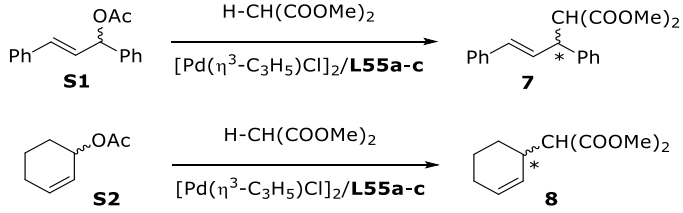
All ligands were stable during purification on neutral silica under an atmosphere of argon and all were isolated as white solids. The ligands were characterized by $^{31}P\{^{1}H\}$, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy and HRMS-ESI. The spectral assignments, based on ^{1}H-^{1}H and ^{13}C-^{1}H correlation measurements, were as expected for these C_1-symmetric ligands.



Scheme 4.3.1. Synthesis of phosphite-hydrazone ligands **L55a**-**c**. (i) Sodium hydroxymethanesulfinate, DMF, 23 h, rt; (ii) α,α-Diphenyl-2-pyrrolidine methanol, BMe_3, $BH_3{\cdot}SMe_2$, THF, 3 h, rt; (iii) MsCl, NEt_3, CH_2Cl_2, 1.5 h, -20 ºC; (iv) hydrazine monohydrate, ^{i}PrOH, 4 ºC, 4 days; (v) salicylaldehyde, toluene, 16 h, rt; (vi) $ClP(OR)_2$ (OR= **a**-**c**), NEt_3, DMAP cat., toluene, 16 h, 80 ºC.

4.3.2.2. Allylic substitution of disubstituted substrates S1 and S2 with dimethyl malonate as nucleophile

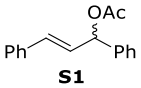
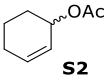
In a first set of experiments we studied the potential of phosphite-hydrazone ligands **L55a**-**c** by applying them in the allylic alkylation of the benchmark linear substrate **S1** and the more challenging cyclic substrate **S2** (Scheme 4.3.2). Generally, **S2** was alkylated with lower enantioselectivities due to the presence of less sterically *anti* substituents, which makes more difficult the control of asymmetric induction for this substrate.



Scheme 4.3.2. Allylic substitution of disubstituted substrates **S1** and **S2** with dimethyl malonate as nucleophile.

The results, which are showed in Table 4.3.1, indicated that unfortunately, the phosphite-hydrazone ligands tested not fulfilled the steric and electronic requirements around the palladium center in the allylic alkylation of **S1**, thus only low enantioselectivities could be achieved (ee's up to 12%, entries 1-3). In contrast, promising enantioselectivities were obtained in the allylic alkylation of substrate **S2** (ee's up to 80% ee). The results indicated that the ligand backbone is not able to control the tropoisomerism of the biaryl phosphite moiety **a** upon coordination to palladium (entry 1 vs 2 and 3). Therefore, the presence of a chiral enantiopure biaryl phosphite moiety is necessary to maximize enantioselectivities. Remarkably, both enantiomers of the alkylated product could be obtained by only changing the configuration of the biaryl phosphite moiety (ee's up to 81%, entries 2-3).

Table 4.3.1. Asymmetric allylic alkylation of **S1** and **S2** with dimethylmalonate using ligands **L55a**-**c**.[a]

		 S1		 S2	
Entry	Ligand	% Conv[b]	% ee[c]	% Conv[d]	% ee[e]
1	**L55a**	100	12 (*R*)	100	7 (*S*)
2	**L55b**	100	7 (*R*)	100	81 (*R*)
3	**L55c**	100	2 (*S*)	100	80 (*S*)

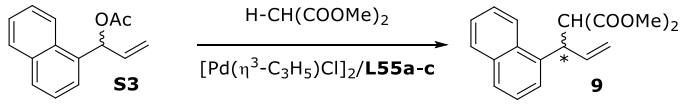
[a] Reaction conditions: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), ligand (0.011 mmol), CH_2Cl_2 as solvent, BSA/KOAc as base, rt. [b] Conversion percentage determined by ^1H NMR after 10 min. [c] Enantiomeric excesses determined by HPLC. [d] Conversions determined by GC after 30 min. [e] Enantiomeric excesses determined by GC.

4.3.2.3. Allylic substitution of the unsymmetrical linear substrate S3 with dimethyl malonate as nucleophile

Finally, we evaluated the potential of **L55a**-**c** in the more challenging monosubstituted linear substrate (*rac*)-1-naphthalen-1-yl)allyl acetate **S3**. For this type of substrates, the catalyst must be able to control the enantioselectivity and also the regioselectivity, due to a mixture of isomers can be obtained. The achiral linear product is often obtained rather than the desired chiral branched isomer.[1]

Catalytic results are summarized in Table 4.3.2. Both regioisomers were obtained in low selectivities towards the branched product (up to 70/40 (b/l)). Moreover, although ligand **L55b** containing a enantiopure biphenyl moiety with (*R*)-configuration was able to induce some enantiocontrol, a low enantioselectivity was obtained for the chiral branched product (21% ee, entry 2).

Table 4.3.2. Pd-catalyzed allylic alkylation of unsymmetrical substrate **S3** with dimethyl malonate using ligands **L55a**-**c**.[a]



Entry	Ligand	% Conv[b]	b/l[c]	%ee[d]
1	**L55a**	100	60/40	4 (*R*)
2	**L55b**	100	70/30	21 (*S*)
3	**L55c**	100	70/30	11 (*R*)

[a] Reaction conditions: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%), ligand (2.2 mol%), CH_2Cl_2 as solvent, BSA/KOAc as base, rt; [b] Conversions measured after 30 min; [c] Regioselectivity measured by ^1H NMR; [d] Enantiomeric excesses determined by chiral HPLC.

4.3.3. Conclusions

The potential of new phosphite-hydrazone ligands **L55a**-**c** were tested in the asymmetric Pd-allylic alkylation of three model substrates **S1**, **S2** and **S3**. Although low enantioselectivities were obtained in the alkylation of model di- (**S1**) and monosubstituted (**S3**) substrates (ee's up to 21%), promising enantioselectivities were achieved for the more challenging cyclic substrate **S2**. For this latter substrate, both enantiomers of the alkylated product were afforded in up to 81% ee by simply varying the configuration of the biaryl phosphite group.

4.3.4. Experimental Section

4.3.4.1. General considerations

All reactions were carried out by using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites were easily prepared in one step from the corresponding binaphthols.[16] Intermediate **1**[13] and **2**[14-15] were prepared as reported previously. Substrates **S1**-**S3**[17] were prepared following the reported procedures. ^1H, ^{13}C and ^{31}P NMR spectra were recorded with 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H and ^{13}C assignments were made based on the results of ^1H-^1H gCOSY and ^1H-^{13}C gHSQC experiments.

4.3.4.2. Procedure for the preparation of hydroxyl-hydrazone compound 6

Salicylaldehyde (366.4 mg, 3 mmol) was added to a stirred solution of the hydrazine **5** (1.0 g, 4.2 mmol) in toluene (6 mL). The reaction mixture was stirred at rt for 16 h, and then the reaction crude was concentrated to dryness and purified by flash chromatography (PE: AcOEt; 9:1) to afford hydroxyl-hydrazone **6** as white solid. Yield: 719 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.88-1.95 (m, 2H, CH2), 2.55-2.64 (m, 2H, CH2), 5.09-5.11 (m, 2H, CH), 6.65-6.78 (m, 4H, CH=), 6.96-7.00 (m, 2H, CH=), 7.24-7.30 (m, 4H, CH=), 7.34-7.38 (m, 4H, CH=). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 32.1 (CH2), 65.5 (CH), 116.2-156.3 (CH=).

4.3.4.3. General procedure for the preparation of phosphite-hydrazone ligands L55a-c

To a solution of *in situ* generated phosphorochloridite (0.55 mmol) in dry toluene (3 mL), triethylamine (0.13 mL, 1.0 mmol) and DMAP (3.4 mg, 0.027 mmol) was added. Then, this solution was placed in a 0 ºC bath. After 2 min at that temperature, a solution of the corresponding hydroxyl compound **3** (196.6 mg, 0.5 mmol), triethylamine (0.13 mL, 1.0 mmol) in toluene (3 mL) was added dropwise at 0 °C. The mixture was left to warm to 80 ºC and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral silica and dry toluene as eluent system (1% NEt_3)) to afford the corresponding deprotected aminophosphine-phosphite compound **L55a**-**c** as white solids.

L55a: Yield: 218.7 mg (56%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 137.6 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.25 (s, 9H, CH_3, ^{t}Bu), 1.30 (s, 9H, CH_3, ^{t}Bu), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.41 (m, 2H, CH_2), 1.48 (s, 9H, CH_3, ^{t}Bu), 2.15 (m, 2H, CH_2), 4.98 (m, 2H, CH), 6.60-6.67 (m, 2H, CH=), 6.74-6.76 (m, 1H, CH=), 6.95-7.12 (m, 11H, CH=), 7.30-7.35 (m, 1H, CH=), 7.40 (dd, 2H, CH=, $^{3}J_{H-H}$= 6.9 Hz, $^{4}J_{H-H}$= 2.4 Hz), 7.56 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.58 (s, 1H, CH=), 7.63 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.88-7.91 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 31.0-31.3 (CH_3, ^{t}Bu and CH_2), 34.4 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 65.1 (CH), 121.4-148.2 (aromatic carbons). MS HR-ESI [found 782.4496, $C_{51}H_{61}N_2O_3P$ $(M+H)^+$ requires 782.4493].

L55b: Yield: 108.7 mg (30%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 130.1 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.40 (s, 9H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.49 (m, 2H, CH_2), 1.73 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.22 (m, 2H, CH_2), 4.96 (m, 2H, CH), 6.56-6.63 (m, 2H, CH=), 6.77 (d, 1H, CH=, $^{3}J_{H-H}$= 7.5 Hz), 6.96-7.19 (m, 11H, CH=), 7.27 (s, 1H, CH=), 7.52 (s, 1H, CH=), 7.85 (d, 1H, CH=, $^{3}J_{H-H}$= 9.0 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.3 (CH_3), 16.6 (CH_3), 20.1 (CH_3), 21.1

(CH_3), 31.2-31.4 (CH_3, ^{t}Bu and CH_2), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 65.1 (CH), 119.6-149.1 (aromatic carbons). MS HR-ESI [found 725.3869, $C_{47}H_{53}N_2O_3P$ $(M+H)^+$ requires 725.3872].

L55c: Yield: 126.9 mg (35%). ^{31}P NMR (161.9 MHz, C_6D_6): δ= 133.4 (s). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.28 (s, 9H, CH_3, ^{t}Bu), 1.44 (m, 2H, CH_2), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.70 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.15 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 4.96 (m, 2H, CH), 6.66-6.68 (m, 2H, CH=), 6.86-6.88 (m, 1H, CH=), 6.96-7.17 (m, 13H, CH=), 7.34 (s, 1H, CH=), 7.47 (s, 1H, CH=), 7.94-7.98 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ= 16.4 (CH_3), 16.8 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.1-31.4 (CH_3, ^{t}Bu and CH_2), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 64.7 (CH), 116.5-147.6 (aromatic carbons). MS HR-ESI [found 725.3870, $C_{47}H_{53}N_2O_3P$ $(M+H)^+$ requires 725.3872].

4.3.4.4. General procedure for the allylic alkylation of substrates S1-S3

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (1.5 mmol), *N,O*-bis(trimethylsilyl)-acetamide (1.5 mmol) and KOAc (3 mg, 0.03 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For substrates **S1** and **S3** conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by chiral HPLC, while for substrates **S2**, conversions and enantiomeric excesses were determined by chiral GC (for more details see previous Section 4.1.5.5).

4.3.5. Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P), European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D.).

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4.4. Theoretical and experimental optimization of a new amino phosphite ligand library for asymmetric palladium-catalyzed allylic substitution

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Abstract: A new library of modular amino-phosphite ligands obtained in a few synthetic steps from enantiopure amino alcohols has been tested in the asymmetric Pd-catalyzed allylic substitution. The modular ligand design has been shown to be crucial in finding highly selective catalysts for each substrate type using a wide range of C-, N- and O-nucleophiles. A DFT study of the species responsible for the enantiocontrol was used for optimizing the ligand structure. By selecting the ligand components, we were able to identify unprecedented catalytic systems that can create new chiral C-C, C-N and C-O bonds in a variety of substrate types (hindered and unhindered) in high yields and enantioselectivities (ee's up to 99%). Further studies on the Pd-π-allyl intermediates provided a deep understanding of the effect of ligand structure in the origin of enantioselectivity. Potential applications of the new Pd/amino-phosphite catalysts were demonstrated by the practical synthesis of a range of chiral carbocycles by simple tandem reactions, with no loss of enantioselectivity.

4.4.1. Introduction

The syntheses of chiral C-X bonds, where X is a C atom or a heteroatom, are the most significant processes in the preparation of complex chiral molecules from simple ones. Of all the C-X bond forming strategies, enantioselective Pd-catalyzed allylic substitution is among the most studied. Some advantages include a high functional group tolerance, mild reaction conditions and high versatility of the alkene functionality of the substrate or further stereoselective functionalization.[1] Most of the top ligands reported to date or Pd-allylic substitution use the capacity of the ligand to direct the nucleophilic attack to one of the allylic terminal atoms, by means of either a secondary ligand-nucleophile interaction[2] or an electronic discrimination[3].[1] The latter approach uses heterodonor ligands to electronically differentiate between the two allylic terminal carbon atoms because of the different *trans* influences of the donor groups. Mixed phosphine/phosphinite-oxazoline ligands have played a dominant role among heterodonor.[1] Our group has also contributed in the Pd-catalyzed allylic substitution with an improved generation of ligands. We have shown that some common limitations of this process, such as low reaction rates and high substrate specificity are overcome

by introducing biaryl-phosphite moieties into the ligand design.[4] As a result increased reaction rates are achieved thanks to the larger π-acceptor ability of the phosphite groups and substrate versatility is increased because the flexibility of the phosphite moieties allows the catalyst chiral pocket to adapt to both hindered and unhindered substrates. We have therefore reported several phosphite-oxazolines as extremely effective ligands for this process.[5] Despite the important advances, the application of P-oxazoline ligands is mainly limited to the use of few nucleophiles, mainly dimethyl malonate and benzylamine. The use of functionalized malonates and alkyl alcohols has scarcely been reported.[1] In addition, only a few catalysts have been efficiently applied in the allylic substitution of a several type of substrates, with different electronic and steric proprieties, using a broad range of nucleophiles.[6] More effort has therefore to be made to expand the range of nucleophiles and substrates with the aim to synthesize more complex chiral organic molecules.

To expand the range of ligands and improve performance, we have recently moved our research towards developing heterodonor ligands that contain groups more robust than oxazolines. In this context, we reported the application of Pd/phosphite-pyridine/thioether catalytic systems in the allylic substitution of several substrate types using a large variety of nucleophiles.[7] A part from this, the successful use in this process of other heterodonor P,X-ligands where X are more robust groups than oxazoline has not been reported yet, and a systematic study of the scope of this family of ligands is still missing. Although other researchers have developed heterodonor phosphine/phosphinite-ligands, containing groups more robust than oxazoline (such as amine,[8] imine,[9] pyridine,[10] thioether,[11] etc), only a few of them have been successfully applied and these are limited in substrate and nucleophile scope (enantioselectivities are mainly high in the allylic substitution of hindered standard substrate *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** using dimethylmalonate as nucleophile). To be of practical interest, substantial improvements in terms of enantioselectivity, chemical yield and substrate and nucleophile versatility are still needed.

To address this point, in this study we prepared and tested a new family of chiral ligands that are readily accessible, easier to handle and that expand the application range. We therefore report a highly modular amino-phosphite ligand library (Figure 4.4.1) for the Pd-allylic substitution of hindered and unhindered substrates with a large number of nucleophiles. These ligands are easily prepared in few steps from readily available enantiopure amino alcohols. They also incorporate the advantages of the robustness of the amine moiety and the additional control provided by either the adaptability of the chiral cavity due to the biaryl phosphite groups and the flexibility of the chiral pocket through a highly modular ligand scaffold. In a simple two/three step procedure (Scheme 4.4.1), several ligand parameters could be easily tuned to maximize the catalyst performance so that we could investigate the effect of systematically changing the substituents (ligands **L56**, **L60** and **L61**) and configuration (ligands **L56**

and **L59**) at the ligand backbone, the amine substituents (ligands **L56**-**L58**) and the substituents and configurations in the biaryl phosphite moiety (**a**-**g**). By judicious choice of the ligand components, we achieved high enantioselectivities and activities in a number of substrates using a wide range of C-, N- and O-nucleophiles. The potential application of these new Pd/amino-phosphite catalytic systems has also been demonstrated by the practical synthesis of chiral carbocycles by simple sequential reactions, with no loss in enantiomeric excess.

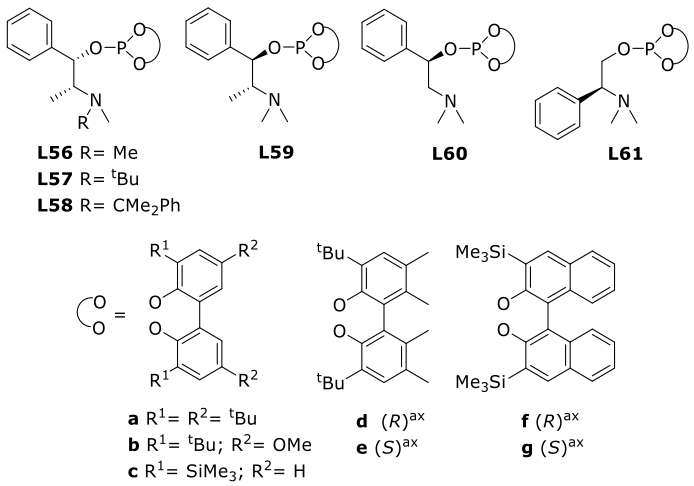


Figure 4.4.1. Phosphite-amino ligand library **L56**-**L61a**-**g**.

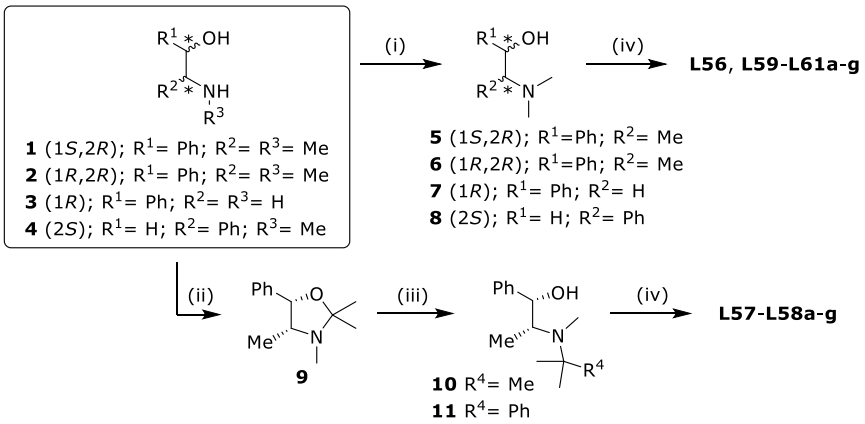
Despite the recent success of Pd/phosphite-nitrogen catalyst systems, the mechanistic aspects of these ligands are not sufficiently understood to predict, a priori, the type of ligand needed to obtain a high selectivity. To address this important point, in this paper we also carried out DFT calculations and the synthesis and characterization of the Pd-π-allyl intermediates in order to explain the origin of enantioselectivity using these highly versatile catalytic systems. It should be noted that these DFT calculations have also been crucial in the optimization of the ligand design.

4.4.2. Results and Discussion

4.4.2.1. Synthesis of ligand library

Ligands **L56**-**L61a**-**g** were synthetized from the corresponding easily accessible enantiopure amino alcohols (**1**-**4**, Scheme 4.4.1). Amino alcohols **1**-**4** already incorporate the desired diversity in the substituents and in the configurations of the amino alcohol backbone. The diversity at the amino group was achieved by either direct methylation of **1**-**4** using formic acid and formaldehyde to afford compounds **5**-**8**[12] (step i) or by formation of oxazolidine **9**[13] (step ii) from **1**, followed by ring-opening with the

corresponding Grignard reagents (compounds **10**-**11**, step iii)[14]. Finally, reaction of amino alcohols **5**-**8**, **10** and **11** with one equivalent of the desired *in situ* formed phosphorocholoridite gave access to amino-phosphite ligands **L56**-**L61a**-**g** (step iv) with the desired substituents and configurations of the biaryl phosphite group (**a**-**g**). Ligands **L56**-**L61a**-**g** were isolated in moderate-to-good yields as white solids after purification on neutral alumina under an atmosphere of argon. Advantageously, they were stable in air and very stable to hydrolysis, so further manipulation/storage was carried out in air. The HRMS-ESI spectra were in agreement with the assigned structure. Ligands **L56**-**L61a**-**g** were also characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments, made using ^{1}H–^{1}H and ^{13}C–^{1}H correlation measurements, were as expected for these C_1-symmetric ligands. One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moieties (**a**-**c**) occurred on the NMR time scale because the expected diastereoisomers were not detected by low-temperature ^{31}P NMR (in CD_2Cl_2 +35 to -85 °C).[15]

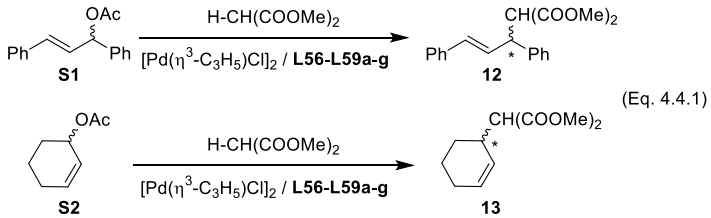


Scheme 4.4.1. Synthesis of amino-phosphites **L56**-**L61a**-**g**. (i) Formic acid, paraformaldehyde, H_2O;[12] (ii) 2,2-dimethoxypropane, toluene;[13] (iii) MeMgBr, Et_2O or PhMgBr, THF [14]; (iv) $ClP(OR)_2$; $(OR)_2$ = **a**-**g**, Py, toluene.

4.4.2.2. Allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene S1 and *rac*-3-acetoxycyclohexene S2 with ephedrine-based ligands L56-L61a-g. Computational study for ligand optimization

First, we tested the efficiency of the ephedrine-based amino-phosphite ligands **L56**-**L59a**-**g**. As mentioned previously, the asymmetric Pd-catalyzed allylic alkylation is highly dependent on the olefin geometry.[1] The effectiveness of the catalyst in transferring the chiral information to the alkylated product mainly depends on its ability to adapt to the variation of the steric demands of the substrate. In order to assess the performance of ligands **L56**-**L59a**-**g** in the allylic alkylation of substrates with different

steric requirements, we initially evaluated them in the asymmetric Pd-catalyzed allylic alkylation of the model substrates *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) and *rac*-3-acetoxycyclohexene (**S2**) (Equation 4.4.1). Because of the presence of less bulky *anti* substituents, the enantioselectivity for cyclic substrate **S2** is more difficult to control.[1] There are, therefore, fewer successful catalysts for **S2**. In all the cases, the catalysts were generated *in situ* from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the corresponding ligand.



(Eq. 4.4.1)

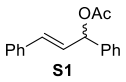
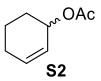
The results, summarized in Table 4.4.1, indicated that enantioselectivity is mainly affected by the substituents/configuration at the biaryl phosphite moiety (**a**-**g**) and by the amine substituents, while the configuration of the ephedrine-backbone affects less. The sense of the enantioselectivity is therefore mostly controlled by the biaryl phosphite moiety, regardless of the configuration of the ephedrine-backbone. The effect of the substituents/configuration of the biaryl phosphite moiety was studied with ligands **L56a-g** (Table 4.4.1, entries 1-7). Results indicate that the presence of trimethylsilyl groups at the *ortho*-positions of the biaryl phosphite moiety affects negatively both the activity and the enantioselectivity (entry 3 vs 1-2 and entries 6-7 vs 4-5). Also, by comparing the results from using ligand **L56a** with the related enantiopure biaryl ligands **L56d** and **L56e** (entry 1 vs 4 and 5), we can conclude that the tropoisomeric biphenyl moiety in ligands **L56a**-**c** is not controlled when coordinated in the Pd-π-allyl intermediate species. The best enantioselectivities are therefore obtained with ligands containing enantiopure biaryl phosphite moieties, with *tert*-butyl groups at the *ortho*-positions (**d** and **e**; entries 4 and 5).

We then evaluated the effect of the amine substituents with ligands **L56**-**L58**. In general, the use of ligands **L56**, with a dimethyl amine group, yielded higher enantioselectivities than ligands **L57** and **L58** (i.e. entries 4 vs 9 and 12). A plausible explanation may be the formation of mixtures of diastereomeric amino complexes with ligands **L57** and **L58** (note that the N atom in ligands **L57** and **L58** becomes a stereogenic center when coordinated to the metal). In addition, **L56** have the advantage that can be synthesized in fewer steps than **L57**-**L58** (Scheme 4.4.1).

Finally, the configuration of the ephedrine backbone was studied by comparing ligands **L56** and **L59**. A cooperative effect between the configurations of both the ephedrine-backbone and the biaryl phosphite moiety was observed. Such a cooperative effect depends of the steric demands of the substrate. While for **S1** the cooperative effect results in a matched combination for ligands **L56d** and **L59d** (81% ee, entries 4

and 15), containing a (*R*)-biphenyl moiety, the matched combination for substrate **S2**, was achieved using *pseudo*-ephedrine ligand **L59e** (70% ee, entry 16), containing a (*S*)-biphenyl phosphite moiety.

Table 4.4.1. Pd-catalyzed allylic alkylation of substrates **S1**-**S2** with dimethyl malonate as nucleophile using ephedrine-based amino-phosphite ligands **L51-L59a**-**g**.[a]

		 **S1**		 **S2**	
Entry	Ligand	Conv (Yield) [%][b]	% ee[c]	Conv (Yield) [%][d]	% ee[e]
1	**L56a**	100 (94)	31 (*R*)	100 (93)	9 (*R*)
2	**L56b**	100 (92)	29 (*R*)	100 (94)	8 (*R*)
3	**L56c**	51 (48)	11 (*R*)	98 (91)	3 (*R*)
4	**L56d**	100 (94)	81 (*R*)	100 (90)	60 (*R*)
5	**L56e**	100 (93)	75 (*S*)	100 (93)	60 (*S*)
6	**L56f**	50 (45)	64 (*R*)	95 (89)	39 (*R*)
7	**L56g**	36 (31)	27 (*S*)	97 (91)	58 (*S*)
8	**L57a**	29 (24)	6 (*S*)	100 (92)	9 (*S*)
9	**L57d**	100 (96)	42 (*R*)	100 (88)	36 (*R*)
10	**L57e**	70 (66)	33 (*S*)	100 (93)	56 (*S*)
11	**L58a**	56 (51)	0	100 (91)	9 (*S*)
12	**L58d**	100 (93)	42 (*R*)	100 (92)	53 (*S*)
13	**L58e**	84 (80)	29 (*S*)	100 (89)	68 (*S*)
14	**L59a**	62 (57)	8 (*R*)	100 (93)	7 (*R*)
15	**L59d**	100 (96)	81 (*R*)	100 (91)	45 (*R*)
16	**L59e**	89 (85)	60 (*S*)	100 (93)	70 (*S*)

[a] Reactions conditions: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), ligand (1 mol%), CH_2Cl_2 as solvent, BSA (3 eq), dimethyl malonate (3 eq), KOAc (3 mg), rt; [b] Conversions and yields determined after 6 h; [c] Enantiomeric excesses determined by HPLC; [d] Conversions and yields determined after 18 h; [e] Enantiomeric excesses determined by GC.

To find what ligand parameters should be further modified to increase enantioselectivity, we performed a DFT computational study of the key intermediates and transition states involved in the enantiocontrol of the Pd-catalyzed allylic substitution of substrate **S1**, using ligands **L59d** and **L59e** as models. The mechanistic studies found in the literature have shown that enantioselectivity is controlled in the effectively irreversible nucleophilic attack, but transition state (TS) for this step can be either early or late depending on the nature of the nucleophile, ligands, and reaction conditions. In an early transition state, the interactions leading to stereochemical differentiation can be understood from the structure of the Pd-allyl intermediate,[16] whereas the late transition state is more reminiscent of the Pd-alkene product

complex.[17] A sterically encumbered ligand can in fact be employed to push the allyl into a more product-like orientation, strongly affecting the regiochemical preference in the nucleophilic attack.[18] In our experience, a diffuse anion like malonate, or a neutral nucleophile like amine, would be expected to give relatively early transition states, whereas a highly concentrated charge like a fluoride anion gives a late TS.[19]

For the early TS case, stereochemistry is governed by both the population of the Pd-η^3-allyl intermediates and the relative electrophilicity of the allylic carbon atoms, with an allyl terminus *trans* to a phosphorus atom generally being more reactive than one *trans* to a nitrogen. When the TS is late, the formation of the most stable Pd-olefin complex controls enantioselectivity. Calculation were carried out using the B3LYP functional, the 6-31G*/LANL2DZ basis set, and the PCM solvent model with parameters for CH_2Cl_2, as implemented in Gaussian 09. The energies were further refined by performing single-point calculations at the 6-311+G** level, and by dispersion correction with the DFT-D3 model. Previous experience has shown that ammonia can be used as a good model nucleophile,[2b,20] avoiding the problems related to charge separation in conjunction with a continuum solvent model. Note that the use of ammonia as nucleophile instead of dimethyl malonate results in the inversion of the CIP descriptor in the 1,3-diphenylallyl case, due to the change in priority of the groups, although the sense of stereoselectivity is maintained.

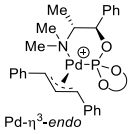
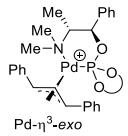
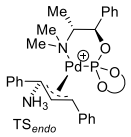
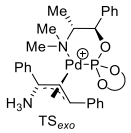
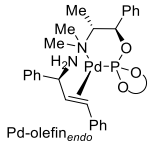
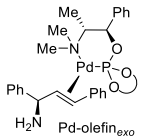
We initially calculated the relative stability of the Pd-η^3-diphenylallyl complexes. Only the two *syn*/*syn* η^3-allyl complexes (named Pd-η^3-*endo* and the Pd-η^3-*exo*, Table 4.4.2) were calculated. In accordance to what has already been described in the literature, the contribution of the other allylic species of higher energy (*anti*/*anti* and *syn*/*anti* Pd-η^3) was neglected.[19] In line with the catalytic results (Table 4.4.1), the DFT results indicate that the configuration of the biaryl-phosphite moiety controls the preferential formation of one of the *syn*/*syn* Pd-allyl intermediates. Thus, while for ligand **L59d** the formation of the Pd-η^3-*exo* is preferred (ΔG = 7.6 kJ/mol), the most stable Pd-allyl intermediate for **L59e** is Pd-η^3-*endo* (ΔG = 8.2 kJ/mol). Assuming that the allyl intermediates are in rapid equilibrium[21] and that the nucleophile will always attack *trans* to phosphorus, we can see that the preferred intermediate leads to the preferred product in this case.

We then calculated the transition states TS_{endo} and TS_{exo}, using NH_3 as nucleophile (Table 4.4.2). The energy differences of the calculated TSs agree with the catalytic results. The energy difference between both TSs of ligand **L59d** ($\Delta G^{\#}$= 4 kJ/mol) is higher than for ligand **L59e** ($\Delta G^{\#}$= 2 kJ/mol). This is in good agreement with the higher enantioselectivities achieved using ligand **L59d** (Table 4.4.1, 81% ee for **L59d** vs 60% ee for **L59e**). In addition, the formation of opposite enantiomers of the substituted product is predicted when using ligands **L59d** and **L59e**.

Finally, we calculated the Pd-olefin intermediates ($Pd\text{-}olefin_{endo}$ and $Pd\text{-}olefin_{exo}$). The results (Table 4.4.2) indicated that the larger energy difference of the Pd-olefin complexes is achieved with ligand **L59e** ($\Delta G^{\#}$= 5 kJ/mol for **L59e** vs 1.8 kJ/mol for

L59d). Thus, in the current case, the product complex energies do not correlate with the transition state energies or with the experimental selectivities. The structural elucidation of the Pd-allyl intermediates and the determination of their relative reactivity towards the nucleophile are therefore crucial to understand their catalytic behavior (see below, Section 4.4.2.5).

Table 4.4.2. Calculated energies for the *endo* and *exo* Pd-η^3-allyl intermediates, TSs and Pd-π-olefin complexes using **S1** and NH_3 as nucleophile.[a]

	L59d	**L59e**
 Pd-η^3-*endo*	0	8.2
 Pd-η^3-*exo*	7.6	0
 TS_{endo}	0	2
 TS_{exo}	4	0
 Pd-olefin$_{endo}$	0	0
 Pd-olefin$_{exo}$	1.8	5

[a] Relative energies in kJ/mol.

Figure 4.4.2 shows the calculated TSs for the major and the minor pathway with both ligands. A special feature of all these TSs is that the methyl substituent of the ephedrine-backbone is pointing in the opposite direction to the coordination sphere. This finding suggests that the methyl group should have little impact on the enantioselectivity. To prove this, we recalculated the TSs by removing the methyl substituent of the ephedrine-backbone (new ligand **L60e**; Figure 4.4.1). Surprisingly, the calculated

energy difference between the two TSs for the formation of both enantiomers of the alkylated product (Figure 4.4.3a) was 8.5 kJ/mol (ligand **L60e**) surpassing the values for ligands **L59d** and **L59e** (4 kJ/mol and 2 kJ/mol, respectively), indicating that ligand **L60e** should provide higher enantioselectivity than the ephedrine-based ligands **L59d** and **L59e**.

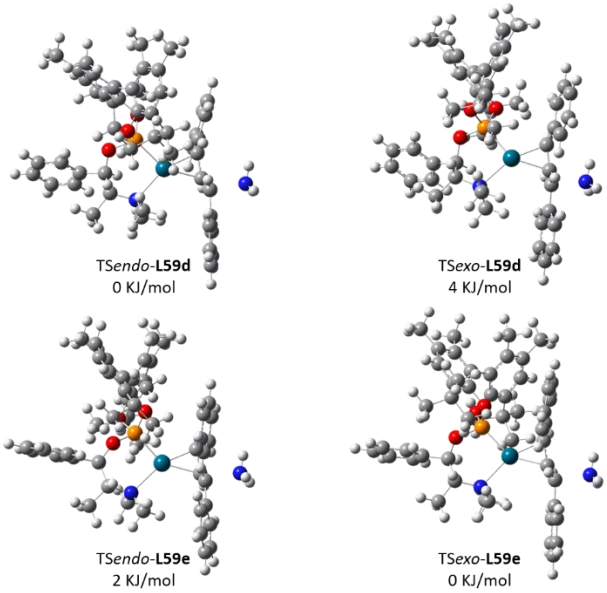


Figure 4.4.2. Calculated transition states using ephedrine-based ligands **L59d** and **L59e**.

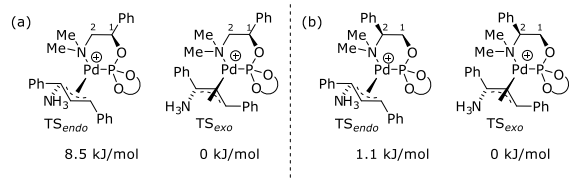


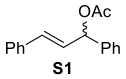
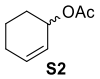
Figure 4.4.3. Calculated energies of transition states (TSs) using (a) ligands **L60e** and (b) **L61e**.

To study the effect of the other stereogenic center of the ephedrine-backbone (C-2), the phenyl substituent was switched from C-1 to C-2 (new ligand **L61e**, Figure 4.4.1). Slightly lower energy difference between the TSs were achieved than using Pd-**L59e** (Figure 4.4.3b), which suggest that this modification should provide lower enantioselectivities than **L59e**.

These theoretical results prompted us to prepare and screen amino-phosphite ligands **L60-L61d**-**e** (Scheme 4.4.1) in the asymmetric allylic substitution of substrates **S1** and **S2**. The experimental results are shown in Table 4.4.3. As predicted by the theoretical calculations, the use of ligand **L60e**, without the methyl substituent at stereogenic C-2

of the ephedrine backbone, in the allylic alkylation of **S1** provided the highest enantioselectivities (Table 4.4.3, entry 2, 94% (*S*) ee), while the use of ligand **L61e** led to similar enantioselectivities to **L59e** (entry 4). The same behavior is observed in the allylic alkylation of cyclic substrate **S2**. Using ligand **L60e** we could therefore increase enantioselectivity from 70% to 82% ee (Table 4.4.3, entry 2). Interestingly, for substrate **S1**, ligand **L60d** provided similar high enantioselectivities like **L60e** did, but in the opposite enantiomer of the substitution product (92% (*R*) ee, entry 1). Both enantiomers of the substitution products can be therefore obtained by simply changing the configuration of the biaryl phosphite moiety in ligands **L60**. All these results show the importance of using modular scaffold to build new ligand systems.

Table 4.4.3. Pd-catalyzed allylic alkylation of substrates **S1** and **S2** with dimethyl malonate using amino-phosphite ligands **L60**-**L61d**-**e**.[a]

		 S1		 S2	
Entry	Ligand	Conv (Yield) [%][b]	% ee[c]	Conv (Yield) [%][d]	% ee[e]
1	**L60d**	100 (94)	92 (*R*)	100 (90)	70 (*R*)
2	**L60e**	100 (96)	94 (*S*)	100 (89)	82 (*S*)
3	**L61d**	100 (92)	41 (*R*)	100 (91)	46 (*R*)
4	**L61e**	100 (93)	62 (*S*)	100 (92)	62 (*S*)
5[f]	**L60e**	100 (95)	97 (*S*)	100 (91)	86 (*S*)
6[g]	**L60e**	98 (91)	92 (*S*)	94 (87)	83 (*S*)
7[h]	**L60e**	38 (32)	89 (*S*)	56 (49)	74 (*S*)

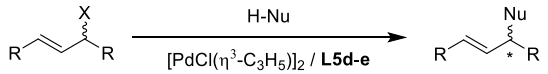
[a] Reaction conditions: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), ligand (1 mol%), CH_2Cl_2 as solvent, BSA (3 eq), dimethyl malonate (3 eq), KOAc (3 mg), rt; [b] Conversions and yields determined after 6 h; [c] Enantiomeric excesses determined by HPLC; [d] Conversions and yields determined after 18 h; [e] Enantiomeric excesses determined by GC; [f] Reactions carried out at 5 °C for 18 h; [g] Reactions carried out at 0 °C for 18 h; [h] Reactions carried out at -15 °C for 18 h.

Enantioselectivity can be improved by controlling not only the structural but also the reaction parameters. We therefore studied these reactions at a low reaction temperature (entries 5-7). Enantioselectivity was further improved (ee's up to 97% for **S1** and 86% for **S2**) by lowering the reaction temperature to 5 ºC (Table 4.4.3, entry 5).

4.4.2.3. Allylic substitution of symmetrical 1,3-disubstituted allylic substrates S1-S10 with other C-, N- and O-nucleophiles. Scope and limitations

With the optimal amino-phosphite ligands **L60e** and **L60d** we investigated the substrate and nucleophile scope. The following linear and cyclic disubstituted substrates with different steric properties were studied (Equation 4.4.2): *rac*-1,3-diphenyl-3-

acetoxyprop-1-ene (**S1**), *rac*-1,3-di(4-tolyl)-3-acetoxyprop-1-ene (**S3**), *rac*-1,3-di(4-bromophenyl)-3-acetoxyprop-1-ene (**S4**), *rac*-1,3-di(3-methoxyphenyl)-3-acetoxyprop-1-ene (**S5**), *rac*-1,3-di(2-tolyl)-3-acetoxyprop-1-ene (**S6**), *rac*-1,3-dimethyl-3-acetoxyprop-1-ene (**S7**), *rac*-*E*-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate (**S8**), *rac*-3-acetoxycyclohexene (**S2**), *rac*-3-acetoxycyclopentene (**S9**) and *rac*-3-acetoxycycloheptene (**S10**). The range of nucleophiles was also expanded, compared to previous work, with special attention to the more challenging and interesting, from a synthetic point of view, functionalized malonates, β-diketones and alkyl alcohols, which have hardly been reported.

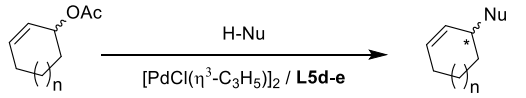


(Eq. 4.4.2)

S1 R= Ph; X= OAc
S3 R= *p*Me-C_6H_4; X= OAc
S4 R= *p*Br-C_6H_4; X= OAc
S5 R= *m*OMe-C_6H_4; X= OAc
S6 R= *o*Me-C_6H_4; X= OAc
S7 R= Me; X= OAc
S8 R= ^{i}Pr; X= OCO_2Et

14 R= Ph; H-Nu= H-CH(CO_2Et)$_2$
15 R= Ph; H-Nu= H-CH(CO_2Bn)$_2$
16 R= Ph; H-Nu= H-CMe(CO_2Me)$_2$
17 R= Ph; H-Nu= H-CAllyl(CO_2Me)$_2$
18 R= Ph; H-Nu= H-CButenyl(CO_2Et)$_2$
19 R= Ph; H-Nu= H-CPentenyl(CO_2Et)$_2$
20 R= Ph; H-Nu= H-Propargyl(CO_2Me)$_2$
21 R= Ph; H-Nu= H-CH($COMe$)$_2$
22 R= Ph; H-Nu= H-NHCH_2Ph
23 R= Ph; H-Nu= H-OCH_2Ph
24 R= Ph; H-Nu= H-OCH_2(*p*Me-C_6H_4)

25 R= Ph; H-Nu= H-OCH_2(*p*CF_3-C_6H_4)
26 R= Ph; H-Nu= H-OCH_2(*m*Me-C_6H_4)
27 R= *p*Me-C_6H_4; H-Nu= H-CH(CO_2Me)$_2$
28 R= *p*Me-C_6H_4; H-Nu= H-CAllyl(CO_2Me)$_2$
29 R= *p*Me-C_6H_4; H-Nu= H-Butenyl(CO_2Et)$_2$
30 R= *p*Br-C_6H_4; H-Nu= H-CH(CO_2Me)$_2$
31 R= *m*OMe-C_6H_4; H-Nu= H-CH(CO_2Me)$_2$
32 R= *o*Me-C_6H_4; H-Nu= H-CH(CO_2Me)$_2$
33 R= Me; H-Nu= H-CH(CO_2Me)$_2$
34 R= Me; H-Nu= H-CMe(CO_2Me)$_2$
35 R= Me; H-Nu= H-CAllyl(CO_2Me)$_2$
36 R= ^{i}Pr; H-Nu= H-CH(CO_2Me)$_2$



S2 n=1
S9 n=0
S10 n=2

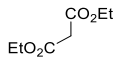
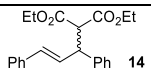
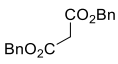
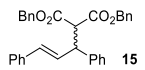
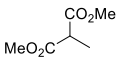
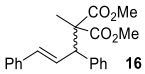
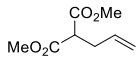
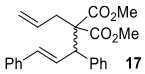
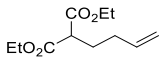
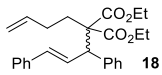
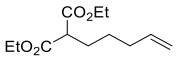
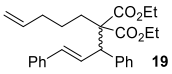
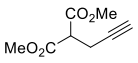
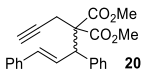
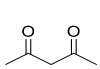
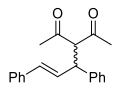
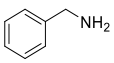
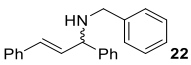
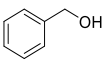
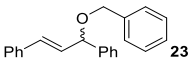
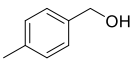
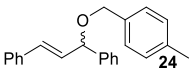
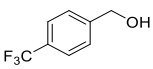
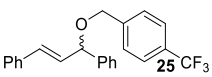
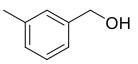
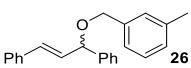
37 n=1; H-Nu= H-CH(CO_2Et)$_2$
38 n=1; H-Nu= H-CMe(CO_2Me)$_2$
39 n=1; H-Nu= H-CAllyl(CO_2Me)$_2$
40 n=1; H-Nu= H-CPropargyl(CO_2Me)$_2$
41 n=1; H-Nu= H-CH($COMe$)$_2$

42 n=0; H-Nu= H-CH(CO_2Me)$_2$
43 n=0; H-Nu= H-CPropargyl(CO_2Me)$_2$
44 n=2; H-Nu= H-CH(CO_2Me)$_2$
45 n=2; H-Nu= H-CPropargyl(CO_2Me)$_2$

The results of Pd/**L60e** and Pd/**L60d** in the allylic substitution of **S1** using a wide range of C-, N- and O-nucleophiles are shown in Table 4.4.4. It can be observed that enantioselectivity was relatively unaffected by a change in the steric nature of the ester groups and in the substituents of the malonate nucleophiles (entries 1-13). Therefore, a variety of malonates, including those α-substituted, reacted cleanly with **S1** to afford products **14**-**20** in high yields, and with enantioselectivities that were as high as or higher than those obtained with dimethyl malonate (ee's up to 99% ee, entries 1-13). Among them, it should be stressed the high enantioselectivities using allyl, butenyl, pentenyl and propargyl substituted malonates (entries 7-13, between 95-99% ee). This is advantageous because the resulting products are important precursors for more complex chiral molecules (see section 4.4.2.4 below). Excellent enantiocontrol was also achieved when the β-diketone acetophenone and the *N*-benzylamine were used as

nucleophiles (ee's up to 99%; entries 14-16). It should be pointed out that the excellent results achieved using benzylamine validates the use of ammonia as nucleophile for the computational model. In all cases, both enantiomers of the substituted product can be obtained in high yields and enantioselectivities.

Table 4.4.4. Allylic substitution of **S1** with other several C-, N- and O-nucleophiles using Pd/**L60d**-**e** catalytic systems.[a]

			L60d		**L60e**	
Entry	Nucleophile	Product	%Yield[b]	% ee[c]	%Yield[b]	% ee[c]
1		 **14**	91	92 (*R*)	92	93 (*S*)
2[d]			88	94 (*R*)	87	95 (*S*)
3		 **15**	93	92 (*R*)	91	94 (*S*)
4[d]			91	94 (*R*)	93	96 (*S*)
5		 **16**	92	95 (*S*)	90	96 (*R*)
6[d]			91	98 (*S*)	92	99 (*R*)
7		 **17**	94	96 (*S*)	93	97 (*R*)
8[d]			92	99 (*S*)	91	99 (*R*)
9[d]		 **18**	95	94 (*S*)	92	95 (*R*)
10		 **19**	93	95 (*S*)	94	97 (*R*)
11[d]			94	97 (*S*)	91	99 (*R*)
12		 **20**	91	94 (*R*)	90	96 (*R*)
13[d]			92	97 (*R*)	93	98 (*R*)
14		 **21**	93	96 (*R*)	94	96 (*S*)
15[d]			91	98 (*R*)	93	99 (*S*)
16		 **22**	89	97 (*S*)	92	99 (*R*)
17[e]		 **23**	92	53 (*S*)	95	56 (*R*)
18[e]		 **24**	91	28 (+)	94	30 (-)
19[e]		 **25**	92	91 (+)	94	94 (-)
20[e]		 **26**	93	68 (+)	91	70 (-)

[a] Reaction conditions: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), CH_2Cl_2 as solvent, ligand (1 mol%), BSA (3 eq), KOAc (3 mg), rt; [b] Full conversions were achieved after 12 h and 24 h for reactions carried out at 23 °C and 5 °C, respectively; [c] Enantiomeric excess determined by chiral HPLC or GC; [d] Reactions carried out at 5 °C for 24 h; [e] Reactions carried out using 2 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol% ligand, Cs_2CO_3 (3 eq). Full conversions were achieved in all cases.

We then went on to study the allylic substitution of **S1** using alkyl alcohols as a challenging class of O-nucleophiles. The stereoselective construction of compounds with ether groups next to a chiral carbon is important for the preparation of biologically active compounds.[22] Although the enantioselective Pd-allylic etherification is currently studied by important research groups, few successful examples have been reported. Among them phenols have been the most studied,[23] while the aliphatic alcohols have been explored less.[11f,24] The reaction of Pd/**L60e** and Pd/**L60d** with several substituted benzylic alcohols also proceeded smoothly to afford both enantiomers of the desired products in high yields (Table 4.4.4, entries 17-20). Furthermore, the enantioselectivity was seen to be influenced by the electronic nature of the substituted benzylic alcohol. The highest enantioselectivity (ee's up to 94%, entry 19) was obtained when the benzylic alcohol contained an electron deficient *para* CF_3 substituent, and the selectivity diminished gradually as the substituent was more electron-rich. This behavior is opposite to that observed in the etherification reaction with Pd/(*S*,*R*p)-FerroNPS catalytic system,[24c] which is one of the few Pd-catalysts that has been specially designed for this purpose and successfully applied. The Hammet plot of this electronic effect shows a linear free-energy relationship (Figure 4.4.4; ρ= 1.78) between enantioselectivity and the electronic character of the substituent.[25] This plot could therefore be used for predicting the enantioselectivity of asymmetric allylic substitution when *para*-substituted benzylic alcohols are used.

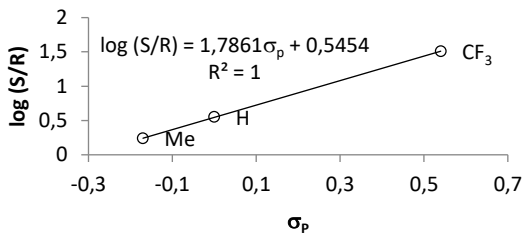


Figure 4.4.4. Hammet plot for the Pd-catalyzed allylic etherification of **S1** with ligand **L60e**.

The scope of Pd/**L60d**-**e** catalytic systems was further studied by using other linear substrates (Equation 2) with different electronic (*rac*-1,3-di(4-tolyl)-3-acetoxyprop-1-ene **S3**, *rac*-1,3-di(4-bromophenyl)-3-acetoxyprop-1-ene **S4** and *rac*-1,3-di(3-methoxyphenyl)-3-acetoxyprop-1-ene **S5**) and steric requirements (*rac*-1,3-di(2-tolyl)-3-acetoxyprop-1-ene **S6**, *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S7** and *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S8**) than substrate **S1** (Figure 5, compounds **27**-**36**). The results using **S3** followed the same trend than for **S1**. High enantioselectivities, in both enantiomers of the substituted product, were obtained in the alkylation of **S3** using several malonates, including those α-substituted with allyl and butenyl groups (ee's up to 99%, compounds **27**-**29**). In addition, catalytic performance is unaffected

by the presence of electronwithdrawing groups at the *para*-position as well as by the introduction of *meta*- and *ortho*-substituents at the phenyl groups. Thus, high enantioselectivities were also achieved for the allylic alkylation of substrates **S4**-**S6** (Figure 4.4.5; ee's up to 94%, compounds **30**-**32**). The allylic substitution of substrate **S7**, which is less sterically demanding and is substituted much less enantioselectively than **S1**,[26] also proceeded smoothly (compounds **33**-**35**). Although enantioselectivity depended on the steric properties of the nucleophile, we were pleased to see that for the more challenging α-substituted malonates enantioselectivities were higher (compounds **34**-**35**, ee's up to 81%) than for the standard dimethyl malonate. Finally, we were pleased to find out that Pd/**L60d**-**e** also provided high enantioselectivity, in both enantiomers of the alkylated product, of the more demanding substrate **S8** (95% ee) which usually reacts with lower yields and enantioselectivities than model substrate **S1**.

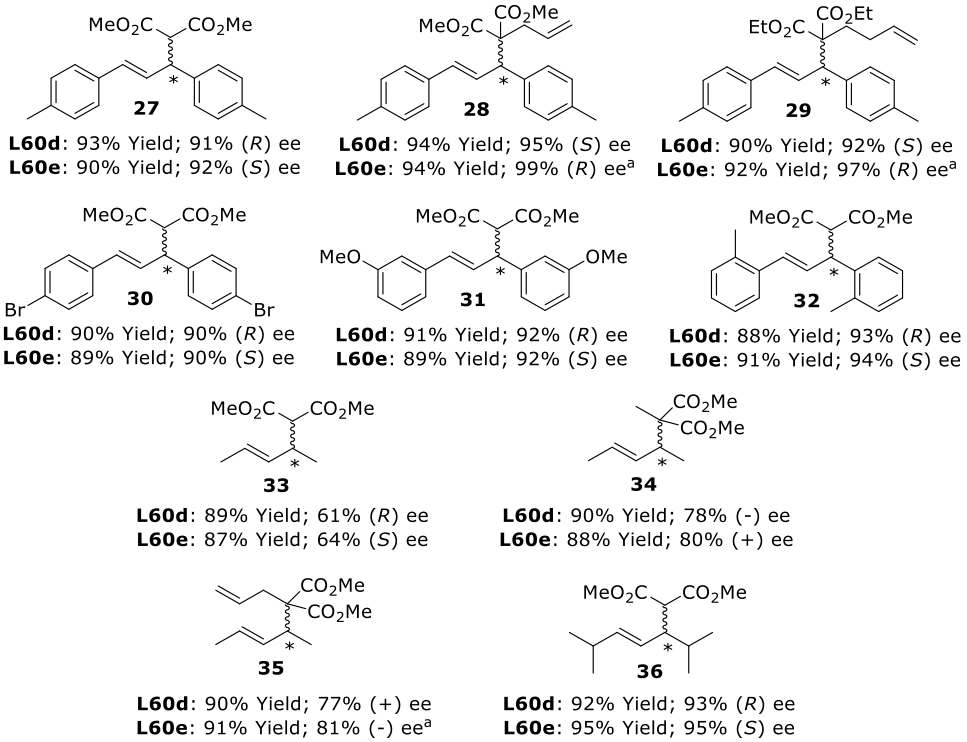
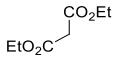
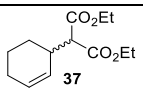
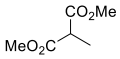
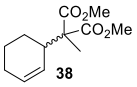
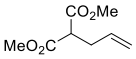
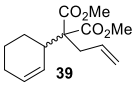
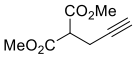
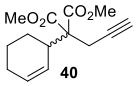
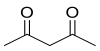
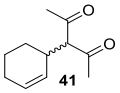
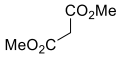
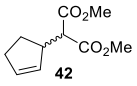
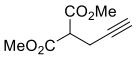
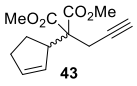
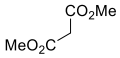
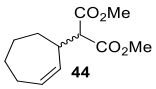
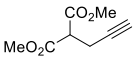
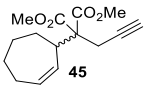


Figure 4.4.5. Pd-allylic substitution of **S3**-**S8** using several C-nucleophiles. Full conversions were achieved in all cases. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, CH_2Cl_2 as solvent, ligand (1 mol%), 23 °C, 18 h. [a] Reaction carried out at 5 °C for 24 h.

Finally, the good performance of Pd/**L60e** was also seen in the allylic substitution of cyclic substrates using a range of C-nucleophiles, including the less studied α-substituted malonates and β-diketones. For substrate **S2**, enantioselectivities were as

high as those obtained with dimethyl malonate (Table 4.4.5, entries 1-5, products **37**-**41**). Even more interesting is the high enantioselectivity achieved using other cyclic substrates with different ring size (*rac*-acetoycyclopentene **S9** and *rac*-acetoxycycloheptene **S10**). The enantiocontrol was high in both cases, even in the allylic substitution of *rac*-3-acetoxycyclopentene (products **42** and **43**), which is usually alkylated much less enantioselectively than 6- and 7-membered cyclic substrates.

Table 4.4.5. Allylic substitution of cyclic substrates **S2**, **S6** and **S7** with other several C-nucleophiles using the Pd/**L60e** catalytic system.[a]

Entry	Substrate	Nucleophile	Product	% Yield[b]	% ee[c]
1	**S2**		 **37**	89	83 (*S*)
2	**S2**		 **38**	91	86 (+)
3	**S2**		 **39**	94	90 (-)
4	**S2**		 **40**	93	87 (*S*)
5	**S2**		 **41**	92	76 (-)
6	**S6**		 **42**	88	75 (-)
7	**S6**		 **43**	92	84 (*S*)
8	**S7**		 **44**	93	91 (*S*)
9	**S7**		 **45**	94	93 (*S*)

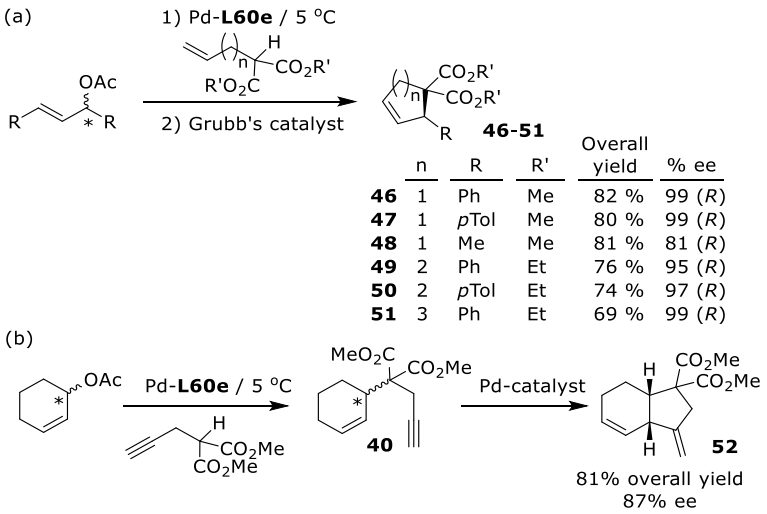
[a] Reaction conditions: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), CH_2Cl_2 as solvent, ligand (1 mol%), BSA (3 eq), KOAc (3 mg), 5 ºC; [b] Full conversions were achieved after 24 h; [c] Enantiomeric excess determined by chiral HPLC or GC.

In summary, by a theoretically-guided optimization of the crucial stereodefining moieties in this new family of modular amino-phosphite ligand library, we have been able to identified one of the very few catalytic systems that can create new C-C, C-N and C-O bonds, in a number of substrate types, with different electronic and steric

proprieties, using a wide range of nucleophiles, in high activities and enantioselectivities.

4.4.2.4. Synthetic applications of the allylic substitution compounds. Preparation of chiral carbocycles

Asymmetric allylic alkylation (AAA) is a relevant method for creating chiral C-C and C-heteroatom bonds. Furthermore, functionalized substrates (see for example the above compounds **17**-**19**, **28**-**29** and **35**, formed by Pd-AAA with nucleophiles containing allyl, butenyl and pentenyl groups) open up new pathways to easily build up more complex molecules. To illustrate these aspects, we have prepared a range of chiral carbocycles (**46**-**51**) by simple tandem reactions involving allylic substitution of the substrate and ring-closing metathesis reactions (Scheme 4.4.2a) or the sequential allylic substitution and cycloisomerization of 1,6-enyne (Scheme 4.4.2b) reactions. Thus, the allylic substitution compounds (**17**-**19**, **28**-**29** and **35**; Equation 2), bearing a terminal alkene, can undergo clean ring-closing metathesis with no loss in enantiomeric excess. A range of 5-, 6- and 7-membered carbocycles with different R substituents (R= Me, Ph, *p*-Tol) were therefore prepared in good yields and high enantioselectivities (compounds **46**-**51**; Scheme 4.4.2a). Also, the carbobicycle hyndrindane **52** is obtained by cycloisomerization of the 1,6-enyne **40**, produced from the AAA of **S2** with dimethyl propargylmalonate, using the methodology described by Uozumi and coworkers (Scheme 4.4.2b).

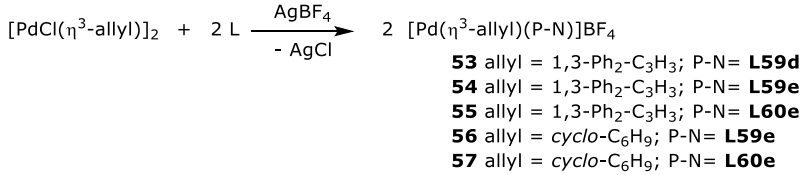


	n	R	R'	Overall yield	% ee
46	1	Ph	Me	82 %	99 (*R*)
47	1	*p*Tol	Me	80 %	99 (*R*)
48	1	Me	Me	81 %	81 (*R*)
49	2	Ph	Et	76 %	95 (*R*)
50	2	*p*Tol	Et	74 %	97 (*R*)
51	3	Ph	Et	69 %	99 (*R*)

Scheme 4.4.2. Preparation of chiral carbocycles via sequential allylic substitution of functionalized olefins/cyclation reactions.

4.4.2.5. NMR study of key Pd-η^3-allyl intermediates

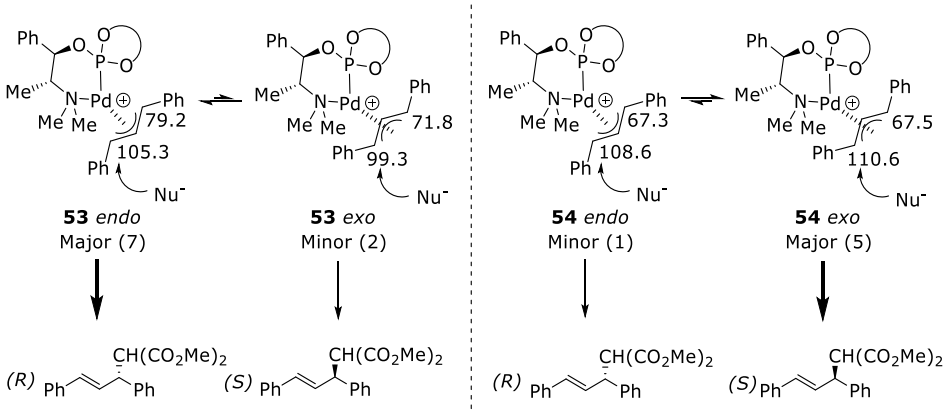
Our DFT studies have shown that enantioselectivity is determined during the nucleophilic attack (see above section 4.4.2.2). Consequently, structural elucidation of the Pd-allyl intermediates and the determination of their relative reactivity towards the nucleophile are essential to understand their catalytic behavior. For this purpose we studied the Pd-η^3-allyl compounds **53**-**57** [Pd(η^3-allyl)(P-N)]BF_4 (P-N= **L59**-**L60d**-**e**) to obtain further insight into how ligand parameters affect catalytic performance (Scheme 4.4.3). These ionic palladium complexes, which contain 1,3-diphenyl or cyclohexenyl allyl groups, were prepared using the previously reported method from the corresponding Pd-allyl dimer and the appropriate ligand in the presence of silver tetrafluoroborate (Scheme 4.4.3).[27] The complexes were characterized by elemental analysis and by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments were based on information from ^{1}H-^{1}H, ^{31}P-^{1}H and ^{13}C-^{1}H correlation measurements in combination with ^{1}H-^{1}H NOESY experiments. Unfortunately, we were unable to obtain crystal of sufficient quality to perform X-ray diffraction measurements.



Scheme 4.4.3. Preparation of [Pd(η^3-allyl)(P-N)]BF_4 complexes **53**-**57**

4.4.2.5.1. Palladium 1,3-diphenyl-allyl complexes

The VT-NMR study (30 ºC to -80 ºC) of Pd-allyl intermediates **53** and **54**, which respectively contains ephedrine-based ligands **L59d** and **L59e**, showed a mixture of two isomers in equilibrium at a ratio of 7:2 and 1:5, respectively.[28] Both isomers were unambiguously assigned by NMR to the two *syn*/*syn* Pd-η^3-*endo* and *exo* isomers (Scheme 4.4.4).



Scheme 4.4.4. Diastereoisomer Pd-allyl intermediates for **S1** with ligands **L59d** and **L59e**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

In all cases, the NOE indicated interactions between the two terminal protons of the allyl group, which clearly indicates a *syn*/*syn* disposition (Figure 4.4.6). In addition, for the major isomer of **53** and the minor isomer of **54**, one of the methyl substituents of the amino group (the one that shows NOE interaction with the hydrogen attached to C-2) showed NOE between the terminal allyl proton *trans* to the phosphite moiety, while this interaction appeared with the central allyl proton in the minor isomer **53** and major isomer of **54** (Figure 4.4.6). Moreover, the other methyl substituent of the amino group (the one that shows NOE with the hydrogen attached to C-1) also shows NOE interaction with the central allyl proton in major isomer **53** and the minor isomer of **54**, while this interaction appears with the terminal allyl proton *trans* to the phosphite moiety for minor and major isomers of **54** and **54**, respectively. Finally, the minor isomer of **53** and major isomer of **54** also showed NOE interactions between the terminal allyl proton *trans* to the amino group with one of the *tert*-butyl substituents at the biaryl phosphite moiety (the one that shows NOE contacts with the hydrogen attached to C-1). These interactions can be explained by assuming a *syn*/*syn endo* disposition for major and minor isomers of **53** and **54**, and a *syn*/*syn exo* disposition for minor and major isomers of **53** and **54** (Scheme 4). Although the population of the Pd-allyl intermediates obtained by DFT calculations is different than those find by NMR, the general trend is reproduced well. Thus, while for Pd/**L59d** the major isomer is Pd-η^3-*endo*, for Pd-**L59e** the major isomer is Pd-η^3-*exo*.

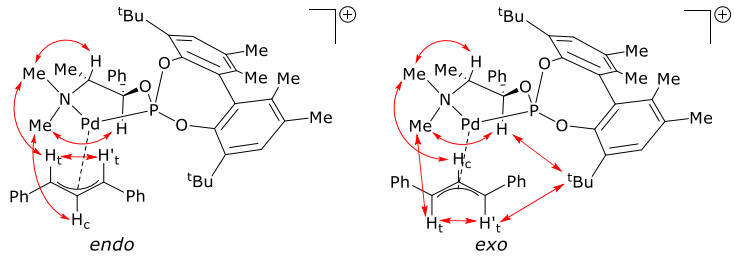
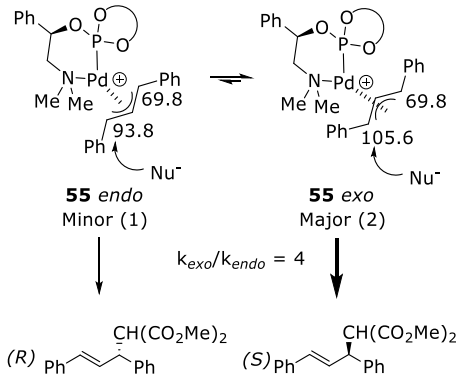


Figure 4.4.6. Relevant NOE contacts from the NOESY experiment of [Pd(η^3-1,3-diphenylallyl)(**L59d**)]BF_4 (**53**) isomers are shown as example. The same NOE contacts were observed for [Pd(η^3-1,3-diphenylallyl)(**L59e**)]BF_4 (**54**) isomers.

In all isomers, the carbon NMR chemical shifts indicate that the most electrophilic allyl carbon terminus is *trans* to the phosphite moiety (Scheme 4.4.4). Assuming that the nucleophilic attack takes place at the more electrophilic allyl carbon terminus,[1] and in line with the DFT calculations, the stereochemical outcome of the reaction is not fully controlled by the population of the Pd-allyl intermediates (note that the diastereomeric excesses differ from the enantiomeric excesses). So, the relative electrophilicity of the terminal allylic carbons of each isomer plays an important role and have to been taken into account. In this respect, Pd/**L59d** catalyst shows higher electronic differentiation between the more electrophilic allylic terminal carbon atoms of both isomers ($\Delta(\delta^{13}C)$= 6 ppm) than in Pd/**L59e** ($\Delta(\delta^{13}C)$= 2 ppm). This higher electronic differentiation makes the major isomer of Pd/**L59d** to react faster than the major isomer of Pd/**L59e** and fully accounts for the higher enantioselectivity achieved with Pd/**L59d** than with Pd/**L59e**.

The VT-NMR study of Pd-allyl intermediate **55** containing ligand **L60e**, which differs from previous Pd/**L59d**-**e** catalysts in that the methyl substituent of the ephedrine ligand backbone has been removed, also had a mixture of two *syn*/*syn* Pd-η^3-*endo* and *exo* isomers, at a ratio 1:2 (Scheme 4.4.5).



Scheme 4.4.5. Diastereoisomer Pd-allyl intermediates for **S1** with ligand **L60e**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

Also, the most electrophilic allyl carbon terminus was *trans* to the phosphite moiety. However, an important difference between complexes **53** and **54** is the higher electronic differentiation between the more electrophilic allylic terminus carbon atoms of both isomers in complex **55** ($\Delta(\delta^{13}C)$= 11 ppm) than in previous complexes **53** and **54** ($\Delta(\delta^{13}C)$= 6 and 2 ppm, respectively). This higher electronic differentiation may explain the higher enantioselectivity obtained with Pd/**L60e** than with Pd/**L59d**-**e**. Accordingly, the reactivity of the Pd-intermediates with sodium malonate at low temperature by in situ NMR indicates that the major Pd-η^3-*exo* isomer reacts 4 times faster than minor Pd-η^3-*endo* isomer (Figure 4.4.7), which fully agrees with the ee obtained experimentally.

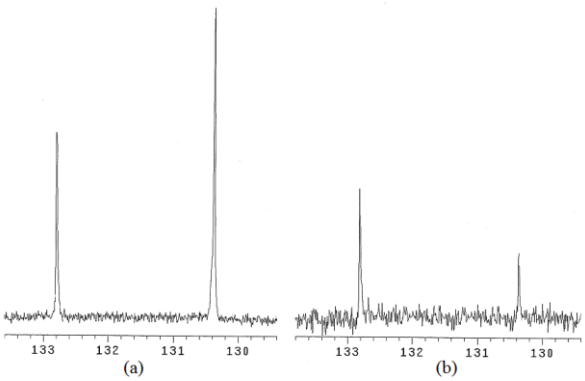


Figure 4.4.7. ^{31}P-{^1H}NMR spectra of [Pd(η^3-1,3-diphenylallyl)(**L60e**)]BF_4 (**55**) in CD_2Cl_2 at -80 °C (a) before the addition of sodium malonate and (b) after the addition of sodium malonate.

4.4.2.5.2. Palladium 1,3-cyclohexenyl-allyl complexes

Finally, in an attempt to provide further information about the positive effect on enantioselectivity observed in the allylic substitution of the unhindered cyclic substrate **S2** when the methyl substituent of the ephedrine backbone was removed, we also studied the Pd-1,3-cyclohexenyl-allyl intermediate **56**, which contains ephedrine-based amino-phosphite ligand **L59e**, and compared it with its related amino-phosphite counterpart (Pd/**L60e**). The VT-NMR (35 °C to –80 °C) of Pd intermediates **56** and **57** showed a mixture of the two possible isomers at a ratio of 10:1 and 20:1, respectively (Scheme 4.4.6). The major isomers were unambiguously assigned by NOE to Pd-η^3-*endo* isomers (Figure 4.4.8). In both cases, the NOE indicates interactions between the central allyl proton and one of the methyl substituents of the amino group (the one that shows NOE with the hydrogen attached to C-1 of the ligand backbone) and with one of the *tert*-butyl substituents at the biaryl phosphite moiety (the one that also shows NOE contact with the hydrogen attached to C-1) (Figure 4.4.8).

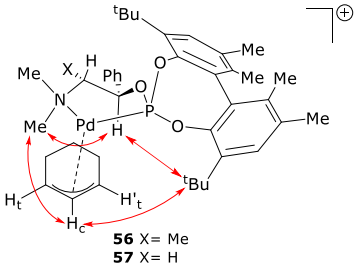
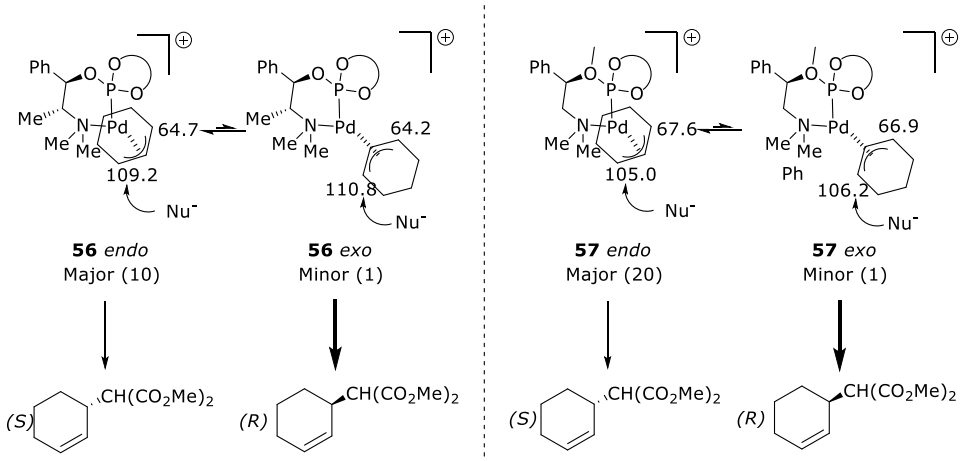


Figure 4.4.8. Relevant NOE contacts from the NOESY experiments for the major isomers of [Pd(η^3-1,3-cyclohexenylallyl)(L)]BF_4 (**56** and **57**; L= **L59e** and **L60e**, respectively).

The carbon NMR chemical shifts indicated that the most electrophilic allylic terminus carbon is *trans* to the phosphite moiety. Assuming that the nucleophilic attack takes place at the most electrophilic allyl carbon terminus, and taking into account the observed stereochemical outcome of the reaction (70% (*S*) for complex **56** and 82% (*S*) for **57**), and the fact that the enantiomeric excesses of alkylation product **13** are different from the diastereoisomeric excesses of the Pd-intermediates (de= 81% (*S*) for **56** and de= 90% (*S*) for **57**), the minor isomers must react slightly faster than major isomers. This is in agreement with the slightly higher electrophilicity of the allylic terminus carbon *trans* to the phosphite moiety located at the minor isomers (i.e. $\Delta(\delta^{13}C)$ around 1 ppm for Pd/**L59e**). The lower enantioselectivities obtained with Pd/ephedrine-based amino-phosphite ligand **L59e** than with related Pd/**L60e** catalytic system can therefore be attributed to the increase in the relative amount of fast reacting isomer *exo* with respect to isomer *endo* compared with the population of *endo* and *exo* isomers in Pd/**L60e**.



Scheme 4.4.6. Diastereoisomer Pd-allyl intermediates for **S2** with ligands **L59e** and **L60e**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

4.4.3. Conclusions

A new library of modular amino-phosphite ligands has been successfully tested in the asymmetric Pd-catalyzed allylic substitution of substrates with different steric and electronic requirements applying a large variety of nucleophiles. These ligands, which are prepared in a few steps from readily available enantiopure amino alcohols, include the benefits of a high stability of the amine moiety and the additional control provided by both the adaptability of the chiral cavity due to the biaryl-phosphite groups and the flexibility of the chiral pocket through a highly modular ligand scaffold. Other advantages of these ligands are that they are solid, stable to air and other oxidizing agents and therefore easy to handle and can be manipulated and stored in air. In simple two or three steps, several ligand parameters have been tuned to maximize the catalyst performance. Enantioselectivity is mainly controlled by the substituents/configuration at the biaryl phosphite moiety and by the amine substituents, while the configuration of the ephedrine-backbone affects less. Theoretically-guided optimization based on DFT studies allowed rationalizing the modifications required in the ligand for improving selectivity. Their results led to identifying one of the very few catalytic systems that can create C-C, C-N and C-O bonds in substrates with a variety of electronic and steric proprieties, using a wide range of nucleophiles, in high yields and enantioselectivities (ee's up to 99%). Further studies on the Pd-π-allyl intermediates provided a deep understanding of the effect of ligand parameters on the origin of enantioselectivity. Potential applications of the new Pd-amino-phosphite catalysts were demonstrated by the synthesis of a range of chiral 5-, 6- and 7-carbocycles by simple tandem reactions with no loss in the enantioselectivity. These results open up the asymmetric Pd-catalyzed allylic substitution of several substrate types with a wide range of nucleophiles to the potential effective use of readily available and highly modular amino-phosphite ligands.

4.4.4. Experimental Section

4.4.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphorochloridites were easily prepared in one step from the corresponding biaryls.[29] Enantiopure amino alcohol compounds **5**-**8**[12] and oxazolidine **9**[13] were prepared as previously described. Racemic substrates **S1**-**S10** were prepared as previously reported.[30] [Pd(η^3-1,3-Ph_2-C_3H_3)(μ-Cl)][31] and [Pd(η^3-cyclohexenyl)(μ-Cl)]$_2$[32] were prepared as previously described. Carbocyclic compound **49** was prepared following the methodology described by Uozumi *et al*.[33] ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra were

recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H, ^{13}C and ^{31}P assignments were made on the basis of ^1H-^1H gCOSY, ^1H-^{13}C gHSQC and ^1H-^{31}P gHMBC experiments.

4.4.4.2. Preparation of (1*S*,2*R*)-2-(*tert*-butyl(methyl)amino)-1-phenylpropan-1-ol 10

Compound **9** (1g, 4.88 mmol) was dissolved in dry ether (20 mL). The solution was stirred in an ice-bath for 5 minutes. Then, MeMgBr (3 M in diethyl ether) (4.96 mL, 14.64 mmol) was added dropwise. The solution was warmed up to reflux and the reaction was kept at that temperature for 8 hours. The reaction was quenched with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the removal of solvents provided **10** as a yellow-pale solid. Yield: 1.0 g (93%). ^1H NMR ($CDCl_3$): δ= 0.94 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 7.2 Hz), 1.06 (s, 9H, ^{t}Bu), 2.0 (s, 3H, CH_3-N), 3.35 (m, 1H, CH-N), 4.50 (m, 1H, CH-O), 7.21-7.32 (m, 4H, CH=). ^{13}C NMR ($CDCl_3$): δ= 12.9 (CH_3), 27.1 (CH_3, ^{t}Bu), 30.9 (CH_3, NMe), 55.1 (C, ^{t}Bu), 55.2 (CH-N), 75.3 (CH-O), 126.7 (CH=), 126.8 (CH=), 127.5 (CH=), 143.1 (C).

4.4.4.3. Preparation of (1*S*,2*R*)-2-(methyl(2-phenylpropan-2-yl)amino)-1-phenylpropan-1-ol 11

Compound **9** (1g, 4.88 mmol) was dissolved in dry THF (20 mL). The solution was stirred in an ice-bath for 5 minutes. Then, PhMgBr (1.M in THF) (14.7 mL, 14.64 mmol) was added dropwise. Then, the reaction was warmed up to reflux and the reaction was kept at that temperature for 8 hours. The reaction was quenched with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over MgSO4. The organic solvents were removed and the crude was purified by silica flash chromatography (AcOEt:light petroleum:NEt_3 6:2:0.1) to afford **11** as a white solid. Yield: 1.2 g (87%). ^1H NMR ($CDCl_3$): δ= 0.95 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 7.1 Hz), 1.34 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.13 (s, 3H, CH_3-N), 3.20 (m, 1H, CH-N), 4.50 (d, 1H, CH-O, $^3J_{H\text{-}H}$= 4.8 Hz), 7.10-7.38 (m, 10H, CH=). ^{13}C NMR ($CDCl_3$): δ = 11.7 (CH_3), 24.8 (CH_3), 25.6 (CH_3), 30.9 (CH_3, NMe), 56.4 (C, CMe_2Ph), 61.0 (CH-N), 77.6 (CH-O), 126.2 (CH=), 126.3 (CH=), 126.4 (CH=), 126.8 (CH=), 127.7 (CH=), 127.9 (CH=), 143.3 (C), 149.0 (C).

4.4.4.4. General procedure for the preparation of amino-phosphite ligands L56-L61a-g

Phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.18 mL, 2.3 mmol) was added. Amino alcohol (1 mmol) was azeotropically dried with toluene (3 x 1 mL) and then dissolved in toluene (5 mL), to which pyridine (0.18 mL, 2.3 mmol) was added. The phosphorochloridite solution was transferred slowly to the solution of amino alcohol. The reaction mixture was stirred at room temperature for 90 hours (ligands **L56**, **L59**-**L61a**-**g**) or 15 hours (ligands **L57**-**L58a**-**g**), and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in alumina (toluene/NEt_3 100:1) to produce the corresponding ligand as white solid.

L56a: Yield: 303 mg (49%). ^{31}P NMR (C_6D_6): δ= 150.5 (s). ^{1}H NMR (C_6D_6): δ= 0.98 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.8 Hz), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.3 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.14 (s, 6H, CH_3, NMe_2), 2.59 (m, 1H, CH-N), 5.55 (dd, 1H, CH-O, $^{3}J_{H-P}$= 8 Hz, $^{3}J_{H-H}$= 4 Hz,), 7.03-7.25 (m, 7H, CH=), 7.33 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.37 (d, 1H, CH=, $^{4}J_{H-H}$= 2.4 Hz), 7.58 (d, 1H, CH=, $^{4}J_{H-H}$= 2.0 Hz), 7.61 (d, 1H, CH=, $^{4}J_{H-H}$= 2.8Hz). ^{13}C NMR (C_6D_6): δ= 8.4 (CH_3), 28.8 (CH_3,^{t}Bu), 28.9 (CH_3, ^{t}Bu), 29.9 (CH_3,^{t}Bu), 30.2 (CH_3,^{t}Bu), 33.2 (C, ^{t}Bu), 34.1 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 40.9 (CH_3, NMe), 41.0 (CH_3, NMe), 64.7 (d, CH-N, $^{3}J_{C-P}$= 9.2 Hz), 76.6 (d, CH-O, $^{2}J_{C-P}$= 9.2 Hz), 122.6-145.4 (aromatic carbons). MS HR-ESI [found 618.4101, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 618.4071].

L56b: Yield: 170 mg (30%). ^{31}P NMR (C_6D_6): δ= 150.2 (s). ^{1}H NMR (C_6D_6): δ= 1.00 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.4 Hz), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 2.14 (s, 6H, CH_3, NMe_2), 2.57 (m, 1H, CH-N), 3.33 (s, 3H, CH_3, OMe), 3.34 (s, 3H, CH_3, OMe), 5.5 (dd, 1H, CH-O, $^{3}J_{H-P}$= 8.0 Hz, $^{3}J_{H-H}$= 4.0 Hz), 6.67 (d, 1H, CH=, $^{4}J_{H-H}$= 2.8 Hz), 6.72 (d, 1H, CH=, $^{4}J_{H-H}$= 3.2 Hz), 7.01-7.26 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 9.5 (CH_3), 30.6 (CH_3,^{t}Bu), 30.7 (CH_3, ^{t}Bu), 35.1(C, ^{t}Bu), 35.2 (C, ^{t}Bu), 41.9 (CH_3, NMe), 42.1 (CH_3, NMe), 54.7 (CH_3, OMe), 65.8 (CH-N), 77.6 (d, CH-O, $^{2}J_{C-P}$ = 9.9 Hz), 112.6-155.9 (aromatic carbons). MS HR-ESI [found 566.3028, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 566.3030].

L56c: Yield: 194 mg (32%). ^{31}P NMR (C_6D_6): δ= 152.4 (s). ^{1}H NMR (C_6D_6): δ= 0.33 (s, 9H, CH_3-Si), 0.44 (s, 9H, CH_3-Si), 0.95 (d, 3H, CH_3, $^{3}J_{H-H}$= 6.8 Hz), 2.10 (s, 6H, CH_3, NMe_2), 2.68 (m, 1H, CH-N), 5.45 (dd, 1H, CH-O, $^{3}J_{H-P}$= 8.8 Hz, $^{3}J_{H-H}$= 5.6 Hz), 7.03-7.46 (m, 11H, CH=). ^{13}C NMR (C_6D_6): δ= 0.0 (CH_3-Si), 0.1 (CH_3-Si), 9.7 (CH_3), 42.1 (CH_3, NMe_2), 65.8 (d, CH-N, $^{3}J_{C-P}$= 2.3 Hz), 78.1 (d, CH-O, $^{2}J_{C-P}$= 4.8 Hz), 124.7-155.2 (aromatic carbons). MS HR-ESI [found 538.2354, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 538.2357].

L56d: Yield: 188 mg (32%). ^{31}P NMR (C_6D_6): δ= 141.1 (s). ^{1}H NMR (C_6D_6): δ= 1.12 (d, 3H, CH_3, $^{3}J_{H-H}$= 7.2 Hz), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H,

CH_3), 2.05 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.16 (s, 6H, CH_3, NMe_2), 2.82 (m, 1H, CH-N), 5.4 (dd, 1H, CH-O, $^3J_{H-P}$= 8.0 Hz, $^3J_{H-H}$= 5.6 Hz), 7.0-7.3 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 8.1 (CH_3), 15.1 (CH_3), 15.3 (CH_3), 19.0 (CH_3), 19.1 (CH_3), 29.9 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 30.4 (CH_3, ^{t}Bu), 33.2 (C, ^{t}Bu), 33.7 (C, ^{t}Bu), 40.5 (CH_3, NMe), 40.6 (CH_3, NMe), 63.9 (d, CH-N, $^3J_{C-P}$= 6.1 Hz), 77.3 (d, CH-O, $^2J_{C-P}$= 6.2 Hz), 124.3-144.6 (aromatic carbons). MS HR-ESI [found 562.3452, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 562.3445].

L56e: Yield: 182 mg (31%). ^{31}P NMR (C_6D_6): δ= 144.9 (s). ^{1}H NMR (C_6D_6): δ= 0.78 (d, CH_3, 3H, $^3J_{H-H}$= 6.4 Hz), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.11 (s, 6H, CH_3, NMe_2), 2.37 (m, 1H, CH-N), 5.41 (dd, 1H, CH-O, $^3J_{H-P}$= 8.0 Hz, $^3J_{H-H}$= 4.0 Hz), 6.95-7.22 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 9.7 (CH_3), 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1(CH_3), 30.9 (d, CH_3, ^{t}Bu, J_{C-P}= 4.6 Hz), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 42.0 (CH_3, NMe), 42.3 (CH_3, NMe), 62.2 (CH-N), 77.2 (d, CH-O, $^2J_{C-P}$= 10.7 Hz), 125.3-146.2 (aromatic carbons). MS HR-ESI [found 562.3448, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 562.3445].

L56f: Yield: 439 mg (69%). ^{31}P NMR (C_6D_6): δ= 155.8 (s). ^{1}H NMR (C_6D_6): δ= 0.40 (s, 9H, CH_3, $SiMe_3$), 0.51 (s, 9H, CH_3, $SiMe_3$), 0.72 (d, CH_3, 3H, $^3J_{H-H}$= 6.8 Hz), 1.96 (s, 6H, CH_3, NMe_2), 2.50 (m, 1H, CH-N), 5.43 (dd, 1H, CH-O, $^3J_{H-P}$= 8.4 Hz, $^3J_{H-H}$= 4.8 Hz), 6.82-7.4 (m, 5H, CH=), 7.4 (d, 1H, CH=, $^3J_{H-H}$= 8.4Hz), 7.70 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.8 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 8.1 (s, 1H, CH=), 7.9 (s, 1H, CH=). ^{13}C NMR (C_6D_6): δ= -0.4 (d, CH_3, $SiMe_3$, J_{C-P}= 4.6 Hz), -0.1 (CH_3, $SiMe_3$), 9.3 (CH_3), 41.8 (CH_3, NMe_2), 66.0 (CH-N), 77.5 (d, CH-O, $^2J_{C-P}$= 5.3 Hz), 122.8-152.6 (aromatic carbons). MS HR-ESI [found 638.2673, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 638.2670].

L56g: Yield: 400 mg (63%). ^{31}P NMR (C_6D_6): δ= 148.5 (s). ^{1}H NMR (C_6D_6): δ= 0.51 (s, 9H, CH_3, $SiMe_3$), 0.52 (s, 9H, CH_3, $SiMe_3$), 1.09 (d, 3H, CH_3, $^3J_{H-H}$= 6.4 Hz), 2.05 (s, 6H, CH_3, NMe_2), 2.87 (m, 1H, CH-N), 5.35 (dd, 1H, CH-O, $^3J_{H-P}$= 8.4 Hz, $^3J_{H-H}$= 6.5 Hz), 6.7-7.3 (m, 6H, CH=), 7.68 (m, 2H, CH=), 7.95 (s, 1H; CH=), 8.05 (s, 1H, CH=). ^{13}C NMR (C_6D_6): δ= -0.2 (d, CH_3, $SiMe_3$, J_{C-P}= 4.6 Hz), -0.1 (CH_3, $SiMe_3$), 9.2 (CH_3), 41.3 (CH_3, NMe_2), 64.3 (d, CH-N, $^3J_{C-P}$= 4.6 Hz), 78.9 (d, CH-O, $^2J_{C-P}$= 2.3 Hz), 122.4-152.3 (aromatic carbons). MS HR-ESI [found 638.2669, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 638.2670].

L57a: Yield: 330 mg (50%). ^{31}P NMR (C_6D_6): δ= 148.4 (s). ^{1}H NMR (C_6D_6): δ= 0.83 (s, 9H, CH_3, ^{t}Bu, N^{t}Bu), 1.21 (d, 3H, CH_3, $^3J_{H-H}$= 6.4 Hz), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H,CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 2.11 (s, 3H, NMe), 3.4 (m, 1H, CH-N), 5.25 (m, 1H, CH-O), 7.0-7.2 (m, 6H, CH=), 7.37 (m, 2H, CH=), 7.60 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz). ^{13}C NMR (C_6D_6): δ= 12.8 (CH_3), 26.8 (CH_3, ^{t}Bu), 29.3 (NMe), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 54.1 (C, ^{t}Bu, N^{t}Bu), 56.6 (d, CH-N, $^3J_{C-P}$= 3.1 Hz), 81.3 (d, CH-

O, $^2J_{C-P}$= 5.43 Hz), 123.8-146.7 (aromatic carbons). MS HR-ESI [found 660.5438, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 660.5438].

L57d: Yield: 422.6 mg (70%). ^{31}P NMR (C_6D_6): δ= 141.1 (s). ^{1}H NMR (C_6D_6): δ= 0.84 (s, 9H, CH_3, ^{t}Bu, N^{t}Bu), 2.15 (d, 3H, CH_3, $^3J_{H-H}$= 6.4 Hz), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H,CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.71 (s, 3H, CH_3,) , 2.04 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.16 (s, 3H, NMe), 3.4 (m, 1H, CH-N), 5.1 (m, 1H, CH-O), 7.0-7.3 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 12.7 (CH_3), 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 26.8 (CH_3, ^{t}Bu), 29.4 (NMe), 31.1 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.4 (CH_3, ^{t}Bu), 34.4(C, ^{t}Bu), 34.7 (C, ^{t}Bu), 54.2 (C, ^{t}Bu, N^{t}Bu), 56.4 (d, CH-N, $^3J_{C-P}$= 5.6 Hz), 81.6 (d, CH-O, $^2J_{C-P}$= 3.0 Hz), 125.3-145.6 (aromatic carbons). MS HR-ESI [found 604.3917, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 604.3914].

L57e: Yield: 392 mg (65%). ^{31}P NMR (C_6D_6): δ= 142.9 (s). ^{1}H NMR (C_6D_6): δ= 0.60 (s, 9H, CH_3, ^{t}Bu, N^{t}Bu), 1.0 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H,CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.75 (s, 3H, CH_3,) , 1.95 (s, 3H, NMe), 2.0 (s, 3H, CH_3), 2.1 (s, 3H, CH_3), 3.2 (m, 1H, CH-N), 5.0 (m, 1H, CH-O), 7.0-7.45 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 13.8 (CH_3), 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 26.8 (CH_3, ^{t}Bu), 28.7 (NMe), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 31.6 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 53.7 (C, ^{t}Bu, N^{t}Bu), 56.7 (d, CH-N, $^3J_{C-P}$= 2.3 Hz), 80.3 (d, CH-O, $^2J_{C-P}$= 5.3 Hz), 125.9-145.6 (aromatic carbons). MS HR-ESI [found 604.3912, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 604.3914].

L58a: Yield: 262 mg (37%). ^{31}P NMR (C_6D_6): δ= 148.90 (s). ^{1}H NMR (C_6D_6): δ= 1.01 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.09 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.86 (s, 9H, CH_3, ^{t}Bu), 2.2 (s, 3H, NMe), 3.2 (m, 1H, CH-N), 5.4 (dd, 1H, CH-O, $^3J_{H-P}$= 9.6 Hz, $^3J_{H-H}$= 4.4 Hz), 7.0-7.4 (m, 12H, CH=), 7.58 (d, 1H, CH=, $^4J_{H-H}$= 2.8 Hz), 7.62 (d, 1H, CH=, $^4J_{H-H}$= 2.8 Hz). ^{13}C NMR (C_6D_6): δ= 9.9 (CH_3), 22.3 (CH_3), 25.2 (CH_3), 28.9 (NMe), 29.9 (CH_3, ^{t}Bu), 30.0 (CH_3, ^{t}Bu), 30.1 (CH_3, ^{t}Bu), 30.2 (CH_3, ^{t}Bu), 33.2 (C, ^{t}Bu), 34.2(C, ^{t}Bu), 34.3 (C, ^{t}Bu), 56.4 (d, CH-N, $^3J_{C-P}$ = 3.8 Hz), 59.8 (C, N-CMe_2Ph), 81.2 (d, CH-O, $^2J_{C-P}$ = 6.9 Hz), 122.7-148.7 (aromatic carbons). MS HR-ESI [found 722.4694, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 722.4697].

L58d: Yield: 244 mg (37%). ^{31}P NMR (C_6D_6): δ= 143.4 (s). ^{1}H NMR (C_6D_6): δ= 1.01 (d, 3H, CH_3, $^3J_{H-H}$= 6.9 Hz), 1.03, (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.8 (s, 3H, CH_3), 1.91 (s, 3H, NMe), 2.06 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.3 (m, 1H, CH-N), 5.3 (m, 1H, CH-O), 7.0-7.3 (m, 12H, CH=). ^{13}C NMR (C_6D_6): δ= 10.9 (CH_3), 15.2 (CH_3), 15.4 (CH_3), 19.0 (CH_3) 23.4 (CH_3), 24.7 (CH_3), 28.2 (NMe), 30.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 30.5 (CH_3, ^{t}Bu), 33.4 (C, ^{t}Bu), 33.7 (C, ^{t}Bu), 56.3 (d, CH-N, $^3J_{C-P}$= 2.3 Hz), 59.4 (C, N-CMe_2Ph), 80.7 (d, CH-O, $^2J_{C-P}$=

6.1 Hz), 124.3-148.8 (aromatic carbons). MS HR-ESI [found 666.4068, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 666.4071].

L58e: Yield: 331.0 mg (50%). ^{31}P NMR (C_6D_6): δ= 148.90 (s). ^1H NMR (C_6D_6): δ= 1.02 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.03 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.01 (s, 3H, CH_3, NMe), 2.06 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.31 (m, 1H, CH-N), 5.3 (m, 1H, CH-O), 7.0-7.4 (m, 12H, CH=). ^{13}C NMR (C_6D_6): δ= 11.9 (CH_3), 16.2 (CH_3), 16.5 (CH_3), 20.1 (CH_3) 24.6 (CH_3), 25.7 (CH_3), 29.2 (NMe), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 57.3 (CH-N), 60.5 (C, N-CMe_2Ph), 81.7 (d, CH-O, $^2J_{C-P}$= 6.1 Hz), 125.3-149.9 (aromatic carbons). MS HR-ESI [found 666.4072, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 666.4071].

L59a: Yield: 276 mg (43%). ^{31}P NMR (C_6D_6): δ= 148.4 (s). ^1H NMR (C_6D_6): δ= 0.47 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.09 (s, 6H, CH_3, NMe_2), 2.78 (m, 1H, CH-N), 5.06 (dd, 1H, CH-O, $^3J_{H-P}$= 8 Hz, $^3J_{H-H}$= 4 Hz), 6.9-7.1 (m, 7H, CH=), 7.27 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.33 (d, 1H, CH=, $^4J_{H-H}$= 2.8 Hz), 7.46 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 7.57 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz). ^{13}C NMR (C_6D_6): δ= 7.9 (CH_3), 30.9 (CH_3,^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 33.2 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 40.9 (CH_3, NMe), 41.0 (CH_3, NMe), 64.7 (d, CH-N, $^3J_{C-P}$= 1.5 Hz), 76.6 (d, CH-O, $^2J_{C-P}$= 9.2 Hz), 123.6-145.8 (aromatic carbons). MS HR-ESI [found 618.4070, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 618.4071].

L59d: Yield: 344 mg (61%). ^{31}P NMR (C_6D_6): δ= 139.0 (s). ^1H NMR (C_6D_6): δ= 0.62 (d, 3H, CH_3, $^3J_{H-H}$ = 7.2 Hz), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.6 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.15 (s, 6H, CH_3, NMe_2), 3.0 (m, 1H, CH-N), 5.1 (dd, 1H, CH-O, $^3J_{H-H}$= 5.6 Hz, $^3J_{H-P}$= 8.0 Hz), 6.9-7.2 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 7.4 (CH_3), 15.1 (CH_3), 15.3 (CH_3), 19.0 (CH_3), 30.0 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 30.4 (CH_3, ^{t}Bu), 33.3 (C, ^{t}Bu), 33.7 (C, ^{t}Bu), 40.1 (CH_3, NMe), 40.2 (CH_3, NMe), 63.9 (d, CH-N, $^3J_{C-P}$= 3.8 Hz), 77.6 (d, CH-O, $^2J_{C-P}$= 10.7 Hz), 126.3-144.6 (aromatic carbons). MS HR-ESI [found 562.3440, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 562.3445].

L59e: Yield: 324 mg (58%). ^{31}P NMR (C_6D_6): δ= 144.7 (s). ^1H NMR (C_6D_6): δ= 0.4 (d, 3H, CH_3, $^3J_{H-H}$= 7.2 Hz), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.11 (s, 6H, CH_3, NMe_2), 2.65 (m, 1H, CH-N), 4.95 (m, 1H, CH-O), 7.05-7.25 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 7.5 (CH_3), 16.2 (CH_3), 16.3 (CH_3), 19.9 (CH_3), 20.1 (CH_3), 30.9 (d , CH_3, ^{t}Bu, J_{C-P}= 4.6 Hz), 31.4 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 42.0 (CH_3, NMe), 42.3 (CH_3, NMe), 64.8 (CH-N), 78.7 (d, CH-O, $^2J_{C-P}$= 13.9 Hz), 127.3-146.7 (aromatic carbons). MS HR-ESI [found 562.3442, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 562.3445].

L59f: Yield: 467 mg (73%). ^{31}P NMR (C_6D_6): δ= 143.7 (s). ^1H NMR (C_6D_6): δ= 0.47 (s, 9H, CH_3, $SiMe_3$) , 0.52 (s, 9H, CH_3, $SiMe_3$), 0.64 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 2.02 (s,

6H, CH_3, NMe_2), 3.0 (m, 1H, CH-N), 5.1 (dd, 1H, CH-O, $^3J_{H-H}$= 6.8 Hz; $^3J_{H-P}$= 10.4 Hz), 6.82-7.27 (m, 5H, CH=), 7.7 (m, 2H, CH=), 8.0 (s, 1H, CH=), 8.1 (s, 1H, CH=). ^{13}C NMR (C_6D_6): δ= -0.0 (CH_3, $SiMe_3$), 9.11 (CH_3), 41.4 (CH_3, NMe_2), 63.9 (d, CH-N, $^3J_{C-P}$= 3.1 Hz), 78.7 (CH-O), 122.0-152.8 (aromatic carbons). MS HR-ESI [found 638.2665, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 638.2670].

L59g: Yield: 666 mg (95%). ^{31}P NMR (C_6D_6): δ= 151. (s). ^{1}H NMR (C_6D_6): δ= 0.4 (s, 9H, CH_3, $SiMe_3$) , 0.47 (s, 9H, CH_3, $SiMe_3$), 0.55 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.85 (s, 6H, CH_3, NMe_2), 2.57 (m, 1H, CH-N), 5.2 (m, 1H, CH-O), 6.79-7.16 (m, 9H, CH=), 7.19 (d, 1H, CH=, $^4J_{H-H}$= 8.0 Hz), 7.32 (d, 1H, CH=, $^4J_{H-H}$= 8.0 Hz), 7.66 (d, 1H, CH=, $^4J_{H-H}$= 8.8 Hz), 7.73 (d, 1H, CH=, $^4J_{H-H}$= 8.4 Hz), 8.0 (s, 2H, CH=). ^{13}C NMR (C_6D_6): δ= -0.3 (d, 9H, CH_3, $SiMe_3$, J_{C-P}= 4.6 Hz), -0.1 ($SiMe_3$), 9.1 (CH_3), 41.2 (CH_3, NMe_2), 64.2 (CH-N), 78.4 (d, CH-O, $^2J_{C-P}$= 2.3 Hz), 122.6-152.9 (aromatic carbons). MS HR-ESI [found 638.2669, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 638.2670].

L60d: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ= 143.7 (s). ^{1}H NMR (C_6D_6): δ= 1.51 (s, 9H, CH_3, ^{t}Bu), 1.76 (s, 9H, CH_3, ^{t}Bu), 1.82 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 2.17 (s, 6H, CH_3, NMe_2), 2.23 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.30 (dd, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz,$^3J_{H-H}$= 5.6 Hz), 2.73 (dd, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz,$^3J_{H-H}$= 6 Hz), 5.33 (m, 1H, CH-O), 7.13-7.4 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 16.1 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (d, CH_3,^{t}Bu, J_{C-P}= 4.6 Hz), 31.3 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 45.5 (CH_3, NMe), 45.6 (CH_3, NMe), 67.6 (CH_2-N), 75.2 (d, CH-O, $^2J_{C-P}$= 13.6 Hz), 125.3-146.3 (aromatic carbons). MS HR-ESI [found 548.3287, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 548.3288].

L60e: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ= 138.1 (s). ^{1}H NMR (C_6D_6): δ= 1.44 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.98 (s, 6H, CH_3, NMe_2), 2.07 (s, 3H, CH_3), 2.1(s, 3H, CH_3), 2.43 (dd, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz,$^3J_{H-H}$= 5.6 Hz), 2.85 (dd, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 6 Hz), 5.1 (m, 1H, CH-O), 6.95-7.19 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 45.6 (CH_3, NMe_2), 66.7 (d, CH_2-N, $^2J_{C-P}$= 3.8 Hz), 75.2 (d, CH-O, $^2J_{C-P}$= 8.4 Hz), 125.3-145.8 (aromatic carbons). MS HR-ESI [found 548.3287, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 548.3288].

L61d: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ= 129.7 (s). ^{1}H NMR (C_6D_6): δ= 1.48 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 6H, CH_3, NMe_2), 3.4 (m, 1H, CH-N), 3.6 (m, 1H, CH_2-O), 4.3 (m, 1H, CH_2-O), 6.95-7.2 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (d, CH_3,^{t}Bu, J_{C-P}= 5.3 Hz), 34.4 (C, ^{t}Bu), 34.5 (C, ^{t}Bu), 42.9 (CH_3, NMe_2), 66.4 (CH_2-O), 70.6 (d, CH-N, $^2J_{C-P}$= 3.0

Hz), 125.3-146.1(aromatic carbons). MS HR-ESI [found 548.3489, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 548.3288].

L61e: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ= 131.1 (s). ^1H NMR (C_6D_6): δ= 1.46 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.06 (s, 6H, CH_3, NMe_2), 3.6 (m, 1H, CH-N), 3.8 (m, 1H, CH_2-O), 4.0 (m, 1H, CH_2-O), 6.95-7.2 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ= 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (d, CH_3,^{t}Bu, $J_{C\text{-}P}$= 5.3 Hz), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 42.9 (CH_3, NMe_2), 66.1 (CH_2-O), 70.6 (d, CH-N, $^2J_{C\text{-}P}$= 2.3 Hz), 125.3-146.1 (aromatic carbons). MS HR-ESI [found 548.3287, $C_{13}H_{17}F_3$ $(M+H)^+$ requires 548.3288].

4.4.4.5. General procedure for the preparation of [Pd(η^3-allyl)(P-S)]BF_4 complexes 53-57

The corresponding ligand (0.05 mmol) and the complex [Pd(μ-Cl)(η^3-1,3-allyl)]$_2$ (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.05 mmol) was added after 30 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over celite under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated as pale-yellow solids by adding hexane.

[Pd(η^3-1,3-diphenylallyl)(L4d)]BF_4 (53). Isomer *endo* (77%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 136.8 (s, 1P). ^1H NMR(CD_2Cl_2, 298 K), δ: 0.50 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 1.22 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 3H, CH_3-Ar), 1.66 (s, 3H, CH_3-Ar), 1.71 (s, 9H, CH_3, ^{t}Bu), 2.13 (s, 3H, CH_3-Ar), 2.29 (s, 3H, CH_3-Ar), 2.75 (s, 3H, CH_3-N), 2.76 (s, 3H, CH_3-N), 3.19 (m, 1H, CH-N), 5.35 (dd, 1H, CH allyl *trans* to N, $^3J_{H\text{-}H}$= 12.0 Hz, $^3J_{H\text{-}P}$= 4.4 Hz), 5.64 (dd, 1H, CH allyl *trans* to P, $^3J_{H\text{-}H}$= 12.0 Hz, $^3J_{H\text{-}P}$= 16.4 Hz), 5.79 (dd, 1H, CH-O, $^3J_{H\text{-}H}$= 4.8 Hz, $J_{C\text{-}P}$= 7.2 Hz), 6.68 (m, 1H, CH allyl central), 6.9-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 10.4 (CH_3), 16.7 (CH_3, Ar), 16.8 (CH_3, Ar), 20.5 (CH_3, Ar), 20.7 (CH_3, Ar), 32.0 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 42.9 (CH_3-N), 48.6 (CH_3-N), 73.5 (CH-N), 79.2 (d, CH allyl *trans* to N, $J_{C\text{-}P}$= 8.3 Hz), 84.6 (d, CH-O, $J_{C\text{-}P}$= 11.5 Hz), 105.3 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 33.8 Hz), 114.8 (d, CH allyl central, $J_{C\text{-}P}$= 12.2 Hz), 123-145 (aromatic carbons). Isomer *exo* (23%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 132.9 (s, 1P). ^1H NMR(CD_2Cl_2, 298 K), δ: 0.50 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 0.91 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 3H, CH_3-Ar), 1.74 (s, 3H, CH_3-Ar), 1.79 (s, 9H, CH_3, ^{t}Bu), 2.17 (s, 6H, CH_3-N and CH_3-Ar), 2.21 (s, 3H, CH_3-N), 2.43 (s, 3H, CH_3-Ar), 3.10 (m, 1H, CH-N), 4.50 (m, 1H, CH allyl *trans* to N), 5.22 (m, 1H, CH-O), 5.45 (m, 1H, CH allyl *trans* to P), 6.59 (m, 1H, CH allyl central), 6.9-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 10.1 (CH_3), 17.1 (CH_3, Ar), 17.3 (CH_3, Ar), 20.4 (CH_3, Ar), 20.8 (CH_3, Ar), 31.9 (CH_3, ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 38.8 (CH_3-N), 50.5 (CH_3-N), 71.8 (d, CH allyl *trans* to N, $J_{C\text{-}P}$= 9.2 Hz), 72.1 (CH-N), 84.0 (d, CH-O, $J_{C\text{-}P}$= 9.1 Hz), 99.3 (d, CH allyl *trans* to P, $J_{C\text{-}}$

$_P$= 33.0 Hz), 113.4 (d, CH allyl central, J_{C-P}= 14.0 Hz), 123-145 (aromatic carbons). Anal. calcd (%) for $C_{50}H_{61}BF_4NO_3PPd$: C 63.33, H 6.48, N 1.48; found: C 63.12, H 6.43, N 1.45.

[Pd(η^3-1,3-diphenylallyl)(L4e)]BF_4 (54). Isomer *endo* (17%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 129.8 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 0.43 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3-Ar), 1.74 (s, 9H, CH_3, ^{t}Bu), 1.84 (s, 3H, CH_3-N), 2.14 (s, 3H, CH_3-Ar), 2.23 (s, 3H, CH_3-Ar), 2.26 (s, 3H, CH_3-N), 2.40 (s, 3H, CH_3-Ar), 3.40 (m, 1H, CH-N), 3.72 (dd, 1H, CH allyl *trans* to N, $^3J_{H-H}$= 10.2 Hz, $^3J_{H-P}$= 6.8 Hz), 4.40 (m, 1H, CH allyl *trans* to P), 5.54 (m, 1H, CH-O), 6.60 (m, 1H, CH allyl central), 6.8-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 10.8 (CH_3), 16.7 (CH_3, Ar), 17.0 (CH_3, Ar), 20.5 (CH_3, Ar), 20.6 (CH_3, Ar), 32.2 (d, CH_3, ^{t}Bu, J_{C-P}= 6.3 Hz), 32.5 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 43.0 (CH_3-N), 49.1 (CH_3-N), 67.3 (d, CH allyl *trans* to N, J_{C-P}= 12.8 Hz), 68.7 (CH-N), 84.9 (CH-O), 108.6 (d, CH allyl *trans* to P, J_{C-P}= 32.4 Hz), 114.5 (d, CH allyl central, J_{C-P}= 12.4 Hz), 127-145 (aromatic carbons). Isomer *exo* (83%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 128.7 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 0.54 (d, 3H, CH_3, $^3J_{H-H}$= 7.2 Hz), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3-Ar), 1.78 (s, 9H, CH_3, ^{t}Bu), 2.11 (s, 3H, CH_3-Ar), 2.19 (s, 3H, CH_3-Ar), 2.40 (s, 3H, CH_3-N), 2.42 (s, 3H, CH_3-Ar), 2.61 (s, 3H, CH_3-N), 3.16 (m, 1H, CH-N), 4.40 (m, 1H, CH allyl *trans* to N), 5.03 (m, 1H, CH-O), 5.73 (m, 1H, CH allyl *trans* to P), 6.60 (m, 1H, CH allyl central), 6.9-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 9.7 (CH_3), 16.9 (CH_3, Ar), 17.3 (CH_3, Ar), 20.5 (CH_3, Ar), 20.7 (CH_3, Ar), 32.0 (CH_3, ^{t}Bu), 32.6 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 42.9 (CH_3-N), 48.8 (CH_3-N), 67.5 (d, CH allyl *trans* to N, J_{C-P}= 12.6 Hz), 69.4 (CH-N), 81.4 (CH-O), 110.6 (d, CH allyl *trans* to P, J_{C-P}= 30.6 Hz), 113.5 (d, CH allyl central, J_{C-P}= 13.8 Hz), 123-145 (aromatic carbons). Anal. calcd (%) for $C_{50}H_{61}BF_4NO_3PPd$: C 63.33, H 6.48, N 1.48; found: C 63.02, H 6.43, N 1.44.

[Pd(η^3-1,3-diphenylallyl)(L5e)]BF_4 (55). Isomer *endo* (33%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 132.7 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 1.45 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3-Ar), 1.71 (s, 3H, CH_3-Ar), 1.73 (s, 9H, CH_3, ^{t}Bu), 2.11 (s, 3H, CH_3-Ar), 2.30 (s, 3H, CH_3-Ar), 2.32 (s, 3H, CH_3-N), 2.42 (m, 1H, CH_2), 2.70 (s, 3H, CH_3-N), 3.56 (dd, 1H, CH_2, $^3J_{H-H}$= 10.0 Hz, $^3J_{H-P}$= 14.4 Hz), 4.49 (m, 1H, CH allyl *trans* to N), 4.84 (m, 1H, CH allyl *trans* to P), 5.23 (m, 1H, CH-O), 6.19 (m, 1H, CH allyl central), 6.7-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 16.5 (CH_3, Ar), 16.7 (CH_3, Ar), 20.0 (CH_3, Ar), 20.1 (CH_3, Ar), 31.9 (CH_3, ^{t}Bu), 32.4 (d, CH_3, ^{t}Bu, J_{C-P}= 4.6 Hz), 34.4-35.3 (C, ^{t}Bu), 48.7 (CH_3-N), 54.3 (CH_3-N), 69.8 (m, CH allyl *trans* to N), 70.9 (CH_2), 74.8 (CH-O), 93.8 (d, CH allyl *trans* to P, J_{C-P}= 39.7 Hz), 114.1 (d, CH allyl central, J_{C-P}= 12.2 Hz), 125-146 (aromatic carbons). Isomer *exo* (67%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 130.3 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 1.31 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3-Ar), 1.74 (s, 3H, CH_3-Ar), 2.16 (s, 6H, CH_3-Ar and CH_3-N), 2.45 (s, 3H, CH_3-Ar), 2.52 (m, 1H, CH_2), 2.75 (s, 3H, CH_3-N), 3.19 (dd, 1H, CH_2, $^3J_{H-H}$= 9.6 Hz, $^3J_{H-P}$= 14.4 Hz),

4.52 (m, 1H, CH allyl *trans* to N), 5.30 (m, 1H, CH-O), 5.61 (m, 1H, CH allyl *trans* to P), 6.54 (m, 1H, CH allyl central), 6.7-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 16.2 (CH_3, Ar), 16.7 (CH_3, Ar), 20.0 (CH_3, Ar), 20.2 (CH_3, Ar), 31.6 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 34.4-35.3 (C, ^{t}Bu), 49.9 (CH_3-N), 51.6 (CH_3-N), 69.8 (m, CH allyl *trans* to N), 71.2 (CH_2), 75.6 (CH-O), 105.6 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 32.0 Hz), 112.3 (d, CH allyl central, $J_{C\text{-}P}$= 10.7 Hz), 125-146 (aromatic carbons). Anal. calcd (%) for $C_{49}H_{59}BF_4NO_3PPd$: C 63.00, H 6.37, N 1.50; found: C 59.61, H 6.31, N 1.46.

[Pd(η^3-1,3-cyclohexenylallyl)(L4e)]BF$_4$ (56). Isomer *endo* (91%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 134.4 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 0.74 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 1.2-1.6 (m, 4H, CH_2), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3-Ar), 1.80 (m, 1H, CH_2), 1.87 (s, 3H, CH_3-Ar), 2.21 (m, 1H, CH_2), 2.23 (s, 3H, CH_3-Ar), 2.34 (s, 3H, CH_3-Ar), 2.82 (s, 3H, CH_3-N), 3.24 (s, 3H, CH_3-N), 3.31 (m, 1H, CH allyl *trans* to N), 3.38 (m, 1H, CH-N), 4.97 (dd, 1H, CH-O, $^3J_{H\text{-}H}$= 7.2 Hz, $^3J_{H\text{-}P}$= 12 Hz), 5.49 (m, 1H, CH allyl central), 5.96 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=).^{13}C NMR (C_6D_6, 298 K), δ: 9.9 (CH_3), 16.7 (CH_3, Ar), 20.5 (CH_3, Ar), 20.6 (CH_3, Ar), 21.4 (b, CH_2), 27.4 (b, CH_2), 21.4 (d, CH_2, $J_{C\text{-}P}$= 8.4 Hz), 31.7 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 35.2-35.4 (C, ^{t}Bu), 44.8 (CH_3-N), 53.4 (CH_3-N), 64.7 (d, CH allyl *trans* to N, $J_{C\text{-}P}$= 10 Hz), 69.7 (CH-N), 82.7 (d, CH-O, $J_{C\text{-}P}$= 6.1 Hz), 109.2 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 40 Hz), 113.5 (d, CH allyl central, $J_{C\text{-}P}$= 10.7 Hz), 127-145 (aromatic carbons). Isomer *exo* (9%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 133.0 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 0.72 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 1.2-1.6 (m, 4H, CH_2), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3-Ar), 1.80 (m, 1H, CH_2), 1.89 (s, 3H, CH_3-Ar), 2.21 (m, 1H, CH_2), 2.27 (s, 3H, CH_3-Ar), 2.29 (s, 3H, CH_3-Ar), 2.68 (s, 3H, CH_3-N), 3.20 (s, 3H, CH_3-N), 3.36 (m, 1H, CH allyl *trans* to N), 3.42 (m, 1H, CH-N), 5.21 (m, 1H, CH-O), 5.68 (m, 1H, CH allyl central), 6.08 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=).^{13}C NMR (C_6D_6, 298 K), δ: 9.2 (CH_3), 16.7 (CH_3, Ar), 16.8 (CH_3, Ar), 20.4 (CH_3, Ar), 20.6 (CH_3, Ar), 21.4 (b, CH_2), 27.4 (b, CH_2), 21.4 (d, CH_2, $J_{C\text{-}P}$= 8.4 Hz), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 35.2-35.4 (C, ^{t}Bu), 45 (CH_3-N), 52.8 (CH_3-N), 64.2 (d, CH allyl *trans* to N, $J_{C\text{-}P}$= 9.2 Hz), 69.7 (CH-N), 81.9 (d, CH-O, $J_{C\text{-}P}$= 7.3 Hz), 110.8 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 38.6 Hz), 113.2 (d, CH allyl central, $J_{C\text{-}P}$= 9.6 Hz), 127-145 (aromatic carbons). Anal. calcd (%) for $C_{41}H_{57}BF_4NO_3PPd$: C 58.90, H 6.87, N 1.68; found: C 58.21, H 6.84, N 1.65.

[Pd(η^3-1,3-cyclohexenylallyl)(L5e)]BF$_4$ (57).[34] Isomer *endo* (96%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 135.2 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 1.25 (m, 1H, CH_2), 1.43 (m, 2H, CH_2), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 1H, CH_2), 1.73 (s, 3H, CH_3-Ar), 1.88 (s, 3H, CH_3-Ar), 1.90 (m, 1H, CH_2), 2.16 (m, 1H, CH_2), 2.24 (s, 3H, CH_3-Ar), 2.35 (s, 3H, CH_3-Ar), 2.71 (d, 1H, CH_2-N, $^3J_{H\text{-}H}$= 14.4 Hz), 2.90 (s, 3H, CH_3-N), 3.12 (s, 3H, CH_3-N), 3.42 (dd, 1H, CH_2-N, $^3J_{H\text{-}H}$= 14.4 Hz, $^3J_{H\text{-}P}$= 9.6 Hz), 3.49 (m, 1H, CH allyl *trans* to N), 5.23 (m, 1H, CH-O), 5.44 (m, 1H, CH allyl central), 6.03 (m, 1H,

CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=).^{13}C NMR (C_6D_6, 298 K), δ: 16.7 (CH_3, Ar), 16.8 (CH_3, Ar), 20.5 (CH_3, Ar), 20.6 (CH_3, Ar),), 20.9 (d, CH_2, J_{C-P}= 2.3 Hz), 27.6 (b, CH_2), 28.5 (d, CH_2, J_{C-P}= 7.6 Hz),31.8 (CH_3, ^{t}Bu), 32.0 (d, CH_3, ^{t}Bu, J_{C-P}= 1.5 Hz)), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 51.8 (CH_3-N), 56.7 (CH_3-N), 67.6 (d, CH allyl *trans* to N, J_{C-P}= 9.1 Hz), 71.8 (CH-N), 77.9 (d, CH-O, J_{C-P}= 6.8 Hz), 105.0 (d, CH allyl *trans* to P, J_{C-P}= 40.3 Hz), 113.5 (d, CH allyl central, J_{C-P}= 10.6 Hz), 126-146 (aromatic carbons). Isomer *exo* (4%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 134.2 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 1.25 (m, 1H, CH_2), 1.43 (m, 2H, CH_2), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 1H, CH_2), 1.74 (s, 3H, CH_3-Ar), 1.90 (bs, 4H, CH_3-Ar and CH_2), 2.16 (m, 1H, CH_2), 2.24 (s, 3H, CH_3-Ar), 2.35 (s, 3H, CH_3-Ar), 2.81 (d, 1H, CH_2-N, $^3J_{H-H}$= 14.0 Hz), 2.91 (s, 3H, CH_3-N), 3.09 (s, 3H, CH_3-N), 3.27 (dd, 1H, CH_2-N, $^3J_{H-H}$= 14.0 Hz, $^3J_{H-P}$= 8.4 Hz), 3.39 (m, 1H, CH allyl *trans* to N), 5.39 (m, 1H, CH-O), 5.54 (m, 1H, CH allyl central), 5.84 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=). Anal. calcd (%) for $C_{40}H_{55}BF_4NO_3PPd$: C 58.44, H 6.74, N 1.70; found: C 58.06, H 6.70, N 1.67.

4.4.4.6. Study of the reactivity of the [Pd(η^3-allyl)(L))]BF$_4$ with sodium malonate by in situ NMR[35]

A solution of *in situ* prepared [Pd(η^3-allyl)(L)]BF_4 (L= phosphite-pyridine, 0.05 mmol) in CD_2Cl_2 (1 mL) was cooled in the NMR at -80 °C. At this temperature, a solution of cooled sodium malonate (0.1 mmol) was added. The reaction was then followed by ^{31}P NMR. The relative reaction rates were calculated using a capillary containing a solution of triphenylphosphine in CD_2Cl_2 as external standard.

4.4.4.7. Typical procedure for the allylic alkylation of linear (S1 and S3-S8) and cyclic (S2, S9 and S10) substrates

A degassed solution of [PdCl(η^3-C_3H_5)]$_2$ (0.9 mg, 0.0025 mmol) and the corresponding amino-phosphite (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), nucleophile (1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (3 mg, 0.03 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For compounds **12**, **14**-**21**, **27**-**32**, **35**, **37**-**39** and **45**, the solvent was removed, conversions were measured by ^{1}H-NMR and enantiomeric excesses were determined by HPLC. For compounds **13**, **33**-**34**, **40**-**41** and **43**-**44**, conversion and enantiomeric excesses were determined by GC. For compounds **36** and **42**, conversions were measured by ^{1}H-NMR

and ees were determined by ^{1}H-NMR using [Eu(hfc)$_3$] (for more details for compounds **12**-**21** and **27**-**45** see previous Section 4.1.5.5).

4.4.4.8. Typical procedure for the allylic amination of substrate S1

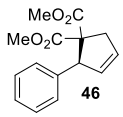
A degassed solution of [PdCl(η^3-C$_3$H$_5$)]$_2$ (0.9 mg, 0.0025 mmol) and the corresponding amino-phosphite ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (0.5 mmol) in dichloromethane (1.5 mL) and benzylamine (131 μL, 1.5 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et$_2$O (5 mL) and saturated NH$_4$Cl (aq) (25 mL) was added. The mixture was extracted with Et$_2$O (3 x 10 mL) and the extract dried over MgSO$_4$. Conversion was measured by ^{1}H-NMR and enantiomeric excess was determined by HPLC (for more details for compound **22** see previous Section 4.2.4.6)

4.4.4.9. Typical procedure for the allylic etherification of substrate S1

A degassed solution of [PdCl(η^3-C$_3$H$_5$)]$_2$ (0.9 mg, 0.0025 mmol) and the corresponding amino-phosphite ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 minutes, Cs$_2$CO$_3$ (122 mg, 0.375 mmol) and alkyl alcohol (0.375 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et$_2$O (5 mL) and saturated NH$_4$Cl (aq) (25 mL) was added. The mixture was extracted with Et$_2$O (3 x 10 mL) and the extract dried over MgSO$_4$. Conversion was measured by ^{1}H-NMR. HPLC was used to determine enantiomeric excesses (for more details for compounds **23**-**26** see previous Section 4.1.5.6)

4.4.4.10. Typical procedure for the preparation of carbocyclic compounds 46-51

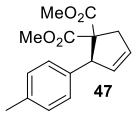
A solution of Grubbs II catalyst (5 mg, 0.006 mmol) and the corresponding alkylated product (0.12 mmol) in CH_2Cl_2 (3 mL) was stirred for 16 h. The solution was directly purified by flash chromatography (95:5; Hex: EtOAc) to obtain the desired carbocycle compounds.



Dimethyl 2-phenylcyclopent-3-ene-1,1-dicarboxylate (46).[7b] Enantiomeric excess determined by HPLC using Chiralpak IC column (87% 2-propanol/hexane, flow 0.5 mL/min, λ= 226 nm). t_R 15.3 min (*S*); t_R 17.0 min (*R*). ^{1}H NMR ($CDCl_3$), δ: 2.76 (d, 1H, CH_2, *J*= 17.4 Hz), 3.06 (s, 3 H,

CH_3), 3.45 (d, 1H, CH_2, *J*= 17.4 Hz), 3.74 (s, 3H, CH_3), 4.86 (s, 1H, CH), 5.68 (m, 1H, CH=), 5.85 (m, 1H, CH=), 7.1-7.3 (m, 5H, CH=).

Dimethyl 2-(p-tolyl)cyclopent-3-ene-1,1-dicarboxylate (47).[7b] Enantiomeric excess determined by HPLC using Chiralpak IA column (98% 2-propanol/hexane, flow 0.5 mL/min, λ= 226 nm). t_R 12.1 min (-); t_R 12.8 min (+). ^{1}H NMR ($CDCl_3$), δ: 2.30 (s, 3H, CH_3), 2.81 (bd, 1H, CH_2, *J*= 12.6 Hz), 3.22 (s, 3 H, CH_3), 3.49 (m, 1H, CH_2), 3.76 (s, 3H, CH_3), 4.86 (s, 1H, CH), 5.71 (m, 1H, CH=), 5.87 (m, 1H, CH=), 7.1-7.3 (m, 4H, CH=).



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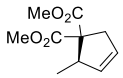
Dimethyl 2-methylcyclopent-3-ene-1,1-dicarboxylate (48).[7b] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (98% 2-propanol/hexane, flow 0.5 mL/min, λ= 226 nm). t_R 15.6 min (-); t_R 16.7 min (+). ^{1}H NMR ($CDCl_3$), δ: 0.96 (d, 3H, CH_3, *J*= 7.6 Hz), 2.72 (d, 1H, CH_2, *J*= 16.8 Hz), 3.26 (d, 1H, CH_2, *J*= 16.8 Hz), 3.62 (q, 1H, CH, *J*= 7.6 Hz), 3.73 (s, 6 H, CH_3), 5.57 (m, 2H, CH=).



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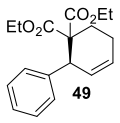
Diethyl 2-phenylcyclohex-3-ene-1,1-dicarboxylate (49).[36] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (98% 2-propanol/hexane, flow 0.5 mL/min, λ= 220 nm). t_R 12.5 min (-); t_R 17.5 min (+). ^{1}H NMR ($CDCl_3$), δ: 1.25 (t, 6H, CH_3, *J*= 7.2 Hz), 1.9-2.3 (m, 4H, CH_2), 3.91 (m, 1H, CH), 4.19 (m, 4H, CH_2), 5.76 (m, 1H, CH=), 5.90 (m, 1H, CH=), 7.1-7.4 (m, 5H, CH=).



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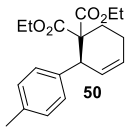
Diethyl 2-(p-tolyl)cyclohex-3-ene-1,1-dicarboxylate (50).[36] Enantiomeric excess determined by HPLC using Chiralpak OJ-H column (98% 2-propanol/hexane, flow 0.5 mL/min, λ= 220 nm). t_R 12.5 min (-); t_R 18.7 min (+). ^{1}H NMR ($CDCl_3$), δ: 1.26 (t, 6H, CH_3, *J*= 7.2 Hz), 1.9-2.2 (m, 4H, CH_2), 2.26 (s, 3H, CH_3), 3.97 (m, 1H, CH), 4.20 (m, 4H, CH_2), 5.73 (m, 1H, CH=), 5.85 (m, 1H, CH=), 7.1-7.4 (m, 4H, CH=).



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4.4.5. Acknowledgments

We would like to thank the Spanish Government for providing grant CTQ2013-40568P the Catalan Government for grant 2014SGR670, COST action CM 1205 Catalytic Routines for Small Molecule Activation (CARISMA) and the ICREA Foundation for providing M. Diéguez and O. Pàmies with financial support through the ICREA Academia awards.

4.4.6. References

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UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull

4.5. Computationally guided design of a readily assembled phosphite-thioether ligand for a broad range of Pd-catalyzed asymmetric allylic substitutions

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In collaboration with the groups of Prof. M. A. Pericàs and Prof. F. Maseras (ICIQ, Tarragona).

Abstract: A modular approach employing indene as common starting material, has enabled the straightforward preparation in three reaction steps of P-thioether ligands for the Pd-catalyzed asymmetric allylic substitution. The analysis of a starting library of P-thioether ligands based on rational design and theoretical calculations has led to the discovery of an optimized anthracenethiol derivative with excellent behavior in the reaction of choice. Improving most approaches reported to date, this ligand presents a broad substrate and nucleophile scope. Excellent enantioselectivities have been achieved for a range of linear and cyclic allylic substrates using a large number of C-, N-, and O-nucleophiles (40 compounds in total). The species responsible for the catalytic activity have been further investigated by NMR in order to clearly establish the origin of the enantioselectivity. The resulting products have been derivatized by means of ring-closing metathesis or Pauson-Khand reactions to further prove the synthetic versatility of the methodology for preparing enantiopure complex structures.

4.5.1. Introduction

The future of chemical production must keep up with the growing demand for fine chemicals while reducing the overall waste production and energy consumption demanded by international regulations (and common sense). Over the last decades, this need for sustainability has driven the shift from suboptimal non-catalyzed processes to high-performing catalytic processes for the production of all sorts of chemicals.[1] This has been especially noteworthy in the production of enantiopure compounds, which play a key role in many technologically and biologically relevant applications.[2] Among the toolkit of catalytic enantioselective transformations, asymmetric Pd-catalyzed allylic substitution stands out for its versatility (as it creates new C-C and C-heteroatom bonds starting from simple precursors), high functional group tolerance and mild reaction conditions. Moreover, the resulting products accept further derivatization thanks to the presence of an alkene functionality.[3] The key role of the ligand in the induction of chirality in this process has motivated several studies concerning the generation and

evaluation of myriad candidates in terms of yield, selectivity, and substrate scope. Heterodonor compounds (phosphine/phosphinite-oxazolines being the paradigmatic example) have proven especially advantageous because the different *trans* influence of the two donor groups generates an efficient electronic differentiation between the two allylic terminal carbon atoms. Indeed, the nucleophilic attack is known to take place predominantly *trans* to the donor group with stronger *trans* influence. On the basis of this premise, we have contributed with mixed ligands bearing biaryl phosphite moieties,[3j,4] which flexible nature allows the catalyst chiral pocket to adapt to the steric demands of the substrate,[4] resulting in a broadened substrate scope.

The vast amount of Pd-catalyzed allylic substitution studies reported in the literature have led to remarkable advances in catalyst design; however, catalysts are still rarely suitable for a wide range of substrates. Instead, the most common scenario is that each allylic precursor requires independent optimization to identify the optimal catalytic system, and a similar situation takes place with the various nucleophiles. Consequently, the identification of "privileged" ligands remains a central task in this type of chemistry. In addition to giving excellent results for a broad range of allylic precursors and nucleophiles (C-, N-, or O-based), such privileged ligands must be readily prepared in both enantiomeric forms from available starting materials and be easy to handle (i.e., solid, robust and stable in air).

To this end, we recently started a research line aimed at identifying suitable alternatives to the labile oxazoline moiety. We were especially interested in the stable and easy to prepare thioether group, which allowed the preparation of a Pd/phosphite-thioether furanoside-based catalyst that creates C-C, C-N, and C-O bonds with different substrates and a variety of nucleophiles.[5] The yields and enantioselectivities obtained were comparable to the best catalytic systems reported in the literature. Although these furanoside ligands were prepared from inexpensive D-xylose, their synthesis was tedious and required a large number of steps. Other researchers have demonstrated the utility of thioether-based P,S-ligands.[6] For instance, the pioneering work in Pd-catalyzed allylic substitution and other relevant asymmetric reactions of Pregosin[7] and Evans,[6a] among others, put the focus on this kind of ligands and spurred their development. Despite the many efforts devoted to develop P,S-ligands, their impact has been limited for two main reasons: (a) even in the most successful cases, they were limited in substrate and nucleophile scope: enantioselectivities were mainly high for the allylic substitution of the standard (and hindered) *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** using dimethylmalonate as nucleophile[6] and (b) thioether-based ligands are prone to producing mixtures of diastereomeric thioether complexes, which tend to interconvert in solution.[8] However, if one could design a scaffold able to control the configuration on sulfur upon coordination of the P,S-ligand, the this would provide an additional chiral element in close proximity to the metal, thus giving rise to simpler

ligands that can be prepared in fewer steps than their oxazoline-phosphine counterparts.

Herein, we give a new push to the study of the catalytic potential of P,S-ligands by screening novel, readily accessible thioether-containing compounds, including a detailed study of the species responsible for the catalytic performance. For this purpose, we designed a small but structurally diverse library of P-thioether ligands **L41**–**L48a**–**g** (Figure 4.5.1) that was tested in the Pd-catalyzed allylic substitution of a broad range of substrates and nucleophiles. These new P,S-ligands are synthesized in only three steps from inexpensive indene (ca. 20 USD/kg in bulk) and, since the corresponding enantiopure epoxide is prepared through Jacobsen epoxidation, both enantiomeric series are equally available. This modular approach[9] greatly expedites the evaluation of several thioether and phosphite/phosphinite moieties, which is deemed crucial for the iterative optimization of the most promising candidates. Consequently, the catalytic performance of the ligands depicted in Figure 4.5.1 has been studied by systematically varying: (a) the electronic and steric properties of the thioether group (**L41**–**L48**), (b) the configuration of the biaryl phosphite moiety (**a**–**c**), and (c) the P-containing group (phosphite (**a**-**c**) vs phosphinite groups (**d**–**g**)).

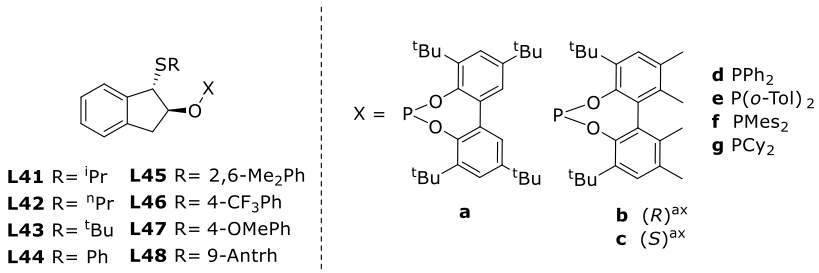


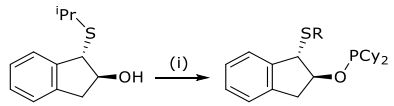
Figure 4.5.1. Phosphite/phosphinite-thioether ligand library **L41**-**L48a**-**g**.

An additional advantage of this set of ligands is the fact that their simplified backbone renders very simple NMR spectra, thus reducing signal overlap, as well as facilitating the identification of relevant intermediates and accelerating the DFT calculations performed to rationalize the behavior of the system. By combining theoretical studies and NMR spectroscopy, we have been able to rationally fine-tune the ligands, improve enantioselectivity and identify the species responsible for the catalytic performance. This optimized ligand has proven active in the Pd-catalyzed allylic substitution of both linear and cyclic substrates with a broad range of C-, N-, and O-nucleophiles (26 examples in total), even with the environmentally friendly propylene carbonate as solvent. Finally, the applicability of the new Pd/P-thioether catalysts has been further demonstrated in the practical synthesis of chiral (poly)carbo- and heterocycles heterocyclic compounds using straightforward sequences of allylic substitution/ring-closing metathesis or allylic alkylation/Pauson-Khand reactions.

4.5.2. Results and Discussion

4.5.2.1. Synthesis of ligands

The synthesis of the new phosphite/phosphinite-thioether ligands **L41g** is shown in Scheme 4.5.1. As previously described in Section 3.10, phosphinite-thioether ligand **L41g** were synthesized by treating the corresponding hydroxyl-thioether **1** with one equivalent of the corresponding chlorophosphine ($ClPR_2$; R= **g**; step i).



1 **L41g**

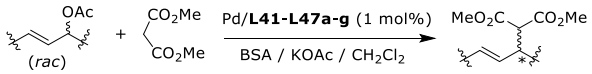
Scheme 4.5.1. Synthesis of new phosphite/phosphinite-thioether ligands **L41g**; (i) $ClPR_2$, NEt_3, DMAP cat., toluene, 20 min.

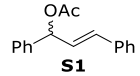
The resulting enantiopure ligand was isolated in a good yield as colorless oil. Ligand **L41g** was characterized by $^{31}P\{^1H\}$, ^1H, and $^{13}C\{^1H\}$ NMR spectroscopy. All data were in agreement with assigned structures. The spectra assignments were supported by the information obtained from ^1H-^1H and ^1H-^{13}C correlation measurements. The $^{31}P\{^1H\}$, ^1H, and $^{13}C\{^1H\}$ NMR spectra showed the expected pattern for the C_1-ligands.

4.5.2.2. Evaluation of the first-generation ligand library in the allylic substitution of symmetrical 1,3-disubstituted allylic substrates

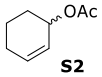
As already mentioned, the catalyst ability to adjust to the steric demands of the substrate is a key factor in transferring the chiral information to the product. To assess the potential of this ligand library in the allylic substitution, we first tested **L41**–**L47a**–**g** in the Pd-catalyzed allylic substitution of two substrates with different steric requirements: the model substrate **S1** and the more challenging cyclic **S2** (Table 4.5.1). Excellent yields were almost invariably obtained under mild reaction conditions (i.e., 1 mol% Pd, ligand-to-palladium ratio of 1.1 at room temperature) with TOF as high as 2000 mol (mol h)$^{-1}$. As for the enantioselectivities, up to 97% ee for **S1** and 88% ee for **S2** could be achieved by using ligands that combine an aryl thioether group with a chiral biaryl phosphite moiety.

Table 4.5.1. Pd-catalyzed allylic alkylation of **S1**–**S2** with dimethyl malonate as nucleophile using ligands **L41**–**L47a**–**g**.[a]





S1



S2

Entry	L	% Conv (h)[b]	% ee[c]	% Conv (h)[b]	% ee[c]
1	**L41a**	100 (0.5)	17 (*R*)	100 (2)	15 (*S*)
2	**L41b**	100 (0.5)	90 (*R*)	100 (2)	66 (*R*)
3	**L41c**	100 (0.5)	75 (*S*)	100 (2)	61 (*S*)
4	**L41d**	100 (0.5)	50 (*R*)	100 (2)	28 (*S*)
5	**L41e**	100 (0.5)	25 (*R*)	100 (2)	11 (*S*)
6	**L41f**	100 (0.5)	4 (*R*)	100 (2)	14 (*R*)
7	**L41g**	5 (0.5)	32 (*R*)	10 (2)	28 (*S*)
8	**L42b**	100 (0.5)	90 (*R*)	100 (2)	62 (*R*)
9	**L43b**	100 (0.5)	84 (*R*)	100 (2)	60 (*R*)
10	**L43e**	100 (0.5)	63 (*R*)	100 (2)	77 (*S*)
11	**L44b**	100 (0.5)[d]	97 (*R*)	100 (2)	85 (*R*)
12	**L45b**	100 (0.5)	96 (*R*)	100 (2)	86 (*R*)
13	**L45c**	100 (0.5)	80 (*S*)	100 (2)	84 (*S*)
14	**L45d**	100 (0.5)	28 (*R*)	100 (2)	13 (*S*)
15	**L45e**	100 (0.5)	40 (*R*)	100 (2)	11 (*S*)
16	**L46b**	100 (0.5)	96 (*R*)	100 (2)	88 (*R*)
17	**L47b**	100 (0.5)	97 (*R*)	100 (2)	87 (*R*)
18[e]	**L45b**	100 (1)	96 (*R*)	100 (4)	85 (*R*)

[a] Reaction conditions: 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch) at rt; [b] Conversion measured by ^1H NMR; [c] Enantiomeric excesses measured by HPLC for dimethyl 2-(1,3-diphenylallyl)-malonate (**2**) and by GC for dimethyl 2-(1,3-cyclohexanylallyl)malonate (**3**); [d] TOF= 2000 mol (mol h)$^{-1}$ calculated after 5 min from catalysis performed at 0.25 mol% of Pd; [e] Reactions carried out using PC as solvent at 40 °C.

In an effort to measure the contribution of the different P-donor groups, we analyzed the results of ligands **L41a**–**g** (entries 1-7). The trend was clearly pointing out to a superior performance of phosphite- over phosphinite-based structures (i.e., entries entry 2 vs. 4-7), even with very bulky ones. We wondered whether the ligand chirality might able to control the conformation around the biphenyl moiety devoid of chiral axis. However, this possibility was ruled out by comparing entries 1-3, where the superior performance of ligands bearing a phosphite with axial chirality was evident (entries 2 and 3). Actually, the chiral axis seems to be the major factor in controlling the enantioselectivity. Indeed, ligands differing only in the configuration of this chiral axis

(but otherwise having the same stereocenters) give rise to products with opposite absolute configuration (entries 2 and 3). Considering the substrates independently, with **S1** a remarkable cooperative effect between the configuration of the biaryl phosphite moiety and the ligand backbone is observed, which results in a matched combination with ligand **L41b**, that bears an (*R*) chiral axis (entry 2 vs 3). This cooperative effect is less pronounced for cyclic substrate **S2**, and both enantiomers of the alkylated products are therefore easily accessible with similar levels of enantioselectivity by simply setting the configuration of the biaryl phosphite moiety (entry 2 vs 3).

Finally, by further comparing ligands **L41**–**L47b**, we found that the electronic and steric properties of the thioether substituent have a small but important effect on the enantioselectivities: ligands with aryl-thioether groups led to higher ee's (especially with cyclic substrate **S2**; i.e., entry 11 vs 2, 8 and 9) than their counterparts with alkyl thioether moieties, even for the bulky *tert*-butyl thiol derivative. In summary, the best enantioselectivities for **S1** (ee's up to 97%) were obtained with ligands **L44**-**L47b**, built from a combination of any aryl thioether group with an (*R*)-biaryl phosphite group: the above-mentioned matched combination (entries 11, 12, 16 and 17). On the other hand, the best enantioselectivities recorded for substrate **S2** (ee's up to 88%), in both enantiomers of the alkylated product, were obtained with ligands **L44**–**L47b**–**c**, containing either an (*R*)- or (*S*)-biaryl phosphite group with an aryl thioether moiety (i.e., entries 11–13 and 16–17).

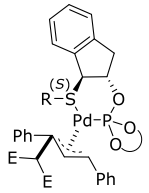
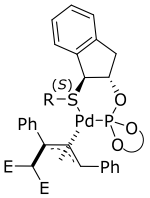
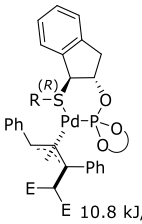
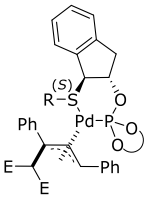
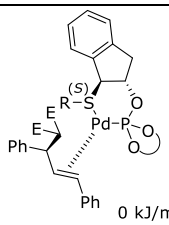
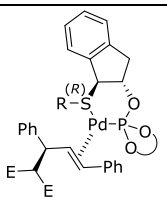
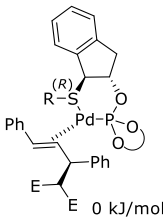
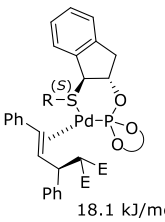
With the aim of improving the sustainability profile of the process, we studied the reactions in 1,2-propylene carbonate (PC), an environmentally friendly alternative to standard organic solvents because of its high boiling point, low toxicity, and "green" synthesis.[10] In spite of these environmental advantages, this solvent it has been scarcely used in asymmetric Pd-catalyzed allylic substitution and mainly limited to the standard **S1** substrate and dimethyl malonate as nucleophile.[4d,10b,11] Thus, we repeated the allylic substitution of substrates **S1** and **S2** in PC (Table 4.5.1, entry 18; see also Table SI.1 in the Supporting Information at the end of this chapter for the use of PC for the allylic substitution of other substrates and nucleophiles). Gratifyingly, the enantioselectivities remained as high as those observed when dichloromethane was used.

4.5.2.3. Optimization of ligand parameters. DFT computational studies towards fine-tuned phosphite-thioether ligands L48

With the ultimate goal of fine-tuning the ligands to increase enantioselectivity, we carried out DFT calculations of the transition states and key Pd-olefin intermediates involved in the enantiodetermining step. Previous mechanistic studies on Pd-catalyzed allylic alkylation have established the irreversible nucleophilic attack as the enantiodetermining step, although the corresponding transition state (TS) can be either

early or late, depending on the nucleophile, ligands, and reaction conditions.[12] In the latter case, if the transition states are very similar to products the enantioselectivity of the process could also be described by the Pd-olefin complexes.

Table 4.5.2. Schematic representation and relative free energies in solution for the most stable (*R*)- and (*S*)-transitions states (in kJ/mol) and most stable (*R*)- and (*S*)-Pd-π-olefin complexes for the substrate **S1** with dimethyl malonate and **L45b** and **L45c** ligands.[a]

	Transition states (TSs)			
Ligand	$TS_{(R)}$	$TS_{(S)}$	$\%ee_{calc}$	$\%ee_{exp}$
L45b	 0 kJ/mol *endo*	 28 kJ/mol *exo*	>99 (*R*)	96 (*R*)
L45c	 10.8 kJ/mol *exo*	 0 kJ/mol *exo*	96 (*S*)	80 (*S*)
	Pd-olefin complexes			
Ligand	Pd-olefin$_{(R)}$	Pd-olefin$_{(S)}$	$\%ee_{calc}$	$\%ee_{exp}$
L45b	 0 kJ/mol	 38.1 kJ/mol	>99 (*R*)	96 (*R*)
L45c	 0 kJ/mol	 18.1 kJ/mol	>99 (*R*)	80 (*S*)

[a] Computational and experimental enantiomeric excesses are also presented. E= CO_2Me

Therefore, we started by calculating the relative stability of the transition states and the Pd-olefin intermediates using the model substrate **S1** and dimethyl malonate as

nucleophile with ligands **L45b**–**c**. The goal was to evaluate the effect of the chiral axis of the biaryl phosphite moiety, as these ligands differ only in the configuration of this biaryl (see Table 4.5.1, entry 12 vs 13). Only the two *syn*/*syn* allyl complexes were calculated, neglecting the contribution of other allylic species of higher energy (*anti*/*anti* and *syn*/*anti*).[3d] In this study, we have taken into account the configuration of the thioether and the attack of the nucleophile *trans* to P and S atoms. In contrast to P,N-ligands, the *trans* influence exerted by the thioether and the phosphite are of a similar magnitude; indeed, previous studies have shown that small changes in the ligand can shift the *trans* preference in P,S-ligands.[5b,13] The results of the most stable transition states ($TS_{(R)}$ and $TS_{(S)}$) and Pd-olefin intermediates ($Pd\text{-}olefin_{(R)}$ and $Pd\text{-}olefin_{(S)}$) leading to the formation of both product enantiomers are shown in Table 4.5.2 (the full set of calculated TSs and Pd-olefin intermediates can be found in the Supporting Information). The energy differences of the calculated TSs match with the results obtained in the catalytic process, the value for **L45b** ($\Delta\Delta G^{\#}$= 28 kJmol^{-1}; ee_{calc} > 99% (*R*)) being therefore higher than that of **L45c** ($\Delta\Delta G^{\#}$= 10.8 kJmol^{-1}; ee_{calc} = 97% (*S*)). This is in agreement with the higher enantioselectivities achieved using **L45b** than **L45c** (96% (*R*) ee for **L45b** vs 80% (*S*) ee for **L45c**; Table 4.5.1, entries 12 and 13). It must be mentioned here that the calculated ee values were obtained using the eight different transition states for each ligand reported in the Supporting Information. If we had only used the two reported in Table 4.5.2, the values for **L45b** and **L45c** would have been 99% (*R*) and 98% (*S*), respectively.

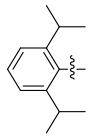
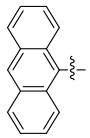
Moreover, DFT correctly predicts the formation of the opposite product enantiomers when **L45b** and **L45c** are applied. It should be noted that, in contrast to what was observed with ligand **L45b**, both enantiomers of the substitution product obtained with ligand **L45c** arise from TSs with *exo* coordination of the substrate, with the nucleophilic attack *trans* to P (for the major enantiomer) and *trans* to S (for the minor enantiomer). Finally, the calculated energies of the Pd-olefin intermediates do not correlate well with the experimental results (Table 4.5.2). For both ligands, the most stable olefin complex corresponds to the (*R*)-enantiomer in more than 99% ee.

Identification of the origin of enantioselectivity from direct inspection of the structures for the two most stable transition states (TSs) with ligands **L45b** and **L45c** (shown in Figure S1 in the Supporting Information at the end of this chapter) is not trivial. We tried to apply a distortion/interaction analysis, also in the Supporting Information at the end of this chapter, but the results were inconclusive. The differences between the two systems were in the distortion part, but their analysis was difficult. A quadrant analysis (see Supporting Information at the end of this chapter, Section 4.5.7.18) was on contrary more indicative. The key to selectivity is in the steric repulsion between one of the phenyl substituents of the substrate and the biaryl phosphite moiety. The modifications between the **L45b** and **L45c** ligands places the steric bulk associated with the biaryl phosphite in a different quadrant, thus favoring different enantiomers.

Interestingly, the steric bulk on the "sulfur side" of the catalyst is also important, as it pushes the sterically active regions of substrate and catalyst closer to each other, thus enhancing selectivity.

Based on the previous findings, we investigated whether the lower enantiomeric excesses recorded with the cyclic substrate **S2** (ee's up to 88%) could be improved by increasing the steric hindrance of the ligand. A simple way to do this is to introduce a thioether group that is bulkier than the 2,6-dimethylphenyl moiety while maintaining the aryl groups (that have been shown to perform better than their alkylic counterparts). For this purpose, we ran analogous TS calculations for **S2** with ligand **L45b** (bearing the 2,6-dimethylphenyl thioether group) and with other ligands containing instead the bulkier 2,6-diisopropylphenyl or anthryl moieties. To accelerate the DFT calculation we used ammonia as model nucleophile.[14]

Table 4.5.3. Comparison between theoretical and experimental results in the Pd-catalyzed allylic substitution of **S2**.

R-S	L	$\Delta\Delta G^{\#}_{calc}$	% ee_{calc}	% ee_{exp}[a]	$\Delta\Delta G^{\#}_{exp}$[a]
	**L45b**	1.2 kJ/mol	9 (*R*)	86 (*R*)	6.3 kJ/mol
	**-**	2.1 kJ/mol	35 (*R*)	-	-
	**L48b**	6.8 kJ/mol	74 (*R*)	94 (*R*)[b]	8.6 kJ/mol

[a] Reaction conditions: 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch) at rt; [b] Ligand **L48c** provided the alkylated product **3** in 93% ee (*S*).

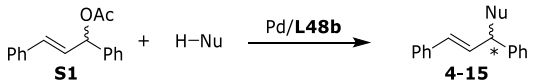
The results show that the enantioselectivity is affected by the steric effects of the thioether group (Table 4.5.3), increasing from 9% (*R*) for ligand **L45b** (with a 2,6-dimethylphenyl thioether group) to 35% (*R*) with a 2,6-diisopropylphenyl thioether, and to 74% (*R*) with an anthryl thioether moiety. The results of these calculations prompted us to prepare two new ligands containing an anthryl thioether group (**L48b** and **L48c**; Figure 4.5.1) and test them in the Pd-catalyzed alkylation of **S2**. To our delight, the introduction of this bulky aromatic moiety did affect positively the enantioselectivity, increasing from 86% ee to 94% ee (Table 4.5.3), as predicted by the theoretical calculations.[15] This result is comparable to the best one reported in the literature for this challenging substrate.[3] Interestingly, ligand **L48b** also provided the highest

enantioselectivity in the alkylation of linear substrate **S1** (ee's up to 99% (*R*), compared to previous best value 97% with ligand **L47b**).

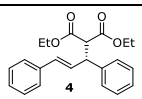
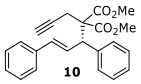
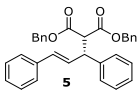
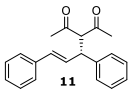
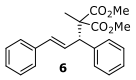
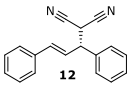
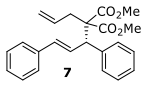
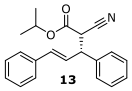
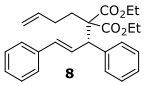
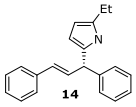
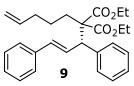
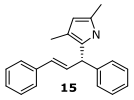
4.5.2.4. Allylic substitution of linear substrate S1 with several nucleophiles. Scope and limitations

We initially considered the allylic substitution of substrate **S1** with an extensive range of C-, N-, and O-nucleophiles. Tables 4.5.4 and 4.5.5 show the results using ligand **L48b**, which had provided the best results in the allylic alkylation of **S1** with dimethyl malonate as model nucleophile.

Table 4.5.4. Pd-catalyzed allylic substitution of linear substrate **S1** with different types of C-nucleophiles using Pd/**L48b** catalytic system.[a]



S1 **4-15**

Entry	Product	%Yield[b]	% ee[c]	Entry	Product	%Yield[b]	% ee[c]
1	 **4**	94	99 (*R*)	7	 **10**	90	99 (*S*)
2	 **5**	92	98 (*R*)	8	 **11**	88	98 (*R*)
3	 **6**	92	97 (*S*)	9	 **12**	84	99 (*R*)
4	 **7**	93	98 (*S*)	10	 **13**	82 (60:40 dr)	98/97[d]
5	 **8**	89	98 (*S*)	11[d]	 **14**	87	96 (*S*)
6	 **9**	91	95 (*S*)	12[d]	 **15**	85	>99(*R*)

[a] Reaction conditions: 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 1.1 mol% ligand, CH_2Cl_2 (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch) at rt for 30 min; [b] Isolated yield; [c] Enantiomeric excesses measured by HPLC or GC; [d] 2 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4.4 mol% ligand CH_2Cl_2 (2 mL), K_2CO_3 (2 equiv) at rt for 18 h.

A variety of malonates, including the allyl-, butenyl-, pentenyl- and propargyl-substituted ones, reacted with **S1** to provide products **4**–**10** in high yields and enantioselectivities (ee's up to 99%, Table 4.5.4, entries 1–7). These substituted

malonates are known to be more challenging nucleophiles for Pd-catalyzed allylic substitution, but they give rise to more interesting products from a synthetic point of view (see Synthetic applications of the allylic substitution compounds, see Section 4.5.2.6). The addition of acetylacetone also proceeded with high enantiocontrol (Table 4.5.4, entry 8, ee's up to 98%). High yields and enantioselectivities were also found in the addition of malononitrile and isopropyl cyanoacetate (products **12** and **13**; ee's up to 99%, Table 4.5.4, entries 9 and 10), albeit the diastereoselectivity of the latter was low, as expected for such an acidic stereocenter.[16]

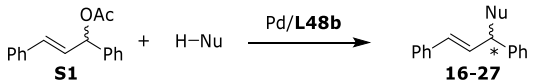
Pyrroles, which are electron-rich *N*-containing heterocycles interesting from the synthetic and biological point of view,[17] also performed well as nucleophiles in this reaction. Despite their importance, as far as we know only one catalytic system has been reported to be successful in the Pd-catalyzed allylic alkylation of **S1**-type substrates with pyrroles, the reaction involving inconvenient low temperature (–20 ºC).[18] The difficulty of the transformation is more evident if we consider that, even two of the most successful ligands developed for this process (Trost diphosphine and phosphine-oxazoline PHOX), did not work with pyrroles.[18] Thus, we were pleased to see that using the Pd/**L48b** system we could reach ee's up to 99% and high yields working at room temperature (Table 4.5.4, entries 11 and 12).

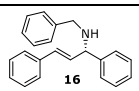
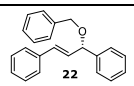
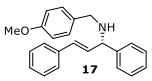
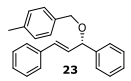
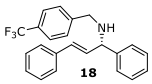
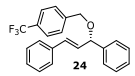
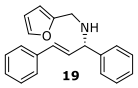
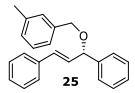
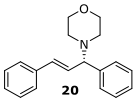
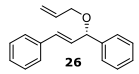
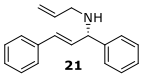
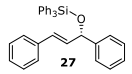
Chiral allylic amines are also ubiquitous in biologically active compounds,[3n] so we next studied the use of amine derivatives as nucleophiles. Benzylamine provided the substitution product **16** in high yield and enantioselectivity (99% ee; Table 4.5.5, entry 1). To test the scope of allylic amination, the reaction of **S1** was evaluated using other *N*-nucleophilic compounds (Table 4.5.5, entries 2–6). The combination Pd/**L48b** also proved highly efficient in the addition of *p*-methoxy- and *p*-trifluoromethylbenzylamines (compounds **17** and **18**) and the furfurylamine **19** (Table 4.5.5, entries 2–4), enantiocontrol being always excellent. The addition of morpholine, a cyclic secondary amine, also gave the expected product with high enantioselectivity (product **20**; Table 4.5.5, entry 5), while allylamine proceeded with comparably high enantioselectivity (97% ee; Table 4.5.5, entry 6). This is especially interesting given the fact that the amination product **21** is a key intermediate in the synthesis of complex molecules. For example, the Boc protected derivative of **21** can be further applied in metathesis reactions for the construction of a dihydropyrrole derivative (see Synthetic applications of the allylic substitution compounds, see Section 4.5.2.6).

The exquisite enantiocontrol observed for C- and N-nucleophiles can also be extended to aliphatic alcohols (compounds **22**–**26**, ee's up to 99%; Table 4.5.5, entries 7–11). The effective allylic substitution with this type of O-nucleophiles opens up new synthetic avenues towards chiral ethers, which are important for the synthesis of biologically active molecules.[19] Despite the potential of the resulting products, a general catalytic solution for the Pd-catalyzed allylic etherification has remained elusive, and most of the few successful examples reported to date deal with phenols,[20] while aliphatic alcohols

have been less studied.[4,6a,6f,21] Moreover, the enantioselectivities reported so far largely depend on the type of aliphatic alcohol and their electronic properties[4,6a,6f,21] can have a large impact on this parameter. Using our streamlined ligand **L48b**, we found that benzylic alcohols gave excellent results regardless of the steric and electronic properties of the aryl group (Table 4.5.5, entries 7–10). Allyl alcohol also furnished the desired product in high yield and ee (Table 4.5.5, entry 11). Even more outstanding are the almost perfect enantioselectivities (ee's up to 99%) and high yields achieved in the etherification of **S1** with triphenylsilanol (Table 4.5.5, entry 12), a rather unusual nucleophile that gives rise to a protected chiral alcohol.[21e] Remarkably, enantioselectivities recorded with O-nucleophiles (Table 4.5.5, entries 7–12) were, at the very least, as high as those obtained with dimethyl malonate.

Table 4.5.5. Pd-catalyzed allylic substitution of linear substrate **S1** with different types of N- and O-nucleophiles using Pd/**L48b** catalytic system.[a]



Entry	Product	%Yield[b]	% ee[c]	Entry	Product	%Yield[b]	% ee[c]
1	 **16**	88	99 (*S*)	7[d]	 **22**	92	99 (*S*)
2	 **17**	81	99 (*S*)	8[d]	 **23**	90	99 (*S*)
3	 **18**	78	99 (*S*)	9[d]	 **24**	91	98 (*S*)
4	 **19**	83	97 (*S*)	10[d]	 **25**	93	98 (*S*)
5	 **20**	87	98 (*S*)	11[d]	 **26**	83	96 (*S*)
6	 **21**	79	97 (*S*)	12[d]	 **27**	78	99 (*R*)

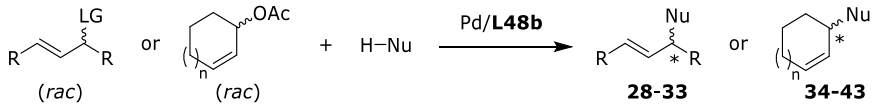
[a] Reaction conditions: 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 1.1 mol% ligand, CH_2Cl_2 (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch) at rt for 30 min; [b] Isolated yield; [c] Enantiomeric excesses measured by HPLC or GC; [d] 2 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4.4 mol% ligand CH_2Cl_2 (2 mL), Cs_2CO_3 (3 equiv) at rt for 18 h.

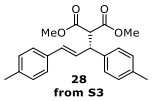
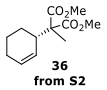
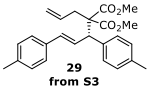
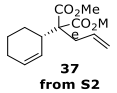
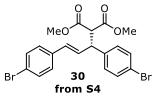
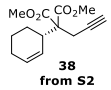
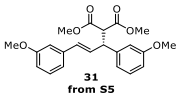
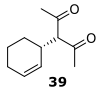
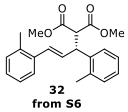
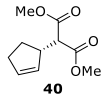
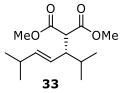
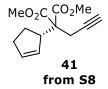
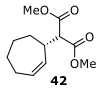
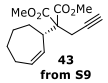
4.5.2.5. Allylic substitution of several linear and cyclic substrates S2-S9 using several C-nucleophiles. Scope and limitations

After the broad scope of nucleophiles displayed by the catalytic system with **S1**, we turned our attention to the use of another five additional linear substrates (**S3**–**S7**) with electronic and steric requirements different from **S1** (Table 4.5.6, entries 1–6). Advantageously, we found that the catalytic performance was neither affected by the introduction of electron-withdrawing, and electron-donating groups (entries 1–3), nor by the introduction of *ortho*- and *metha*-substituents at the phenyl groups of the substrate (entries 4–5). A remarkable enantioselectivity (entry 6) was still achieved in the Pd-catalyzed allylic alkylation of **S7**, a challenging substrate that typically gives rise to the corresponding substitution products in much lower enantioselectivities than **S1** in otherwise identical conditions.

Finally, we wanted to see if the high enantioselectivities achieved in the allylic substitution of linear substrates were retained for their notoriously difficult cyclic analogues. To this end, a number of cyclic substrates with different ring sizes were tested using ligand **L48b** (Table 4.5.6, entries 7–16; for the results using the Pd/**L48c** catalytic system see Table SI.2 in the Supporting Information at the end of this chapter). For substrate the cyclohexenyl derivative **S2**, a range of C-nucleophiles proved to give yields and enantioselectivities as high, if not higher, as those recorded with dimethyl malonate (ee's up to 97%, entries 7–11). The only exception was acetylacetone that led to somewhat lower enantioselectivity (entry 12). High enantioselectivities in both enantiomers of the substitution products were thus obtained using methyl-, allyl-, and propargyl-substituted malonates (compounds **36**–**38**; Table 4.5.6; entries 9–11 and Table SI.2). Furthermore, the biaryl phosphite group in Pd/**L48b** and Pd/**L48c** can adapt its chiral pocket to efficiently mediate the substitution of other cyclic substrates (entries 13–16). Excellent yields and enantioselectivities, comparable to the best reported in the literature, were obtained in the allylic alkylation of a 7-membered cyclic substrate with different C-nucleophiles (products **42** and **43**; entries 15 and 16). Even more interesting is that the good performance could be also extended to the allylic alkylation of a more challenging 5-membered cyclic substrate (compounds **40** and **41**; entries 13 and 14).

Table 4.5.6. Pd-catalyzed allylic substitution of substrates **S2**–**S9** with several C-nucleophiles using Pd/L8b catalytic system.[a]



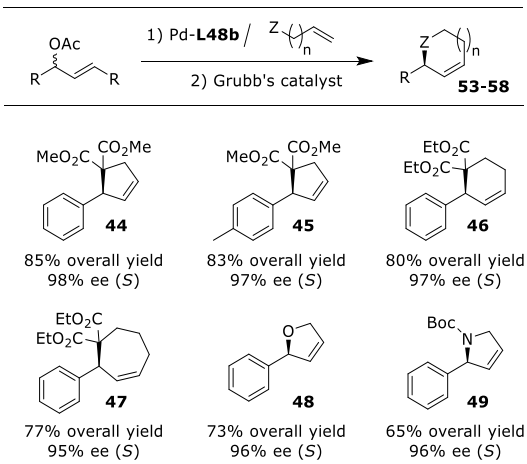
Entry	Product	%Yield[b]	% ee[c]	Entry	Product	%Yield[b]	% ee[c]
1	 **28** **from S3**	98	98 (*R*)	9	 **36** **from S2**	87	91 (*R*)
2	 **29** **from S3**	87	97 (*R*)	10	 **37** **from S2**	84	94 (*R*)
3	 **30** **from S4**	89	96 (*R*)	11	 **38** **from S2**	86	97 (*R*)
4	 **31** **from S5**	91	97 (*R*)	12	 **39** **from S2**	82	80 (-)
5	 **32** **from S6**	87	99 (*R*)	13	 **40** **from S8**	80	84 (-)
6	 **33** **from S7**	91	95 (*R*)	14	 **41** **from S8**	83	85 (-)
7	 **34** **from S2**	87	95 (*R*)	15	 **42** **from S9**	90	96 (*R*)
8	 **35** **from S2**	84	95 (*R*)	16	 **43** **from S9**	92	96 (*R*)

[a] Reaction conditions: 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 1.1 mol% ligand, CH_2Cl_2 (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch) at rt for 2 h; [b] Isolated yield; [c] Enantiomeric excesses measured by HPLC, GC or ^{1}H-NMR using $[Eu(hfc)_3]$.

4.5.2.6. Synthetic applications of the allylic substitution compounds. Preparation of chiral functionalized (poly)carbocyclic and heterocyclic compounds 44-49

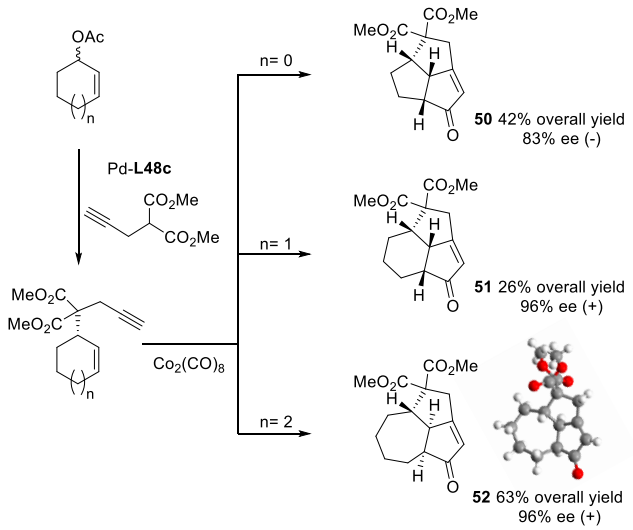
To illustrate the synthetic versatility of the compounds obtained from the enantioselective Pd-catalyzed allylic substitution, we have prepared a range of chiral functionalized carbocycles (**44**–**47**), heterocycles (**48**–**49**), and polycarbocycles (**50**–**52**) from the enantioenriched allylic substitution products. These compounds have been synthesized by straightforward reaction sequences involving allylic substitution of the appropriate substrates followed by either ring-closing metathesis (Scheme 4.5.2) or Pauson-Khand enyne cyclization (Scheme 4.5.3).

According to this strategy, the alkylated compounds **7**–**9** (see Table 4.5.4 above) and **29** (see Table 4.5.6 above) undergo clean ring-closing metathesis with no loss of enantiopurity, furnishing a number of 5-, 6-, and 7-membered carbocyles in high yields and enantioselectivities (ee's ranging from 95–98%; Scheme 4.5.2). In an analogous manner, the O-heterocycle (*S*)-**48** is achieved by sequential allylic etherification of **S1** with allylic alcohol and ring-closing metathesis reaction (Scheme 4.5.2); the corresponding *N*-heterocycle **49** performs similarly, although it requires protection of the amine with Boc prior to the ring-closing metathesis reaction, presumably owing to the azophilicity of ruthenium.



Scheme 4.5.2. Preparation of chiral functionalized carbo- and heterocyclic compounds **44**–**49**.

The second derivatization we tackled was the Pauson-Khand reaction of the propargylated derivatives **38**, **41** and **43** (see Table 4.5.6 above), which differ only in the size of the cycloalkene ring. Formation of the complex with $Co_2(CO)_8$, followed by thermal decomposition, gave rise to the [2+2+1] cycloadducts **50**–**52**, which feature an architecturally complex tricyclic system (Scheme 4.5.3).

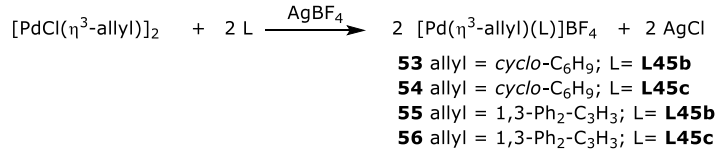


Scheme 4.5.3. Preparation of chiral functionalized polycarbocyclic compounds **50**–**52**. X-ray structure of compound **52** is also included.

Remarkably, the chiral information on the allylic substitution products was reliably conveyed to the final products, which were isolated as single diastereomers and with ee's replicating those of the starting materials. The relative configuration of ketone **52** was assigned to be *trans-cis* on the basis of a single-crystal X-ray diffraction image, **50** and **51** being assigned as the *cis-cis* diastereomer according to literature precedents.[22]

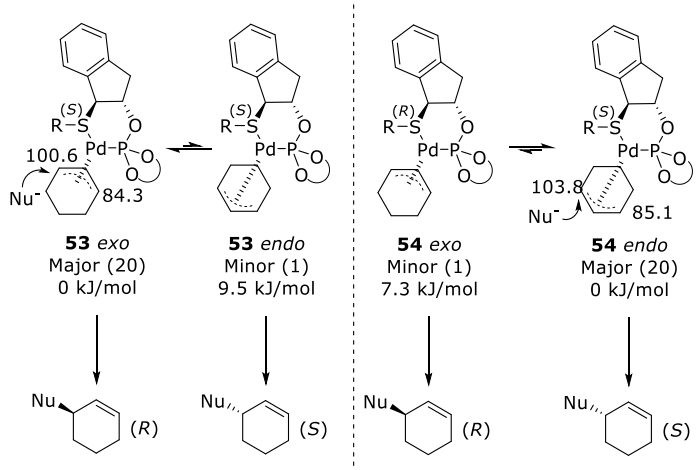
4.5.2.7. Study of the Pd-π-allyl intermediates

Our DFT calculations have established the nucleophilic attack as the enantiodetermining step (see Optimitzation of ligand parameters, Section 4.5.2.3, vide supra). With the aim of better understanding the catalytic process, we decided to prepare and characterize the Pd-allyl intermediates and determine their relative reactivity towards the nucleophile. Consequently, we studied the Pd-π-allyl compounds **53**–**56** [Pd(η^3-allyl)(**L**)]BF_4 (L = **L45b**–**c**) by NMR and DFT studies. These Pd-intermediates containing cyclohexenyl and 1,3-diphenyl allyl groups were synthesized as previously reported (Scheme 4.5.4). All complexes were characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy[23] and mass spectrometry. Unfortunately, we were unable to obtain crystals of sufficient quality to perform X-ray diffraction measurements. The ESI-HR-MS showed the heaviest ions at m/z corresponding to the cation.



Scheme 4.5.4. Preparation of [Pd(η³-allyl)(P,S)]BF_4 (P,S= **L45b**-**c**) complexes **53**–**56**.

To understand why the configuration of the enantiomer of the alkylated product changes with the configuration of the biaryl phosphite group in the substitution of cyclic substrate **S2**, we compared the Pd-1,3-cyclohexenyl-allyl intermediate **53**, which contains ligand **L45b** with its related counterpart Pd/**L45c** intermediate (**54**). The VT-NMR study (30 ºC to –80 ºC) showed the presence of essentially single isomers (ratio ca. 20:1; Scheme 4.5.5) for both intermediates (**53** and **54**). The major isomers were unambiguously assigned by NMR to be the *exo* isomer for **53** and the *endo* isomer for **54** (see Supporting Information for NOE details). In both cases, the thioether group had an (*S*)-configuration. The assignments are in agreement with the DFT calculations of the Pd-η³-cyclohexenyl complexes (see Supporting Information for the results of the full set of calculated Pd-η³-allyl intermediates).



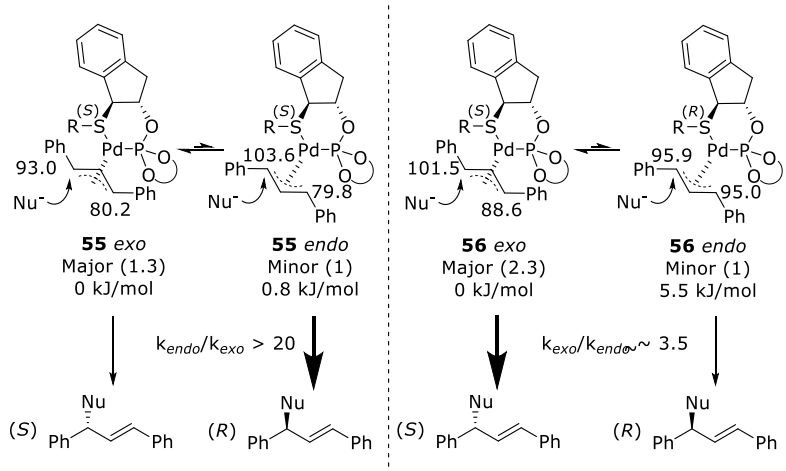
Scheme 4.5.5. Diastereoisomeric Pd-η³-allyl intermediates for **S2** with ligands **L45b** and **L45c**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons and the computed relative free energies in solution between *endo* and *exo* Pd-allyl intermediates are also shown for compounds **53** and **54**, in kJ/mol.

Thus, for Pd/**L45b** the major Pd-η³-*exo* isomer is 9.5 kJ/mol more stable than the most stable *endo* isomer, while for Pd/**L45c** the Pd-η³-*endo* isomer energy is 7.3 kJ/mol lower than the most stable *exo* isomer. The ^{13}C NMR chemical shifts indicate that for both major isomers the most electrophilic electron-deficient allylic terminal carbon is

trans to the phosphite group. Assuming that the nucleophilic attack takes place at the more electrophilic electron-deficient allyl carbon terminus, the fact that the observed stereochemical outcome of the reaction (86% ee (*R*) for Pd/**L45b** and 84% ee (*S*) for Pd/**L45c**) is similar to the diastereoisomeric excess (de 90%) of the Pd-intermediates indicates that both major and minor species react at a similar rate. In summary, the study of Pd-allyl intermediates shows that changes in the configuration of the phosphite moiety lead to changes in the ratio of the species that provide both enantiomers of the alkylated product. The enantioselectivity is therefore mainly controlled by the population of the Pd-allyl intermediates.

Finally, to assess the impact of the phosphite chiral axis configuration on the enantioselectivity obtained for **S1**, we compared the corresponding Pd allylic intermediates with ligands **L45b** and **L45c** (**55** and **56**, respectively). In this case, **L45b** provided high enantioselectivity whereas **L45c** proved less selective, which is in contrast to the observation made for the alkylation of the cyclic substrate **S2**. The VT-NMR study (30 ºC to −80 ºC) of intermediates **55** and **56** showed a mixture of two isomers in equilibrium with ratios 1.3:1 and 2.3:1, respectively (Scheme 4.5.6). All isomers were assigned to be *syn*/*syn*, according to the NOE interaction between the two terminal protons of the allyl group. Unfortunately, the NOE contacts are not conclusive enough to unambiguously assign the 3D structure of these isomers. The final assignment of these Pd-allyl intermediates was performed by DFT studies (see Supporting Information) and further assessed by studying the reactivity of the Pd-intermediates with sodium dimethyl malonate at low temperature by *in situ* NMR studies (Figure S3 of the Supporting Information at the end of this chapter). The DFT-calculated population of the different Pd-allyl species (i.e., ratio of 1.4:1 for complex **55**) is in good agreement with the population obtained experimentally (i.e., ratio 1.3:1 for **55**). Calculations indicate that for both systems, the most stable Pd-allyl intermediate is the *exo* isomer, the *endo* isomer being higher in energy (0.8 kJ/mol for Pd/**L45b** and 5.5 kJ/mol for Pd/**L45c**). On the other hand, the reactivity study of the Pd-intermediate **55** with sodium dimethyl malonate at low temperature reveals that the minor *endo* isomer reacts faster than the major isomer (Figure S3 of the Supporting Information at the end of this chapter; $k_{endo}/k_{exo} > 20$). This reactivity pattern is in agreement with the previously presented TS calculations (see Section 4.5.2.3), which indicate that the most favorable (lowest in energy) transition state arises from the nucleophilic attack to the Pd-allyl *endo* intermediate, being the pathway for the *exo* TS of much higher energy ($\Delta\Delta G^{\#} = 28$ kJ/mol; Table 4.5.2). All these evidences further support the DFT calculations that suggest that for intermediates **55** the major isomer has an *exo* disposition, while the minor isomer has an *endo* spatial arrangement. In contrast, the reactivity study of the Pd-allyl complex **56** indicates that the major *exo* isomer is the isomer that reacts faster with a nucleophile (Figure S3 of the Supporting Information at the end of this chapter; $k_{exo}/k_{endo} \approx 3.5$). Again, this finding is in agreement with the DFT calculations (*vide*

supra, $\Delta\Delta G^{\#}$= 10.8 kJ/mol, Table 4.5.2) and corroborates the DFT isomer assignment of the Pd-allyl intermediates observed in solution, having the major isomer an *exo* arrangement.



Scheme 4.5.6. Diastereoisomer Pd-η^3-allyl intermediates for **S1** with ligands **L45b** and **L45c**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons and the relative DFT-calculated energies are also shown.

It should be pointed out that, albeit for the Pd/**L45c** catalytic system the relative population of the faster reacting isomer is much higher than that of Pd/**L45b**, the latter provides higher enantioselectivity (96% ee for Pd/**L45b** vs 80% ee for Pd/**L45c**). Hence, in the case of **S1** the enantioselectivity seems to be controlled by the different reactivity of the allyl intermediates towards the nucleophile (rather than their population, as was the case for **S2**). These results are in line with the previous TS DFT calculations (see Table 4.5.2) and therefore further corroborate that the energy gap between the most stable TSs leading to each of the product enantiomers is higher for the Pd/**L45b** catalytic system than for Pd/**L45c**.

4.5.3. Conclusions

A new and small library of P-thioether ligands has been testes in the Pd-catalyzed allylic substitution reactions. The modular architecture of the ligands has allowed the iterative optimization of the ligand parameters in order to fine control the chiral cavity in which the allyl system is embedded. The robustness of the thioether group adds another advantage to these ligands. Compared to the previously reported P,S-ligand library, the new library is easier to synthetize, in only three steps, from inexpensive indene. The simpler backbone of these ligands give rise to neat NMR spectra with less signal overlap, which facilitates the identification of relevant intermediates and accelerates the DFT calculations in the search for better catalysts. The combination of

experimental and theoretical studies has therefore lead us to the rational design of an optimal, solid, air-stable P,S-ligand for the Pd-catalyzed enantioselective allylic substitution. This ligand consistently gave excellent enantioselectivities for 40 compounds involving linear and cyclic substrates and a broad range C-, N-, and O-nucleophiles. The results were maintained using the propylene carbonate as green solvent. In comparison with previous furanoside-based P,S-ligands, which have emerged as some of the most successful catalyst for this process, the new P,S-ligand also provided a better activity and a wider nucleophile scope (i.e., including the addition of pyrroles and a broader range of amines). The species responsible for the catalytic performance were also identified by mechanistic studies based on NMR spectroscopy, thus rationalizing the origin of the enantioselectivity. For enantioselectivities to be high, the ligand parameters therefore need to be correctly chosen to either increase the difference in population of the possible Pd-allyl intermediates (for cyclic substrates) or to increase the relative rates of the nucleophilic attack for each of the possible Pd-allyl complexes (for linear substrates). Finally, to assess the potential impact of this catalytic system in synthesis, the products have been employed in ring-closing metathesis or Pauson-Khand reactions, giving rise to a set of chiral (poly)carbo- and heterocyclic compounds with faithful transmission of the chiral information. The results presented here compete very well with a few other ligands that also provide high catalytic performance in several substrate and nucleophiles.

4.5.4. Experimental Section

4.5.4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphorochloridites were easily prepared in one step from the corresponding biaryls.[24]. Ligands **L41**-**L48a**-**f** have been prepared as described in Section 3.10. Racemic substrates **S1**-**S9**[25] and Pd-allyl complexes $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(\mu\text{-}Cl)]_2$[26] and $[Pd(\eta^3\text{-}cyclohexenyl)(\mu\text{-}Cl)]_2$[27] were prepared as previously reported. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H, ^{13}C, and ^{31}P assignments were made on the basis of ^1H-^1H gCOSY, ^1H-^{13}C gHSQC, and ^1H-^{31}P gHMBC experiments.

4.5.4.2. Procedure for the preparation of phosphinite-thioether ligand L41g

Thioether-hydroxyl compound **1** (104.1 mg, 0.5 mmol) and DMAP (6.7 mg, 0.055 mmol) were dissolved in toluene (1 ml), and triethylamine was added (0.09 ml, 0.65

mmol) at rt, followed by the addition of the corresponding chlorodicylohexylphosphine (0.12 mL, 0.55 mmol) via syringe. The reaction was stirred for 20 min at rt. The solvent was removed *in vacuo*, and the product was purified by flash chromatography on alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as an oil. Yield: 128.9 mg (61%). ^{31}P NMR (161.9 MHz, C_6D_6): δ=140.4 (s). ^1H NMR (400 MHz, C_6D_6): δ=1.08-1.20 (m, 6H, CH_2, Cy), 1.22 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.4 Hz), 1.25-1.35 (m, 5H, CH_2, Cy), 1.38 (d, 3H, CH_3, ^{i}Pr, $^3J_{H-H}$ =6.4 Hz), 1.48-1.61 (m, 5H, CH_2, Cy), 1.69 (b, 5H, CH, CH_2, Cy), 1.86 (m, 2H, CH_2, Cy), 2.98 (d, 1H, CH_2, $^2J_{H-H}$ =16.0 Hz), 3.10-3.17 (m, 1H, CH ^{i}Pr), 3.41 (dd, 1H, CH_2, $^2J_{H-H}$ =16.4 Hz, $^3J_{H-H}$ =5.6 Hz), 4.51-4.54 (m, 2H, CH-S, CH-OP), 6.99-7.15 (m, 3H, CH=), 7.40 (d, 1H, CH=, $^3J_{H-H}$ =8.0 Hz), 7.52 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6): δ=23.3 (CH_3, ^{i}Pr), 24.0 (CH_3, ^{i}Pr), 26.5-27.1 (CH_2, Cy), 28.1 (CH_2, Cy), 28.3 (CH_2, Cy), 28.5 (CH_2, Cy), 35.2 (CH, ^{i}Pr), 37.6 (d, CH, $^1J_{C-P}$ =8.5 Hz), 37.8 (d, CH, $^1J_{C-P}$ =9.9 Hz), 39.3 (d, CH_2, $^3J_{C-P}$ =6.1 Hz), 54.8 (d, CH-S, $^3J_{C-P}$ =6.1 Hz), 87.7 (d, CH-OP, $^2J_{C-P}$ =18.4 Hz), 124.8-141.5 (aromatic carbons).

4.5.4.3. Typical procedure for the allylic alkylation of disubstituted linear (S1 and S3-S7) and cyclic (S2 and S8-S9) substrates

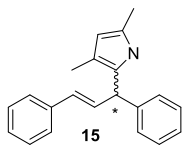
A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), nucleophile (1.5 mmol), N,O-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^1H NMR and enantiomeric excesses were determined either by HPLC (compounds **2**, **4**-**12**, **28**-**32** and **34**-**37**) or by GC (compounds **3**, **38**-**39** and **41**-**43**) or by ^1H NMR using $[Eu(hfc)_3]$ (compounds **33** and **40**) (for more details for compounds **2**-**10** and **28**-**43** see previous Section 4.1.5.5 and for compounds **12**-**13** see previous Section 4.2.4.4).

4.5.4.4. Typical procedure for the allylic alkylation of disubstituted linear substrate S1 using pyrroles

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the corresponding phosphite/phosphinite-thioether (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), the corresponding pyrrole (0.4 mmol) and K_2CO_3 (110 mg, 0.8 mmol) were added. The reaction mixture was stirred at room temperature. After 18

h, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^1H NMR and enantiomeric excesses were determined by HPLC (for more details for compound **14** see previous Section 4.2.4.5).

3,5-Dimethyl-2-(1,3-diphenyl-2-propenyl)pyrrole (15).[6a] Enantiometic excess determined by HPLC using Chiralpak AD-H column (99,5% hexane/2-propanol, flow 0.7 mL/min, λ= 254 nm) t_R 17.8 min; t_R 19.7 min. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.96 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 4.94 (d, 1H, CH=, *J*=6.8 Hz), 5.73 (m, 1H, CH=), 6.31 (d, 1H, CH=, *J*=15.6 Hz), 6.56 (dd, 1H, CH=, *J*=15.6 Hz, *J*= 6.8 Hz), 7.37−7.18 (m, 11H, CH=).



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4.5.4.5. Typical procedure for the allylic amination of disubstituted linear substrate S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (0.5 mmol) in dichloromethane (1.5 mL), the corresponding amine (1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 2 hours, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^1H NMR and enantiomeric excesses were determined by HPLC (for more details for compounds **16**-**21** see previous Section 4.2.4.6).

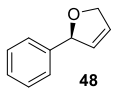
4.5.4.6. Typical procedure for the allylic etherification and silylation of disubstituted linear substrate S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 minutes, Cs_2CO_3 (122 mg, 0.375 mmol) and the corresponding alcohol or silanol (0.375 mmol) were added. The reaction mixture was stirred at room temperature. After 18 h, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^1H NMR and enantiomeric excesses were determined by HPLC (for more details for compounds **22**-**27** see previous Section 4.1.5.6).

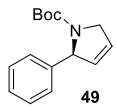
4.5.4.7. Typical procedure for the preparation of chiral carbo- and heterocyclic compounds 44-49

A solution of Grubbs II catalyst (5 mg, 0.006 mmol) and the corresponding alkylated product (0.12 mmol) in CH_2Cl_2 (3 mL) was stirred for 16 h. The solution was directly purified by flash chromatography (Hex/EtOAc 95:5) to obtain the desired compounds (for more details for compounds **44**-**47** see previous Section 4.4.4.10).

(S)-2-Phenyl-2,5-dihydrofuran (48).[37] Enantiomeric excess determined by GC using Chiralsil-Dex CB column (105 kPa H_2, 90 °C for 30 min, 10 °C/min, to 180 °C). t_R 17.4 min (*S*); t_R 18.3 min (*R*).^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.76 (m, 1H), 4.87 (m, 1H), 5.79 (m, 1H), 5.88 (m, 1H), 6.03 (m, 1H), 7.2-7.4 (m, 5H).


48

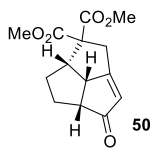
tert-Butyl (S)-2-phenyl-2,5-dihydro-1H-pyrrole-1-carboxylate (49).[38] Enantiomeric excess determined by HPLC using Chiracel IC column (hexane/2-propanol=95/5, 0.5 mL/min, 210 nm). t_R 18.3 min (*R*); t_R 19.9 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.21 (s, 9H), 4.33 (s, 2H), 5.37 (s, 1H), 5.73 (s, 1H), 5.84 (s, 1H), 7.1-7.3 (m, 5H).


49

4.5.4.8. Typical procedure for the preparation of chiral tricyclic compounds 50-52

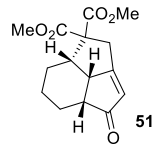
A solution of the starting enyne (0.187 mmol) in 1 mL of *tert*-butylbenzene was added to a solution of $Co_2(CO)_8$ (83 mg, 0.243 mmmol) in 0.5 mL of *tert*-butylbenzene under air. The flask was rinsed with 0.5 mL more of the same solvent. The resulting mixture was stirred at room temperature for 1 h, until full consumption of the starting material was observed by TLC. After that, the system was heated at 170 °C for a further hour. Then, it was cooled to room temperature, filtered on Celite with CH_2Cl_2 and concentrated in vacuo. The crude mixture was purified by flash column chromatography on silica gel eluting with cyclohexane/EtOAc (gradient form 90:10 to 70:30) to furnish the desired tricyclic compound as a white solid.

Dimethyl (2aS,2a^{1}S,4aR)-5-oxo-2a,2a^1,3,4,4a,5-hexahydrocyclopenta[cd]pentalene-2,2(1H)-dicarboxylate (50). Enantiomeric excess determined by SFC using Daicel Chiralpak ID-3 column (100 x 4.6 mm, 3 μm), 35 °C, CO_2/MeOH (85:15), ABPR = 1500 psi, flow rate 3.0 mL/min, λ = 227 nm. t_{major}= 1.32 min; t_{minor}= 1.15 min. The relative configuration has been assigned by comparison with literature precedents.[22b, 22c] ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (tdd, 1H, *J*=12.9 Hz, *J*=11.5 Hz, *J*=7.0 Hz), 1.58 (dt, 1H, *J*=12.9 Hz, *J*=7.0 Hz), 1.79 (dd, 1H, *J*=13.3 Hz, *J*=7.0 Hz), 1.94 (tdd, 1H, *J*=13.3 Hz, *J*=10.1 Hz, *J*=6.8 Hz), 2.84 (dd, 1H, *J*=10.1 Hz, *J*=5.3 Hz),


50

2.91 (ddd, 1H, *J*=17.5 Hz, *J*=2.0 Hz, *J*=1.2 Hz), 3.13 (dt, 1H, *J*=11.5 Hz, *J*=7.4 Hz), 3.55 (t, 1H, *J*=6.2 Hz), 3.66 (d, 1H, *J*=17.5 Hz), 3.71 (s, 3H), 3.78 (s, 3H), 6.02 (t, 1H, *J*=2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.4, 31.0, 35.7, 46.1, 51.4, 52.6, 53.1, 57.4, 62.5, 129.2, 169.8, 172.2, 183.8, 212.2. $[\alpha]_D$: –132.4 (*c* 1.18, CH_2Cl_2). TOF-MS (ESI+): *m/z* calcd. for $C_{14}H_{16}NaO_5$ $[M+Na]^+$: 287.0890, found: 287.0890.

Dimethyl (2a^{1}S,4aR,7aS)-4-oxo-2,2a^1,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[cd]indene-1,1-dicarboxylate (51). Enantiomeric excess determined by SFC using Daicel Chiralpak ID-3 column (100 x 4.6 mm, 3 μm), 35 °C, CO_2/MeOH (85:15), ABPR = 1500 psi, flow rate 3.0 mL/min, λ = 227 nm. t_{major} = 1.20 min; t_{minor} = 1.33 min. The relative configuration has been assigned by comparison with literature precedents.[22c, 22a, 39] ^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.84 (dtd, 1H, *J*=2.8 Hz, *J*=1.9 Hz, *J*=0.7 Hz), 3.77 (s, 3H), 3.76 (s, 3H), 3.62 (dt, 1H, *J*=20.7 Hz, *J*=2.0 Hz), 3.36 (t, 1H, *J*=7.3 Hz), 3.15 (ddd, 1H, *J*=20.7 Hz, *J*=2.2 Hz, *J*=1.1 Hz), 2.96 (ddd, 1H, *J*=13.3 Hz, *J*=7.8 Hz, *J*=6.4 Hz), 2.70 (td, 1H, *J*=6.1 Hz, *J*=9.5 Hz), 2.08-2.00 (m, 1H), 1.69-1.61 (m, 1H), 1.47-1.38 (m, 1H), 1.30-1.15 (m, 1H), 1.01 (tdd, 1H, *J*=13.6 Hz, *J*=9.9 Hz, *J*=3.8 Hz), 0.68 (qd, 1H, *J*=12.8, *J*=2.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.8, 23.1, 25.1, 34.1, 41.9, 46.2, 49.3, 52.7, 53.1, 65.7, 123.0, 169.4, 171.9, 183.0, 213.1. $[\alpha]_D$: +10.7 (*c* 0.55, $CHCl_3$). TOF-MS (ESI+): *m/z* calcd. for $C_{15}H_{18}NaO_5$ $[M+Na]^+$: 301.1046, found: 301.1043.



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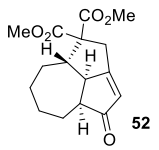
Dimethyl (2a^{1}R,4aS,8aS)-4-oxo-2a^1,4,4a,5,6,7,8,8a-octahydrocyclopenta[cd]-azu-lene-1,1(2H)-dicarboxylate (52). Enantiomeric excess determined by SFC using Daicel Chiralpak IB-3 column (100 x 4.6 mm, 3 μm), 35 °C, CO_2/^{i}PrOH (90:10), ABPR = 1500 psi, flow rate 3.0 mL/min, λ = 225 nm: t_{major} = 1.55 min; t_{minor} = 1.66 min. The absolute configuration has been assigned by X-ray diffraction (*vide infra*) ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30-1.10 (m, 3H), 1.45-1.30 (m, 1H), 2.00-1.90 (m, 1H), 2.18-2.00 (m, 3H), 2.25-2.20 (m, 1H), 2.55 (ddd, 1H, *J*=12.9 Hz, *J*=7.7 Hz, *J*=5.7 Hz), 3.00 (dt, 1H, *J*=18.5 Hz, *J*=1.1 Hz), 3.16 (dddt, 1H, *J*=13.3 Hz, *J*=7.1 Hz, *J*=2.2 Hz, *J*=1.4 Hz), 3.58 (ddt, 1H, *J*=18.5 Hz, *J*=2.2 Hz, *J*=1.1 Hz), 3.77 (s, 3H), 3.78 (s, 3H), 5.86 (td, 1H, *J*=2.1 Hz, *J*=1.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.2, 28.2, 30.2, 30.4, 36.4, 48.8, 49.5, 52.7, 52.8, 54.1, 62.3, 124.8, 171.2, 171.3, 182.8, 211.4. $[\alpha]_D$: +264.7 (*c* 1.09, CH_2Cl_2). TOF-MS (ESI+): *m/z* calcd. for $C_{16}H_{21}O_5$ $[M+H]^+$: 293.1384, found: 293.1375.



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4.5.4.9. General procedure for the preparation of [Pd(η^3-allyl)(L)]BF$_4$ complexes 53-56

The corresponding ligand (0.05 mmol) and the complex [Pd(μ-Cl)(η^3-1,3-allyl)]$_2$ (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon.

$AgBF_4$ (9.8 mg, 0.05 mmol) was added after 30 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over celite under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated as pale-yellow solids by adding hexane.

[Pd(η³-1,3-cyclohexenyl)(L45b)]BF_4 (53). ^{31}P NMR (CD_2Cl_2, 298 K): δ= 106.7 (s, 1P). ^{1}H NMR (CD_2Cl_2, 298 K): δ= 0.78 (m, 1H, CH_2, allyl), 1.03 (m, 1H, CH_2, allyl), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.42-1.56 (m, 2H, CH_2, allyl), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.62-1.71 (m, 2H, CH_2, allyl), 1.81 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.68 (s, 3H, CH_3, SR group), 2.91 (s, 3H, CH_3, SR group), 3.23 (dd, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 7.2 Hz), 3.51 (dd, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 6.4 Hz), 4.00 (m, 1H, CH allyl *trans* to S), 4.81 (m, 1H, CH-O), 5.15 (d, 1H, CH-S, $^3J_{H-H}$= 6.8 Hz), 5.24 (m, 1H, CH allyl central), 5.46 (m, 1H, CH allyl *trans* to P), 6.71 (d, 1H, CH=, $^3J_{H-H}$= 6 Hz), 7.18 (m, 1H, CH=), 7.3-7.5 (m, 7H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K): δ= 18.1 (CH_3), 18.2 (CH_3), 20.9 (CH_2 allyl), 21.9 (CH_3), 22.0 (CH_3), 24.5 (CH_3, SR group), 25.7 (CH_3, SR group), 28.6 (CH_2 allyl), 29.6 (CH_2 allyl), 32.9 (CH_3, ^{t}Bu), 33.5 (CH_3, ^{t}Bu), 36.6 (C, ^{t}Bu), 36.9 (C, ^{t}Bu), 39.4 (d, CH_2, J_{C-P}= 6 Hz), 55.2 (CH-S), 83.6 (d, CH-O, J_{C-P}= 4.8 Hz), 84.3 (d, CH allyl *trans* to S, J_{C-P}= 6.5 Hz), 100.6 (d, CH allyl *trans* to P, J_{C-P}= 30.5 Hz), 115.0 (d, CH allyl central, J_{C-P}= 8.7 Hz), 125.5-147.3 (aromatic carbons). MS HR-ESI [found 839.2869, $C_{47}H_{58}O_3PPdS$ $(M\text{-}BF_4)^+$ requires 839.2874].

[Pd(η³-1,3-cyclohexenyl)(L45c)]BF_4 (54). ^{31}P NMR (CD_2Cl_2, 298 K): δ= 106.2 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K): δ= 1.18 (m, 1H, CH_2, allyl), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.51-1.72 (m, 3H, CH_2, allyl), 1.84 (s, 3H, CH_3), 1.86 (m, 1H, CH_2, allyl), 2.14 (s, 3H, CH_3), 2.14 (m, 1H, CH_2), 2.38 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.58 (s, 3H, CH_3, SR group), 2.70 (s, 3H, CH_3, SR group), 3.29 (dd, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 6.8 Hz), 3.56 (dd, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 6 Hz), 4.08 (m, 1H, CH allyl *trans* to S), 5.20 (m, 1H, CH allyl *trans* to P), 5.28 (m, 2H, CH-S and CH allyl central), 5.34 (m, 1H, CH-O), 6.14 (d, 1H, CH=, $^3J_{H-H}$= 6.4 Hz), 7.04 (m, 1H, CH=), 7.3-7.5 (m, 7H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K): δ= 18.1 (CH_3), 18.2 (CH_3), 21.0 (CH_2 allyl), 21.9 (CH_3), 22.0 (CH_3), 24.7 (CH_3, SR group), 24.8 (CH_3, SR group), 29.5 (CH_2 allyl), 30.96 (CH_2 allyl), 33.1 (CH_3, ^{t}Bu), 33.5 (CH_3, ^{t}Bu), 36.6 (C, ^{t}Bu), 36.8 (C, ^{t}Bu), 40.1 (d, CH_2, J_{C-P}= 5.4 Hz), 56.8 (d, CH-S, J_{C-P}= 3.2 Hz), 85.1 (m, CH-O and CH allyl *trans* to S), 103.8 (d, CH allyl *trans* to P, J_{C-P}= 28.6 Hz), 115.0 (d, CH allyl central, J_{C-P}= 7.9 Hz), 125.4-147.0 (aromatic carbons). MS HR-ESI [found 839.2870, $C_{47}H_{58}O_3PPdS$ $(M\text{-}BF_4)^+$ requires 839.2874].

[Pd(η³-1,3-diphenylallyl)(L45b)]BF_4 (55). Major isomer (57%): ^{31}P NMR (CD_2Cl_2, 298 K): δ= 102.8 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K): δ= 1.25 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.97 (s, 3H, CH_3, SR group), 2.18 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.95 (s, 3H, CH_3, SR group), 2.97 (m, 1H, CH_2), 3.41 (dd, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 7.2 Hz), 4.70 (m, 1H, CH-S), 4.75 (m, 1H, CH allyl *trans* to S), 4.85 (m, 1H, CH-O), 5.46 (m, 1H, CH allyl *trans* to P), 6.18 (dd, 1H,

CH allyl central, $^3J_{H-H}$= 10.8 Hz, $^3J_{H-H}$= 9.2 Hz), 6.36 (d, 1H, CH=, $^3J_{H-H}$= 6.0 Hz), 6.71-7.52 (m, 14H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K): δ= 16.9 (CH_3), 17.3 (CH_3), 20.7 (CH_3), 20.9 (CH_3), 22.5 (CH_3, SR group), 24.0 (CH_3, SR group), 31.5 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 36.4 (C, ^{t}Bu), 36.6 (C, ^{t}Bu), 37.6 (b, CH_2), 53.6 (CH-S), 80.2 (d, CH allyl *trans* to S, J_{C-P}= 7.3 Hz), 80.4 (d, CH-O, J_{C-P}= 6.8 Hz), 93.0 (d, CH allyl *trans* to P, J_{C-P}= 21.2 Hz), 110.8 (d, CH allyl *trans* to P, J_{C-P}= 8.4 Hz), 122.7-144.5 (aromatic carbons). Minor isomer (43%): ^{31}P NMR (CD_2Cl_2, 298 K): δ= 102.6 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K): δ= 1.50 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.20 (s, 3H, CH_3, SR group), 2.42 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.14 (s, 3H, CH_3, SR group), 2.97 (m, 1H, CH_2), 3.30 (dd, 1H, CH_2, $^2J_{H-H}$= 12.4 Hz, $^3J_{H-H}$= 7.2 Hz), 4.15 (m, 1H, CH allyl *trans* to S), 4.89 (m, 1H, CH-O), 5.02 (m, 1H, CH-S), 5.39 (m, 1H, CH allyl *trans* to P), 6.36 (d, 1H, CH=, $^3J_{H-H}$= 6.0 Hz), 6.52 (t, 1H, CH allyl central, $^3J_{H-H}$= 9.6 Hz), 6.71-7.52 (m, 14H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K): δ= 16.9 (CH_3), 17.3 (CH_3), 20.8 (CH_3), 20.8 (CH_3), 22.5 (CH_3, SR group), 23.3 (CH_3, SR group), 30.6 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 36.5 (C, ^{t}Bu), 36.8C, ^{t}Bu), 37.6 (b, CH_2), 53.5 (CH-S), 79.8 (d, CH allyl *trans* to S, J_{C-P}= 6.3 Hz), 92.3(d, CH-O, J_{C-P}= 6.2 Hz), 103.2 (d, CH allyl *trans* to P, J_{C-P}= 23 Hz), 112.1 (d, CH allyl *trans* to P, J_{C-P}= 10 Hz), 122.7-144.5 (aromatic carbons). MS HR-ESI [found 951.3184, $C_{56}H_{62}O_3PPdS$ $(M\text{-}BF_4)^+$ requires 951.3187].

[Pd(η^3-1,3-diphenylallyl)(L45c)]BF_4 (56). Major isomer (70%): ^{31}P NMR (CD_2Cl_2, 298 K): δ= 104.3 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K): δ= 1.41 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.77 (s, 12H, CH_3, ^{t}Bu and CH_3), 2.27 (s, 3H, CH_3), 2.47 (s, 3H, CH_3, SR group), 3.06 (s, 3H, CH_3, SR group), 3.01 (m, 1H, CH_2), 3.36 (dd, 1H, CH_2, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 6.8 Hz), 5.01 (m, 1H, CH-O), 5.06 (m, 1H, CH-S), 5.12 (m, 1H, CH allyl *trans* to S), 5.26 (d, 1H, CH allyl *trans* to P, $^3J_{H-H}$= 10 Hz), 5.95 (d, 1H, CH=, $^3J_{H-H}$= 6.0 Hz), 6.73 (m, 1H, CH allyl central), 6.87-7.51 (m, 14H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K): δ= 18.0 (CH_3), 18.4 (CH_3), 21.9 (CH_3), 22.1 (CH_3), 24.4 (CH_3, SR group), 25.8 (CH_3, SR group), 33.8 (CH_3, ^{t}Bu), 34.2 (CH_3, ^{t}Bu), 36.7 (C, ^{t}Bu), 36.9 (C, ^{t}Bu), 40.0 (d, CH_2, J_{C-P}= 6.7 Hz), 56.9 (d, CH-S, J_{C-P}= 2.7 Hz), 84.7 (d, CH-O, J_{C-P}= 5.4 Hz), 88.6 (d, CH allyl *trans* to S, J_{C-P}= 5.2 Hz), 101.5 (d, CH allyl *trans* to P, J_{C-P}= 25.7 Hz), 112.9 (d, CH allyl *trans* to P, J_{C-P}= 8.3 Hz), 124.7-146.9 (aromatic carbons). Minor isomer (30%): ^{31}P NMR (CD_2Cl_2, 298 K): δ= 107.1 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K): δ= 1.64 (s, 9H, CH_3, ^{t}Bu), 1.72 (s, 9H, CH_3, ^{t}Bu), 1.74 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.38 (s, 3H, CH_3, SR group), 2.60 (s, 3H, CH_3, SR group), 3.01 (m, 1H, CH_2), 3.47 (dd, 1H, CH_2, $^2J_{H-H}$= 12.8 Hz, $^3J_{H-H}$= 6.8 Hz), 4.85 (d, 1H, CH-S, $^3J_{H-H}$= 5.6 Hz), 5.21 (m, 1H, CH allyl *trans* to S), 5.51 (m, 1H, CH-O), 5.70 (d, 1H, CH allyl *trans* to P, $^3J_{H-H}$= 10 Hz), 6.00 (d, 1H, CH=, $^3J_{H-H}$= 6.0 Hz), 6.58 (m, 1H, CH allyl central), 6.87-7.51 (m, 14H, CH=). ^{13}C NMR (CD_2Cl_2, 298 K): δ= 18.2 (CH_3), 18.3 (CH_3), 21.9 (CH_3), 22.0 (CH_3), 24.2 (CH_3, SR group), 26.1 (CH_3, SR group), 32.8 (CH_3, ^{t}Bu), 34.1 (CH_3, ^{t}Bu), 36.6 (C, ^{t}Bu), 36.7 (C, ^{t}Bu), 39.6 (d, CH_2, J_{C-P}= 7.5 Hz), 58.1 (d, CH-S, J_{C-P}=

2.5 Hz), 86.7 (d, CH-O, $J_{C\text{-}P}$= 7.5 Hz), 95.0 (d, CH allyl *trans* to S, $J_{C\text{-}P}$= 5.4 Hz), 95.9 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 23.7 Hz), 113.0 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 9.1 Hz), 124.7-146.9 (aromatic carbons). MS HR-ESI [found 951.3182, $C_{56}H_{62}O_3PPdS$ $(M\text{-}BF_4)^+$ requires 951.3187].

4.5.4.10. Study of the reactivity of the [Pd(η^3-allyl)(L))]BF_4 with sodium dimethyl malonate by in situ NMR[28]

A solution of *in situ* prepared [Pd(η^3-allyl)(L)]BF_4 (L= phosphite-thioether, 0.05 mmol) in CD_2Cl_2 (1 mL) was cooled in the NMR at –80 °C. At this temperature, a solution of cooled sodium dimethyl malonate (0.1 mmol) was added. The reaction was then followed by ^{31}P NMR. The relative reaction rates were calculated using a capillary containing a solution of triphenylphosphine in CD_2Cl_2 as external standard.

4.5.4.11. Computational details

Geometries of all transition states and intermediates were optimized using the Gaussian 09 program,[29] employing the B3LYP[30] density functional and the LANL2DZ[31] basis set for palladium and the 6-31G* basis set for all other elements.[32] All energies presented correspond to single point calculations with the B3LYP-D3 functional[33] and the larger 6-311+G(d,p)[34] basis set for all elements except Pd. Solvation correction was taken into account along optimization and single points through the use of the PCM continuum model with the default parameters for dichloromethane.[35] No symmetry constraints were applied. The validity of the model was confirmed by a series of geometry optimizations at the B3LYP-D3 level on the four key transition states. The qualitative trends were unchanged: ligand L42b favored the (R) product (corrected ee of 64 vs uncorrected ee of 99.99) and ligand L42c favored the (S) product (corrected ee of 99.6 vs uncorrected ee of 97.5). Normal mode analysis of all transition states revealed a single imaginary frequency corresponding to the expected nucleophilic attack of the nucleophile to one of the two allylic termini carbons. All energies reported are Gibbs free energies in solution at 298.15 K and calculated as $G_{reported} = G_{B3LYP/6\text{-}31G*} + (E_{B3LYP\text{-}D3/6\text{-}311+G**} - E_{B3LYP/6\text{-}31G*})$. A data set collection of the computational results is available in the ioChem-BD repository, and can be accessed via https://doi.org/doi:10.19601/iochem-bd-1-69.[36]

4.5.5. Acknowledgments

We all acknowledge MINECO for INTECAT network CTQ2016-81293-REDC/AEI. The URV members gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P) and European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2014SGR670), and the

ICREA Foundation (ICREA Award to M.D.). The ICIQ members gratefully acknowledge financial support from CERCA Programme/Generalitat de Catalunya, the Spanish Ministry of Economy and Competitiveness (CTQ2015-69136-R, CTQ2017-87792-R, AEI/MINECO/FEDER, UE, and Severo Ochoa Excellence Accreditation 2014-2018, SEV-2013-2019), and DEC Generalitat de Catalunya (Grant No. 2014SGR827). The CELLEX Foundation is also acknowledged for financing the High Throughput Experimentation (HTE) laboratory.

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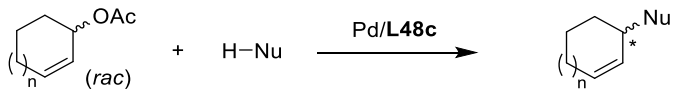
4.5.7. Supporting Information

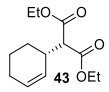
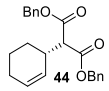
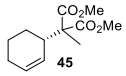
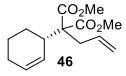
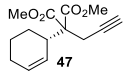
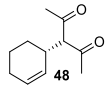
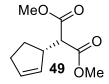
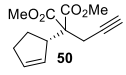
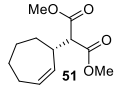
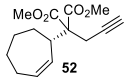
4.5.7.1. Table SI.1. Selected results for the Pd-catalyzed allylic substitution of S1–S9 with Pd-L48b catalytic system in PC as a solvent

Entry	Substrate	H-Nu	Product	% Conv (H)[b]	% Yield	% ee[c]
1	**S1**	H-CH(COOMe)$_2$	**11**	100 (0.5)	89	97 (*R*)
2	**S1**	H-CMe(COOMe)$_2$	**15**	100 (0.5)	90	96 (*S*)
3	**S1**	H-CAllyl(COOMe)$_2$	**16**	100 (0.5)	92	96 (*S*)
4	**S1**	H-CButenyl(COOMe)$_2$	**17**	100 (0.5)	88	97 (*S*)
5	**S1**	H-CPentenyl(COOMe)$_2$	**18**	100 (0.5)	87	93 (*S*)
6	**S1**	H-CPropargyl(COOMe)$_2$	**19**	100 (0.5)	86	99 (*S*)
7	**S1**	H-CH(COMe)$_2$	**20**	100 (0.5)	84	96 (*R*)
8	**S1**	H-NHCH$_2$Ph	**25**	100 (2)	86	96 (*S*)
9	**S2**	H-CH(COOMe)$_2$	**12**	100 (6)	91	90 (*R*)
10	**S3**	H-CH(COOMe)$_2$	**37**	98 (1)	88	97 (*R*)
11	**S4**	H-CH(COOMe)$_2$	**39**	100 (1)	93	96 (*R*)
12	**S5**	H-CH(COOMe)$_2$	**40**	99 (1)	87	96 (*R*)
13	**S6**	H-CH(COOMe)$_2$	**41**	100 (1)	88	98 (*R*)
14	**S7**	H-CH(COOMe)$_2$	**42**	100 (24)	90	>95 (*R*)
15	**S8**	H-CH(COOMe)$_2$	**49**	100 (6)	83	82 (+)
16	**S9**	H-CH(COOMe)$_2$	**51**	100 (6)	88	92 (*R*)

[a] All reactions were run at 40 °C, 0.5 mol% [PdCl(η^3-C$_3$H$_5$)]$_2$, 1 mol% ligand. [b] Conversion measured by GC or ^{1}H-NMR. Reaction time shown in parentheses. [c] Enantiomeric excesses. Absolute configuration shown in parentheses.

4.5.7.2. Table SI.2. Pd-catalyzed allylic substitution of several cyclic substrates S2, S9–S10 with several C nucleophiles using Pd/L48c catalytic system

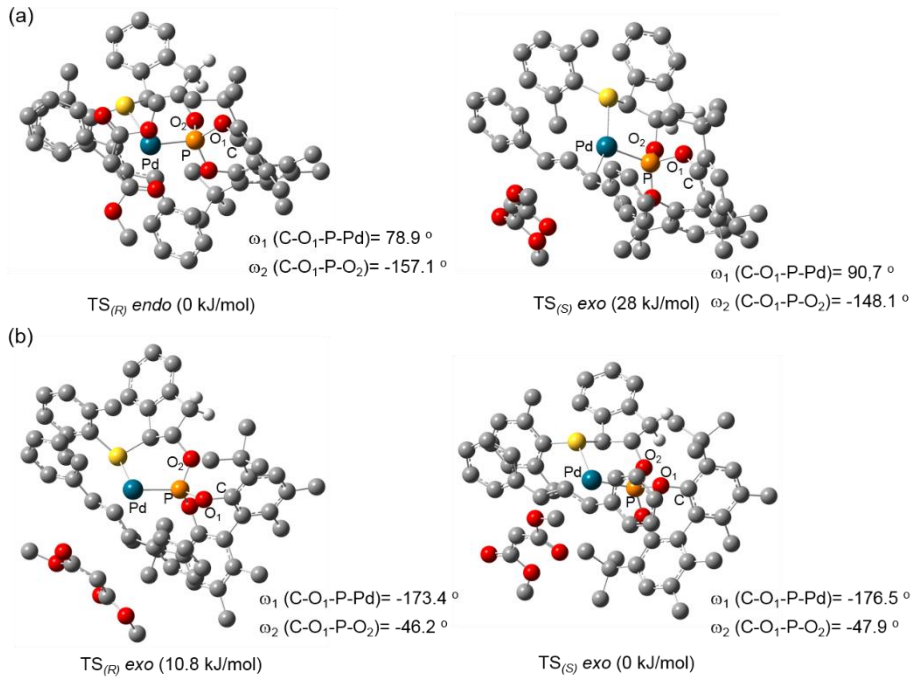


Entry	Substrate	Product	% Yield[b]	% ee[c]
1	**S2**	 **43**	81	92 (*S*)
2	**S2**	 **44**	78	94 (*S*)
3	**S2**	 **45**	84	89 (*S*)
4	**S2**	 **46**	91	91 (*S*)
5	**S2**	 **47**	79	94 (*S*)
6	**S2**	 **48**	74	78 (+)
7	**S8**	 **49**	69	82 (+)
8	**S8**	 **50**	84	83 (+)
9	**S9**	 **51**	86	95 (*S*)
10	**S9**	 **52**	89	94 (*S*)

[a] Reactions were performed at room temperature with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), CH_2Cl_2 as solvent, ligand (1 mol%), BSA (3 equiv.), KOAc, 24 h. Full conversions were achieved in all cases. [b] Isolated yields. [c] Enantiomeric excesses determined by chiral HPLC, GC or ^{1}H-NMR. Absolute configuration shown in parentheses.

4.5.7.3. Figure SI.1

Figure S1. Structure of the two most stable calculated *R*- and *S*- transition states for substrate **S1** and dimethyl malonate using ligands (a) **L45b** and (b) **L45c** (all hydrogen atoms have been omitted for clarity except those of the methylene group of the ligand backbone). Relative free energies in solution and in kJ/mol respect to the corresponding lowest energy transition state.



4.5.7.4. SI.1. NOESY assignments for the major isomer of compounds 55 and 56

For complex **55**, the NOE indicated interactions between one of the *tert*-butyl groups of the phosphite moiety with the terminal allyl proton *trans* to the thioether group, whereas for compound **56** this interaction appeared with the methinic hydrogen of the CH-O group (Figure S2). The *exo* arrangement of the allyl group in complex **55** is further confirmed by a NOE interaction of the terminal allyl proton *trans* to the phosphite moiety with one of the methyl groups of the thioether moiety, while the other methyl of the thioether group presents a NOE interaction with the methinic hydrogen of the CH-S group (Figure S2). Similarly, the *endo* disposition of the allyl group in the complex **56** is further confirmed by the presence of NOE interactions with one of the methyls of the 2,6-dimethylphenyl thioether group with the methinic hydrogen of the CH-S group, the central allyl proton and the terminal allyl proton *trans* to the phosphite moiety.

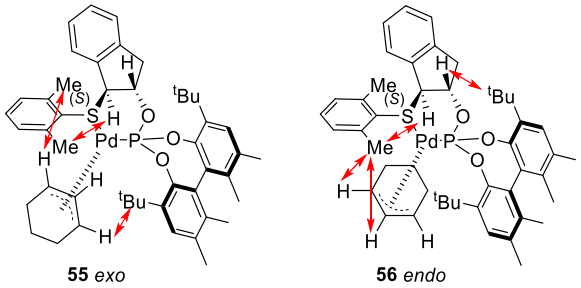


Figure S2. Relevant NOE contacts from the NOESY experiment of Pd-η^3-allyl intermediates **55** and **56**.

4.5.7.5. Figure SI.3

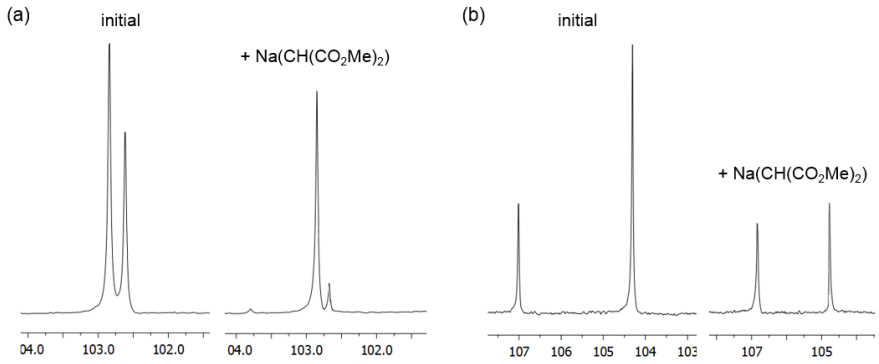


Figure S3. ^{31}P-{^{1}H}NMR spectra before and after the addition of sodium dimethyl malonate in CD_2Cl_2 at −80 °C of: (a) [Pd(η^3-1,3-diphenylallyl)(**L45b**)]BF_4 (**55**) (b) [Pd(η^3-1,3-diphenylallyl)(**L45c**)]BF_4 (**56**).

4.5.7.6. Quadrant analysis on the origin of the enantioselectivity

Figure S4, shows a schematic representation of the most stable transition states using ligands **L45b** and **L45c**. There is a discriminatory effect on the phosphite side, and it is of steric nature. The most stable orientation of the substrate corresponds to the one that fits the substrate in the "free quadrants" avoiding the steric effects on the phosphite. However, this is a simplification of the real system, please see Figure S1, and substitution on the thioether group is also important and it strongly contributes to the overall constraint of the system.

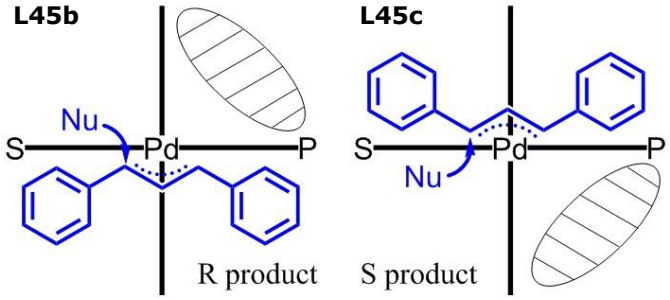


Figure S4. Schematic representation of the most stable transition states for Pd/**L45b** and Pd/**L45c**. Steric effects on the phosphate are represented with stripes. The substrate and nucleophile are presented in blue.

4.5.7.7. Distortion and interaction energies for the transition states of ligands L45b–c and substrate S1

We split the energies of the transition states for the systems Pd/**L45b** and Pd/**L45c** in three terms: distortion of the [Pd/**L45b**-**c**] moiety, distortion of the [substrate-nucleophile] moiety and interaction energy between the two moieties. The aim of this analysis is to observe if there are important changes in the distortion energies of the catalyst. The geometries at the transition states are cut in two moieties: the catalyst [Pd/**L45b**-**c**] and the reactants [substrate-nucleophile] and single point calculations of each moiety performed. The distortion energies of the [Pd/**L45b**-**c**] moiety in the different transition states is computed according to Eq. 1, as the difference in energy between the [Pd/**L45b**-**c**] moiety of the considered transition state TSx and the free catalyst (Pd^0). The distortion energy of [substrate-nucleophile] is achieved in a similar way. However in this case, the energy we call distortion does not only corresponds to the distortion but also to the formation of the acid. The interaction energies correspond to the difference between the single point energies of the two fragments and the TS.

$$\Delta E^{TSx}_{def(Pd\text{-}ligand)} = E^{TSx}_{(Pd\text{-}ligand)} - E^{free}_{(Pd\text{-}ligand)} \qquad \text{(Eq 1)}$$

The results obtained are presented in the following Tables SI.3 and SI.4. The differences between the two ligands cannot be seen in the interaction energies that are in both cases similar. The distortion energies of the [Pd/**L45b**-**c**] are the ones showing a difference between **L45b** and **L45c**, they are larger for **L45b** than for **L45c**. For the [Pd/**L5b**] moiety the distortion is higher in the transition states producing the *S* products than for the equivalent transitions states leading to the *R* products. For [Pd/**L45c**] the tendencies are not as clear. Distortion energies of the [substrate-nucleophile] are similar for both ligands. The distortion of the [Pd/**L45b**-**c**] alone is not enough to explain the overall reactivity, tendencies on the other energies are less clear and the overall results are rather inconclusive.

Table SI.3. Distortion energy of [Pd/L45b], distortion energy of [substrate-nucleophile] and interaction energies for transitions states of ligand L45b and substrate S1[a]

	$\Delta E_{dist(Pd/L45b)}$	$\Delta E_{dist(substrate\text{-}nucleophile)}$	$\Delta E_{interaction}$	ΔE	Product
TS_{endo}	38.9	179.5	-150.6	67.8	(*R*)
TS_{endoS}	27.6	166.1	-162.8	31.0	(*R*)
TS_{exo}	44.8	164.8	-152.7	56.9	(*S*)
TS_{exoS}	34.7	164.0	-154.0	44.8	(*S*)
$TS_{endotrans}$	72.0	174.5	-143.5	102.9	(*S*)
$TS_{endoStrans}$	31.4	180.7	-140.6	71.5	(*S*)
$TS_{exotrans}$	41.0	165.7	-151.9	54.4	(*R*)
$TS_{exoStrans}$	26.8	156.9	-150.2	33.5	(*R*)

[a] All energies correspond to potential energies in solution and in kJ/mol. TS_{endo} and TS_{exo} refer to the attack trans to P and (*R*)-configuration in the sulfur atom. TS_{endoS} and TS_{exoS} refer to the attack trans to P and (*S*)-configuration in the sulfur atom. $TS_{endotrans}$ and $TS_{exotrans}$ refer to the attack trans to S and (*R*)-configuration in the sulfur atom. $TS_{endoStrans}$ and $TS_{exoStrans}$ refer to the attack trans to S and (*S*)-configuration in the sulfur atom.

Table SI.4. Distortion energy of [Pd/L45c], distortion energy of [substrate-nucleophile] and interaction energies for transitions states of ligand L45c and substrate S1[a]

	$\Delta E_{dist(Pd\text{-}L45c)}$	$\Delta E_{dist(substrate\text{-}nucleophile)}$	$\Delta E_{interaction}$	ΔE	Product
TS_{endo}	28.0	173.2	-161.5	40.2	(*R*)
TS_{endoS}	20.1	173.2	-159.8	33.9	(*R*)
TS_{exo}	31.8	164.0	-161.5	34.3	(*S*)
TS_{exoS}	17.6	160.2	-151.5	26.4	(*S*)
$TS_{endotrans}$	27.2	153.1	-145.2	35.1	(*S*)
$TS_{endoStrans}$	17.2	154.0	-142.7	28.5	(*S*)
$TS_{exotrans}$	35.6	156.5	-145.6	46.4	(*R*)
$TS_{exoStrans}$	24.7	156.9	-141.0	40.6	(*R*)

[a] All energies correspond to potential energies in solution and in kJ/mol. TS_{endo} and TS_{exo} refer to the attack trans to P and (*R*)-configuration in the sulfur atom. TS_{endoS} and TS_{exoS} refer to the attack trans to P and (*S*)-configuration in the sulfur atom. $TS_{endotrans}$ and $TS_{exotrans}$ refer to the attack trans to S and (*R*)-configuration in the sulfur atom. $TS_{endoStrans}$ and $TS_{exoStrans}$ refer to the attack trans to S and (*S*)-configuration in the sulfur atom.

4.6. Application of P*-stereogenic *N*-phosphine-phosphite ligands to enantioselective Pd-catalyzed allylic alkylation

Biosca, M.; Pàmies, O.; Diéguez, M. *Preliminary results*.

Abstract: The previously P*-stereogenic *N*-phosphine-phosphinite ligand library **L51**-**L54a**-**c** has also been applied in the asymmetric Pd-catalyzed allylic substitution of different benchmark substrates using dimethyl malonate as nucleophile. Moderate enantioselectivities were achieved in the allylic alkylation of linear hindered substrate **S1** (ee's up to 86%), and promising results in the more challenging cyclic substrate **S2** (ee's up to 85%). These ligands were also applied in the alkylation of the difficult monosubstituted linear substrate **S3** but unfortunately, low regio- and enantioselectivities were achieved.

4.6.1. Introduction

The development of methods for enantioselective formation of carbon-carbon and carbon-heteroatom bond are particularly useful in the synthesis of complex molecules of biological and industrial interest. A versatile method for achieving this is the asymmetric Pd-catalyzed allylic substitution reaction.[1] Therefore, this reaction has been extensively studied over the past years and a large number of chiral ligands have been developed. Most of the chiral ligands applied in this process have been designed using three main strategies; the use of pendant group able to interact with the nucleophile and direct its approach to the substrate,[2] the use of C_2-symmetrical ligands scaffolds in order to restrict the number of diastereomeric transition states[3] or the use of strong and weak donor groups to control the nucleophilic attack due to the different *trans* influence of the donor functionalities[4]. The latter one is the most studied approach giving rise to the discovery of a wide range of efficient heterodonor ligands for the Pd-catalyzed allylic substitution reaction. Nevertheless, in most of them the asymmetric induction is highly dependent on the steric demand of the substrate or the nucleophile scope is limited, or both. More recently, our group found that the presence of a flexible π-acceptor biaryl phosphite moiety improve these limitations. In addition, in the allylic substitution of monosubstituted linear substrates, it improve the regioselectivity towards the desired branched isomer due to the π-acceptor ability of the phosphite moiety that together with the steric effect of the ligand favors the nucleophilic attack at this carbon atom.[5]

As previously mentioned Pd-catalyzed allylic substitutions have been extensively studied however, there are, however, not many reports concerning the use of heterodonor P,P'-ligands compared to other classes of ligands (i.e. P,N-ligands).[6] Moreover, only few of them contain a P*-stereogenic phosphine ,[7] although the presence of P*-stereogenic donor unit has demonstrated its usefulness potential in several

catalytic transformations[8]. The first example on the use of this class of ligands was reported by van Leeuwen *et al*. who applied a family of P*stereogenic phosphine-phosphite ligands (**1** and **2**; Figure 4.6.1) achieving enantioselectivities up to 82% ee in the allylic alkylation of benchmark (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene substrate with dimethyl malonate.[7a] Later, Grabulosa *et al*. applied ligands containing a P*-stereogenic phosphine and a phosphinite, phosphite or phosphorodiamidite moiety (**3**, **4** and **5**; Figure 4.6.1).[7b] The best results were obtained when the more π-acceptor phosphorous moieties were present (phosphite and phosphorodiamidite; ligands **4** and **5**) which agrees with what our group found (ee's up to 95% in the alkylation of (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene).

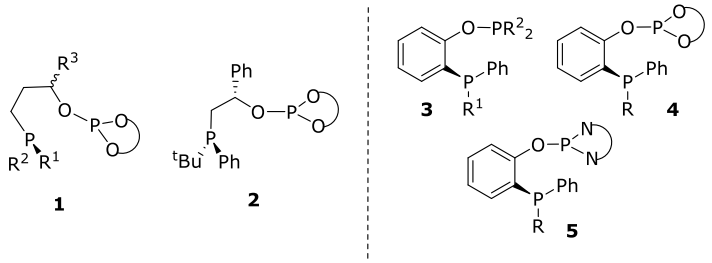


Figure 4.6.1. P*-stereogenic phosphine-other phosphorous ligands

To further investigate the potential of this class of ligands, in this section we reported the application of P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**L54a**-**c** (Figure 4.6.2) in the palladium allylic alkylation of the benchmark substrates (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**), (*rac*)-3-acetoxycylohexene (**S2**) and (*rac*)-1-(naphtalen-1-yl)allyl acetate (**S3**) using dimethyl malonate as nucleophile. This family of ligands allows us to systematically study the effect of the substituents in the P*-stereogenic *N*-phosphine group (**L51**-**L52**), the configuration of the biaryl phosphite moiety (**a**-**c**) as well as the effect of the rigidity of the ligand backbone (**L51-L52** vs **L54**). In addition, for comparative purpose we also synthetized ligands **L53b**-**c** without chirality on the *N*-phosphine moiety.

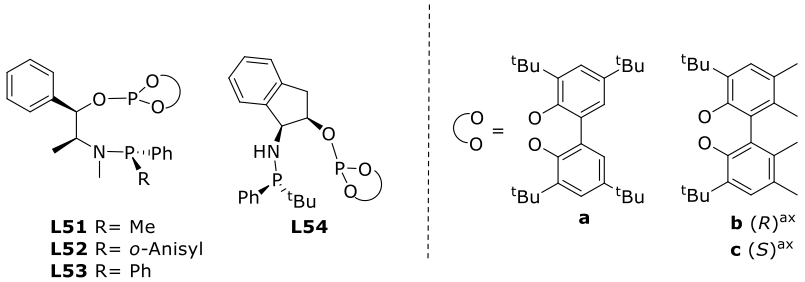


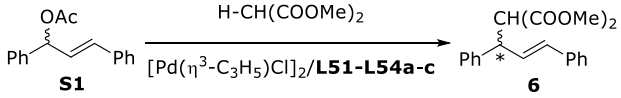
Figure 4.6.2. *N*-phosphine-phosphite ligand library **L51**-**L54a**-**c**.

4.6.2. Results and Discussions

4.6.2.1. Allylic alkylation of symmetrical linear disubstituted substrate (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene (S1)

We initially screened P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**54a**-**c** in the allylic alkylation of the benchmark linear disubstituted substrate **S1**. Table 4.6.1 shows the catalytic results which indicated that the asymmetric induction is highly affected by the substituents on the *N*-phosphine, the configuration of the phosphite group and the rigidity of the ligand backbone.

Table 4.6.1. Pd-catalyzed allylic alkylation of model substrate **S1** with dimethyl malonate using **L51**-**L54a**-**c**.[a]



Entry	Ligand	% Conv[b]	%ee[c]
1	**L51a**	100	76 (*S*)
2	**L51b**	100	32 (*R*)
3	**L51c**	100	84 (*S*)
4	**L52b**	100	44 (*R*)
5	**L52c**	100	85 (*S*)
6	**L53b**	100	54 (*R*)
7	**L53c**	100	58 (*S*)
8	**L54a**	100	86 (*R*)
9	**L54b**	100	2 (*S*)
10	**L54c**	100	53 (*R*)

[a] Reaction conditions: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), ligand (0.011 mmol), CH_2Cl_2 as solvent, BSA/KOAc as base, rt; [b] Conversion percentage determined by ^1H NMR after 30 min; [c] Enantiomeric excesses determined by HPLC.

We first studied the effect of the configuration of the phosphite moiety with ligands **L51a**-**c**. The results indicated that the presence of chiral biphenyl moiety with (*S*)-configuration is necessary to obtain the highest enantioselectivity (**L51c**, 84% ee, entry 3), thus there is a matched combination of all stereocenters of the ligands when this (*S*)-configuration is present. Nevertheless, the result obtained with the inexpensive achiral biphenyl moiety **a** was also satisfactory (**L51a**, 76% ee, entry 1).

The nature of the substituent at the P*-stereogenic *N*-phosphine group has a little effect on the enantioselectivity (**L51**-**L52**, entries 2-5). However, the use of ligands **L53** without chirality at the *N*-phosphine moiety led to lower enantioselectivities than when

using P*-analogues **L51** and **L52** (e.g. entry 7 vs 3 and 5), which supports that the presence of P*-stereogenic unit is crucial to maximize enantioselectivities.

Next, we studied the effect increasing the rigidity of the backbone with ligands **L54a**-**c**. In contrast with previous ligands tested, the presence of chiral biphenyl phosphite moiety has a negative effect on the enantioselectivity (**L54b**-**c**, entries 9-10) and the highest results was obtained with the ligand that contains an inexpensive achiral biphenyl moiety (**L54a**, 86% ee, entry 8).

In summary, enantioselectivities up to 86% ee were achieved for the allylic alkylation for **S1** with dimethyl malonate. Moreover, by carefully selecting the ligand parameters both enantiomers of the alkylated product could be obtained (entries 5 and 8).

4.6.2.2. Allylic alkylation of the unhindered cyclic disubstituted substrate (*rac*)-3-acetoxycyclohexene (S2)

We subsequently tested ligands **L51**-**L54a**-**c** in the Pd-catalyzed allylic alkylation of the model cyclic substrate **S2**. The allylic alkylation of **S2** is more difficult to control due to the presence of less sterically demanding *anti* substituents.[1] The results are found in Table 4.6.2 and indicated that again the enantioselectivity is highly affected by all the ligand parameters.

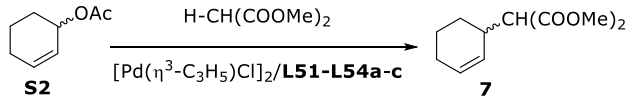
The effect of the configuration of the biaryl phosphite moiety, which was studied with ligands **L51a**-**c**, follow similar trend than in the alkylation of **S1**. Thus, the highest enantioselectivities were obtained with ligands that contains a (*S*)-biaryl phosphite moiety **c** or the inexpensive biaryl phosphite group **a** (ee's up to 64%, entries 1-3).

As observed for **S1**, the presence of a P*-stereogenic moiety is again crucial to maximize enantioselectivities (**L51**-**L52** vs **L53**, entries 2-5 vs 6-7). Nevertheless. in contrast to the alkylation of model substrate **S1**, for **S2** the increment of the bulkiness in the P*-stereogenic phosphine moiety has a positive effect on the enantioselectivity (**L51** vs **L52**, entries 2-3 vs 4-5). Thus, the use of ligand **L52c**, with an *ortho*-anysil group at the P*-stereogenic *N*-phosphine group, provides higher enantioselectivities (up to 85% ee) than when using ligand **L51c** with a methyl substituent in the P*-group (entry 5 vs 3).

When a more rigid backbone is present on the ligand design enantioselectivities were also satisfactory (**L54a**-**c**, ee's up to 79%, entries 8-10). Interestingly, with these ligands, again the inexpensive biaryl phosphite group **a** provided a satisfactory result (78% ee, entry 8). However in contrast to the previous ephedrine-based ligands tested, the highest enantioselectivity was achieved using the ligand containing an (*R*)-biaryl phosphite moiety (ligand **L54b**, 79% ee, entry 9).

In summary, by carefully selecting the ligand parameters a high enantioselectivity could be obtained for this more challenging cyclic substrate **S2** (85% ee, entry 5).

Table 4.6.2. Pd-catalyzed allylic alkylation of model substrate **S2** with dimethyl malonate using **L51**-**L54a**-**c**.[a]



S2 **7**

Entry	Ligand	% Conv[b]	%ee[c]
1	**L51a**	100	64 (*S*)
2	**L51b**	100	25 (*R*)
3	**L51c**	100	60 (*S*)
4	**L52b**	100	64 (*R*)
5	**L52c**	100	85 (*S*)
6	**L53b**	100	55 (*R*)
7	**L53c**	100	74 (*S*)
8	**L54a**	100	78 (*S*)
9	**L54b**	100	79 (*R*)
10	**L54c**	100	21 (*S*)

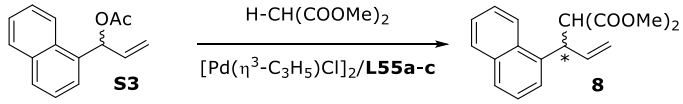
[a] Reaction conditions: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), ligand (0.011 mmol), CH_2Cl_2 as solvent, BSA/KOAc as base, rt; [b] Conversions determined by GC after 2 h; [c] Enantiomeric excesses determined by GC.

4.6.2.3. Allylic alkylation of the unsymmetrical linear substrate (*rac*)-1-(naphthalene-1-yl)allyl acetate (S3)

Finally, the potential of P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**L54a**-**c** were evaluated Pd-catalyzed allylic alkylation of the more challenging monosubstituted linear substrate **S3**. For this kind of unsymmetrical substrates not only does the enantioselectivity need to be controlled but also the regioselectivity is a problem because a mixture of isomers can be obtained.[1]

The catalytic results are found in Table 4.6.3 and showed that unfortunately Pd/**L51**-**L54a**-**c** catalysts were not able to control the regioselectivity of the process, thus low regioselectivities towards the formation of the desired branched isomer were obtained. Furthermore, the results also showed that the enantioselectivity of the branched isomer is mainly affected by the configuration of the biaryl phosphite group. Ligands that contains a chiral (*R*)-biphenyl phosphite moiety provided the highest results, albeit they were unsatisfactory (ee's up to 36%).

Table 4.6.3. Pd-catalyzed allylic alkylation of model substrate **S3** with dimethyl malonate using **L51**-**L54a**-**c**.[a]



Entry	Ligand	% Conv[b]	b/l	%ee[c]
1	**L51a**	100	35/65	2 (*R*)
2	**L51b**	100	30/70	33 (*R*)
3	**L51c**	100	30/70	7 (*R*)
4	**L52b**	100	45/55	30 (*R*)
5	**L52c**	100	40/60	4 (*R*)
6	**L53b**	100	30/70	36 (*R*)
7	**L53c**	100	30/70	10 (*R*)
8	**L54a**	100	35/65	14 (*R*)
9	**L54b**	100	25/75	24 (*S*)
10	**L54c**	100	50/50	15 (*S*)

[a] Reaction conditions: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol%), ligand (2.2 mol%), CH_2Cl_2 as solvent, BSA/KOAc as base, rt; [b] Conversions measured after 30 min; [c] Regioselectivity measured by ^1H NMR; [d] Enantiomeric excesses determined by chiral HPLC.

4.6.3. Conclusions

A family of P*-stereogenic *N*-phosphine-phosphinite ligands **L51**-**L54a**-**c** has been applied in the asymmetric Pd-catalyzed allylic substitution of three model substrates (*rac*)-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**), (*rac*)-3-acetoxycylohexene (**S2**) and (*rac*)-1-(naphtalen-1-yl)allyl acetate (**S3**) using dimethyl malonate as nucleophile. These ligands allow the study of the effect of several factors; the rigidity of the ligand backbone, the substituents at the P*-stereogenic *N*-phosphine group and the configuration of the biaryl phosphite moiety. By carefully tuning the ligand parameters, moderate enantioselectivities were achieved in the allylic alkylation of linear hindered substrate **S1** (ee's up to 86%) and promising results in the more challenging cyclic substrate **S2** (ee's up to 85%). These ligands were also applied in the alkylation of the difficult monosubstituted linear substrate **S3** but unfortunately, low regio- towards the branched isomer and enantioselectivities were achieved.

4.6.4. Experimental Section

4.6.4.1. General considerations

All reactions were carried out by using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. The synthesis of

P*-stereogenic *N*-phosphine-phosphite ligands **L51**-**L54a**-**c** has been previously described in Section 3.12. Substrates **S1**-**S3**[9] were prepared following the reported procedures.

4.6.4.2. General procedure for the allylic alkylation of substrates S1-S3

A solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-hydrazone ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (1.5 mmol), *N,O*-bis(trimethylsilyl)-acetamide (1.5 mmol) and KOAc (3 mg, 0.03 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For substrates **S1** and **S3** conversions were measured by ^1H NMR and enantiomeric excesses were determined by chiral HPLC, while for substrates **S2**, conversions and enantiomeric excesses were determined by chiral GC (for more details see previous Section 4.1.5.5).

4.6.5. Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P), European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D.).

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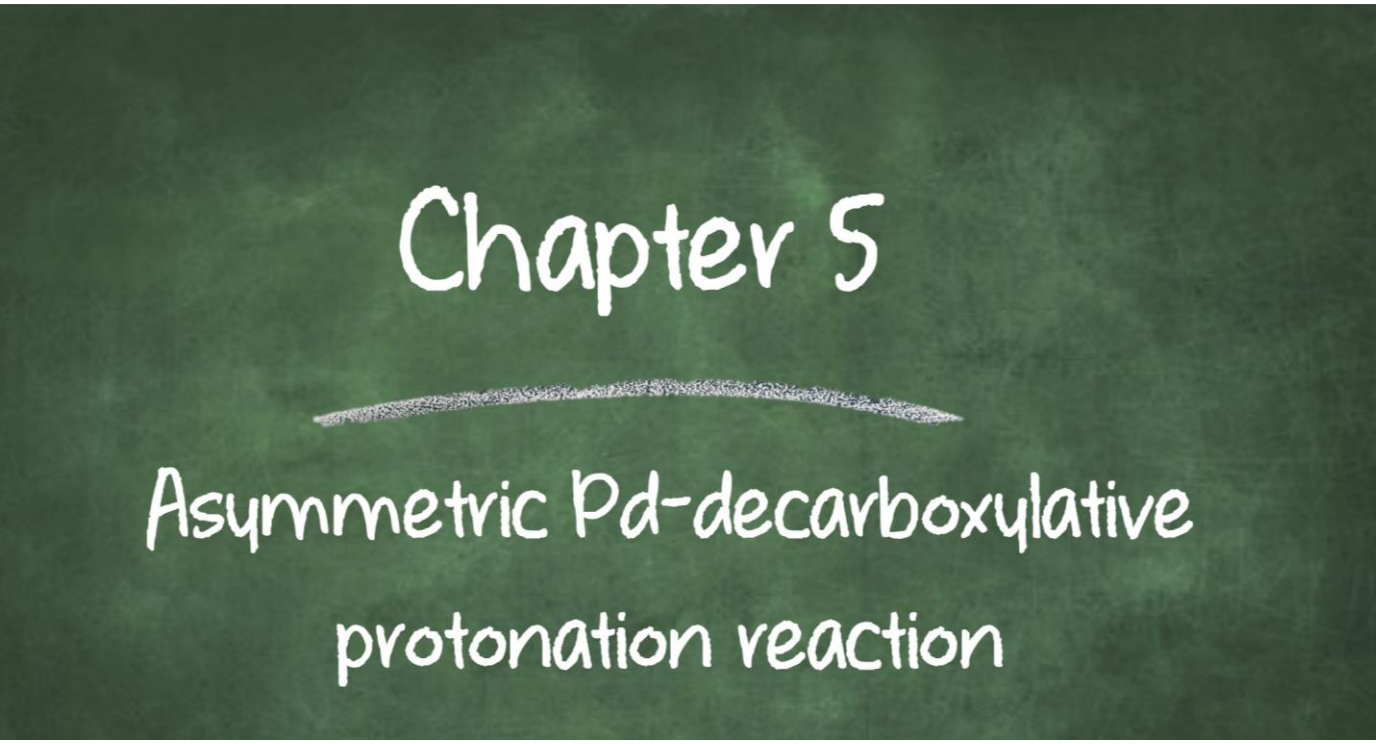

Chapter 5
Asymmetric Pd-decarboxylative protonation reaction

UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull

5.1. Enantioselective synthesis of sterically hindered tertiary α-aryl oxindoles via Palladium-catalyzed decarboxylative protonation. An experimental and theoretical mechanistic investigation

Biosca, M.*; Jackson, M.*; Magre, M.*; Pàmies, O.; Norrby, P.O.; Diéguez, M.; Guiry, J. P. *Adv. Synth. Catal.* **2018**, *360*, 3124. *These authors contributed equally to this study.

In collaboration with the group of Prof. J. P. Guiry (University College of Dublin) and Prof. P.-O. Norrby (AstraZeneca, Sweden).

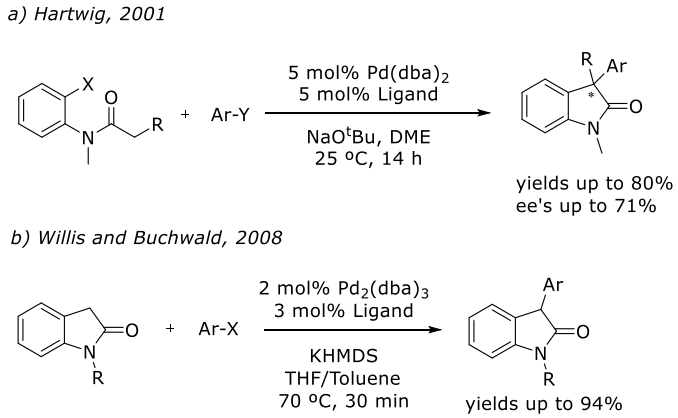
Abstract: We have developed the first catalytic asymmetric preparation of sterically hindered tertiary α-aryl oxindoles via enantioselective palladium-catalyzed decarboxylative protonation of the corresponding α-aryl-β-amido allyl esters. The reaction occurs under very mild conditions and in short reaction times, providing excellent yields and promising enantioselectivities (ee's up to 78%). We have also performed an experimental investigation of the reaction mechanism and employed theoretical calculations to understand the nature of the enantioselectivity-determining step.

5.1.1. Introduction

The enantioselective formation of C-C bond between an aryl group and a carbon α-to a carbonyl group is one of the most challenging problems in organic chemistry.[1] The asymmetric synthesis of α-aryl carbonyl-containing molecules has attracted much attention over the last decade, due to the presence of this structural motif in a wide range of naturally occurring and biologically active compounds.[2]

Oxindoles are endogenous aromatic organic compounds that are found in the tissues and body fluids of mammals. The oxindole skeleton is also present in many natural products which exhibit anti-viral, anti-bacterial and anti-carcinogenic properties.[3]

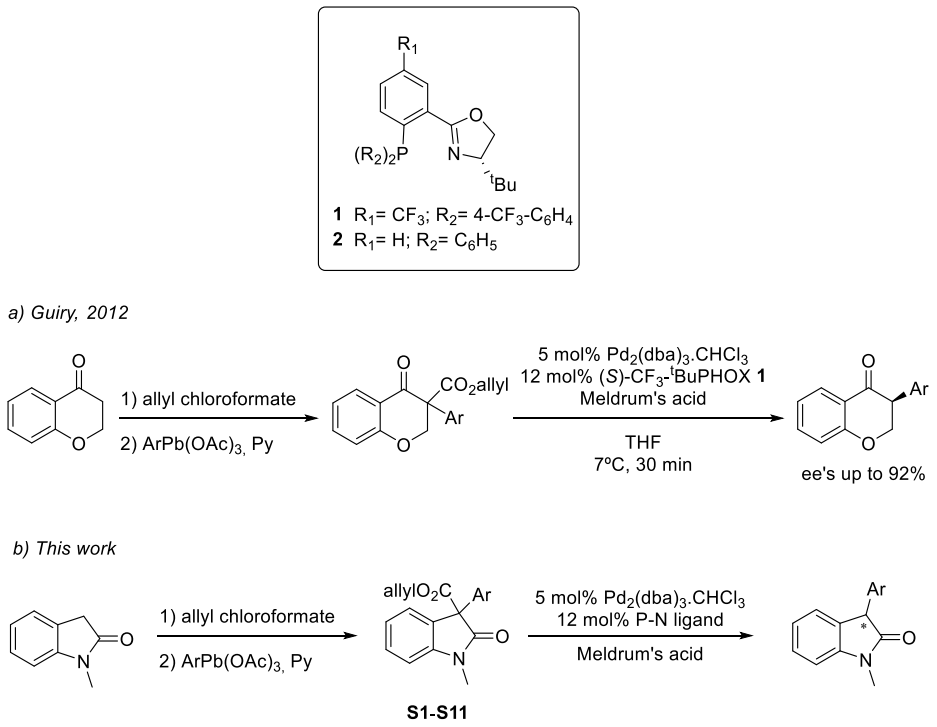
The first approach to the asymmetric synthesis of oxindoles was reported by Hartwig (Scheme 5.1.1a) in 2001. They reported the preparation of 3,3-disubstituted oxindoles using a Pd-catalyzed intramolecular cyclization with excellent conversions and promising enantioselectivities (ee's up to 71%).[4] However, such an approach was not suitable when the substrate had an oxindole core and only quaternary α-aryl oxindoles were prepared. In contrast to the catalytic asymmetric synthesis of quaternary α-aryl carbonyl stereocenters, the synthesis of the corresponding tertiary α-aryl carbonyl containing compounds remains a challenge due to the ease at which such compounds racemize. As an alternative to the cyclization method, direct metal-catalyzed α-arylation of carbonyl compounds emerged for a wide range of nucleophiles such as enolates of ketones, esters, nitriles, and amides.[1b,5]



Scheme 5.1.1. Previous methodologies for the preparation of α-aryl oxindoles.

The first metal-catalyzed α-arylation of oxindoles was reported by Willis'[6] and Buchwald's[7] groups independently in 2008 (Scheme 5.1.1b). They applied Pd-phosphine complexes to catalyze the α-arylation of oxindoles with several aryl halides with good to excellent yields. The application of strong bases (such as NaO^{t}Bu or KHMDS) is necessary to deprotonate the amidic α-proton in these approaches to the α-arylation of oxindoles. However, due to such strong basic media, the asymmetric α-arylation of oxindoles has not been reported yet because the ease of racemization of tertiary stereocenter.

An alternative path to catalytic asymmetric α-arylation of carbonyls without using strong bases is to perform a Pd-catalyzed decarboxylative protonation of α-aryl-β-keto allyl esters (Scheme 5.1.2). With this idea, Guiry has reported the preparation of chiral α-aryl ketones and isoflavanones via Pd-decarboxylative protonation in excellent yields and enantioselectivities with (*S*)-CF_3-tBuPHOX ligand **1** (Scheme 5.1.2a).[8] This methodology was based in the pioneering work of Stoltz who used Pd-decarboxylative protonation of allyl β-ketoesters to prepare α-alkyl cyclic ketones using the ^{t}BuPHOX ligand **2**.[9] A relevant finding of Guiry's group was that the electron deficient phosphine-oxazoline ligand (*S*)-CF_3-^{t}BuPHOX **1** provided much higher enantioselectivity than the ^{t}BuPHOX ligand **2**. The Guiry group has also extensively studied the preparation of sterically hindered α-allyl-α-arylcarbonyl containing compounds possessing all-carbon quaternary stereocenters,[10] including oxindoles which required the preparation of a series of α-aryl-β-amido esters **S1**-**S11**.[11] With these substrates at hand, containing aryl substituents with different electronic and steric properties, we now wish to report the first catalytic asymmetric synthesis of chiral tertiary α-aryl oxindoles by Pd-catalyzed decarboxylative protonation (Scheme 5.1.2b).



Scheme 5.1.2. Synthesis of chiral α-aryl isoflavones (Scheme 5.1.2a) and oxindoles (Scheme 5.1.2b) by a lead mediated arylation followed by an enantioselective Pd-catalyzed decarboxylative protonation.

Because the use of electron deficient ligands was seen to facilitate the asymmetric Pd-decarboxylative protonation of α-aryl-β-keto allyl esters (Scheme 5.1.2a),[8a] we focused in electron deficient P,N-ligands and applied several π-acceptor phosphite-N ligand families (Figure 5.1.1) that Diéguez's group had developed previously. They found that in some asymmetric catalytic transformations the biaryl π-acceptor phosphite groups in the ligands have a positive effect on activity and widen substrate versatility.[12] The higher flexibility of a biaryl phosphite compared with a phosphine moiety allows these P,N-ligands to accommodate a wider range of substrates, thereby yielding excellent enantioselectivities for a broad range of substrates and catalytic reactions.[12] In the present study we applied three phosphite-N ligand families in the Pd-decarboxylative protonation of α-aryl-β-amido esters (Figure 5.1.1).[13] These phosphite-oxazoline ligands are based on three main ligand structures. The first one is based on the phosphine-oxazoline PHOX ligands **2**, in which the phosphine moiety has been replaced by biaryl phosphite groups (ligands **L3**-**L6**).[13a-c] In the second one the flat *ortho*-phenylene tether in **L3**-**L6** has been replaced by an alkyl chain bonded to carbon 4 of the oxazoline moiety, which shifts the chirality from the oxazoline to the alkyl chain (ligands **L62**-**L65**).[13d-g] In the third one the oxazoline group has been replaced by a

more robust pyridine group (ligands **L66**-**L73**).[13h,i] Several configuration/substituents on the biaryl phosphite moiety will be also studied (**a**-**e**). Finally, we have also performed an experimental investigation of the reaction mechanism and used theoretical studies primarily to understand the nature of the selective-determining step.

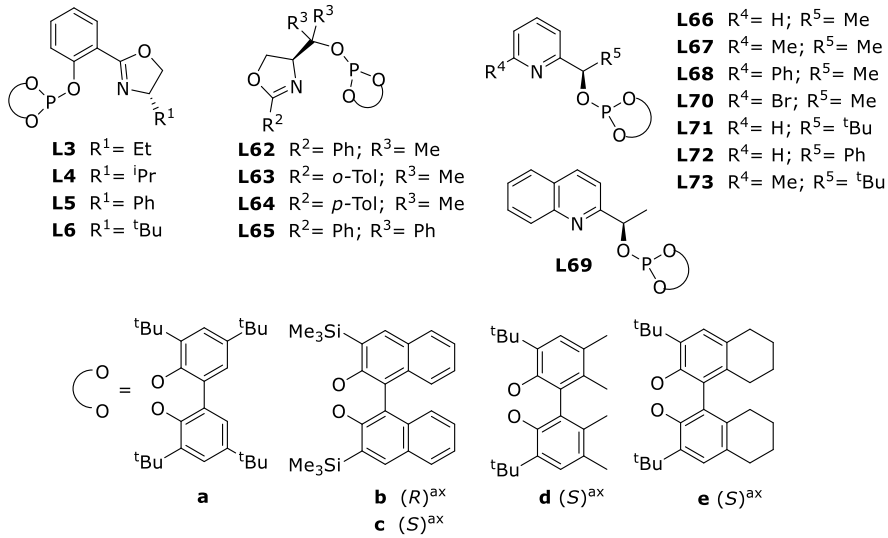


Figure 5.1.1. Phosphite-nitrogen ligand libraries.

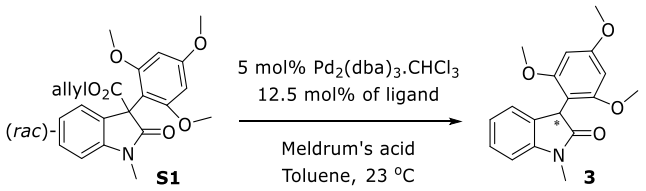
5.1.2. Results and Discussion

5.1.2.1. Catalytic reactions

In a first set of experiments we used allyl 1-methyl-2-oxo-3-(2',4',6'-trimethoxyphenyl)indoline-3-carboxylate **S1** as a model substrate using previously developed reaction conditions (Table 5.1.1).[8] Reactions were therefore performed at room temperature, using 5 mol% of *in situ* generated catalyst $Pd_2(dba)_3{\cdot}CHCl_3$ and the corresponding ligand in the presence of Meldrum's acid (Table 5.1.1). In this protocol catalysts need to be preactivated during 30 min at 40 ºC. All catalytic systems were found to give full conversion in less than 2 hours. Disappointingly, the use of the electron deficient phosphine-oxazoline ligand **1** afforded low enantioselectivity (37% ee, Table 5.1.1, entry 1).[14] The use of related phosphite-oxazoline ligands **L3**-**L6a**, in which the phosphine moiety in ligand **1** has been replaced by a biaryl phosphite group, provided even lower enantioselectivities (ee's up to 3%, Table 5.1.1, entries 2-5). The use of ligands **L62**-**L65a** provided also lower enantioselectivities than those achieved with ligand **1** (Table 5.1.1, entries 6-9). In these cases we found that enantioselectivity is affected by the substituent at the alkyl backbone chain. Thus, the best enantioselectivity (18% ee, entry 9) was achieved with ligand **L65a** which contains phenyl substituents on the alkyl backbone. Similar levels of enantioselectivity were achieved using more

robust phosphite-pyridine ligands **L66**-**L73a** (entry 12, 20% ee). By varying the substituent of the ligand backbone (R_4 and R_5) with ligands **L66**-**L73a** we found that the best enantioselectivity was obtained with **L66a** (entry 12), which contain a hydrogen in R_4 and a Me in R_5.

Table 5.1.1. Initial ligand screening of Pd-catalyzed decarboxylative protonation of **S1**.



Entry[a]	Ligand	t (min)	% Conv[b]	% ee[c]
1	**1**	60	100	37 (+)
2	**L3a**	60	100	1 (+)
3	**L4a**	60	100	2 (+)
4	**L5a**	60	100	1 (+)
5	**L6a**	60	100	3 (+)
6	**L62a**	60	100	4 (+)
7	**L63a**	60	100	3 (+)
8	**L64a**	60	100	10 (+)
9	**L65a**	60	100	18 (+)
10	**L65b**	60	100	11 (+)
11	**L65c**	60	100	38 (+)
12	**L66a**	60	100	20 (+)
13	**L66b**	60	100	9 (+)
14	**L66c**	120	100	49 (+)
15	**L66d**	60	100	5 (+)
16	**L66e**	60	100	4 (+)
17	**L67a**	120	100	3 (+)
18	**L68a**	120	100	1 (-)
19	**L69a**	120	100	2 (-)
20	**L70a**	120	100	1 (-)
21	**L71a**	120	100	8 (-)
22	**L72a**	120	100	17 (-)
23	**L73a**	120	100	2 (-)

[a] Reaction conditions: 50 mg substrate (0.125 mmol), 5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 12.5 mol% ligand, 2.5 eq. Meldrum's acid; [b] Determined by ^1H NMR spectroscopy; [c] Determined by SFC.

To improve the enantioselectivities further we used ligands **L65**-**L66a**-**e** to study the effect of the biaryl phosphite moiety. The results indicated that enantioselectivity could

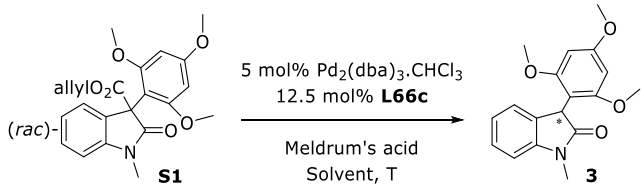
be increased with the adequate configuration and substituent at the biaryl phosphite moiety (ligand **L66c**, up to 49% ee, entry 14). Thus, ligands **L65**-**L66c** (entries 11 and 14) with an (*S*)-biaryl phosphite group provided higher enantioselectivities than ligands **L65**-**L66b** containing an (*R*)-biaryl group (entries 10 and 13). On the other hand, enantioselectivities are very sensitive to variations in the substituents of the biaryl and therefore sensitive to the dihedral angle of the biaryl phosphite group. Accordingly, the use of ligands **L66d**-**e** (entries 15 and 16), which also contains (*S*)-biaryl phosphite groups, provided lower enantioselectivities than ligand **L66c**.

Optimization of reaction conditions

We next optimized the reaction conditions for ligand **L66c** that had provided the best results (Table 5.1.2). The screening of seven solvents (toluene, chloroform, dichloromethane, 1,4-dioxane, tetrahydrofuran, diethyl ether, and methyl *tert*-butyl ether (MTBE)) showed that enantioselectivities were higher when ethereal solvents were used (Table 5.1.2, entries 1, 4-7 vs 2-3). Of the solvents, MTBE had the most positive effect on enantioselectivity (ee's increased to 70%; Table 5.1.2, entry 7), albeit with isolated yields up to 64%. This lower yield with MTBE were attributed to the difficulty of a quantitative transfer of the substrate solution to the catalyst mixture due to the low solubility of the substrate in MTBE. To improve the yields, both Meldrum's acid and substrate were added as solids to the preactivated solution of the catalyst precursor and ligand. This increased the isolated yields while maintaining the enantioselectivity (entry 11). Another strategy tested, using mixtures of solvents (entries 8-10), was unsuccessful and enantioselectivity decreased, although yields were higher than when using MTBE alone. We also found that catalyst did not need to be preactivated to achieve high yields and ees, although the reaction time required to achieve full conversions increased (entry 12).

Finally, by decreasing the temperature to 5 ºC, enantioselectivity increased up to 78% ee while maintaining the excellent yield (Table 5.1.2, entry 13 vs entry 12). Further decreasing the temperature to -20 ºC led to a decrease in conversion and enantioselectivity (Table 5.1.2, entry 14). We also tested the reaction at 40 ºC, since the literature indicated that higher temperatures could provide better enantioselectivities,[8c] but enantioselectivity did not improve (Table 5.1.2, entry 15).

Table 5.1.2. Reaction optimization: solvent and temperature with ligand **L66c.**



Entry[a]	Solvent	T (ºC)	t (h)	% Conv[b]	%ee[c]
1	Toluene	23	2	100 (94)	49 (+)
2	$CHCl_3$	23	1	<5 (nd)	5 (+)
3	CH_2Cl_2	23	1	100 (93)	17 (+)
4	1,4-Dioxane	23	1	100 (93)	54 (+)
5	THF	23	1	100 (94)	46 (+)
6	Et_2O	23	1	100 (64)	63 (+)
7	MTBE	23	1	100 (60)	70 (+)
8	MTBE:Dioxane (2:1)	23	1	100 (92)	50 (+)
9	MTBE:Dioxane (4:1)	23	1	100 (93)	33 (+)
10	MTBE:Toluene (1:1)	23	1	100 (91)	36 (+)
11[d]	MTBE	23	1	100 (92)	66 (+)
12[e]	MTBE	23	3	100 (93)	70 (+)
13[e]	MTBE	5	3	100 (92)	78 (+)
14[e]	MTBE	-20	3	43 (nd)	63 (+)
15[e]	1,4-Dioxane	40	1	97 (nd)	17 (+)

[a] Reaction conditions: 50 mg substrate (0.125 mmol), 5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 12.5 mol% **L66c**, 2.5 eq. Meldrum's acid; [b] Determined by ^1H NMR; [c] Determined by SFC; [d] Substrate and Meldrum's acid added as solids; [e] Catalyst precursor, ligand, Meldrum's acid and substrate all together in the schlenk without catalyst preactivation.

Substrate scope

After optimizing the reaction, substrates **S2**-**S11**, with different electronic and steric aryl substituents on the oxindole, were studied. These aryl substituents were chosen due to the facile synthesis of the required aryllead triacetate and the high yields obtained in the arylation of the β-amido allyl esters. In addition, previous results from Guiry had demonstrated the importance of strongly electron-donating substituents in the *ortho*- and *para*-positions for obtaining high enantioselectivities.[8-9] The results (Figure 5.1.2) underline the importance of bulkiness and of the presence of electron-donating substituents for the enantioselectivity.[15] The best enantioselectivities (ee's up to 78%) were therefore obtained with the bulkiest and electronically rich substrates **S1** and **S2**. When other substrates that had less bulky aryl substituents (**S3** and **S4**) were tested, the enantioselectivity decreased due to the removal of one *ortho*-substituent.

Comparing the results for **S3** with those of **S4** we can also determine that substituents at *meta*-position have almost no effect on the catalytic performance. When *para*-methoxy group was removed (**S5**), the enantioselectivity decreased but it was higher than those with only one *ortho*-methoxy substituent (**S3** and **S4**). As expected, when non-*ortho*-substituted aryl groups were studied (**S6** and **S7**) almost racemic compounds were obtained.

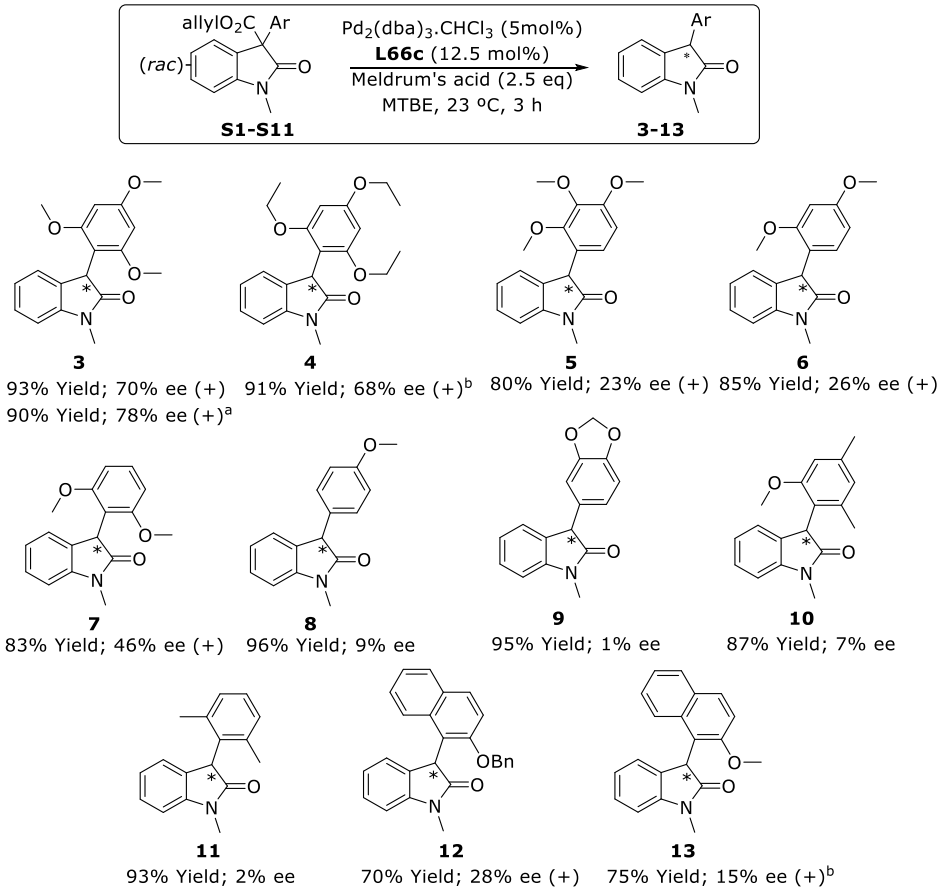
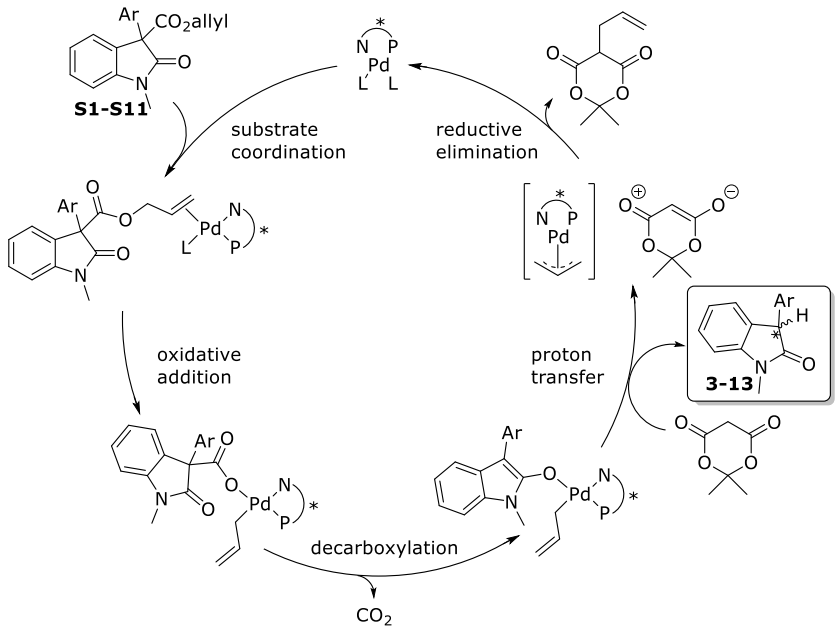


Figure 5.1.2. Pd-decarboxylative protonation of **S1**-**S11**. Reaction conditions: substrate (0.125 mmol), 5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 12.5 mol% **L66c**, 2.5 eq. Meldrum's acid. [a] Reaction carried out at 5 ºC; [b] Reaction carried out in Et_2O due to insolubility of **S2** and **S11** in MTBE.

The importance of an *ortho*-alkoxy substituent was corroborated by its sequential replacement by methyl groups. Products **10** and **11** were obtained with lower ee's than **3** and **7**, respectively. Accordingly, substrates with *ortho*-substituted naphthyl groups (**S10** and **11**) provided moderate levels of enantioselectivities, comparable to those found when using **S3** and **S4** (ee's up to 28% and 15%, respectively). As a summary, for enantioselectivities to be high, the aryl group of the substrate must contain substituents in *ortho*- and *para*-positions.

5.1.2.2. Study of the key intermediates. Experimental and theoretical studies

Although the mechanism for the asymmetric decarboxylative allylation of allyl β-keto esters with Pd-catalysts has been investigated both experimentally and computationally, the mechanism for decarboxylative protonation is not well understood.[8d,9c] The current mechanistic hypothesis for decarboxylative protonation mainly relies on kinetic experiments carried out by Stoltz with allyl β-keto esters.[9b,16] They studied the variation of the substrate concentration over time by NMR spectroscopy and found a zero-order dependence on substrate concentration which indicates that the substrate reacts very fast.[17] However, this only gives information about the first two steps of the catalytic cycle, namely the coordination of the substrate and the oxidative addition (Scheme 5.1.3).



Scheme 5.1.3. Proposed catalytic cycle for the enantioselective decarboxylative protonation of allyl β-amido esters.

To obtain a clearer picture of the kinetic profile for the decarboxylative protonation with our allyl β-amido esters, we performed a detailed kinetic study with substrate **S1** using the Pd/**L66c** catalytic system. Initially, we studied the effect of the Pd loading (0.5–2 mM) on activity. It was found that the rate of product formation is proportional to the Pd concentration (Figure 5.1.3a). This indicates a first order-dependence and excludes the possibility of polinuclear species as competent catalysts for this transformation. Next, we studied the effect of the substrate concentration on activity.

Figure 5.1.3b shows that the rate of product formation is independent on the substrate concentration (0.01-0.05M), which is in agreement with Stoltz's observations. This indicates that the most likely rate determining step is either the decarboxylation or the subsequent proton transfer (Scheme 5.1.3). We therefore next studied the effect of the Meldrum's acid concentration on activity. The rate of the decarboxylative protonation of **S1** did not depend on concentration of the Meldrum's acid (0.05-0.2 M; Figure 5.1.3c). This zero-order dependence agrees with a rapid protonation step. Further mechanistic insights into the rate determining step of the reaction were obtained by studying the kinetic isotope effect (KIE) of the decarboxylative protonation of **S1** using Meldrum's acid and d_2-Meldrum's acid (Figure 5.1.3d). Reaction monitoring by ^{1}H-NMR revealed a practically null KIE (KIE≈ 1.05). This result further confirms that the decarboxylation is the rate determining step.

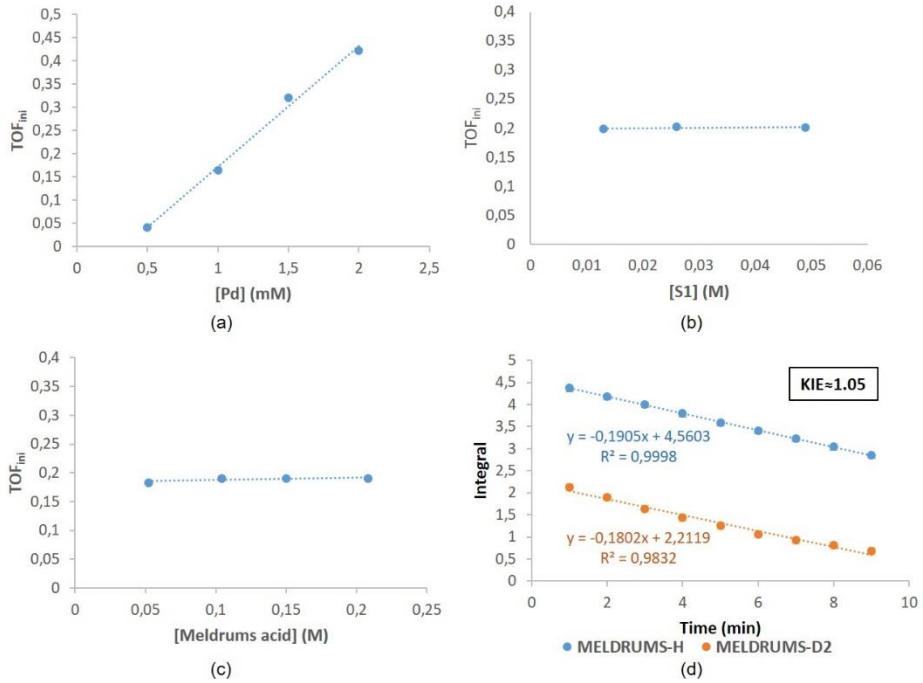
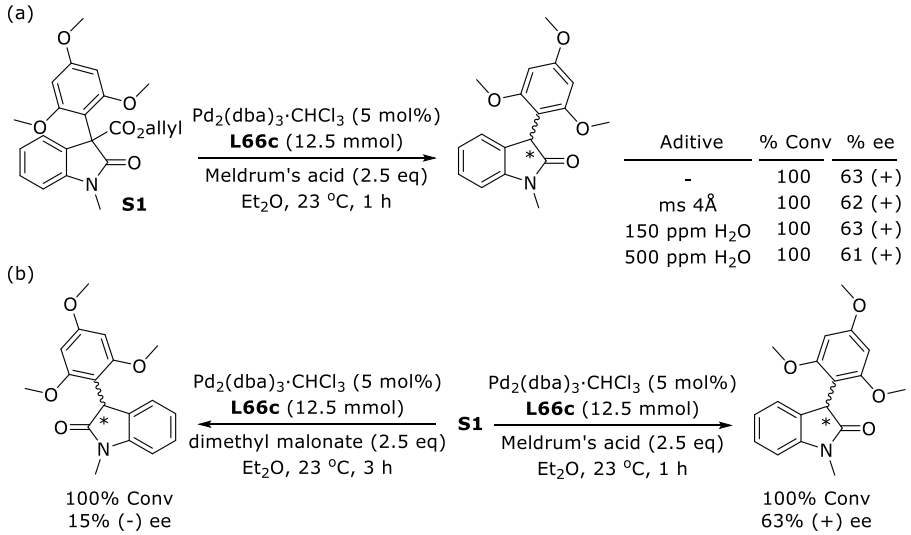


Figure 5.1.3. Kinetic and kinetic isotope effect measurements of the decarboxylative protonation of **S1** using Pd/**L66c**. (a) Plot of TOF_{ini} (measured after 5 min) versus [Pd]; (b) Plot of TOF_{ini} (measured after 5 min) versus [**S1**]; (c) Plot of TOF_{ini} (measured after 5 min) versus Meldrum's acid concentration; (d) Plots of consumption of substrate **S1** using Meldrum's acid and d_2-Meldrum's acid measured by ^{1}H NMR integral vs time.

Once the rate determining step had been well established, we moved to study the enantioselectivity-determining step – the proton transfer – by theoretical calculations. However, studying protonation by DFT is complex because there are many reaction pathways that must be considered. These included the direct transfer of the hydrogen

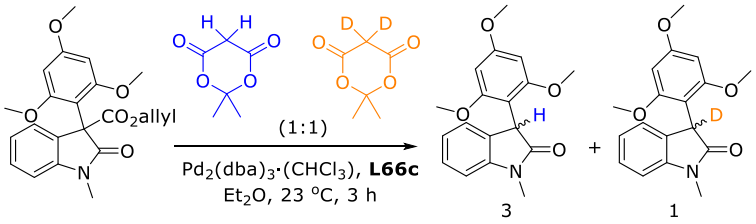
from the proton source to the enolate with or without the involvement of water molecules, or a multiple step process in which the proton source protonates the pyridine[18] followed by direct transfer of the hydrogen either to the enolate or to the Pd-center (see Figure S1 in the Supporting Information at the end of this chapter). In order to discard reaction pathways, the following tests were performed. Firstly, the involvement of water molecules in the transition states (TSs) were studied. We carried out the decarboxylative protonation of **S1** using different amounts of water (including the use of molecular sieves) (Scheme 5.1.4a). The same enantioselectivity was obtained in all cases, which allows us to discard the involvement of water in the TSs. We then studied the effect of the proton source on enantioselectivity by replacing Meldrum's acid with dimethyl malonate, leading to 63% ee (+) using Meldrum's acid and a 15% ee (-) using dimethyl malonate) (Scheme 5.1.4b).



Scheme 5.1.4. Decarboxylative protonation of **S1** using (a) different amounts of water and (b) different proton sources.

This experiment indicated that the type of proton source is important in the enantioselectivity determining step and therefore excluded the possibility of a multistep process in which the proton source transfers the proton to the Pd-intermediate prior to the protonation of the enolate. Both experiments agreed with an outer-sphere protonation mechanism in which the Meldrum's acid directly protonates the prochiral enolate formed after the decarboxylation of the allyl β-amido ester (Scheme 5.1.3). In preliminary experiments in the asymmetric decarboxylative protonation using the (*S*)-^{t}BuPHOX ligand and our model substrate **S1**, we have also investigated a series of proton sources – cyclopentanone ethyl ester, phenyl sulfonyl acetone, and formic acid - all proton sources originally screened by Stoltz.[9b] However, these afforded very low

levels of enantioselectivity (6-13% ee). In addition, the employment of acetic acid did not lead to any conversion, highlighting the need, not just for a proton source, but also a reagent that can successfully sequester the allyl unit from palladium. In this case, Meldrum's acid has proven optimal on both counts.



Scheme 5.1.5. Competitive decarboxylative protonation of **S1** in the presence of a 1:1 mixture of Meldrum's acid and d_2-Meldrum's acid.

Finally, to study whether the proton transfer is reversible or irreversible, we carried out the decarboxylative protonation of **S1** in a 1:1 mixture of Meldrum's acid and d_2-Meldrum's acid (Scheme 5.1.5). This time a significant KIE was observed (KIE≈ 3), indicating that the protonation is irreversible.[19]

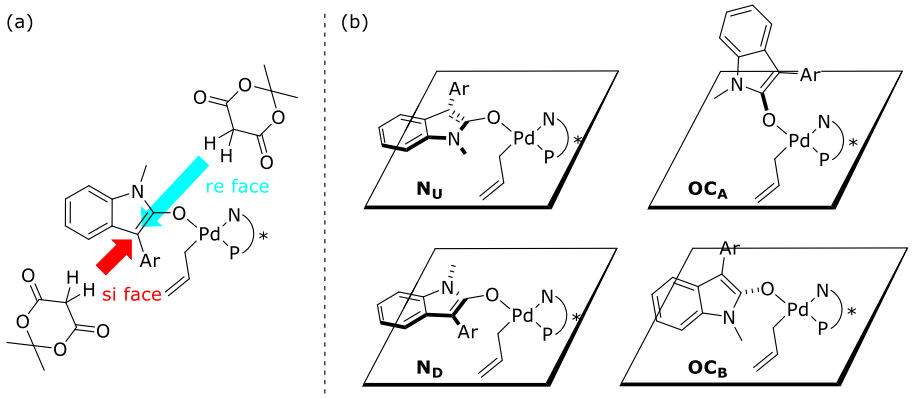
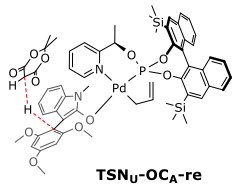
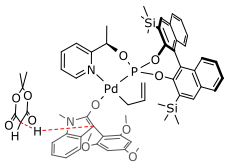
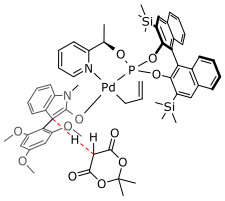
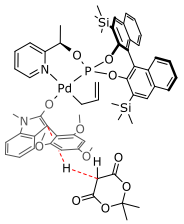
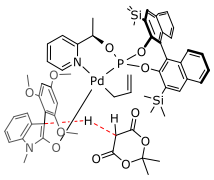
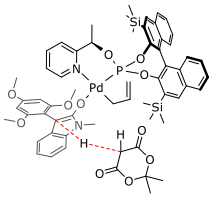
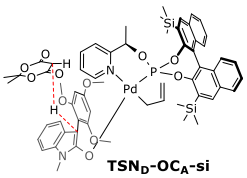
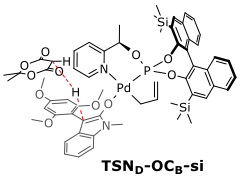


Figure 5.1.4. (a) Representation of the protonation (through either the *re*- and *si*-faces) to the Pd-enolates *trans* to the phosphite moiety; (b) Representation of the different relative dispositions of the enolate took into account in the TSs calculations.

Taking into consideration these conclusions about the nature of the TS a computational study of the TSs arising from the outer-sphere protonation mechanism was performed in an attempt to explain the enantioselectivity achieved in the Pd-decarboxylative protonation of **S1** using Pd/**L66c**. Only the TSs derived from the Pd-enolates *trans* to the phosphite moiety were calculated (Figure 5.1.4a), since it has been shown that o-allyl complexes with anionic ligands prefer the anion to be *trans* to P than to N.[20]

Table 5.1.3 shows the calculated energies of all the TSs. These TSs correspond to (a) different relative dispositions of the *N*-methyl group of the enolate after coordination to Pd (pointing up (**N_U**) or down (**N_D**), Figure 5.1.4b), (b) different relative dispositions of the oxindole core of the enolate after coordination to Pd (above or below the coordination N-P-Pd-O-C plane, (**OC_A** and **OC_B** in Figure 5.1.4b)); and (c) different attack of the Meldrum's acid (through the either *re*- or *si*-faces of the Pd-enolate, Figure 5.1.4a).[21]

Table 5.1.3. Calculated energies for the transition states with substrate **S1** using Pd/**L66c**.

Transition state	Energy	Product configuration	Transition state	Energy	Product configuration
 **TSN_U-OC_A-re**	21.8 kJ/mol	(*R*)	 **TSN_U-OC_B-re**	0 kJ/mol	(*R*)
 **TSN_U-OC_A-si**	53.9 kJ/mol	(*S*)	 **TSN_U-OC_B-si**	11.4 kJ/mol	(*S*)
 **TSN_D-OC_A-re**	28.0 kJ/mol	(*R*)	 **TSN_D-OC_B-re**	30.9 kJ/mol	(*R*)
 **TSN_D-OC_A-si**	19.2 kJ/mol	(*S*)	 **TSN_D-OC_B-si**	26.5 kJ/mol	(*S*)

The results (Table 5.1.3) show that the two most stable TSs (**TSN_U-OC_B-re** and **TSN_U-OC_B-si**) arise from the proton attack on either the enantiotopic *re*-face or the enantiotopic *si*-face of the same Pd-enolate. In this Pd-enolate, the substrate is coordinated in such a way that the *N*-methyl group is pointing up and the oxazole core

is below the coordination plane. The most stable TS, **TSN$_U$-OC$_B$-re**, provides de (*R*)-product.[22]

The structure of these two most stable calculated TSs, Figure 5.1.5, indicates that the **TSN$_U$-OC$_B$-si** is destabilized due to a steric repulsion between one of the *ortho*-methoxy groups of the substrate and the *ortho*-substituent of the biaryl phosphite moiety. This unfavorable interaction is reflected in a larger dihedral angle ω(C-Pd-P-O) in **TSN$_U$-OC$_B$-re** than in **TSN$_U$-OC$_B$-si**. Thus, in **TSN$_U$-OC$_B$-si** the steric interaction pushes the biaryl phosphite moiety away leading to a lower ω dihedral angle. In the most stable TS, it is also interesting to note the close proximity of the migrating proton and the oxygen of one of the *ortho*-methoxy groups of the substrate. This suggests that the proton transfer is supported by this *ortho*-methoxy group of the substrate, and explains the lower enantioselectivity achieved when the *ortho*-methoxy groups are replaced by *ortho*-methyls (Figure 5.1.2, 70% ee for **3** vs 2% ee for **11**).

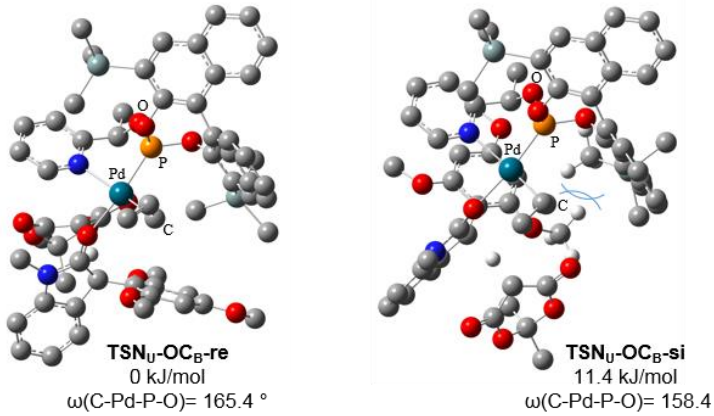


Figure 5.1.5. Most stable calculated **TSN$_U$-OC$_B$-re** and **TSN$_U$-OC$_B$-si** transition states for substrate **S1** and Meldrum's acid using ligand **L66c**. For clarity, only the hydrogens involved in the protonation are shown. For the **TSN$_U$-OC$_B$-si**, the hydrogens involved in the steric interaction are also shown. Relative free energies in solution and in kJ/mol respect to the corresponding lowest energy transition state.

The analysis of all calculated DFT structures can be reflected in a quadrant diagram that explains the stereoselectivity. In this quadrant model, the pyridine group of the ligand blocks the upper left quadrant and one of the aryls of the biaryl phosphite group partly occupies the lower right quadrant making it semi-hindered (Figure 5.1.6a). Also, the allyl ligand occupies the upper right quadrant (Figure 5.1.6a). In this way, the ligand and the allyl group impose a very sterically hindered chiral environment so that, in the most stable TSs, the oxindole core occupies the free lower left quadrant and only the aryl group slightly occupies the semi-hindered lower right quadrant (Figure 5.1.6b).

However, for the less stable TSs, in which the oxindole core is placed above the coordination plane (**TSsN$_X$-OC$_A$**), the oxindole core is forced to partially occupy the upper quadrants (Figure 5.1.6c), which causes its destabilization. This quadrant model also helps to rationalize the lack of enantiocontrol found with ligands **L66d** and **L66e** (Table 5.1.1, entries 15 and 16). These ligands contain less bulky *ortho*-substituents in the biaryl phosphite moiety than **L66c**, which results in a lower occupancy of the semi-hindered lower right quadrant. Therefore, the above mentioned steric interaction between one of the *ortho*-methoxy substituent of the substrate and the substituent of the biaryl phosphite moiety diminishes considerably and therefore the two TSs leading to opposite product enantiomers have a more similar energy.

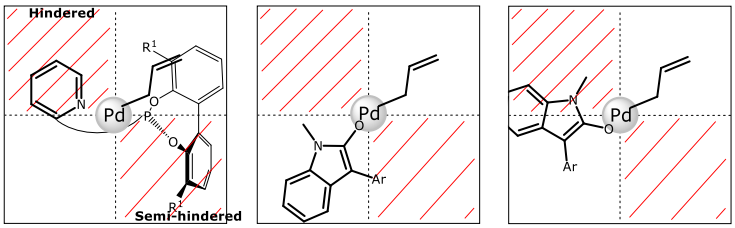


Figure 5.1.6. Quadrant diagram describing the enantioselective substrate-ligand interactions.

Finally, to study the effect of the *ortho*-substitution of the aryl moiety of the substrate in enantioselectivity, we ran analogous calculations for substrates **S4** and **S6**. The results, which can be found in the Supporting Information, indicate that again the most stable TSs for both substrates are the **TSN$_U$-OC$_B$-re** and **TSN$_U$-OC$_B$-si** (Figure 5.1.7). The results also indicate that due to the lack of the one or both *ortho*-substituents the energy difference between the two most stable TSs is smaller than for the two most stable TSs for substrate **S1** (ΔΔGcalc≈ 1.5 kJ/mol for **S4** and **S6** vs ΔΔGcalc≈ 11.4 kJ/mol for **S1**). This can be attributed to two main reasons. Firstly, the above mentioned sterically hindrance between the *ortho*-substituent and the biaryl phosphite moiety is less important and therefore the dihedral angle ω for the TSs, leading to opposite enantiomers for each substrate, are very similar. Secondly, the presence of two *ortho*-methoxy groups is needed to ensure that one methoxy group is in a good position to stabilize the proton and support its migration.

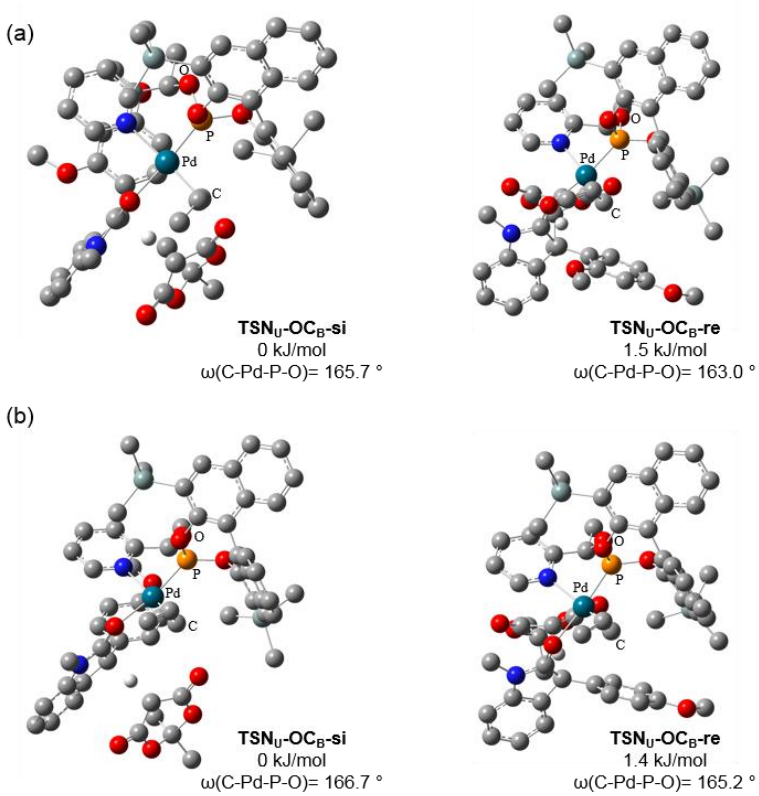


Figure 5.1.7. Most stable calculated **TSN$_U$-OC$_B$-re** and **TSN$_U$-OC$_B$-si** transition states for substrates (a) **S4** and (b) **S6** with Meldrum's acid using ligand **L66c**. All hydrogens atoms have been omitted for clarity except those involve in the protonation. Relative free energies in solution and in kJ/mol respect to the corresponding lowest energy transition state.

5.1.3. Conclusions

We have developed the first catalytic asymmetric preparation of tertiary sterically hindered α-aryl oxindoles via enantioselective Pd-catalyzed decarboxylative protonation of the corresponding α-aryl-β-amido allyl esters. The method utilizes readily accessible α-aryl-β-amido allyl esters and commercially available Meldrum's acid as the proton donor. The reaction occurs under very mild conditions and in short reaction times, providing excellent yields and promising enantioselectivities (ee's up to 78%). After the screening of three large series of phosphite-N (N= oxazoline and pyridine) ligand families we found that the best results were obtained with a readily accessible phosphite-pyridine ligand library. The introduction of an enantiopure (*S*)-biaryl phosphite moiety with bulky substituents in the *ortho*-positions played an essential role in increasing the enantioselectivity of the Pd-catalytic systems. For enantioselectivities to be high, the aryl group of the substrate must contain substituents in *ortho*- and *para*-

positions. In this study we have been therefore able to identify a readily accessible phosphite-pyridine palladium catalytic system (Pd/**L66c**) that can be used in the preparation of hindered and electronrich α-aryl oxindoles with excellent yields (up to 96%) and promising enantioselectivities (ee's up to 78%). Kinetic studies in a practical regime and KIE experiments indicated that the decarboxylation is the rate determining step. The combination of experimental investigation and theoretical studies were used to understand the nature of the selective-determining step, the proton transfer. The enantioselectivity and the effect of the ligand parameters could be rationalized in terms of a simple quadrant model.

5.1.4. Experimental Section

5.1.4.1. General considerations

All reactions were performed under an inert atmosphere of nitrogen in flame-dried glassware with magnetic stirring. All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Anhydrous methyl *tert*-butyl ether (MTBE) was dried refluxing it over sodium and benzophenone. All other solvents were obtained from dry solvent dispenser. Aryl lead triacetates ($ArPb(OAc)_3$) were synthesized according to literature procedures.[8a] α-Aryl-β-amido allyl esters **S1** and **S3**-**S11** have been synthesized and characterized following a reported procedure.[11] $Pd_2dba_3.CHCl_3$ was freshly synthesized following reported method.[23] Meldrum's acid was recrystallized from ethyl acetate before its use. Ligands **1**,[8a] **L3**-**L6**,[13a] **L62**-**L65**,[13d] **L66**-**L73**[13h] and d_2-Meldrum's acid[24] were prepared as previously described. Hydroxyl-pyridine intermediate for the preparation of ligands **L66e** was prepared following the reported procedure.[13h] Phosphorochloridite was easily prepared in one step from the corresponding binaphthol.[25] Thin layer chromatography (TLC) was performed on aluminum plates precoated with silica gel F254. They were visualized with UV-light (254 nm) fluorescence quenching, or by charring with acidic vanillin solution (vanillin, H_2SO_4 in ethanol). $[\alpha]_D^{20}$ values have been determined using PE MC240 apparatus with a sodium (Na) lamp at 589 nm. ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H, ^{13}C, and ^{31}P assignments were made on the basis of ^1H-^1H gCOSY, ^1H-^{13}C gHSQC, and ^1H-^{31}P gHMBC experiments.

5.1.4.2. Preparation of allyl 1-methyl-2-oxo-3-(2',4',6'-triethoxyphenyl)-indoline-3-carboxylate S2

(2,4,6-Triethoxyphenyl)lead triacetate. To a stirred solution of lead (IV) tetraacetate (2 g, 4.50 mmol) in anhydrous $CHCl_3$ (0.3 M) at room temperature was

added, dropwise over 15 min, arene (2.55 g, 12.15 mmol) in anhydrous $CHCl_3$ (3 M). The reaction mixture was stirred for 18 h. Then water was added (2 x 100 mL) and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (3 x 50 mL) and the combined organic layers were filtered through Celite. The organic phase concentrated and added dropwise to pentane (500 mL) wherein the aryllead triacetate precipitated out. Yield: 3.56 g (50%) as bright yellow crystalline solid. ^{1}H NMR ($CDCl_3$): δ= 1.39 (m, 9H, CH_3, OEt), 2.05 (s, 9H, CH_3, OAc), 3.99 (q, 2H, CH_2, OEt, $^3J_{H-H}$= 5.6 Hz), 4.02 (q, 4H, CH_2, OEt, $^3J_{H-H}$= 6.8 Hz), 6.18 (s, 2H, CH=, $^4J_{H-Pb}$= 84.8 Hz). ^{13}C NMR ($CDCl_3$): δ= 14.3 (CH_3, OEt), 14.6 (CH_3, OEt), 20.4 (CH_3, OAc), 64.0 (CH_2, OEt), 64.8 (CH_2, OEt), 92.9 (CH=, $^3J_{C-Pb}$= 43.2 Hz), 159.5 (C), 163.9 (C), 179.0 (C-Pb). TOF-HRMS (ESI+): m/z = 595.1421, calcd. for $C_{18}H_{26}O_9Pb$ $[M+H]^+$: 595.1418.

Allyl 1-methyl-2-oxo-3-(2',4',6'-triethoxyphenyl)indoline-3-carboxylate S2: To a flame dried Schlenk flask was added LDA (1.1 equiv.) in THF (20 mL g^{-1} of starting material) and the mixture was cooled to −78 °C. *N*-Methyl-oxindole (1 equiv.) was added and the reaction was stirred for 1 h. To the solution was added allyl chloroformate (1.1 equiv., 1.134 g mL^{-1}) and the reaction was warmed to −55 °C. After stirring for 12 h, chloroform (5 mL), pyridine (3.3 equiv.) and $ArPb(OAc)_3$ (0.9 equiv.) were added and the reaction was brought to 40 °C for a further 18 h. The reaction mixture was stirred in 6% H_2SO_4 (50 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were filtered through Celite. The organic layer was reduced *in vacuo* and the product was purified by silica gel flash column chromatography. Yield: 850.6 mg (80%) as yellowish solid. ^{1}H NMR (DMSO d^6, 100 ºC): δ= 1.14 (b, 6H, CH_3, OEt), 1.30 (t, 3H, CH_3, OEt, $^3J_{H-H}$= 8.0 Hz), 3.16 (s, 3H, NCH_3), 3.90 (b, 4H, CH_2, OEt), 4.04 (q, 1H, CH_2, OEt, $^3J_{H-H}$= 8.0 Hz), 4.53 (m, 2H, CH_2allyl), 5.11 (m, 2H, CH_2allyl), 5.80 (m, 1H, CHallyl), 6.18 (s, 2H, CH=), 6.93 (m, 2H, CH=), 7.21 (m, 2H, CH=). ^{13}C NMR (DMSO d^6, 100 ºC): δ= 14.7 (CH_3, OEt), 14.9 (CH_3, OEt), 26.9 (CH_3, NCH_3), 60.0 (C), 63.9 (CH_2, OEt), 64.5 (CH_2, OEt), 65.5 (CH_2, OEt), 93.9 (CH=), 94.0 (CH=), 108.0 (CH=), 108.5 (C), 117.3 (CH=), 122.3 (CH=), 124.9 (CH=), 128.4 (CH=), 130.4 (CH=), 132.8 (CH=), 144.2 (C), 158.3 (C), 160.127 (C), 168.3 (C=O), 172.3 (C=O). TOF-HRMS (ESI+): m/z = 440.2073, calcd. for $C_{25}H_{30}NO_6$ $[M+H]^+$: 440.2069.

5.1.4.3. Preparation of phosphite-pyridine ligand L66e

The corresponding phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL), and pyridine (0.19 mL, 2.3 mmol) was added. The corresponding hydroxyl-pyridine compound (1 mmol) was dried azeotropically with toluene (3 x 2 mL) and then dissolved in toluene (5 mL) to which pyridine (0.19 mL, 2.3 mmol) was added. The phosphorochloridite solution was transferred slowly at room temperature to the solution of hydroxyl-pyridine. Reaction was left at 80 ºC for 90 min. Pyridine salts were

removed through filtration. Evaporation of the solvent gave white foam, which was purified by using flash chromatography under argon in dry alumina (toluene:hexane: NEt_3, 5:5:0,1) to produce the corresponding ligand as a white solid. Yield: 345.9 mg (56%). ^{31}P NMR (C_6D_6): δ= 136.8 ppm (s). ^1H NMR (C_6D_6): δ= 1.10-1.30 (m, 6H, CH_2), 1.38 (s, 9H, CH_3, ^tBu), 1.45 (d, 3H, CH_3, $^3J_{H-H}$= 6.7 Hz), 1.57 (s, 9H, CH_3, ^tBu), 2.10-2.60 (m, 10H, CH_2), 5.35 (m, 1H, CH-O), 6.54 (m, 1H, CH=), 6.90-7.21 (m, 4H, CH=), 8.30 (m, 1H, CH=). ^{13}C NMR (C_6D_6): δ= 22.7 (CH_2), 22.9 (CH_2), 23.1 (CH_2), 23.2 (CH_2), 23.6 (CH_3), 27.2 (CH_2), 27.5 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 30.8 (CH_3, ^tBu), 31.0 (CH_3, ^tBu), 34.3 (C, ^tBu), 34.6 (C, ^tBu), 75.7 (d, CH-O, $^2J_{C-P}$= 9.3 Hz), 119.7-162.9 (aromatic carbons). MS HR-ESI [found 557.3062, $C_{35}H_{44}NO_3P$ $(M)^+$ requires 557.3059].

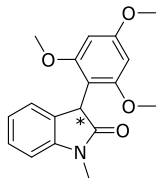
5.1.4.4. General procedure for the preparation of racemic protonated compounds (3-13)

$Pd(OAc)_2$ (0.0063 mmol) and 1,2-bis(diphenylphosphino)ethane (dppe) (0.0078 mmol) were added to a flame dried Schlenk flask and dry 1,4-dioxane (1.5 ml) were added. The suspension was stirred at 40 ºC for 90 min and formic acid (0.37 mmol) was added followed immediately by a solution of the corresponding substrate (0.063 mmol) in 1,4-dioxane (1.5 ml). The reaction mixture was stirred at 40 ºC for 10 h, cooled to room temperature and solvent was removed under vacuum and the resulting residue was purified by silica gel column chromatography (pentane:EtOAc) to afford the corresponding α-aryl oxindole.

5.1.4.5. General procedure for enantioenriched protonated compounds (3-13)

$Pd_2(dba)_3{\cdot}CHCl_3$ (0.0125 mmol, 6.6 mg), phosphite-pyridine **L66c** (0.016 mmol, 9 mg), substrate (0.125 mmol), Meldrum's acid (2.5 eq, 0.31 mmol, 42.4 mg) were added to a flame dried Schlenk flask and dry methyl *tert*-buthyl ether (MTBE) (for **S1**, **S3**-**S10**) or diethyl ether (for **S2** and **S11**) (5 ml) were added. The suspension was stirred at room temperature for 3 hours. The solvent was removed under vacuum and the resulting residue was purified by silica gel column chromatography (pentane: EtOAc), to achieve the corresponding product.

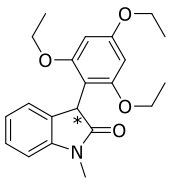
1-Methyl-3-(2',4',6'-trimethoxyphenyl)indolin-2-one (3). Yield: 36.4 mg (93%) as yellowish solid. $[\alpha]_D^{20}$: +24.4º (*c* 0.82 in CH_2Cl_2) for 70% *ee*). Enantiomeric excess determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 70:30 $scCO_2$:MeOH; λ= 254.0 nm). tr (+): 1.71 min (major), tr (-): 2.29 min (minor). ^1H NMR ($CDCl_3$): δ= 3.32 (s, 3H, NCH_3), 3.41 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.08 (s, 1H, CH), 6.03 (d, 1H, CH=, $^4J_{H-H}$= 2.6 Hz), 6.21 (d, 1H, CH=,



3

$^4J_{H-H}$= 2.6 Hz), 6.8 (d, 1H, CH=, $^3J_{H-H}$= 10.5 Hz), 6.95 (m, 2H, CH=), 7.2 (t, 1H, CH=, $^3J_{H-H}$= 10.6 Hz). ^{13}C NMR ($CDCl_3$): δ= 26.1 (CH_3, NCH_3), 42.0 (CH), 55.2 (CH_3, OCH_3), 56.1 (CH_3, OCH3), 91.1 (CH=), 92.0 (CH=), 106.8 (C), 107.1 (CH=), 122.0 (CH=), 123.1 (CH=), 127.1 (CH=), 130.2 (C), 144.2 (C), 158.3 (C), 159.1 (C), 160.3 (C), 178.0 (C=O). TOF-HRMS (ESI+): m/z = 314.1389, calcd. for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1392.

1-Methyl-3-(2′,4′,6′-triethoxyphenyl)indolin-2-one (4). Yield: 40.4 mg (91%) as white solid ($[\alpha]_D^{20}$: +30.0º (*c* 0.98 in CH_2Cl_2) for 68% *ee*). Enantiomeric excess determined by SFC using Chiralpack IA column (flow: 3 ml/min, 90:10 $scCO_2$:MeOH; λ= 254.0 nm). tr (-): 1.55 min (minor), tr (+): 2.42 min (major). ^{1}H NMR ($CDCl_3$): δ= 0.89 (t, 3H, CH_3, OEt, $^3J_{H-H}$= 6.8 Hz), 1.38 (t, 3H, CH3, OEt, $^3J_{H-H}$= 7.2 Hz), 1.41 (t, 3H, CH_3, OEt, $^3J_{H-H}$= 7.2 Hz), 3.26 (s, 3H, NCH_3), 3.56 (m, 1H, CH_2, OEt), 3.78 (m, 1H, CH_2, OEt), 4.05 (m, 2H, CH_2, OEt), 4.11 (m, 2H, CH_2, OEt), 5.12 (s, 1H, CH), 5.97 (d, 1H, CH=, $^4J_{H-H}$= 2.0 Hz), 6.18 (d, 1H, CH=, $^4J_{H-H}$= 2.4 Hz), 6.80 (d, 1H, CH=, $^3J_{H-H}$= 7.2 Hz), 6.95 (m, 2H, CH=), 7.22 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 14.2 (CH_3, OEt), 14.8 (CH_3, OEt), 14.9 (CH_3, OEt), 26.2 (CH_3, NCH_3), 42.1 (CH), 63.4 (CH_2, OEt), 64.2 (CH_2, OEt), 92.0 (CH=), 92.2 (CH=), 107.0 (CH=), 121.8 (C), 123.2 (CH=), 127.0 (CH=), 130.5 (C), 144.6 (C), 158.0 (C), 158.7 (C), 159.9 (C), 178.0 (C=O). TOF-HRMS (ESI+): m/z = 356.1862, calcd. for $C_{21}H_{26}NO_4$ $[M+H]^+$: 356.1860.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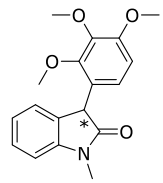
1-Methyl-3-(2′,3′,4′-trimethoxyphenyl)indolin-2-one (5). Yield: 31.3 mg (80%) as white solid ($[\alpha]_D^{20}$: +3.5º (*c* 0.77 in CH_2Cl_2) for 23% *ee*). Enantiomeric excess determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 70:30 $scCO_2$:MeOH; λ= 254.0 nm). tr (+): 2.77 min (major), tr (-): 5.85 min (minor). ^{1}H NMR ($CDCl_3$): δ= 3.28 (s, 3H, NCH_3), 3.62 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.62 (s, 1H, CH), 6.6 (d, 1H, CH=, $^3J_{H-H}$= 6.4 Hz), 6.8 (d, 1H, CH=, $^3J_{H-H}$= 6.8 Hz), 6.88 (d, 1H, CH=, $^3J_{H-H}$= 6.5 Hz), 7.0 (m, 2H, CH=), 7.24 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.1 (CH_3, NCH_3), 48.0 (CH), 56.1 (CH_3, OCH_3), 60.2 (CH_3, OCH_3), 107.4 (CH=), 107.9 (CH=), 122.4 (CH=), 124.0 (C), 124.2 (CH=), 124.4 (CH=), 128.0 (CH=), 130.1 (C), 142.1 (C), 144.2 (C), 152.3 (C), 153.9 (C), 176.2 (C=O). TOF-HRMS (ESI+): m/z = 314.1387, calcd. for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1392.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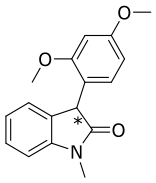
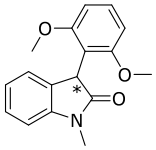
3-(2′,4′-Dimethoxyphenyl)-1-methylindolin-2-one (6). Yield: 33.3 mg (85%) as yellowish solid ($[\alpha]_D^{20}$: +2.40º (*c* 0.75 in CH_2Cl_2) for 26% *ee*). Enantiomeric excess determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 90:10 $scCO_2$:MeOH; λ= 254.0 nm). tr (+): 7.43 min (major), tr (-): 8.19 min (minor). ^{1}H NMR ($CDCl_3$): δ= 3.27 (s, 3H, NCH_3), 3.68 (s. CH_3, OCH_3), 3.80 (s, 3H, OCH_3), 4.80 (s, 1H, CH), 6.48 (m, 2H, CH=), 6.83 (d, 1H, CH=, $^3J_{H-H}$= 6.8 Hz), 6.94 (m, 2H, CH=),

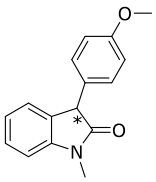

6

7.02 (m, 1H, CH=), 7.25 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.1 (CH_3, NCH_3), 47.1 (CH), 55.5 (CH_3, OCH_3), 55.8 (CH_3, OCH_3), 99.1 (CH=), 104.3 (CH=), 107.8 (CH=), 118.1 (C), 122.0 (CH=), 124.1 (CH=), 127.9 (CH=), 129.9 (C), 130.1 (CH=), 144.1 (C), 158.3 (C), 160.2 (C), 176.8 (C=O). TOF-HRMS (ESI+): m/z = 284.1282, calcd. for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1287.

3-(2′,6′-Dimethoxyphenyl)-1-methylindolin-2-one (7). Yield: 29.4 mg (83%) as white solid ($[\alpha]_D^{20}$: +14.6º (*c*= 0. 28 in CH_2Cl_2) for 46% *ee*). Enantiomeric excess determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 90:10 $scCO_2$:MeOH; λ= 254.0 nm). tr (+): 6.75 min (major), tr (-): 7.52 min (minor). ^{1}H NMR ($CDCl_3$): δ= 3.28 (s, 3H, NCH_3), 3.44 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.16 (s, 1H, CH), 6.44 (d, 1H, CH=, $^3J_{H\text{-}H}$= 6.5 Hz), 6.64 (d, 1H, CH=, $^3J_{H\text{-}H}$= 6.6 Hz), 6.82 (d, 1H, CH=, $^3J_{H\text{-}H}$ = 6.8 Hz), 6.92 (m, 2H, CH=), 7.1 (m, 2H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.0 (CH_3, NCH_3), 42.0 (CH), 56.1 (CH_3, OCH_3), 104.1 (CH=), 105.2 (CH=), 107.5 (CH=), 114.2 (C), 122.0 (CH=), 123.7 (CH=), 127.7 (CH=), 129.1 (CH=), 130.0 (C), 144.2 (C), 158.1 (C), 159.0 (C), 176.7 (C=O). TOF-HRMS (ESI+): m/z = 284.1280, calcd. for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1287.


7

3-(4′-Methoxyphenyl)-1-methylindolin-2-one (8). Yield: 30.4 mg (96%) as white solid (9% ee). Enantiomeric excess determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 70:30 $scCO_2$:MeOH; λ= 254.0 nm). tr (major): 1.79 min, tr (minor): 2.04 min. ^{1}H NMR ($CDCl_3$): δ= 3.24 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 4.57 (s, 1H, CH), 6.87 (m, 3H, CH=), 7.06 (m, 1H, CH=), 7.15 (m, 3H, CH=), 7.33 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 26.1 (CH_3, NCH_3), 51.1 (CH), 55.2 (CH_3, OCH_3), 108.0 (CH=), 114.2 (CH=), 122.5 (CH=), 124.8 (CH=), 128.0 (CH=), 128.2 (C), 129.0 (C), 129.5 (CH=), 144.2 (C), 159.0 (C), 176.0 (C=O). TOF-HRMS (ESI+): m/z = 254.1181, calcd. for $C_{16}H_{17}NO_2$ $[M+H]^+$: 254.1173.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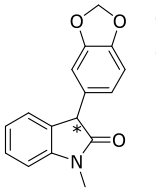
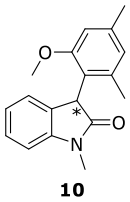
3-(Benzo[d][1,3]dioxol-5-yl)-1-methylindolin-2-one (9). Yield: 31.7 mg (95%) as yellowish solid (1% ee). Enantiomeric excess determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 70:30 $scCO_2$:MeOH; λ= 254.0 nm). tr (major): 1.88 min, tr (minor): 2.07 min. ^{1}H NMR ($CDCl_3$): δ= 3.26 (s, 3H, NCH_3), 4.51 (s, 1H, CH), 5.91 (s, 2H, CH_2), 6.60 (s, 1H, CH=), 6.69 (m, 1H, CH=), 6.76 (m, 1H, CH=), 6.87 (d, 1H, CH=, $^3J_{H\text{-}H}$= 6.4 Hz), 7.08 (t, 1H, CH=, $^3J_{H\text{-}H}$= 6.5 Hz), 7.18 (d, 1H, CH=, $^3J_{H\text{-}H}$= 6.6 Hz), 7.35 (t, 1H, CH=, $^3J_{H\text{-}H}$= 6.7 Hz). ^{13}C NMR ($CDCl_3$): δ= 26.1 (CH_3, NCH_3), 51.5 (CH), 101.2 (CH_2), 108.0 (CH=), 108.2 (CH=), 122.0 (CH=), 122.8 (CH=), 124.8 (CH=), 128.3 (CH=), 128.5 (C), 130.0 (C), 144.2 (C), 147.1 (C), 148.0 (C), 176.0 (C=O). TOF-HRMS (ESI+): m/z = 268.0967, calcd. for $C_{16}H_{14}NO_3$ $[M+H]^+$: 268.0974.


9

3-(2'-Methoxy-4',6'-dimethylphenyl)-1-methylindolin-2-one (10). Yield: 30.6 mg (87%) as white solid (7% ee). Enantiomeric excess determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 85:15 $scCO_2$:MeOH; λ= 210.0 nm). tr (major): 2.78 min, tr (minor): 3.17 min. ^{1}H NMR ($CDCl_3$): δ= 1.62 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.31 (s, 3H, NCH_3), 3.68 (s, 3H, OCH_3), 4.67 (s, 1H, CH), 6.41 (s, 1H, CH=), 6.72 (s, 1H, CH=), 6.83 (m, 2H, CH=), 6.93 (m, 2H, CH=). ^{13}C NMR ($CDCl_3$): δ= 20.3 (CH_3), 21.6 (CH_3), 26.1 (CH_3, NCH_3), 46.2 (CH), 56.0 (CH_3, OCH_3), 107.6 (CH=), 109.7 (C), 111.1 (CH=), 122.0 (CH=), 122.2 (C), 122.8 (CH=), 123.6 (CH=), 124.2 (C), 127.5 (CH=), 138.1 (CH=), 144.1 (C), 157.3 (C), 177.8 (C=O). TOF-HRMS (ESI+): m/z = 284.1280, calcd. for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1287.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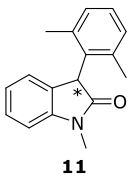
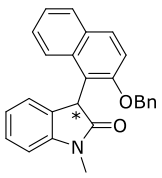
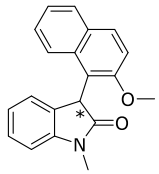
3-(2',6'-Dimethylphenyl)-1-methylindolin-2-one (11). Yield: 29.2 mg (93%) as white solid (2% ee). Enantiomeric excess determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 90:10 $scCO_2$:MeOH; λ= 254.0 nm). tr (major): 3.02 min, tr (minor): 4.31 min. ^{1}H NMR ($CDCl_3$): δ= 1.64 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.32 (s, 3H, NCH_3), 5.05 (s, 1H, CH), 6.9 (m, 3H, CH=), 6.97 (m, 1H, CH=), 7.12 (m, 2H, CH=), 7.30 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$): δ= 18.6 (CH_3), 21.8 (CH_3), 26.2 (CH_3, NCH_3), 48.1 (CH), 107.9 (CH=), 122.5 (CH=), 122.8 (CH=), 127.8 (CH=), 127.9 (CH=), 128.1 (CH=), 128.2 (CH=), 128.3 (C), 129.5 (CH=), 133.5 (C), 137.2 (C), 138.0 (C), 142.0 (C), 176.1 (C=O). TOF-HRMS (ESI+): m/z = 252.1385, calcd. for $C_{17}H_{19}NO$ $[M+H]^+$: 252.1388.


11

1-Methyl-3-(2'-phenoxynaphthalen-1-yl)indolin-2-one (12). Yield: 33.2 mg (70%) as yellowish solid ($[\alpha]_D^{20}$: +47.5º (*c*= 0.61 in CH_2Cl_2) for 28% ee). Enantiomeric excess determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 70:30 $scCO_2$:MeOH; λ= 254.0 nm). tr (+): 2.9 min (major), tr (-): 3.23 min (minor). ^{1}H NMR ($CDCl_3$): δ= 2.68 (s, 3H, NCH_3), 4.80 (d, 1H, CH_2, $^2J_{H-H}$= 11.4 Hz) 4.85 (d, 1H, CH_2, $^2J_{H-H}$= 11.4 Hz), 5.29 (s, 1H, CH), 6.61 (d, 1H, CH=, $^3J_{H-H}$= 6.4 Hz), 6.92 (m, 4H, CH=), 7.27 (m, 6H, CH=), 7.43 (m, 1H, CH=), 7.61 (m, 1H, CH=), 7.85 (m, 1H, CH=), 8.15 (d, 1H, CH=, $^3J_{H-H}$= 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ= 25.6 (CH_3, NCH_3), 44.6 (CH), 70.7 (CH_2), 107.8 (CH=), 114.1 (CH=), 118.9 (C), 121.9 (CH=), 122.3 (CH=), 123.2 (CH=), 123.6 (CH=), 127.3 (CH=), 127.9 (C), 128.3 (CH=), 128.5 (C), 128.6 (CH=), 128.8 (CH=), 129.4 (CH=), 129.5 (CH=), 129.6 (CH=). 134.1 (C), 136.2 (C), 144.6 (C), 153.8 (C), 177.1 (C=O). TOF-HRMS (ESI+): m/z = 380.1651, calcd. for $C_{26}H_{22}NO_2$ $[M+H]^+$: 380.1638.


12

3-(2'-Methoxynaphthalen-1-yl)-1-methylindolin-2-one (13). Yield: 30.3 mg (80%) as white solid ($[\alpha]_D^{20}$: +25.2º (*c*= 0.61 in CH_2Cl_2) for 15% ee). Enantiomeric excess determined by SFC using Chiralcel IC-3 column (flow: 3 ml/min, 90:10 $scCO_2$:MeOH; λ= 254.0 nm). tr (+): 9.63 min (major), tr (-): 11.36 min (minor). ^{1}H NMR ($CDCl_3$): δ= 3.37 (s, 3H, NCH_3), 3.61 (s, 3H, OCH_3), 5.28 (s, 1H, CH), 6.90 (m, 3H, CH=), 7.21 (m, 2H, CH=), 7.42 (m, 1H, CH=), 7.58 (m, 1H, CH=), 7.85 (m, 2H, CH=), 8.15 (d, 1H, CH=, $^3J_{H-H}$= 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ= 26.6 (CH_3, NCH_3), 44.5 (CH), 57.2 (CH_3), 107.5 (CH=), 114.6 (CH=), 122.1 (CH=), 122.4 (CH=), 122.6 (C), 122.8 (C), 123.4 (CH=), 122.3 (CH=), 123.7 (CH=), 126.9 (C), 127.7 (CH=), 128.6 (C), 129.6 (CH=), 130.1 (CH=). 133.9 (C), 154.7 (C), 177.0 (C=O). TOF-HRMS (ESI+): m/z = 303.1259, calcd. for $C_{20}H_{18}NO_2$ $[M+H]^+$: 303.1265.



13

5.1.4.6. Procedure for kinetic experiments

In a flame-dried Schlenk tube, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0019 mmol, 2.0 mg), phosphite-pyridine **L66c** (0.0049 mmol, 2.8 mg), substrate **S1** (25 mg, 0.0630 mmol), Meldrum's acid (2.5 eq, 0.1575 mmol, 22.7 mg) and hexamethylbenzene (1.7 mg, 0.0105 mmol) as internal standard were placed. Dry C_6D_6 (3 mL) was added and 0.7 mL of this mixture were rapidly transferred to a NMR tube with a septum cap, immediately before recording the NMR. Previously, the NMR tube was placed under vacuum and backfilled with N_2 (x3). The reaction was followed by recording the ^{1}H-NMR spectrum with a 1 min interval.

5.1.4.7. Computational details

The geometries of all transition states were optimized employing B3LYP[26] functional including a D3 empirical dispersion correction as implemented in Gaussian 09 program.[27] LANL2DZ[28] basis set were used for palladium and the 6-31G* basis set for all other elements.[29] Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for diethylether.[30] The energies were further refined by performing single-point calculations using the parameters mentioned before, with the exception that the 6-311+G**[31] basis set was used for all elements except palladium. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported}=G_{6\text{-}31G^*} + (E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*})$.

5.1.5. Acknowledgements

We gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P), European Regional Development Fund

(AEI/FEDER, UE), the Catalan Government (2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D.) M.M. thanks to MINECO for fellowship. M.J. acknowledges the financial support for his PhD programme received from Molecular Medicine Ireland as part of the Clinical & Translational Research Scholars Programme (CTRSP), funded under the Programme for Research in Third Level Insititutions (PRTLI) Cycle 5, and co-funded under the European Regional Development Fund (ERDF).

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[14] Disappointingly, the application of other successful ligands for Pd-decarboxylative reactions, such as the (*R*,*R*)-ANDEN-phenyl Trost and (*R*,*R*)-DACH-phenyl Trost ligands, provided the desired product in racemic form.

[15] Similar behavior has been reported previously in the Pd-catalyzed decarboxylative protonation of α-aryl-β-keto allyl esters, for which the enantioselectivity also decreases for substrates lacking *ortho*-methoxy substituents, see Ref 8a.

[16] On the other hand, based on experimental results, Guiry has proposed that in the key Pd-enolate intermediate using ligand **1**, the preferential attack of the proton electrophile thorugh one of the enolate faces is controlled by both the oxazoline substituent and the presence of the *ortho*-substituents in the aryl group, see Ref 8a.

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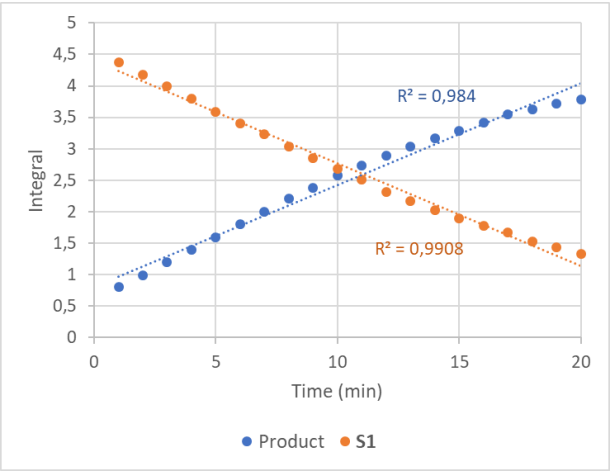
5.1.7. Supporting Information

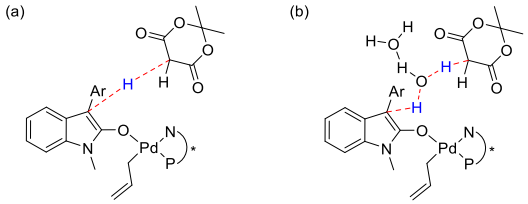
5.1.7.1. Plot of consumption of substrate S1 and product formation measured by NMR



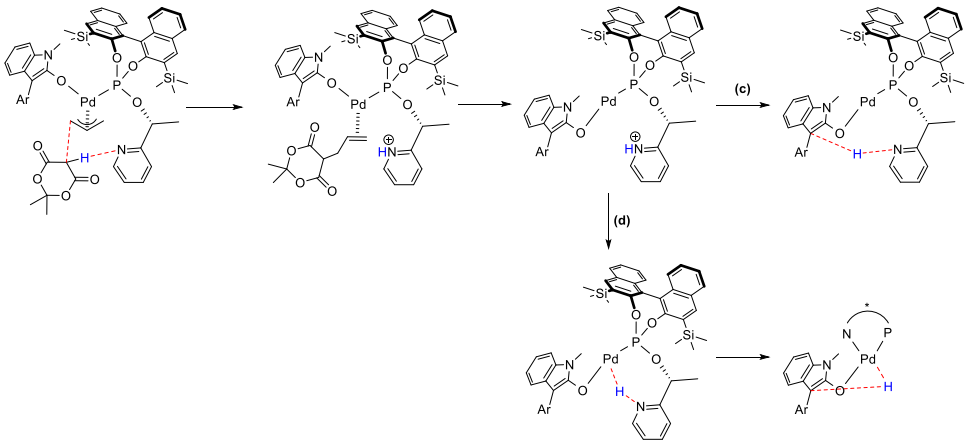
Although the R^2 value for the plots of the product formation (blue) and substrate consumption (red) over time are in good agreement with a zero-order fit, they look curved by the end of the reaction. A possible explanation for this is that CO_2 pressure is building up in the sealed NMR tube during the reaction, which slows down the reaction at high CO_2 concentrations. To provide further proof for the zero zero-order dependence on substrate concentration, we studied the initial rate (TOF_{ini}) of product formation at different substrate concentrations (see Figure 5.1.3b of the manuscript). The results indicate that the TOF_{ini} is independent on the substrate concentration, which confirms the zero-order in [**S1**].

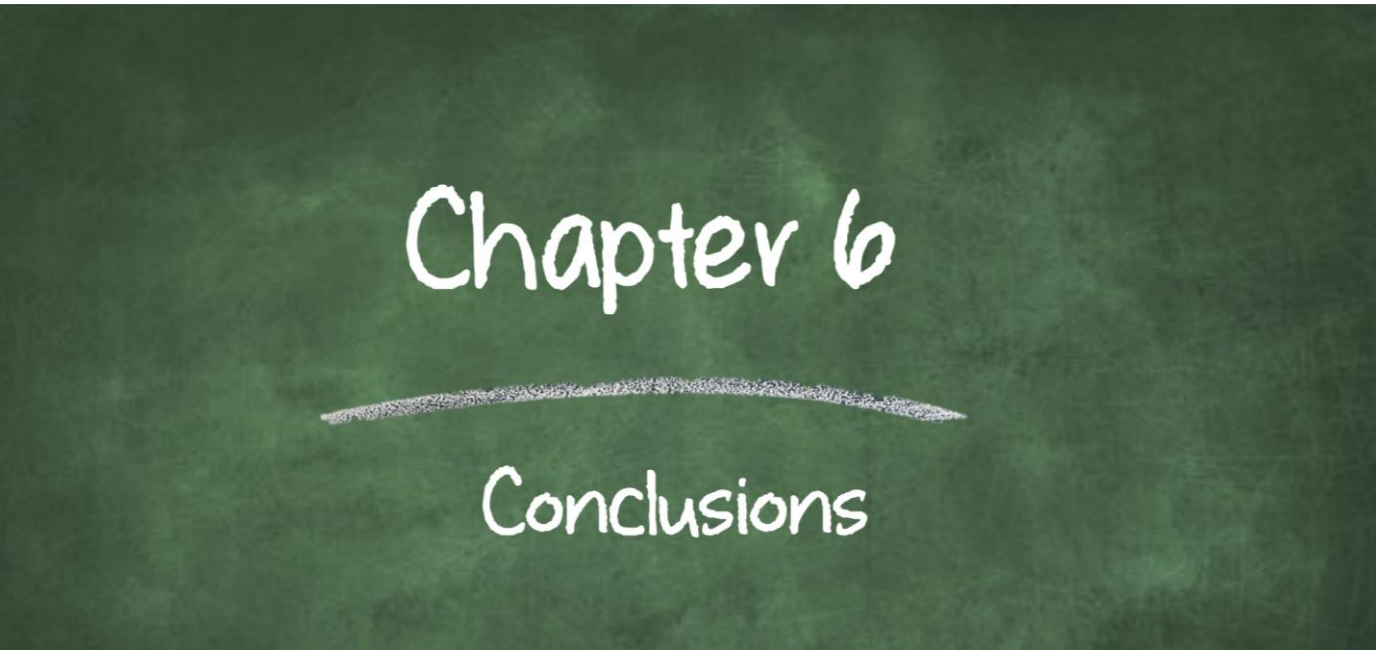
5.1.7.2. Figure S1. Possible pathways for the proton transfer

- Direct transfer of the hydrogen from the proton source to the enolate (a) with or (b) without the involvement of water molecules



- Multiple step process in which the proton source protonates the pyridine followed by direct transfer of the hydrogen either (c) to the enolate or (d) to the Pd-center




Chapter 6
Conclusions

UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull

6. Conclusions

1. Chapter 3. *Asymmetric hydrogenation of olefins*. The conclusions of this chapter can be summarized as follows:

Twelve different phosphorus-containing ligand libraries have been successfully synthesized and applied to Rh- and Ir-catalyzed asymmetric hydrogenation of functionalized and minimally functionalized olefins.

- In Section 3.1, we have successfully synthetized and applied an Ir-phosphoroamidite-oxazoline/thiazole catalysts library in the hydrogenation of a wide range of minimally functionalized olefins, including *E*- and *Z*-tri- and disubstituted substrates, with examples containing poorly coordinative neighboring polar groups (ee's up to 99%). These catalyst precursors were derived from previous successful generation of Ir-bicyclic *N*-phosphane-oxazoline/thiazole catalysts, by replacing the *N*-phosphane group of the ligand with a π-acceptor biaryl phosphoroamidite moiety. We demonstrated that the introduction of phosphoroamidite moiety in the ligand design extended the range of olefins that could be successfully hydrogenated. Moreover, compared to their analogous, the new ligands have an additional advantage because they are solid and air stable.

- In Section 3.2, we have identified readily accessible Ir- and Rh-phosphite-oxazoline PHOX-based catalytic systems that can successfully hydrogenate, for the first time, a broad range of minimally functionalized and functionalized olefins (62 examples in total with ee's up to >99%). Moreover, the new Ir- and Rh-catalyst precursors maintain their enantioselectivities when environmentally friendly propylene carbonate is used as solvent. These ligands showed to be superior to the privileged analogous phosphine-oxazoline ligands (PHOX), due to they improved the enantioselectivities achieved for challenging minimally functionalized *Z*-olefins, 1,1'-disubstituted olefins with poorly coordinative groups and cyclic β-enamides. Remarkably, in all cases both enantiomers of the hydrogenated product could be obtained, either by changing the configuration of the biaryl phosphite moiety (for minimally functionalized olefins) or by simply changing the metal from Ir to Rh (for cylic β-enamides). Another advantage of the new ligands over the PHOX ligands is that the best ligands are derived from affordable (*S*)-phenylglycinol rather than from expensive (*S*)-*tert*-leucinol.

- In Section 3.3, we have presented a family of air stable Ir/P-oxazoline catalysts which has been synthesized in a few steps from inexpensive starting materials. They differ from previous PHOX-based phosphite-oxazoline ligands (Section 3.2) in the presence of a chiral alkyl chain instead of the flat *ortho*-phenylene tether. The right choice of either a phosphite group or phosphinite group gives the first catalytic family

that is able to successfully hydrogenate di-, tri- and tetrasubstituted minimally functionalized olefins, the challenging 1,2-dihydro-naphthalene and also a range of the most elusive acyclic olefins with unprecedented enantioselectivities under mild reaction conditions (ee's up to 99%). The catalysts could tolerate different functional groups very well and in addition an unprecedented high tolerance to the geometry and steric constrains of the olefin. Thus, a broad range of olefins containing both minimally coordinative groups (e.g. α,β-unsaturated carboxylic esters, enones, lactams, vinyl boronates and enol phosphinates) and coordinative groups (the challenging β-enamides) could be hydrogenated with high asymmetric induction.

- In Section 3.4, we successfully carried out the inclusion of a modified phosphite-oxazoline ligand and its corresponding Ir-catalyst precursor [Ir(L)(acac)] in a supramolecular metallocage. High binding constant was extracted from the entrapped free phosphite-oxazoline ligand in the nanocage, thus we can conclude that the *meta*-pyridine groups of the biaryl phosphite moiety interact with Zn-porphyrins building blocks of the supramolecular metallocage in a ditopic fashion. In the near future, this entrapped catalyst precursor will be further applied in the asymmetric hydrogenation of minimally functionalized olefins.

- In Section 3.5, an Ir/P-stereogenic P,N-catalyst library (Ir-MaxPHOX) with a simple modular architecture was successfully applied in the asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins. These air stable Ir-MaxPHOX catalysts can be easily prepared in a few steps from readily available sources. They are able to efficiently reduce several indenes and also a range of more acyclic olefins with high enantioselectivities up to 99% ee under mild reaction conditions. In addition, the reactions could be performed at low pressure with no loss of catalytic performance. The preliminary results in the application of asymmetric hydrogenation of α,β-unsaturated esters shows enantioselectivities up to >99% ee.

- In Section 3.6, a new family of Ir-catalyst precursors, that combine the robustness of the sulfoximine group with the flexibility and modularity of the biaryl phosphite moiety, was synthetized in five steps. We presented their preliminary results in the asymmetric hydrogenation of a wide range of minimally functionalized olefins. These new catalyst precursors provided high levels of enantiocontrol in the hydrogenation trisubstituted α,β-unsaturated enones (ee's up to 97%), surpassing the results achieved using previously described phosphine-sulfoximine analogues. In addition, this high catalytic performance was also extended to other relevant substrates such as trisubstituted α,β-unsaturated esters and δ-lactams (ee's up to 97%) and in the reduction of a trisubstituted alkenyl boronic ester (>99% ee).

- In Section 3.7, we successfully synthetized novel chelating TADDOL-based cationic phosphonite-pyridine ligands. The formation of these ligands has been confirmed by ^{31}P, ^{1}H and ^{13}C NMR and HRMS-ESI. The unique electronic characteristic of these ligand architecture lead us to think that they can be optimal ligands for a future application in the enantioselective Ir-hydrogenation of minimally functionalized olefins.

- In Section 3.8, we present one of our first thioether containing ligand family. In this context, we have synthetized and applied a family of ferrocene-based P,S-ligands in the asymmetric hydrogenation of minimally functionalized olefins. By carefully selecting the ligand parameters, these Ir-catalyst precursors provided excellent enantioselectivities in the reduction of model trisubstituted α,β-unsaturated esters and di- and trisubstituted enol phosphinates (ee's up to 99%). Moreover, good enantioselectivities have been achieved for challenging cyclic enones and alkenes bearing benzyl amide and δ-lactone groups (ee's up to 90%).

- In Section 3.9, we have successfully reported the Ir-hydrogenation of 40 minimally functionalized olefins with Ir-phosphite/phosphinite-thioether catalysts, which are synthesized in only two steps from commercially accessible cyclohexene oxide. These ligands provided enantioselectivities up to 99% ee in a variety of olefins, including examples with poorly coordinative groups. Interestingly, these catalysts showed to be very efficient in the reduction of terminal aryl-substituted boronic esters (ee's up to 98%). Moreover, the simpler backbone of these thioether-phosphite/phosphinite ligands yields to simple NMR spectra which facilitates the identification of the catalytically competent Ir-dihydride alkene species. Therefore, by combining HP-NMR spectroscopy and theoretical studies, we found that, similarly to the classical Halpern-mechanism for asymmetric hydrogenation with Rh-catalysts, the minor intermediate, which is less stable, is converted to the major product enantiomer.

- In Section 3.10, a phosphite/phosphinite-thioether ligand library with an indene structure has been synthetized and their preliminary results in the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins and cyclic β-enamides are presented. By carefully selecting the ligand components, high enantioselectivities were achieved in a range of trisubstituted olefins with poorly coordinative polar groups (ee's up to 98%) and in the reduction of more challenging 1,1'-disusbtituted olefins and cyclic β-enamides (ee's up to 98%).

- In Section 3.11, a phosphite/phosphinite-thioether ligand family, with a very simple architecture, was successfully synthesized in only four steps from commercially available (*R*,*R*)-hydrobenzoin. Preliminary results on their application in the Ir-catalyzed hydrogenation of minimally functionalized olefins showed that both phosphorus and thioether groups have been found to be highly important for the enantioselectivity of the

process and they must be suitable selected for each substrate in order to maximize enantioselectivities. High enantioselectivities were achieved in the asymmetric hydrogenation of several *E*- and *Z*-trisubstituted and 1,1'-disubstituted olefins, including examples with poorly coordinative neighboring polar groups (ee's up to 99%). In addition, promising enantioselectivities were also obtained in the asymmetric hydrogenation of more challenging tetrasubstituted olefins (ee's up to 77%).

- In Section 3.12, we reported the synthesis and the preliminary results of the application of a new family of P*-stereogenic *N*-phosphine-phosphite ligands in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins. By suitable tuning the ligand parameters, we have been able to achieve moderate-to-high enantioselectivities in the hydrogenation of a variety of functionalized substrates, including examples of more challenging β-dehydroamino acid derivatives and β-enamides (ee's ranging from 60% to >99%).

2. Chapter 4. *Asymmetric Pd-allylic substitution reactions*. The conclusions of this chapter can be summarized as follows:

Six different families of phosphorus-containing ligands have been applied in the Pd-catalyzed enantioselective allylic substitution.

- In Section 4.1, we reported the successful application of some of previously presented PHOX-based phosphite-oxazoline ligands (see Section 3.2) in the Pd-catalyzed asymmetric allylic substitution. Improving previous results reported in the literature, we have been able to largely expand the substrate and the nucleophile scope for this reaction. Therefore, excellent activities, regio- and enantioselectivities up to >99% ee have been achieved in several substrates with different electronic and steric properties and using a wide range of nucleophiles (49 compounds in total). Furthermore, NMR and DFT studies have been carried out to fully understand the catalytic behavior of those privileged phosphite-oxazoline ligands.

- In Section 4.2, the previously new generation of phosphite-oxazoline PHOX-based ligand library presented in Section 3.3 have been successfully applied in the Pd-catalyzed allylic substitution of several substrate and nucleophile types. The enantioselectivities obtained with these new ligands are similar to the ones with previous Pd/PHOX-based phosphite-oxazoline catalysts (ee's up to >99%), with the added advantage that the activity is much higher (TOF's up to >8640 mol substrate·(mol Pd·h)$^{-1}$ for new Pd/PHOX-based catalysts vs >2400 mol substrate·(mol Pd·h)$^{-1}$ for previous Pd/PHOX-based catalysts). Moreover, with these family of ligands we expanded the range of non-symmetric substrates obtaining good levels of regio- and enantioselectivity. In addition, the enantiopure alkylated products were used for the

preparation of more complex chiral molecules without loss of enantioselectivity through cycloisomerization or Pauson-Khand reactions. Finally, the use of DFT calculations in combination with NMR studies helped us to better understand the origin of enantioselectivity.

- In Section 4.3, we reported the application of a family new phosphite-hydrazone ligands in the asymmetric Pd-allylic alkylation of three model substrates (linear hindered, cyclic and monosubstituted ones). Preliminary results showed that these Pd-catalysts were able to achieve promising enantioselectivities in the allylic alkylation of the more challenging cyclic substrate. Furthermore, both enantiomers of the alkylated product were afforded by changing the configuration of the biaryl phosphite moiety in enantioselectivities up to 81% ee.

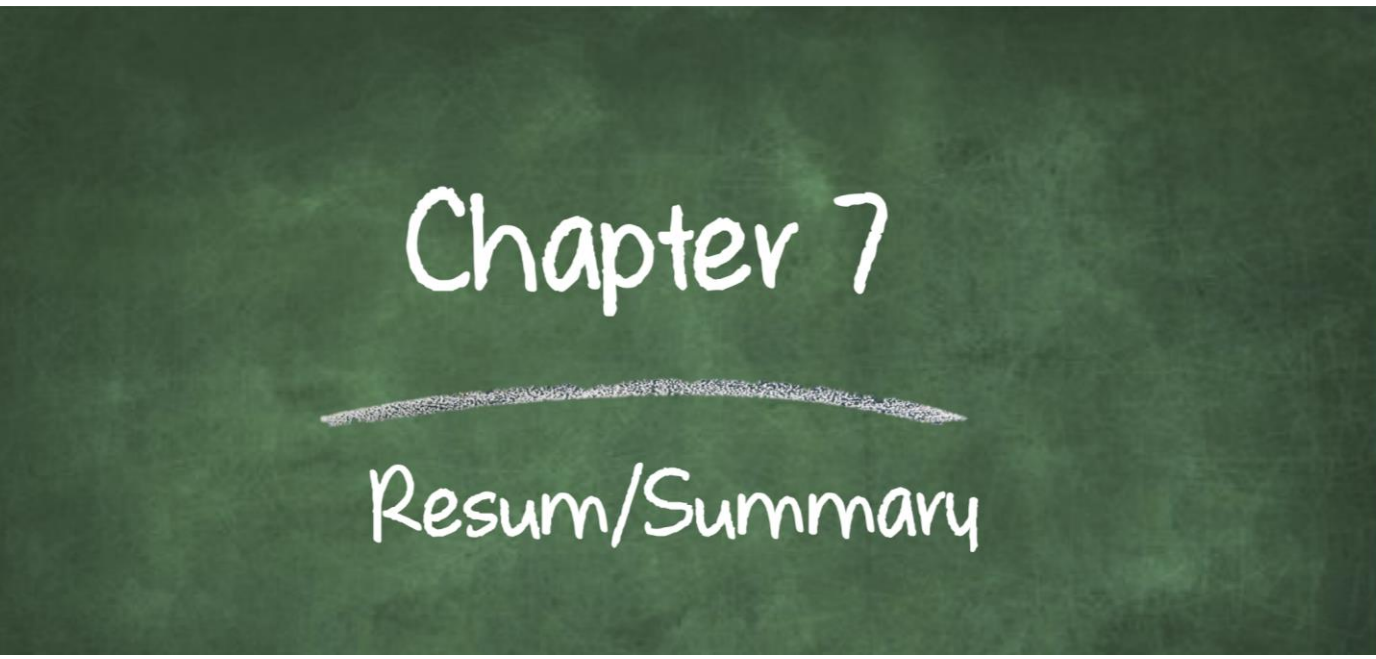
- In Section 4.4, we reported the application of a new library of modular phosphite-amino ligands in the asymmetric Pd-catalyzed allylic substitution of substrates with different steric and electronic requirements applying a large variety of nucleophiles (ee's up to 99%). These air stable phosphite-amino ligands are prepared in a few steps from readily available enantiopure aminoalcohols and combine the benefits of a high stability of the amine moiety and the flexibility of the biaryl-phosphite groups and the chiral pocket through a highly modular ligand scaffold. The results indicated that the replacement of oxazoline moiety by a more robust N-donor group such as amine could be beneficial in this catalytic process. With the help of DFT calculations we have been able to understand the influence of the ligand in the enantioselectivity and guide the ligand optimization, which led us to the synthesis of a simplest and most efficient amino-phosphite ligand.

- In Section 4.5, we present the application of the previously described thioether ligand family (see Section 3.10) in the Pd-catalyzed asymmetric allylic substitution reactions. Experimental and theoretical studies has been carried out in order to perform a rational design of an optimal, solid and air-stable P,S-ligand for the Pd-catalyzed enantioselective allylic substitution. The new optimal ligand provides excellent enantioselectivities for 40 compounds involving linear and cyclic substrates and a broad range C-, N-, and O-nucleophiles (ee's up to >99%). Remarkably, the results were maintained using the propylene carbonate as green solvent. Moreover, the enantioenriched alkylated products obtained with these catalysts precursors were further transformed to chiral (poly)carbo- and heterocyclic compounds through ring-closing metathesis or Pauson-Khand reactions without loss of enantioselectivity. The species responsible for the catalytic performance were also identified by mechanistic studies based on NMR spectroscopy, thus rationalizing the origin of the enantioselectivity.

- In Section 4.6, we showed the preliminary results of the application of the previously presented P*-stereogenic *N*-phosphine-phosphinite ligand family (see Section 3.12) in the asymmetric Pd-catalyzed allylic substitution of model substrates with different steric requirements using dimethyl malonate as nucleophile. By carefully selecting the ligand components, promising enantioselectivities were achieved in the allylic alkylation of linear hindered substrate and in the more challenging cyclic substrate (ee's up to 86% ee).

3. Chapter 5. *Asymmetric Pd-decarboxylative protonation reaction.* The conclusions of this chapter can be summarized as follows:

- We have developed the first catalytic asymmetric preparation of tertiary sterically hindered α-aryl oxindoles via enantioselective Pd-catalyzed decarboxylative protonation of the corresponding α-aryl-β-amido allyl esters in excellent yields and promising enantioselectivities (ee's up to 78%). Three large series of phosphite-N (N= oxazoline and pyridine) ligand families have been tested in this process and we found that the best results were obtained with a readily accessible phosphite-pyridine ligand library. Among these phosphite-pyridine ligands, the combination of enantiopure (*S*)-biaryl phosphite moiety with bulky substituents in the *ortho*-positions provided the best enantioselectivities. The substituents of the substrate in *ortho*- and *para*-positions play a crucial role for obtaining high enantioselectivities. Moreover, we carried out kinetic studies in a practical regime and KIE experiments that indicated that the decarboxylation is the rate determining step. The combination of experimental investigation and theoretical studies allows us to understand the nature of the selective-determining step, the proton transfer and rationalize the enantioselectivity and the effect of the ligand parameters in a simple quadrant model.


Chapter 7
Resum/Summary

UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull

7. Resum/Summary

Degut a la creixent demanda de compostos enantiomèricament purs en la producció de productes naturals, farmacèutics i de química fina, el descobriments de noves rutes sintètiques per preparar aquests compostos és un dels objectius més importants en química. La catàlisis asimètrica és una de les tecnologies més emprades en la formació de molècules quirals ja que generalment proporciona elevades activitats i selectivitats a la vegada que és respectuosa amb el medi ambient. Generalment amb aquesta estratègia un complex de metall de transició que conté un lligand quiral catalitza la transformació d'un substrat proquiral a un dels enantiòmer majoritàriament. Per tal de maximitzar la reactivitat i selectivitat de les reaccions catalítiques enantioselectives un dels paràmetres més important és el disseny del lligand quiral. Per tant, la síntesi de nous lligands quirals és essencial pel desenvolupament de nous sistemes catalítics que donin lloc a bons resultats en catàlisi asimètrica. A més a més, perquè aquests lligands siguin d'alt interès industrial és fonamental que siguin estables i fàcils de manipular a la vegada que la seva síntesis no sigui complexa i es pugui dur a terme a partir de compostos de partida accessibles.

En aquest context, l'objectiu principal d'aquesta tesi es centra en el desenvolupament de diverses famílies de lligands quirals i la seva posterior aplicació a diferents reaccions asimètriques d'elevat interès industrial i acadèmic com són la reacció d'hidrogenació d'olefines funcionalitzades i mínimament funcionalitzades catalitzada per Rh i Ir, la reacció de substitució al·lílica i la reacció de protonació descarboxilativa d'oxindoles ambdues catalitzades per Pd. Més concretament, s'han sintetitzat diverses famílies de lligands heterodadors P-oxazolina (P= fosfina, fosfinit, fosfit, fosforamidit), P-altres grups N-dadors (P= fosfit, fosforamidit, fosfonit i N= tiazol, sulfoximina, hidrazona, amina, piridina), P-tioèter (P= fosfina, fosfinit, fosfit) i una família de lligands fosfina quiral-fosfit.

El primer capítol (Introducció) consisteix en un repàs dels trets més rellevants de cadascuna de les reaccions estudiades en aquesta tesis així com també una explicació del mecanisme i els lligands més significatius.

En el segon capítol (Objectius) es recullen els diferents objectius en els que es basa aquesta tesis.

En el tercer capítol es presenten dotze apartats on es discuteix la síntesis i aplicació de dotze llibreries de lligands en reaccions d'hidrogenació d'olefines. El primer apartat consta del manuscrit titulat "*Extending the substrate scope of bicyclic P-oxazoline/thiazole ligands for Ir-catalyzed hydrogenation of unfunctionalized olefins by introducing a biaryl phosphoramidite group*" on es descriu l'obtenció i ús de compostos Ir/fosforamidit-oxazolina/tiazol com a precursors de catalitzador en la hidrogenació d'olefines mínimament funcionalitzades. Aquests precursors de catalitzadors estan basats en una família de catalitzadors Ir/fosfina-oxazolina/tiazol aplicada prèviament

amb èxit en aquest procés. En aquest apartat es demostra que la introducció d'un grup fòsfor més π-acceptor com és el fosforamidit proporciona més versatilitat a aquests sistemes catalítics.

En el segon apartat es presenta el manuscrit "*Alternatives to phosphinooxazoline (^{t}BuPHOX) ligands in the metal-catalyzed hydrogenation of minimally functionalized olefins and cyclic β-enamides*" on es descriu la síntesi i aplicació dels lligands fosfit-oxazolina basats en els lligands fosfina-oxazolina (PHOX). Aquests lligands proporcionen elevades enantioselectivitats en una amplia gamma d'olefines mínimament funcionalitzades i també en β-enamides cícliques, inclús utilitzant carbonat de propilè com a solvent. Cal remarcar que d'ambdós enantiòmers del producte hidrogenat són fàcilment accessibles canviant la configuració del grup biaril fosfit per olefines mínimament funcionalitzades o bé canviant el metall utilitzat en la hidrogenació (Ir o Rh) per β-enamides cícliques.

En el tercer apartat s'inclou el manuscrit "*Asymmetric hydrogenation of di-, tri- and tetrasubstituted minimally functionalized olefins and cyclic β-enamides with easily accessible Ir-P,oxazoline catalysts*" on es descriu la síntesi i aplicació dels lligands fosfit-oxazolina, que es diferencien dels prèviament esmentats perquè introdueixen un nou centre estereogènic a la cadena del esquelet del lligand. L'aplicació en la hidrogenació asimètrica d'olefines mínimament funcionalitzades catalitzada per Ir d'aquests lligands dona lloc a la primera lligandoteca capaç d'hidrogenar amb elevades enantioselectivitats una amplia gama de olefines trisubstituïdes i disubstituïdes a la vegada que olefines tetrasubstituted, les qual representen un gran repte en aquest camp. A més a més, aquests sistemes catalítics també són capaços d'hidrogenar amb elevades enantioselectivitats olefines funcionalitzades com són les β-enamides cícliques.

El quart apartat consta del treball anomenat "*Inclusion of Ir-catalyst containing phosphite-oxazoline ligand in a supramolecular metallocage*" on es mostra l'encapsulament d'un lligand fosfit-oxazolina, derivat d'una de les millors famílies desenvolupades per aquesta reacció, i també l'encapsulament del corresponent precursor d'Ir ([Ir(L)(acac)]). En un futur propè, aquest precursor de catalitzador serà aplicat en la hidrogenació d'olefines mínimament funcionalitzades.

En el cinquè apartat es presenta el manuscrit "*Highly enantioselective hydrogenation of unfunctionalized tetrasubstituted olefins using Ir-P* aminophosphine-oxazoline catalysts*" on s'inclou l'aplicació dels lligands MaxPHOX en la hidrogenació d'olefines tetrasubstituïdes mínimament funcionalitzades catalitzada per Ir. Aquests catalitzadors donen lloc a l'obtenció d'elevades enantioselectivitats sota condicions de reacció suaus en una amplia gama d'olefines tetrasubstituïdes cícliques i acícliques. També es presenten els resultats preliminars en la hidrogenació d'esters α,β-insaturats on també s'obtenen elevades enantioselectivitats.

El sisè apartat consisteix en el treball titulat "Screening of a phosphite-sulfoximine ligand library in the asymmetric Ir-hydrogenation of minimally functionalized olefins" on

es discuteix la síntesi i cribratge dels lligands fosfit-sulfoximina en la hidrogenació d'olefines mínimament funcionalitzades catalitzada per Ir. Aquests lligands són capaços d'hidrogenar diverses cetones, esters i lactames α,β-insaturats i esters alquenil boronics en elevats nivells d'enantioselectivitat.

En el setè apartat es presenta el treball titulat "*Synthesis of novel cationic phosphonite-pyridine ligands for Ir-catalyzed enantioselective hydrogenation of minimally functionalized olefins*" on es descriu la síntesis de dos lligands catiònics fosofonit-piridina. Aquests lligands han estat dissenyat per la seva posterior aplicació en la hidrogenació d'olefines mínimament funcionalitzades catalitzada per Ir.

En el vuitè apartat es presenta el manuscrit "*Chiral ferrocene-based P-S ligands for Ir-catalyzed hydrogenation of minimally functionalized olefins. Scope and limitations*" on s'inclou l'aplicació de lligands fosfina-tioèter que contenen un ferrocè en l'estructura del lligand. Aquests sistemes catalítics proporcionen elevades enantioselectivitats en la hidrogenació d'esters α,β-insaturats trisubstituïts i també en la reducció d'enol fosfinats di- i trisubstituïts.

En el novè apartat es mostra el manuscrit "*Ir-catalyzed asymmetric hydrogenation with simple cyclohexane-based P/S ligands: In situ HP-NMR and DFT calculations for the characterization of reaction intermediates*" on es descriu la síntesi i aplicació d'una nova família de lligands fosfinit/fosfit-tioèter en una amplia gama d'olefines mínimament funcionalitzades. A més a més, s'han realitzat estudis computacionals i de RMN per tal d'identificar els intermedis de reacció i entendre l'origen de l'enantioselectivitat.

El desè apartat consta del treball titulat "Enantioselective hydrogenation of minimally functionalized olefins and cyclic β-enamides with indene-based Ir-phosphite/phosphinite-thioether catalysts" on es discuteix la síntesi d'una nova família de lligands fosfinit-tioèter derivats de l'indè, els quals s'obtenen en només tres passos a partir de productes de fàcil disponibilitat. També es presenta la seva aplicació en la hidrogenació de diversos substrats, on s'obtenen enantioselectivitats elevades.

En el onzè apartat es presenta el treball "*The application of phosphite/phosphinite-thioether ligands to enantioselective Ir-catalyzed hydrogenation of unfunctionalized olefins*". Els lligands presentats s'obtenen en quatre passos i a partir de productes de partida fàcilment accessibles. Seleccionant els paràmetres adequats del lligand, s'han pogut identificar lligands capaços de reduir diverses olefines di- i trisubstituïdes amb altes enantioselectivitats i també olefines tetrasubstituïdes en enantioselectivitats prometedores.

En dotzè apartat es mostra el treball anomenat "Rh-catalyzed asymmetric hydrogenation of functionalized olefins using P*-stereogenic *N*-phosphine-phosphite ligands" on s'inclou la síntesi i cribratge de nous lligands *N*-fosfina quiral-fosfit en la hidrogenació d'olefines funcionalitzades catalitzada per Rh. Aquests sistemes catalítics són capaços d'hidrogenar olefines amb diferents requeriments estèrics i electrònics en enantioselectivitats de moderades a altes.

En el quart capítol es presenten sis apartats on es discuteix l'aplicació de sis famílies de lligands en reaccions de substitució al·lílica catalitzada per Pd. El primer apartat consta del manuscrit titulat "*Conformational preferences of a tropos biphenyl phosphinooxazoline – a ligand with wide substrate scope*" on es descriu l'aplicació de lligands fosfit-oxazolina prèviament utilitzats en la hidrogenació (veure Secció 3.2) en la reacció de substitució al·lílica asimètrica catalitzada per Pd. S'han obtingut elevades activitats i enantioselectivitats per una amplia gamma de substrats i nucleòfils. Tanmateix, es demostra el potencial d'aquests lligands mitjançant l'ús de reaccions tàndem que han donat lloc a la preparació de molècules quirals més complexes. A més a més, els d'estudis computacionals ha permès entendre l'origen d'aquesta elevada enantioselectivitat.

El segon apartat consta del manuscrit "*Tailor-made ligands for highly active and enantioselective Pd-catalyzed allylic substitution reactions. Ligands with an exceptionally wide substrate and nucleophile scope*" on s'inclou l'aplicació d'una segona generació lligands fosfit-oxazolina amb la presencia d'un centre quiral addicional en l'esquelet del lligand i que han estat prèviament utilitzats en la hidrogenació (veure Secció 3.3). Un gran nombre de substrats i nucleòfils han estat cribats en èxit, obtenint excel·lents enantioselectivitats comparables a les obtingudes en l'apartat anterior però millorant les activitats. En aquest apartat, també s'ha dut a terme la síntesi de diferents carbobicícles i ciclopentenones quirals mitjançant reaccions tàndem. A més a més, s'han realitzat estudis computacionals mitjançant càlculs DFT i estudis de RMN els quals han estat claus per estudiar l'origen de les enantioselectivitats obtingudes.

El tercer apartat consisteix en el treball titulat "*Asymmetric Pd-catalyzed allylic alkylation using hydrazone-phosphite ligands*" on es mostra la síntesis i aplicació d'una família de lligands fosfit-hidrazona en la reacció de substitució al·lílica catalitzada per Pd. Els resultats preliminars mostren que aquests lligands tenen un prometedor potencial en l'alquilació de substrats cíclics. A més a més, ambdós enantiòmers del producte alquilat es poden obtenir amb el simple canvi de la configuració dels grup fosfit.

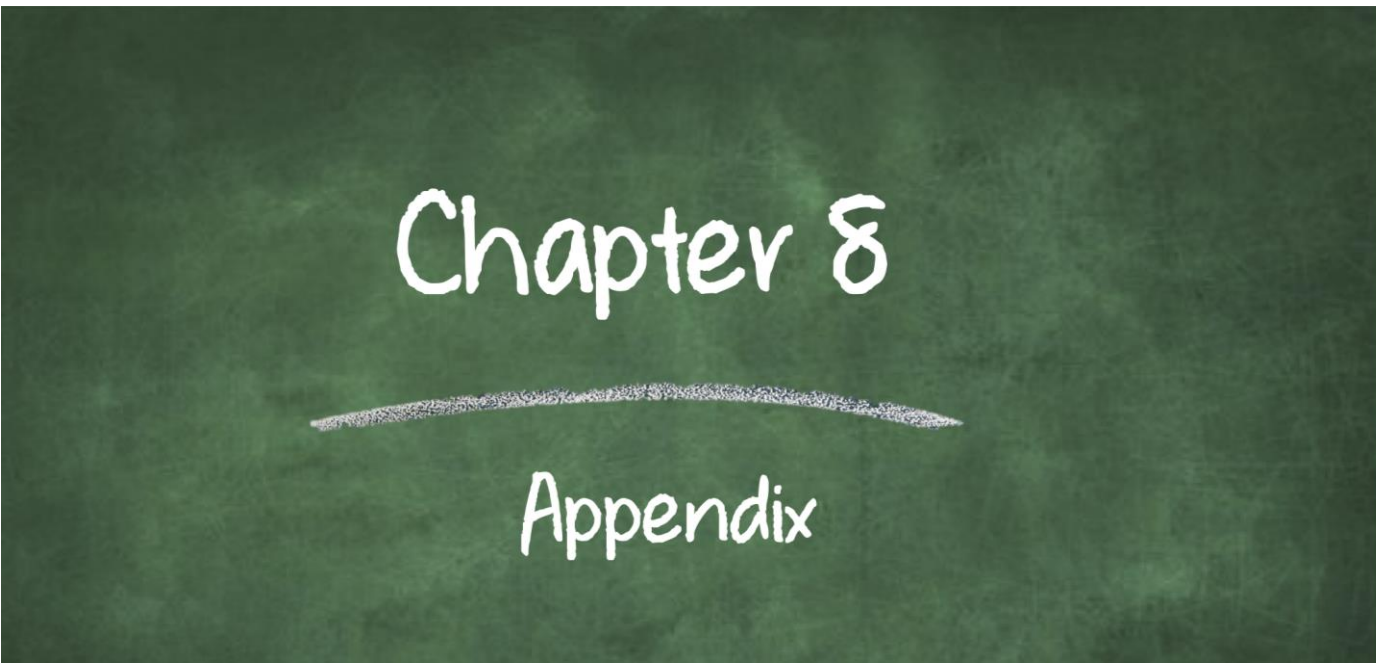
En el quart apartat es presenta el manuscrit "*Theoretical and experimental optimization of a new amino-phosphite ligand library for asymmetric palladium-catalyzed allylic substitution*" on es descriu la síntesi i aplicació de lligands fosfit-amina. La major robustesa del grup amina respecte el grup oxazolina confereix a aquests lligands una major estabilitat, oferint a vegada elevades activitats i enantioselectivitats per un ampli ventall de substrats i nucleòfils. Gràcies a alternar la química computacional i els assajos experimentals s'ha pogut trobar el lligand òptim per aquest procés dins d'aquesta família. A més a més, els estudis de RMN dels intermedis Pd-π-al·lil i la seves reactivitats ens han permès esbrinar els paràmetres del lligand que són responsables de les altes enantioselectivitats obtingudes.

En el cinquè apartat es mostra el manuscrit titulat "*Computationally guided design of a readily assembled phosphite-thioether ligand for a broad range of Pd-catalyzed asymmetric allylic substitutions*" on es descriu l'aplicació dels lligands fosfinit/fosfit-tioèter derivats de l'indè prèviament utilitzats en la hidrogenació (veure Secció 3.10) en la reacció de substitució al·lílica catalitzada per Pd utilitzant diferents substrats i una gran varietat de nucleòfils. En aquest apart, s'ha demostrat el valor sintètic d'aquest procés transformant els productes obtingut en divers carbo- i heterocicles. A més a més, s'han realitzat estudis computacional per guiar l'optimització del lligand i estudis de RMN que han clarificar l'origen de les enantioselectivitats obtingudes.

En el sisè apartat es presenta el treball anomenat "A*pplication of P*-stereogenic N-phosphine-phosphite ligands to enantioselective Pd-catalyzed allylic alkylation*" on es presenten els resultats preliminars d'aplicació de lligands *N*-fosfina quiral-fosfinit prèviament utilitzats en la hidrogenació (veure Secció 3.12), donant lloc a l'obtenció d'enantioselectivitats prometedores en substrats amb diferents requeriments estèrics.

Finalment en el cinquè capítol s'inclou el manuscrit "*Enantioselective synthesis of sterically hindered tertiary α-aryl oxindoles via Palladium-catalyzed decarboxylative protonation. An experimental and theoretical mechanistic investigation*", on es descriu l'aplicació de tres famílies de lligands fosfit-nitrogen, prèviament sintetitzades i aplicades en el nostre grup, en la protonació descarboxilativa asimètrica catalitzada per Pd de substrats del tipus α-aril-β-amido al·lil. Els millors resultats s'han obtingut amb lligands fosfit-piridina i substrats que contenen grups aril molt impedits estèricament i rics en densitat electrònica. A més a més, la combinació d'assaigs experimentals i estudis computacionals han permet ampliar el coneixement del mecanisme d'aquests procés i els factors que afecten a la etapa responsable de l'enantioselectivitat. Cal remarcar que aquest és el primer cas de síntesi enantioselectiva d'α-aril oxindoles a la bibliografia.

UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
THEORETICALLY GUIDED LIGAND DESIGN AND MECHANISTIC INVESTIGATIONS
Maria Biosca Brull


Chapter 8
Appendix

UNIVERSITAT ROVIRA I VIRGILI
FITTING THE CATALYSTS FOR EFFECTIVE ENANTIOSELECTIVE C-X BOND FORMING REACTIONS.
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8. Appendix

8.1. List of papers

1. Magre, M.; Biosca, M.; Pàmies, O.; Diéguez, M. Filling the Gaps in the Challenging Asymmetric Hydroboration of 1,1-Disubstituted Alkenes with Simple Phosphite-Based Phosphinooxazoline Iridium Catalysts. *ChemCatChem* **2015**, *7*, 114. Selected to be in the back cover.

2. Biosca, M.; Paptchikhine, A.; Pàmies, O.; Andersson, P.G.; Diéguez, M. Extending the Substrate Scope of Bicyclic P-Oxazoline/Thiazole Ligands for Ir-Catalyzed Hydrogenation of Unfunctionalized Olefins by Introducing a Biaryl Phosphoroamidite Group. *Chem. Eur. J.* **2015**, *21*, 3455.

3. Orgue, S.; Flores-Gaspar, A.; Biosca, M.; Pàmies, O.; Diéguez, M.; Riera, A.; Verdaguer, X. Stereospecific S_N2@P reactions: novel access to bulky P-stereogenic ligands. *Chem. Comm.* **2015**, *51*, 17548.

4. Magre, M.; Biosca, M.; Pàmies, O.; Norrby, P.-O.; Diéguez, M. Theoretical and experimental optimization of a new amino phosphite ligand library for asymmetric palladium-catalyzed allylic substitution. *ChemCatChem* **2015**, *7*, 4091.

5. Borràs, C.; Biosca, M.; Pàmies, O.; Diéguez, M. Iridium-Catalyzed Asymmetric Hydrogenation with Simple Cyclohexane-Based P/S Ligands: In Situ HP-NMR and DFT Calculations for the Characterization of Reaction Intermediates. *Organometallics* **2015**, *34*, 5321.

6. Biosca, M.; Coll, M.; Lagarde, F.; Brémond, L.; Routaboul, L.; Manoury, E.; Pàmies, O.; Poli, R.; Diéguez, M. Chiral ferrocene-based P,S-ligands for Ir-catalyzed hydrogenation of minimally functionalized olefins. Scope and limitations. *Tetrahedron* **2016**, *72*, 2623. Special issue: Chiral Sulfur Ligands/Catalysts in Asymmetric Catalysis.

7. Bellini, R.; Magre, M.; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M.; Moberg, C. Conformational Preferences of a Tropos Biphenyl Phosphinooxazoline - A Ligand with Wide Substrate Scope. *ACS Catal*. **2016**, *6*, 1701.

8. Biosca, M.; Magre, M.; Coll, M.; Pàmies, O.; Diéguez, M. Alternatives to Phosphinooxazoline (^{t}BuPHOX) Ligands in the Metal-Catalyzed Hydrogenation of Minimally Functionalized Olefins and Cyclic β-Enamides. *Adv. Synth. Catal*. **2017**, *359*, 2801.

9. Biosca, M.; Margalef, J.; Caldentey, X.; Besora, M.; Rodriguez-Escrich, C.; Saltó, J.; Cambeiro, X.; Maseras, F.; Pàmies, O.; Diéguez, M.; Pericàs, M. Computationally-guided design of a readily assembled phosphite-thioether ligand for a broad range of Pd-catalyzed asymmetric allylic substitutions. *ACS Catal*. **2018**, *8*, 3587.

10. Biosca, M.; Jackson, M.; Magre, M.; Pàmies, O.; Norrby, P.-O.; Diéguez, M.; Guiry, P. Enantioselective Synthesis of Sterically Hindered Tertiary α-Aryl Oxindoles via Pd-Catalyzed Decarboxylative Protonation. An Experimental and Theoretical Mechanistic Investigation. *Adv. Synth. Catal.* **2018**, *360*, 3124.

11. Biosca, M.; Magre, M.; Pàmies, O.; Diéguez, M. Asymmetric Hydrogenation of Di-, Tri- and Tetrasubstituted Minimally Functionalized Olefins and Cyclic β-Enamides with Easily Accessible Ir-P,oxazoline Catalysts. *Submitted to ACS. Catal.*

12. Biosca, M.; Salomó, E.; Riera, A.; Verdaguer, X.; Pàmies, O.; Diéguez, M. Highly enantioselective hydrogenation of unfunctionalized olefins using Ir-P* aminophosphine-oxazoline catalysts. Submitted to *Adv. Synth. Catal.*

8.2. Meeting contributions

1. **Authors:** Biosca, M.; Pàmies, O.; Diéguez, M.; Andersson, P.G.
   Title: "Phosphoroamidite-oxazoline/thiazole ligands for enantioselective Ir-catalyzed hydrogenation of unfunctionalized olefins"
   Type of contribution: Poster and Member of Organization Committee
   Congress: GEQOXXXII – Grupo Especializado Química Organometálica (RSEQ)
   Place: Tarragona, Spain
   Date: 17th-19th September 2014

2. **Type of contribution:** Member of Organization Committee and Attendance.
   Congress: COST-CARISMA- Catalytic Routines For Small Molecules Activation
   Place: Tarragona, Spain
   Date: 18th-20th March 2015

3. **Authors:** Biosca, M.; Pàmies, O.; Andersson, P.G.; Diéguez, M.
   Title: "A new generation of bicyclic P-oxazoline/thiazole ligands for Ir-catalyzed hydrogenation of minimally functionalized olefins. Improving substrate scope by introducing a biaryl phosphoroamidite group"
   Type of contribution: Poster and flash presentation
   Congress: VIII International School on Organometallic Chemistry Marcial Moreno Mañas
   Place: Sevilla, Spain
   Date: 15th-17th June 2015

4. **Authors:** Biosca, M.; Paptchikhine, A.; Pàmies, O.; Andersson, P.G.; Diéguez, M.
   Title: "New P,N-ligands for enantioselective Ir-catalyzed hydrogenation of minimally functionalized olefins"
   Type of contribution: Poster
   Congress: Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS 18)
   Place: Sitges, Spain
   Date: 28th June-2nd July 2015

5. **Authors:** Biosca, M.; Magre, M.; Pàmies, O.; Norrby, P.O.; Diéguez, M.
   Title: "Development of new catalysts for asymmetric reduction and C-X coupling reactions. Theoretically guided ligand optimization"
   Type of contribution: Oral Communication
   Congress: 1st GDRI-HC3A Meeting
   Place: Toulouse, France
   Date: 26th-27th January 2016

6. **Authors:** Biosca, M.; Magre, M.; Pàmies, O.; Norrby, P.O.; Diéguez, M.
   Title: "New simple and readily available catalysts for enantioselective reduction and C-X coupling reactions. Theoretically-guided ligand optimization"
   Type of contribution: Oral Communication
   Congress: IX Trobada de Joves Investigadors dels Països Catalans
   Place: Perpignan, France
   Date: 03th-05th February 2016

7. **Authors:** Biosca, M.; Magre, M.; Pàmies, O.; Diéguez, M.
   Title: "Asymmetric hydroboration of 1,1-disubstituted olefins"
   Type of contribution: Poster
   Congress: EuCheMS International Organometallic Conference XXII (EUCOMC 2017)
   Place: Amsterdam, Netherlands
   Date: 09th-13th July 2017

8. **Authors:** Biosca, M.; Saltó, J; Norrby, P.O.; Pàmies, O.; Diéguez, M.
   Title: "Development of new catalysts for asymmetric reduction and C-X coupling reactions. Theoretically guided ligand optimization"
   Type of contribution: Oral Communication
   Congress: 2nd GDRI-H3CA Meeting
   Place: Toulouse, France
   Date: 18th-19th January 2018

9. **Authors:** Biosca, M.; Magre, M.; Jackson, M.; Guiry, P.; Norrby, P.O.; Pàmies, O.; Diéguez, M.
   Title: "Novel approach for the synthesis of chiral tertiary α-aryl oxindoles via Pd-catalyzed decarboxylative protonation. An experimental and theoretical mechanistic investigation"
   Type of contribution: Oral Communication and Member of Organization Committee
   Congress: 2nd Trans Pyrenean Meeting in Catalysis
   Place: Tarragona, Spain
   Date: 18th-19th October 2018

8.3. PhD research abroad

1. Place: Biomedical Center (BMC, Uppsala)
Course in Molecular Modelling and Computational Medicinal Chemistry
Duration: 12/01/2015-06/02/2015
Supervisor: Prof. P.-O. Norrby and Dr. C. Sköld
Grant: Cost Action CM1205 (CARISMA)

2. Place: University of Göttingen, Göttingen (Germany)
Synthesis of novel cationic phosphonite-pyridine ligands for Ir-catalyzed enantioselective hydrogenation of minimally functionalized olefins
Duration: 01/02/2017 – 31/05/2017
Supervisor: Prof. Manuel Alcarazo
Grant: Ajuts URV Fundació Bancària La Caixa per realitzar estades de recerca a l'estranger

ChemPubSoc Europe
DOI: 10.1002/cctc.201402822
CHEMCATCHEM Full Papers

Filling the Gaps in the Challenging Asymmetric Hydroboration of 1,1-Disubstituted Alkenes with Simple Phosphite-Based Phosphinooxazoline Iridium Catalysts

Marc Magre, Maria Biosca, Oscar Pàmies,* and Montserrat Diéguez*[a]

We have identified a readily accessible phosphinooxazoline-based phosphite-oxazoline catalytic system, (*S*)-4-isopropyl-2-{2-[(3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite]-phenyl}-2-oxazoline (**L1 a**), that can hydroborate a range of 1,1-disubstituted aryl olefins with high enantioselectivity (up to 94%), excellent yields and perfect regioselectivity. The new phosphite-oxazoline ligands efficiently hydroborate a broader range of olefins than previous phosphinooxazoline ligands. In particular, a wide range of α-*tert*-butylstyrenes can be hydroborated that bear aryl substituents with different electronic and steric properties, which complements previous results with N-heterocyclic copper catalysts, the only other system reported to date that has achieved these reactions.

Introduction

Many of today's pharmaceutical, fragrance and agrochemical compounds, and the chemicals used in functional materials are required as pure enantiomers.[1] As a result, the industrial production of enantiopure chiral compounds is gaining importance and synthetic procedures are constantly evolving towards high selectivity and productivity, atom economy, operational simplicity, cost efficiency, environmental friendliness and low energy consumption. In comparison to other synthetic approaches, asymmetric catalysis is a smart strategy. A small amount of catalyst can produce large quantities of the desired chiral compound with only a few reaction steps and synthetic operations, thus bringing down the overall production cost, and decreasing the amount of by-products.

Chiral organoboron compounds have received a great deal of attention lately.[2] They are valuable organic intermediates because the C–B bond can be readily transformed to chiral C–N, C–O and C–C bonds.[2c,3] The synthesis of these compounds by transition-metal catalyzed asymmetric hydroboration is attracting considerable interest. However, whereas the asymmetric hydroboration of monosubstituted olefins (i.e., styrenes) and internal 1,2-disubstituted olefins (i.e., norbornadiene) has been well studied, the hydroboration of 1,1-disubstituted olefins remains a challenge.[2,4] This is because the chiral transition metal catalyst has difficulty in controlling not only the specific boration at the desired terminal β position rather than at the more substituted α-position (most catalysts favour Markovnikov regioselectivity)[5] but also the face selectivity coordination (due to the presence of the two relatively similar substituents at the geminal position). To date, high regio- and enantioselectivities have been reported in only three publications, with limited substrate scope (Scheme 1).[6] In 2008 Soderquist and co-workers reported the hydroboration of 1,1-disubstituted alkenes by using stoichiometric quantities of chiral boranes with *ee* values between 28 and 92% (Scheme 1 a).[6a] The highest *ee* was observed only with 2,3,3-trimethylbut-1-ene.

Subsequently, two important breakthroughs in the asymmetric hydroboration of 1,1-disubstituted olefins were reported (Scheme 1 b). They both included metal-catalyzed hydroboration processes instead of expensive and sacrificial stoichiometric chiral auxiliaries. One of them, reported by Hoveyda and co-workers, showed the asymmetric hydroboration of 1,1-disubstituted aryl-alkyl olefins with chiral copper-based bidentate N-heterocyclic carbene catalysts.[6b] A range of α-methylstyrenes and some aryl olefins with alkyl substituents other than the typical methyl unit and exocyclic alkenes were hydroborated with high regioselectivities and enantioselectivities in the range 61–92% *ee*. Despite this important advance, high catalyst loading (7.5%), long reaction times (48 h), low temperature (from −15 °C to −50 °C) and the presence of an almost equimolar amount of base were required (Scheme 1 b). Mazet and Gérard also reported the hydroboration of a range of 1,1-disubstituted aryl-alkyl olefins with excellent yields and regioselectivities (with exclusive attack at the desired β position) in which the iridium catalyst was modified with the readily accessible (*S*)-4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline ligand (PHOX-*t*Bu, Scheme 1 b).[6c] Enantioselectivity (up to 92% *ee*), however, was only high in the hydroboration of α-methylstyrene **S1**. The introduction of substituents at the aryl ring or the increase in steric requirements at the alkyl substituent of the substrate decreased the enantioselectivity consider-

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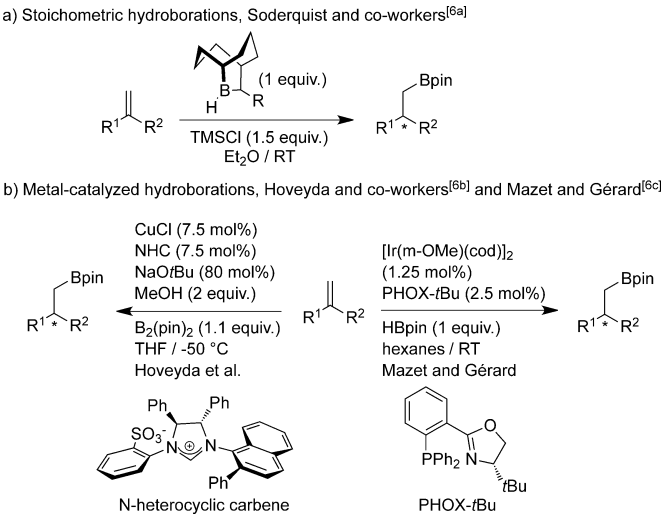
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201402822.



Scheme 1. State-of-the-art asymmetric hydroboration of challenging 1,1-disubstituted olefins. Bpin = Pinacolato.

ably. Although fewer substrates were hydroborated than with the copper carbene-based catalysts, the PHOX iridium catalysts allowed this transformation to take place under milder reaction conditions and with lower catalyst loading (Scheme 1 b), which would be advantageous for sustainable industrial process. Owing to the limited substrate scope of the three advances mentioned, new developments in this field are still needed.

In most asymmetric transformations involving olefins as prochiral reagents (e.g., epoxidation, hydrogenation), 1,1-disubstituted olefins are systematically challenging substrates,[7] mainly due to face selectivity issues (as in the hydroboration reaction). We recently demonstrated the highest reported enantioselectivities in the iridium-catalyzed hydrogenation of a very large range of simple 1,1-disubstituted olefins by introducing a biaryl phosphite moiety into the ligand.[7c–d,8] Inspired by the work of Mazet and Gérard[6c] and the similarities of the elementary steps involved in hydroboration and hydrogenation, we studied here whether the introduction of a biaryl phosphite moiety into the ligand was also beneficial for iridium-catalyzed hydroboration. To this end, we took the previously successful PHOX ligand family and replaced the phosphine group with biaryl phosphite moieties (ligands **L1**–**L4 a**–**c**, Figure 1). Herein, we present the application of the phosphite-oxazoline ligands **L1**–**L4 a**–**c** in the asymmetric iridium-catalyzed hydroboration of 1,1-disubstituted olefins. These ligands incorporate the advantages of biaryl phosphites such as higher resistance to oxidation than phosphines, facile synthesis from readily available chiral alcohols and a straightforward modular construction.[9] We investigated the catalytic performance by systematically varying the electronic and steric properties of the oxazoline substituents **L1**–**L4** and using different substituents and configurations in the biaryl phosphite group (**a**–**c**).

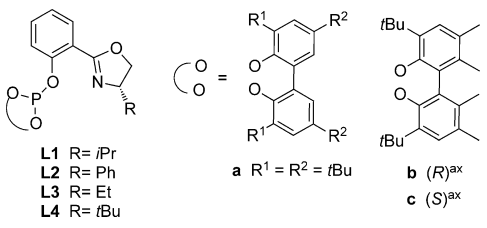
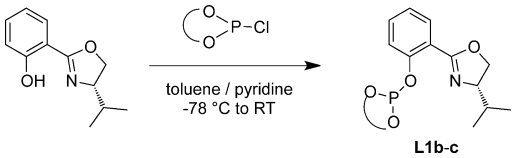


Figure 1. Phosphite-oxazoline PHOX-based ligands **L1**–**L4 a**–**c**.



Scheme 2. Synthetic route for the synthesis of new phosphite-oxazoline PHOX-based ligands **L1 b** and **L1 c**.

Results and Discussion

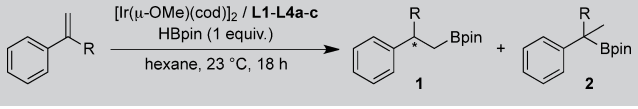
Ligand synthesis

The new phosphite-oxazoline PHOX-based ligands **L1 b** and **L1 c** can be synthesized easily by following the procedure previously described for ligands **L1**–**L4 a**[10] (Scheme 2). They were prepared in one step by coupling the oxazoline-alcohol (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol with one equivalent of the in situ-formed phosphorochloridite (**b**–**c**) under basic conditions (Scheme 2). All ligands were isolated in good yields as white solids after purification on neutral alumina. Advantageously, they were stable in air and very stable to hydrolysis, so further manipulation and storage was performed in air. The high-resolution electrospray ionization (ESI) mass spectra were in agreement with the assigned structures. **L1 b** and **L1 c** were also characterized by $^{31}P\{^{1}H\}$, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy. The spectral assignments, made by using ^{1}H–^{1}H and ^{13}C–^{1}H correlation measurements, were as expected for these C_1-symmetric ligands.

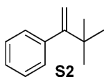
Initial screening experiments of phosphite-oxazoline PHOX-based ligands

As previously mentioned, the effectiveness of the catalyst in transferring the chiral information to the hydroborated product

Table 1. Asymmetric hydroboration of α-methylstyrene **S1** and α-*tert*-butylstyrene **S2**.[a]




S1


S2

Entry	L	Conv.[b] [%] (**1a**/**2a**)	*ee*[c] [%]	Conv.[b] [%] (**1b**/**2b**)	*ee*[c] [%]
1	**L1a**	100 (>99:1)	44 (*S*)	100 (>99:1)	88 (*S*)
2	**L1b**	50 (>99:1)	7 (*S*)	46 (>99:1)	43 (*S*)
3	**L1c**	60 (>99:1)	41 (*S*)	59 (>99:1)	79 (*S*)
4	**L2a**	100 (>99:1)	42 (*S*)	100 (>99:1)	86 (*S*)
5	**L3a**	100 (>99:1)	17 (*S*)	100 (>99:1)	43 (*S*)
6	**L4a**	96 (>99:1)	43 (*S*)	84 (>99:1)	88 (*S*)
7	PHOX-*t*Bu	100 (>99:1)	92 (*S*)[6c]	0	–

[a] All reactions performed in duplicate with 1 mmol of substrate, 1.25 mol% of [Ir(μ-OMe)(cod)]$_2$, 2.5 mol% of ligand and 2 mL of hexane. [b] Determined by using ^{1}H NMR, in all cases regioselectivities were >99%. [c] Determined by using HPLC after conversion to the corresponding alcohols.

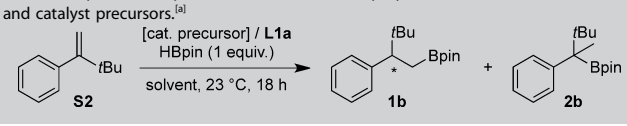
that ligands with an *S* biaryl phosphite group provided better enantioselectivities than ligands with an *R* biaryl phosphite group (Table 1, entry 2 vs 3). This is an advantage because it means that the inexpensive 3,3′,5,5′-tetra-*tert*-butyl-[1,1′-biphenyl]-2,2′-diyl phosphite moiety (**a**) can be used. For the oxazoline substituent, the enantioselectivities are highest with bulky isopropyl and *tert*-butyl groups (ligands **L1a** and **L4a**, Table 1, entries 1 and 6) but the activities are best if the steric demand on the oxazoline substituents is decreased. The trade-off between activities and enantioselectivities is therefore best with ligand **L1a** (Table 1, entry 1). This result contrasts with the one described by Mazet and Gérard, which required the presence of a *tert*-butyl oxazoline substituent to achieve high enantioselectivity, and it has an economic advantage because **L1a** is derived from L-valinol, which is around eight times cheaper than the L-*tert*-leucinol required for the synthesis of the PHOX-*t*Bu ligand.

depends mainly on its ability to sterically differentiate between the two geminal substituents of the olefin. To assess the potential of the phosphite-oxazoline PHOX-based ligands **L1**–**L4a**–**c** in the hydroboration of substrates with different steric requirements, we initially evaluated them in the asymmetric iridium-catalyzed hydroboration of model substrate **S1**[2,6] and the hydroboration of more demanding **S2** (Table 1).

For purposes of comparison, we first tested **L1**–**L4a**–**c** under the same optimal reaction conditions found in the previous study of Mazet and Gérard with related PHOX iridium catalytic systems.[6c] Reactions were performed at room temperature, with 2.5 mol% of in situ-generated catalyst ([Ir(μ-OMe)(cod)]$_2$/L) and hexane as solvent.[6c] The results are collected in Table 1. All of the ligands favoured the attack at the β position and the desired primary (pinacolato)boron adduct **1** was achieved with perfect regiocontrol (**1**/**2** ratio >99). Although enantioselectivities were moderate for α-methylstyrene **S1**, an unprecedentedly high enantioselectivity was achieved for the more challenging α-*tert*-butylstyrene **S2** (*ee* values up to 88%). Notably, the hydroboration of **S2** by using the related PHOX-*t*Bu ligand provided no conversion under the same reaction conditions (Table 1, entry 7). These important results indicate that both PHOX-based ligand families are complementary, thus, we can hydroborate both substrate types by the correct combination of substrate and ligand type (phosphine/oxazoline or phosphite/oxazoline).

As far as the effect of the ligand parameters on activities and enantioselectivities is concerned, we found that bulky *tert*-butyl groups are needed at the *ortho* and *para* positions of the biaryl phosphite moiety to achieve the highest activities and enantioselectivities (Table 1, entry 1 vs 2 and 3). We also found

Table 2. Asymmetric hydroboration of α-*tert*-butylstyrene **S2**: effect of the solvent and catalyst precursors.[a]

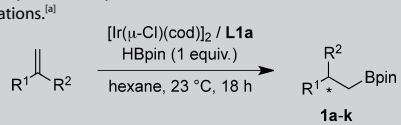


Entry	Solvent	[Cat. precursor]	Conv.[b] [%] (**1b**/**2b**)	*ee*[c] [%]
1	hexane	[Ir(μ-OMe)(cod)]$_2$	100 (>99:1)	88 (*S*)
2	THF	[Ir(μ-OMe)(cod)]$_2$	88 (>99:1)	76 (*S*)
3	CH_2Cl_2	[Ir(μ-OMe)(cod)]$_2$	100 (>99:1)	80 (*S*)
4	toluene	[Ir(μ-OMe)(cod)]$_2$	96 (>99:1)	83 (*S*)
5	hexane	[Ir(μ-Cl)(cod)]$_2$	100 (>99:1)[d]	92 (*S*)
6	hexane	[Ir(cod)**L1a**]BAr$_F$[e]	61 (>99:1)	66 (*S*)

[a] All reactions performed in duplicate with 1 mmol of substrate, 1.25 mol% of iridium catalyst precursor, 2.5 mol% of ligand and 2 mL solvent. [b] Determined by using ^{1}H NMR. [c] Determined by using HPLC after conversion to the corresponding alcohol. [d] 91% isolated yield. [e] BAr$_F$ = [B{3,5-(CF$_3$)$_2$C$_6$H$_3$}$_4$]$^-$.

We next optimized the reaction conditions by evaluating a variety of solvents and catalyst precursors with ligand **L1a**, which had provided the best results (Table 2). Although in all cases regioselectivity towards the desired β adduct **1** remained excellent, activity and enantioselectivity were highly dependent on the solvent and the nature of the catalyst precursor. The combination of hexane and [Ir(μ-Cl)(cod)]$_2$ (cod = 1,5-cyclooctadiene) as catalyst precursor was found to be optimal (Table 2, entry 5). Under these new reaction conditions we were therefore able to increase the enantioselectivity to 92% while maintaining the excellent yield and regioselectivity of the desired β compound **1**. To the best of our knowledge, iridium–**L1a** is the first catalytic system that can hydroborate **S2** with perfect regioselectivity, excellent yield and high enantioselectivity.

Table 3. Asymmetric hydroboration of 1,1-disubstituted olefins: scope and limitations.[a]



1a-k

Entry	Substrate	R^1	R^2	**1/2**	Yield[b] [%]	*ee*[c] [%]
1	**S1**	C_6H_5	Me	>99:1	93	50 (*S*)
2	**S2**	C_6H_5	*t*Bu	>99:1	91	92 (*S*)
3	**S3**	C_6H_5	Et	>99:1	90	55 (*S*)
4	**S4**	C_6H_5	*i*Bu	>99:1	88	56 (*S*)
5	**S5**	C_6H_5	*i*Pr	>99:1	89	58 (*S*)
6	**S6**	4-Me-C_6H_4	*t*Bu	>99:1	92	94 (*S*)
7	**S7**	4-OMe-C_6H_4	*t*Bu	>99:1	91	93 (*S*)
8	**S8**	4-CF_3-C_6H_4	*t*Bu	>99:1	94	90 (*S*)
9	**S9**	2-naphthyl	*t*Bu	>99:1	89	87 (*S*)
10	**S10**	3-Me-C_6H_4	*t*Bu	>99:1	90	92 (*S*)
11	**S11**	4-OMe-C_6H_4	CF_3	>99:1	88	18 (*S*)
12[d]	**S11**	4-OMe-C_6H_4	CF_3	–	0	n.d.

[a] All reactions performed in duplicate with 1 mmol of substrate, 1.25 mol% of $[Ir(\mu\text{-Cl})(cod)]_2$, 2.5 mol% of **L1a** and 2 mL hexane. [b] Determined by using ^{1}H NMR. [c] Determined by using HPLC or GC after conversion to the corresponding alcohol. [d] Reaction performed by using PHOX-*t*Bu iridium catalyst; hydrogenated product isolated in 45% yield and 0% *ee*.

Asymmetric hydroboration of other 1,1-disubstituted olefins: scope and limitations

The unprecedented results obtained up to this point with the iridium–**L1a** catalyst in the hydroboration of **S2** encouraged us to test iridium–**L1a** in the hydroboration of other 1,1-disubstituted olefins (Table 3).

First, we studied the hydroboration of several phenyl and alkyl olefins bearing alkyl substituents with different steric demands (**S3**–**S5**, Table 3, entries 3–5). Excellent regioselectivities of the desired β adduct **1** were achieved. Enantioselectivities were moderate regardless of the steric demands of the alkyl substituent (entries 3–5). However, enantioselectivities were not as low as those observed with related PHOX iridium catalysts with increased steric hindrance on the alkyl substituents (i.e., *ee* values decreased from 92 to 31% on replacing Me by Et substituent).[6c]

We next studied several α-*tert*-butylstyrenes that had aryl substituents with different electronic and steric properties (**S6**–**S10**, Table 3, entries 6–10). Advantageously, iridium–**L1a** is very tolerant to variations in the substituents of the aryl ring and can hydroborate a wide range of α-*tert*-butylstyrenes with comparably high enantioselectivities (up to 94%) and yields and perfect regioselectivity. Accordingly, our results with several *para*-substituted α-*tert*-butylstyrenes (**S6**–**S8**) indicated that the enantioselectivity was relatively insensitive to the electronic effects in the aryl ring (*ee* values of 90–94%, entries 2, 6–8). Enantioselectivities were, however, highest in the hydroboration of electron-rich olefins **S6** and **S7** (entries 6–7). Enantioselectivities were also excellent in the hydroboration of *meta*-substituted olefins (**S9**–**S10**, entries 9–10). Again, these results contrasted with the ones described by Mazet and Gérard with related PHOX iridium catalysts for which the introduction of any type of substituent at the aryl ring of the substrate had a negative effect on enantioselectivity.[6c]

We then looked into the hydroboration of aryl and trifluoromethyl olefins. Owing to the unique properties of the fluorine, the efficient hydroboration of these substrates opened up an appealing route for obtaining organic intermediates for the preparation of drugs, agrochemicals and materials. To the best of our knowledge, only Hoveyda and co-workers have attempted the hydroboration of this substrate class with their N-heterocyclic carbene copper catalysts, although they obtained undesired difluoroallylboronates.[6b] Here, we have tested the new iridium–**L1a** and related PHOX iridium catalysts in the hydroboration of the model 1-methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene **S11** substrate (Table 3, entries 11 and 12). Although PHOX-*t*Bu iridium was found to be inadequate because it provided exclusively the hydrogenated product in racemic form, the iridium–**L1a** catalyst gave the desired hydroborated product with perfect regioselectivity and good yield, albeit with low enantiocontrol. This result opens up new possibilities for further research and it demonstrates once again that the behaviour is not that observed with PHOX iridium catalysts.

Conclusion

We have identified a readily accessible phosphinooxazoline (PHOX)-based phosphite-oxazoline iridium catalytic system (iridium–**L1a**) that can hydroborate a range of 1,1-disubstituted aryl olefins with high enantioselectivity (up to 94%), excellent yields and perfect regioselectivity. The new phosphite-oxazoline PHOX-based ligands could efficiently hydroborate a broader range of olefins than previous PHOX ligands. Particularly, we could hydroborate a wide range of α-*tert*-butylstyrenes, with aryl substituents that had different electronic and steric properties, thus complementing the results of N-heterocyclic carbene copper catalysts, the only other system reported to date that has attempted these reactions. In addition, the introduction of a biaryl phosphite moiety allowed, for the first time, the highly regioselective hydroboration of aryl and trifluoromethyl olefins. Another advantage over previous PHOX ligands was that the new ligands were stable to air and therefore easier to handle, manipulate and store. This contribution opens up the path for the synthesis of new iridium phosphite-based catalysts for the challenging hydroboration of 1,1-disubstituted olefins. Further studies on the design of new phosphite-based iridium catalysts to further broaden the scope of this hydroboration reaction are currently underway.

Experimental Section

General

All reactions were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Phosphorochloridites were prepared easily in one step from the corresponding binaphthols.[11] Intermediate compound (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol,[12] ligands **L1**–**L4a**[10] and substrates **S2**,[13] **S3**,[14] **S4**,[15] **S5**[13]

and **S11**[7c] were prepared as previously reported. Substrates **S6–S10** were prepared by using the Wittig olefination procedure (for details, see the Supporting Information). ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded by using a 400 MHz spectrometer. Chemical shifts are relative to those of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H, ^{13}C and ^{31}P assignments were made on the basis of ^{1}H–^{1}H gCOSY and ^{1}H–^{13}C gHSQC NMR analyses.

Preparation of phosphite-oxazoline ligands L1–L4 a–c

General procedure: The corresponding phosphorochloridite (1.1 mmol) produced in situ was dissolved in toluene (5 mL) and pyridine (0.36 mL, 4.6 mmol) was added. Hydroxyl-oxazoline intermediate (1 mmol) was azeotropically dried with toluene (3×1 mL) and then dissolved in toluene (5 mL), to which pyridine (0.36 mL, 4.6 mmol) had been added. The hydroxyl-oxazoline solution was transferred slowly at −78 °C to the solution of phosphorochloridite. The reaction mixture was allowed to warm to RT and stirred overnight. The pyridine salts were then removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography (Al_2O_3, toluene/NEt_3 = 100:1) to produce the corresponding ligand.

(*S*)-4-isopropyl-2-{2-[(*R*)-3,3′-di-*tert*-butyl-5,5′,6,6′-tetra-methyl-1,1′-biphenyl-2,2′-diyl)phosphite]phenyl}-2-oxazoline (L1 b): Yield: 423 mg (72%); ^{31}P NMR (C_6D_6): δ = 132.6 ppm (s); ^{1}H NMR (C_6D_6): δ = 0.62 (d, 6H, $^3J_{H-H}$ = 6.4 Hz, CH_3, *i*Pr), 1.27 (s, 9H, CH_3, *t*Bu), 1.37 (s, 9H, CH_3, *t*Bu), 1.39 (m, 1H, CH, *i*Pr), 1.61 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 3.03 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 5.2 Hz, CH_2–O), 3.12 (dd, 1H, $^2J_{H-H}$ = 11.2 Hz, $^3J_{H-H}$ = 5.2 Hz, CH_2–O), 4.22 (m, 1H, CH–N), 6.7–7.5 (m, 6H, CH=), 8.59 ppm (d, 1H, $^3J_{H-H}$ = 6.4 Hz, CH=); ^{13}C NMR (C_6D_6): δ = 16.2 (CH_3, *i*Pr), 16.4 (CH_3, *i*Pr), 17.8 (CH_3), 19.1 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 28.6 (CH, *i*Pr), 31.0 (d, CH_3, *t*Bu, J_{C-P} = 5.3 Hz), 31.3 (CH_3, *t*Bu), 34.4 (C, *t*Bu), 34.8 (C, *t*Bu), 45.3 (CH_2-O), 55.4 (CH-N), 118.4–150.9 (C_{Ar}), 163.4 ppm (C=N); HRMS (ESI): *m/z*: calcd for $C_{36}H_{46}NO_4P + Na^+$: 610.3062 [*M*–Na]$^+$, found 610.3067.

(*S*)-4-isopropyl-2-{2-[(*S*)-3,3′-di-*tert*-butyl-5,5′,6,6′-tetra-methyl-1,1′-biphenyl-2,2′-diyl)phosphite]phenyl}-2-oxazoline (L1 c): Yield: 376 mg (64%); ^{31}P NMR (C_6D_6): δ = 133.9 ppm (s); ^{1}H NMR (C_6D_6): δ = 0.55 (d, 3H, $^3J_{H-H}$ = 6.4 Hz, CH_3, *i*Pr), 0.63 (d, 3H, $^3J_{H-H}$ = 6.8 Hz, CH_3, *i*Pr), 1.35 (s, 9H, CH_3, *t*Bu), 1.39 (s, 9H; CH_3, *t*Bu), 1.42 (m, 1H, CH, *i*Pr), 1.65 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.35 (m, 2H, CH_2–O), 4.28 (m, 1H, CH–N), 6.7–7.7 (m, 6H, CH=), 8.60 ppm (d, 1H, $^3J_{H-H}$ = 8.0 Hz, $^4J_{H-H}$ = 2.0 Hz, CH=); ^{13}C NMR (C_6D_6): δ = 16.2 (CH_3, *i*Pr), 16.6 (CH_3, *i*Pr), 18.1 (CH_3), 19.1 (CH_3), 20.0 (CH_3), 21.4 (CH_3), 28.6 (CH, *i*Pr), 31.2 (d, CH_3, *t*Bu, J_{C-P} = 4.6 Hz), 31.4 (CH_3, *t*Bu), 34.4 (C, *t*Bu), 34.7 (C, *t*Bu), 45.6 (CH_2–O), 55.5 (CH–N), 119.3–150.4 (C_{Ar}), 163.4 ppm (C=N); HRMS (ESI): *m/z*: calcd for $C_{36}H_{46}NO_4P + Na^+$: 610.3062 [*M*–Na]$^+$, found 610.3068.

Asymmetric hydroboration of 1,1-disubstituted substrates

General procedure: The corresponding ligand (2.5×10^{-2} mmol) and $[Ir(\mu\text{-Cl})(cod)]_2$ (8.4 mg, 2.5×10^{-5} mmol) were dissolved in hexane (2 mL) and stirred for 10 min at RT. Then, the slightly turbid solution was cooled to 0 °C and the desired 1,1-disubstituted olefin (1.0 mmol) slowly added. After 5 min, pinacolborane (150 μL, 1.0 mmol) was added dropwise. The ice bath was then removed and the reaction stirred at RT. After 18 h, the volatiles were evaporated and the crude mixture purified by column chromatography (SiO_2, Et_2O/cyclohexane = (9:1) to give the hydroborated product as a colourless oil.

ee Values were determined after oxidation of the pinacolborane derivatives to the corresponding alcohols. Pinacolborane derivative (0.25 mmol) was dissolved in Et_2O (2 mL) and cooled to 0 °C. NaOH (3 N, 2.0 mL) and H_2O_2 (30%, 1.5 mL) were then added. The resulting solution was stirred at RT for 2 h. Then, the solution was extracted twice with Et_2O (2 mL) and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2, Et_2O/cyclohexane = 4:1) to yield the desired chiral primary alcohol.

4,4,5,5-Tetramethyl-2-(2-phenylpropyl)-1,3,2-dioxaborolane (1 a): ^{1}H NMR ($CDCl_3$): δ = 1.08 (s, 12H, CH_3, Bpin), 1.09 (m, 2H, CH_2), 1.20 (d, $^3J_{H-H}$ = 8 Hz, 3H, CH_3), 2.95 (m, 1H, CH), 7.0–7.2 ppm (m, 5H, CH=); ^{13}C NMR ($CDCl_3$): δ = 24.6 (CH_3, Bpin), 24.7 (CH_3, Bpin), 24.9 (CH_3), 35.8 (CH), 82.9 (C, Bpin), 125.7 (CH=), 126.6 (CH=), 128.1 (CH=), 149.2 ppm (C); HRMS elemental analysis calcd (%) for $C_{15}H_{23}BO_2$ [M^+]: 246.1791, found: 246.1794.

ee Values were determined after oxidation to phenylpropan-1-ol: ^{1}H NMR ($CDCl_3$): δ = 1.23 (d, $^3J_{H-H}$ = 8 Hz, 3H, CH_3), 2.95 (m, 1H, CH), 3.71 (m, 2H, CH_2), 7.2–7.4 ppm (m, 5H, CH=);^{13}C NMR ($CDCl_3$): δ = 17.5 (CH_3), 42.4 (CH), 68.7 (CH_2), 126.7 (CH=), 127.4 (CH=), 128.6 (CH=), 143.6 ppm (C); HRMS elemental analysis calcd (%) for $C_9H_{12}O$ [M^+]: 136.0888, found: 136.0885; *ee* (HPLC, Chiracel IA column, hexane/2-propanol = 99:1, 0.5 mL min^{-1}, λ = 254 nm): t_R = 38.9 (*R*), 41.7 min (*S*).

2-(3,3-Dimethyl-2-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 b): ^{1}H NMR ($CDCl_3$): δ = 0.83 (s, 9H, CH_3, *t*Bu), 0.91 (s, 6H, CH_3, Bpin), 0.96 (s, 6H, CH_3, Bpin), 1.18 (m, 2H, CH_2), 2.67 (m, 1H, CH), 7.05–7.20 ppm (m, 5H, CH=); ^{13}C NMR ($CDCl_3$): δ = 24.2 (CH_3, Bpin), 24.5 (CH_3, Bpin), 27.7 (CH_3, *t*Bu), 34.0 (C, *t*Bu), 51.6 (CH), 82.7 (C, Bpin), 125.6 (CH=), 127.1 (CH=), 129.7 (CH=), 144.3 ppm (C); HRMS elemental analysis calcd (%) for $C_{18}H_{29}BO2$ [M^+]: 288.2261, found: 288.2259.

ee Values were determined after oxidation to 3,3-dimethyl-2-phenylbutan-1-ol: ^{1}H NMR ($CDCl_3$): δ = 0.87 (s, 9H, CH_3, *t*Bu), 2.65 (m, 1H, CH), 4.01 (m, 2H, CH_2), 7.05–7.35 ppm (m, 5H, CH=); ^{13}C NMR ($CDCl_3$): δ = 28.4 (CH_3, *t*Bu), 33.1 (C, *t*Bu), 58.9 (CH), 62.6 (CH_2), 125.6 (CH=), 126.8 (CH=), 127.1 (CH=), 128.2 (CH=), 140.2 ppm (C); HRMS elemental analysis calcd (%) for $C_{12}H_{18}O$ [M^+]: 178.1358, found: 178.1357; *ee* (HPLC, Chiracel IA column, hexane/2-propanol = 98:2, 0.5 mL min^{-1}, λ = 220 nm): t_R = 23.0 (*S*), 25.2 min (*R*).

4,4,5,5-Tetramethyl-2-(2-phenylbutyl)-1,3,2-dioxaborolane (1 c): ^{1}H NMR ($CDCl_3$): δ = 0.73 (t, $^3J_{H-H}$ = 8.0 Hz, 3H, CH_3), 1.08 (s, 12H, CH_3, Bpin), 1.12 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 2.65 (m, 1H, CH), 7.0–7.2 ppm (m, 5H, CH=); ^{13}C NMR ($CDCl_3$): δ = 12.2 (CH_3), 24.6 (CH_3, Bpin), 24.7 (CH_3, Bpin), 35.8 (CH), 43.3 (CH_2), 82.9 (C, Bpin), 125.7 (CH=), 127.4 (CH=), 128.0 (CH=), 147.2 ppm (C); HRMS elemental analysis calcd (%) for $C_{16}H_{25}BO_2$ [M^+]: 260.1948, found: 260.1947.

ee Values were determined after oxidation to 2-phenylbutan-1-ol: ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, $^3J_{H-H}$ = 8.0 Hz, 3H, CH_3), 1.5–1.8 (m, 2H, CH_2), 2.65 (m, 1H; CH), 3.75 (m, 2H, CH_2), 7.20–7.35 ppm (m, 5H, CH=); ^{13}C NMR ($CDCl_3$): δ = 12.5 (CH_3), 25.7 (CH_2), 50.5 (CH), 67.3 (CH_2), 126.7 (CH=), 128.1 (CH=), 128.6 (CH=), 142.2 ppm (C); HRMS elemental analysis calcd (%) for $C_{10}H_{14}O$ [M^+]: 150.1045, found: 150.1043; *ee* (GC, CP-Chirasil-Dex CB column, 90 kPa H_2, 110 °C isotherm): t_R = 8.8 (*S*), 9.2 min (*R*).

4,4,5,5-Tetramethyl-2-(4-methyl-2-phenylpentyl)-1,3,2-dioxaborolane (1 d): ^{1}H NMR ($CDCl_3$): δ = 0.81 (d, $^3J_{H-H}$ = 6.0 Hz, 3H, CH_3,

*i*Bu), 0.85 (d, $^3J_{H-H}$ = 8.0 Hz, 3H, CH_3, *i*Bu), 1.02 (s, 12H, CH_3, Bpin), 1.2–1.6 (m, 5H), 2.95 (m, 1H, CH), 7.1–7.3 ppm (m, 5H, CH=); ^{13}C NMR ($CDCl_3$): δ = 22.0 (CH_3, *i*Bu), 23.4 (CH_3, *i*Bu), 24.6 (CH_3, Bpin), 24.7 (CH_3, Bpin), 29.6 (CH_2, *i*Bu), 39.2 (CH, *i*Bu), 49.0 (CH), 82.8 (C, Bpin), 125.6 (CH=), 127.4 (CH=), 128.0 (CH=), 147.6 ppm (C); HRMS elemental analysis calcd (%) for $C_{18}H_{29}BO_2$ [M^+]: 288.2261, found: 288.2262.

ee Values were determined after oxidation to 4-methyl-2-phenylpentan-1-ol: ^{1}H NMR ($CDCl_3$): δ = 0.79 (m, 6H, CH_3, *i*Bu), 1.2–1.6 (m, 5H), 2.85 (m, 1H, CH), 3.62 (m, 2H, CH_2), 7.1–7.3 ppm (m, 5H, CH=); ^{13}C NMR ($CDCl_3$): δ = 21.8 (CH_3, *i*Bu), 23.5 (CH_3, *i*Bu), 25.3 (CH_2, *i*Bu), 41.1 (CH, *i*Bu), 46.4 (CH), 68.0 (CH_2), 126.7 (CH=), 128.1 (CH=), 128.6 (CH=), 142.4 ppm (C); HRMS elemental analysis calcd (%) for $C_{12}H_{18}O$ [M^+]: 178.1358, found: 178.1356; *ee* (HPLC using Chiracel IA column, hexane/2-propanol = 98:2, 0.5 mL min^{-1}, λ = 220 nm): t_R = 22.5 (*S*), 24.3 min (*R*).

4,4,5,5-Tetramethyl-2-(3-methyl-2-phenylbutyl)-1,3,2-dioxaborolane (1 e): ^{1}H NMR ($CDCl_3$): δ = 0.65 (d, $^3J_{H-H}$ = 8.0 Hz, 3H, CH_3, *i*Pr), 0.87 (d, $^3J_{H-H}$ = 8.0 Hz, 3H, CH_3, *i*Pr), 1.02 (s, 12H, CH_3, Bpin), 1.04 (s, 12H, CH_3, Bpin), 1.0–1.2 (m, 2H, CH_2), 1.68 (m, 1H, CH, *i*Pr), 2.55 (m, 1H, CH), 7.0–7.2 ppm (m, 5H, CH=);^{13}C NMR ($CDCl_3$): δ = 20.4 (CH_3, *i*Pr), 20.6 (CH_3, *i*Pr), 24.4 (CH_3, Bpin), 24.6 (CH_3, Bpin), 35.3 (CH, *i*Pr), 48.3 (CH), 82.7 (C, Bpin), 125.6 (CH=), 127.7 (CH=), 128.3 (CH=), 146.1 ppm (C); HRMS elemental analysis calcd (%) for $C_{17}H_{27}BO_2$ [M^+]: 274.2104, found: 274.2102.

ee Values were determined after oxidation to 3-methyl-2-phenylbutan-1-ol: ^{1}H NMR ($CDCl_3$): δ = 0.75 (d, $^3J_{H-H}$ = 8.0 Hz, 3H, CH_3, *i*Pr), 1.02 (d, $^3J_{H-H}$ = 8.0 Hz, 3H, CH_3, *i*Pr), 1.93 (m, 1H, CH, *i*Pr), 2.55 (m, 1H, CH), 3.8–4.0 (m, 2H, CH_2), 7.2–7.4 ppm (m, 5H, CH=); ^{13}C NMR ($CDCl_3$): δ = 21.0 (CH_3, *i*Pr), 21.1 (CH_3, *i*Pr), 30.1 (CH, *i*Pr), 55.8 (CH), 65.2 (CH_2), 126.7 (CH=), 128.5 (CH=), 128.7 (CH=), 141.6 ppm (C); HRMS elemental analysis calcd (%) for $C_{11}H_{16}O$ [M^+]: 164.1201, found: 164.1202; *ee* (HPLC, Chiracel IA column, hexane/2-propanol = 98:2, 0.5 mL min^{-1}, λ = 210 nm): t_R = 25.2 (*S*), 26.5 min (*R*).

2-(3,3-Dimethyl-2-(p-tolyl)butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 f): ^{1}H NMR ($CDCl_3$): δ = 0.85 (s, 9H, CH_3, *t*Bu), 0.94 (s, 6H, CH_3, Bpin), 0.97 (s, 6H, CH_3, Bpin), 1.21 (m, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.67 (m, 1H, CH), 6.9–7.1 ppm (m, 4H, CH=); ^{13}C NMR ($CDCl_3$): δ = 20.9 (CH_3), 24.2 (CH_3, Bpin), 24.5 (CH_3, Bpin), 27.7 (CH_3, *t*Bu), 34.0 (C, *t*Bu), 51.2 (CH), 82.7 (C, Bpin), 127.7 (CH=), 129.5 (CH=), 134.9 (C), 141.2 ppm (C); HRMS elemental analysis calcd (%) for $C_{19}H_{31}BO_2$ [M^+]: 302.2417, found: 302.2415.

ee Values were determined after oxidation to 3,3-dimethyl-2-(p-tolyl)butan-1-ol: ^{1}H NMR ($CDCl_3$): δ = 0.88 (s, 9H, CH_3, *t*Bu), 2.33 (s, 3H, CH_3), 2.64 (m, 1H, CH), 4.0 (m, 2H, CH_2), 7.1–7.2 ppm (m, 4H, CH=); ^{13}C NMR ($CDCl_3$): δ = 21.0 (CH_3), 28.4 (CH_3, *t*Bu), 33.0 (C, *t*Bu), 58.9 (CH), 62.5 (CH_2), 128.9 (CH=), 129.6 (CH=), 136.3 (C), 136.7 ppm (C); HRMS elemental analysis calcd (%) for $C_{13}H_{20}O$ [M^+]: 192.1514, found: 192.1511; *ee* (GC using Chiradex B-DM column, 77 kPa H_2, 110 °C isotherm): t_R = 26.5 (*S*), 27.5 min (*R*).

2-(2-(4-Methoxyphenyl)-3,3-dimethylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 g): ^{1}H NMR ($CDCl_3$): δ = 0.83 (s, 9H, CH_3, *t*Bu), 0.90 (s, 6H, CH_3, Bpin), 0.97 (s, 6H, CH_3, Bpin), 1.22 (m, 2H, CH_2), 2.65 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 6.75 (d, 2H, $^3J_{H-H}$ = 8.0 Hz, CH=), 7.07 ppm (d, 2H, $^3J_{H-H}$ = 8.0 Hz, CH=); ^{13}C NMR ($CDCl_3$): δ = 24.2 (CH_3, Bpin), 24.6 (CH_3, Bpin), 27.6 (CH_3, *t*Bu), 34.1 (C, *t*Bu), 50.7 (CH), 55.2 (OCH_3), 82.7 (C, Bpin), 112.5 (CH=), 130.4 (CH=), 136.6 (C), 157.7 ppm (C); HRMS elemental analysis calcd (%) for $C_{19}H_{31}BO_3$ [M^+]: 318.2366, found: 318.2365.

ee Values were determined after oxidation to 2-(4-methoxyphenyl)-3,3-dimethylbutan-1-ol: ^{1}H NMR ($CDCl_3$): δ = 0.87 (s, 9H, CH_3, *t*Bu), 2.63 (m, 1H, CH), 3.82 (s, 3H, CH_3O), 3.97 (m, 2H, CH_2), 6.87 (d, 2H, $^3J_{H-H}$ = 8.4 Hz, CH=), 7.14 ppm (d, 2H, $^3J_{H-H}$ = 8.4 Hz, CH=); ^{13}C NMR ($CDCl_3$): δ = 28.3 (CH_3, *t*Bu), 33.1 (C, *t*Bu), 55.2 (OCH_3), 58.1 (CH), 62.5 (CH_2), 113.6 (CH=), 130.6 (CH=), 131.6 (C), 158.4 ppm (C); HRMS elemental analysis calcd (%) for $C_{13}H_{20}O_2$ [M^+]: 208.1463, found: 208.1460; *ee* (GC, CP-Chirasil-Dex CB column, 90 kPa H_2, 110 °C for 40 min, 5 °C min^{-1} until 150 °C, 20 °C min^{-1} until 170 °C): t_R = 49.6 (*S*), 49.9 min (*R*).

2-(3,3-Dimethyl-2-(4-(trifluoromethyl)phenyl)butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 h): ^{1}H NMR ($CDCl_3$): δ = 0.86 (s, 6H, CH_3, Bpin), 0.88 (s, 6H, CH_3, Bpin), 0.95 (s, 9H, CH_3, *t*Bu), 1.27 (m, 2H, CH_2) 2.77 (m, 1H, CH), 7.28 (d, 2H, $^3J_{H-H}$ = 8.0 Hz, CH=), 7.47 ppm (d, 2H, $^3J_{H-H}$ = 8.0 Hz, CH=); ^{13}C NMR ($CDCl_3$): δ = 24.1 (CH_3, Bpin), 24.5 (CH_3, Bpin), 27.6 (CH_3, *t*Bu), 29.7 (C, *t*Bu), 51.6 (CH), 82.9 (C, Bpin), 124.1 (CH=), 132.2 (CH=), 128.9 (C), 152.3 ppm (C); HRMS elemental analysis calcd (%) for $C_{19}H_{28}BF_3O_2$ [M^+]: 356.2134, found: 356.2133.

ee Values were determined after oxidation to 3,3-dimethyl-2-(4-(trifluoromethyl)phenyl)butan-1-ol: ^{1}H NMR ($CDCl_3$): δ = 0.87 (s, 9H, CH_3, *t*Bu), 2.76 (m, 1H, CH), 4.06 (m, 2H, CH_2), 7.34 (d, 2H, $^3J_{H-H}$ = 7.6 Hz, CH=), 7.59 ppm (d, 2H, $^3J_{H-H}$ = 7.6 Hz, CH=); ^{13}C NMR ($CDCl_3$): δ = 28.3 (CH_3, *t*Bu), 32.1 (C, *t*Bu), 58.8 (CH), 62.5 (CH_2), 125.0 (CH=), 130.6 (CH=), 145.8 (C), 160.0 ppm (C); HRMS elemental analysis calcd (%) for $C_{13}H_{17}BF_3O$ [M^+]: 246.1231, found: 246.1229; *ee* (HPLC, Chiracel IA column, hexane/2-propanol = 98:2, 0.5 mL min^{-1}, λ = 220 nm): t_R = 32.7 (*S*), 38.4 min (*R*).

2-(3,3-Dimethyl-2-(naphthalen-2-yl)butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 i): ^{1}H NMR ($CDCl_3$): δ = 0.81 (s, 9H, CH_3, *t*Bu), 0.87 (s, 6H, CH_3, Bpin), 0.91 (s, 6H, CH_3, Bpin), 1.2–1.4 (m, 2H, CH_2), 2.89 (m, 1H, CH), 7.4–7.8 ppm (m, 7H, CH=); ^{13}C NMR ($CDCl_3$): δ = 24.1 (CH_3, Bpin), 24.5 (CH_3, Bpin), 27.8 (CH_3, *t*Bu), 34.4 (C, *t*Bu), 51.7 (CH), 82.7 (C, Bpin), 124.4 (CH=), 125.4 (CH=), 126.3 (CH=), 127.3 (CH=), 127.7 (CH=), 132.2 (C), 133.0 ppm (C); HRMS elemental analysis calcd (%) for $C_{22}H_{31}BO_2$ [M^+]: 338.2417, found: 338.2415.

ee Values were determined after oxidation to 3,3-dimethyl-2-(naphthalen-2-yl)butan-1-ol: ^{1}H NMR ($CDCl_3$): δ = 0.83 (s, 9H, *t*Bu), 2.79 (m, 1H, CH), 4.07 (m, 2H, CH_2), 7.30–7.77 ppm (m, 7H, CH=); ^{13}C NMR ($CDCl_3$): δ = 28.5 (CH_3, *t*Bu), 33.7 (C, *t*Bu), 59.1 (CH), 62.6 (CH_2), 125.5 (CH=), 126.1 (CH=), 127.5 (CH=), 127.6 (CH=), 127.7 (CH=), 132.5 (C), 133.2 (C), 137.7 ppm (C); HRMS elemental analysis calcd (%) for $C_{16}H_{20}O$ [M^+]: 228.1514, found: 228.1513; *ee* (HPLC, Chiracel IA column, hexane/2-propanol = 98:2, 0.5 mL min^{-1}, λ = 220 nm): t_R = 40.4 (*S*), 44.5 min (*R*).

2-(3,3-Dimethyl-2-(*m*-tolyl)butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 j): ^{1}H NMR ($CDCl_3$): δ = 0.93 (s, 9H, CH_3, *t*Bu), 0.95 (s, 6H, CH_3, Bpin), 0.96 (s, 6H, CH_3, Bpin), 1.23 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.68 (m, 1H, CH), 6.9–7.1 ppm (m, 5H, CH=); ^{13}C NMR ($CDCl_3$): δ = 21.4 (CH_3), 24.2 (CH_3, Bpin), 24.5 (CH_3, Bpin), 27.7 (CH_3, *t*Bu), 34.0 (C, *t*Bu), 51.5 (CH), 82.6 (C, Bpin), 126.2 (CH=), 127.0 (CH=), 136.3 (CH=), 138.0 (C), 144.3 ppm (C); HRMS elemental analysis calcd (%) for $C_{19}H_{31}BO_2$ [M^+]: 302.2417, found: 302.2414.

ee Values were determined after oxidation to 3,3-dimethyl-2-(*m*-tolyl)butan-1-ol: ^{1}H NMR ($CDCl_3$): δ = 0.89 (s, 9H, CH_3, *t*Bu), 2.35 (s, 3H, CH_3), 2.65 (m, 1H, CH), 4.01 (m, 2H, CH_2), 7.05–7.2 ppm (m, 5H, CH=); ^{13}C NMR ($CDCl_3$): δ = 21.6 (CH_3), 28.4 (CH_3, *t*Bu), 33.0 (C, *t*Bu), 58.9 (CH), 62.6 (CH_2), 126.8 (CH=), 128.05 (CH=), 137.7 ppm (C); HRMS calcd for $C_{13}H_{20}O$ [M^+]: 192.1514, found: 192.1512; *ee* (GC,

CP-Chirasil-Dex CB column, 90 kPa H_2, 110 °C isotherm): $t_R = 20.1$ (*S*), 21.9 min (*R*).

4,4,5,5-Tetramethyl-2-(3,3,3-trifluoro-2-(4-methoxyphenyl)propyl)-1,3,2-dioxaborolane (1 k): ^{1}H NMR ($CDCl_3$): $\delta = 1.03$ (s, 6H, CH_3, Bpin), 1.09 (s, 6H, CH_3, Bpin), 1.40 (m, 2H, CH_2), 3.54 (m, 1H, CH), 3.79 (s, 3H, CH_3O), 6.84 (d, 2H, $^3J_{H-H} = 8.4$ Hz, CH=), 7.23 ppm (d, 2H, $^3J_{H-H} = 8.4$ Hz, CH=); ^{13}C NMR ($CDCl_3$): $\delta = 24.3$ (CH_3, Bpin), 24.4 (CH_3, Bpin), 44.8 (q, CH, $^3J_{H-F} = 28.1$ Hz), 55.2 (CH_3O), 83.0 (C, Bpin), 113.6 (CH=), 128.5 (d, C, $J_{C-F} = 29.7$ Hz), 128.7 (C), 130.0 (CH=), 159.2 ppm (C); HRMS elemental analysis calcd (%) for $C_{16}H_{22}BF_3O_3$ [M^+]: 330.1614, found: 330.1612.

ee Values were determined after oxidation to 3,3,3-trifluoro-2-(4-methoxyphenyl)propan-1-ol: ^{1}H NMR ($CDCl_3$): $\delta = 3.45$ (m, 1H, CH), 3.8 (s, 3H, CH_3O), 3.98 (m, 1H, CH_2), 4.16 (m, 1H, CH_2), 6.92 (d, 2H, $^3J_{H-H} = 8.4$ Hz, CH=), 7.25 ppm (d, 2H, $^3J_{H-H} = 8.4$ Hz, CH=); ^{13}C NMR ($CDCl_3$): $\delta = 51.5$ (q, CH, $J_{C-F} = 25.4$ Hz), 55.2 (CH_3O), 61.2 (CH_2), 114.3 (CH=), 124.6 (d, C, $J_{C-F} = 30.2$ Hz), 130.2 (CH=), 159.7 ppm (C); HRMS elemental analysis calcd (%) for $C_{10}H_{11}F_3O$ [M^+]: 220.0711, found: 220.0712; *ee* (GC, CP-Chirasil-Dex CB column, 90 kPa H_2, 110 °C isotherm): $t_R = 28.2$ (*S*), 29.4 min (*R*).

Acknowledgements

We thank the Spanish Government for providing grant CTQ2013–40568, the Catalan Government for grant 2014SGR670, and the ICREA Foundation for providing M.D. and O.P. with financial support through the ICREA Academia awards.

Keywords: alkenes · asymmetric catalysis · hydroboration · iridium · phosphite-oxazoline ligands

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Received: October 14, 2014
Published online on November 17, 2014

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