Author:
Aldhous, Tim

Title:
Development of Ir(I)-catalysed Hydrofunctionalisation Methodologies

Development of Ir(I)-catalysed Hydrofunctionalisation Methodologies

Timothy P. Aldhous

A Thesis submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Science

School of Chemistry, March 2023

Word count: 64,205

Abstract

This Thesis presents the development of multiple Ir(I)-catalysed hydrofunctionalisation methodologies. Following the introduction of enantioselective intermolecular Murai-type hydroarylation reactions in **Chapter 1**, **Chapter 2** describes the synthesis of chiral bisphosphonite and bisphosphite ligands. Building upon previous work in the group, **Chapter 3** begins by exploring the use of these ligands in enantioselective hydroheteroarylation reactions of styrene to promote high enantio- and branch-selectivity.

Chapter 3 proceeds to describe the optimisation of hydroheteroarylation reactions of styrene using furan substrates through judicious modification of the directing group. This process exhibits broad substrate scope for a wide variety of styrenes and aliphatic alkenes and the products were obtained in high: (i) yield, (ii) site-selectivity, (iii) branch-selectivity and (iv) enantioselectivity. Further utility of this reaction was demonstrated by use of an α-chiral alkene to deliver a product bearing contiguous 1,2-stereocentres in a catalyst-controlled, diastereoselective process. A methodology for the hydro(hetero)arylation of 1,1-disubstituted alkenes was also developed and exemplified to install challenging quaternary stereocentres.

Chapter 4 discusses the development of hydroheteroarylation reactions using alkenyl silanes by extensive screening of a range of phosphine-derived ligands. The methodology is applicable to a range of vinyl and allyl silanes using a broad scope of furan, thiophene and pyrrole substrates. The products are formed in excellent yields and in very high alkene regiocontrol.

Finally, **Chapter 5** begins by disclosing investigations into enantioselective hydroalkylation reactions using 1,3-dicarbonyl compounds. A related process for enantioselective hydroalkylations using α-aminoamides is then described. This tolerates of a wide variety of styrenes to form branched products with excellent control over absolute and relative stereochemistry. Further investigations demonstrate the catalysis products can be further derivatised into various α-amino analogues (such as α-amino acids) as well as other pharmaceutically-active motifs.

Author's Declaration

I declare that the work in this Thesis was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

Signed:

Date: 14/03/2023

Acknowledgements

First and foremost, I would like to thank Prof. John Bower for his expertise, enthusiasm and support throughout my time in his group. John sets high standards for himself and his students, and has a meticulous eye for detail, which together have pushed me to improve all aspects of my work. The skills and traits I have learnt from being in the Bower group will be invaluable to my future career. His door was always open (or emails regularly checked) to chat about chemistry, or otherwise, and I will always be grateful for that. I wish John all the best for the rest of his academic career and will eagerly monitor the progress of his laboratory.

I would also like to thank Dr. Natalie Fey and Dr. Paul Kemmitt for their input and insightful discussions throughout.

To tackle this chronologically: I would like to thank Prof. Kevin Booker-Milburn, Dr. Laura Chavda, Mar Ruiz-Molina and the rest of the Chemical Synthesis CDT management team for allowing me to pursue Ph.D. studies at the University of Bristol. I thoroughly enjoyed my time within the CDT, which was no doubt enhanced by those in the 2018 Cohort – thank you all for putting up with me, and making those years in Bristol (and days in Spain) the most fun. Thank you to Dr Alastair Lennox and Prof. Robin Bedford for allowing me to undertake placements in their groups and to Sayad Doobary, Ben Rowsell and Olivia Boyd for their mentoring. A particular mention to Sayad, who sacrificed many evenings to help me out in the lab when I first started out in Bristol. Thanks also to Paul Lawrence, Sam Ferrins, Prof. Craig Butts and the rest of the NMR team for their help and tuition.

I have had the privilege to work alongside excellent chemists (decent people too) during my time in the Bower group who vastly enriched my Ph.D. experience and made the lab a fun and positive place to "work", so thanks to: Steven Stanton, Josh Farndon, Olivia Boyd, Olga Sokolova, Jamie Cadge, Lauren O'Neil, Ben Jones, Madelene Waldron, Wenbin Tu as well as post-docs: Xiaofeng Ma, Gangwei Wang, James Wood and Javier García Cárceles.

When I accepted a Ph.D. position at the University of Bristol, little did I know that I would end up spending a large portion of time at the University of Liverpool. Thanks to everyone behind the scenes who made the move go as (surprisingly) smoothly as possible, and to everyone who supported me in Liverpool. Luckily, this allowed me to work with a whole new set of chemists, so thanks to Bower group 2.0: Erin Boddie, Matt Smith, Peter Ledwith, Davide Sella, Ross Adams, Jake Painter, Tom Ball, Romi Aggarwal, Karim Bahou, David Dailler, Charlotte Lorton, Changcheng Jing, Daniel Zhu and Wenbin Mao for being a part of it all.

For those that continue to read this Thesis, it is clear that teamwork makes the dream work, and so I would like to give a special mention to Andrew Dalling, Phillippa Cooper, Raymond Chung and Fenglin Hong for their incredible contributions to various projects which are described within. Thank you all for your amazing efforts, ideas and most importantly, spirocyclic ligands.

Also, thanks to Dr. Shirley Leung for day-to-day troubleshooting of the lab, and to Dr. Konstantin Luzyanin and Richard Roberts for their NMR and other analytical expertise at Liverpool.

Last, but certainly not least, I would like to give my warmest thanks to my parents, grandparents and brother for their love and encouragement – not only during this endeavour, but throughout my entire education. Thanks for "listening" to my "ramblings" about "molecular LEGO®" and "tiny scaffolds". We may only be a small unit, but we are tightly-knit, and I would not want it any other way.

Abbreviations

acac	acetylacetone
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BOM	benzyloxymethyl acetal
cod	1,4-cyclooctadiene
coe	cyclooctene
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
(–)-DBNE	(1*S*,2*R*)-(−)-2-(dibutylamino)-1-phenyl-1-propanol
1,2-DCB	1,2-dichlorobenzene
1,2-DCE	1,2-dichloroethane
1,2-DCP	1,2-dichloropropane
d^Fppb	1,4-bis(di(pentafluorophenyl)-phosphino)butane
DFT	density functional theory
DG	directing group
DMAc	dimethylacetamide
e.e.	enantiomeric excess
IMes	1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
KIE	kinetic isotope effect
Mes	mesityl
MOM	methoxymethyl ether
PMB	*para*-methoxybenxyl
PMP	*para*-methoxyphenyl
SFC	supercritical fluid chromatography
SPINOL	2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol
TBME	*tert*-butyl methyl ether
TMEDA	tetramethylethylenediamine

Table of Contents

Chapter 1

Enantioselective Intermolecular Murai-Type Alkene Hydroarylation Reactions

Chapter 1 – Enantioselective Intermolecular Murai-Type Alkene Hydroarylation Reactions

Sections of this chapter have been adapted from the following publication:

*T. P. Aldhous, R. W. M. Chung, A. G. Dalling, J. F. Bower, Synthesis, 2021, **53**, 2961.*[1]

1.1 Cross-coupling strategies for the formation of tertiary benzylic stereocentres

Tertiary benzylic stereocentres are key structural features in numerous pharmaceutical agents, including Naproxen[2] (an anti-inflammatory), Tapentadol[3] (an opioid analgesic) and Sertraline[4] (an antidepressant, **Figure 1**). Large-scale methods to prepare these molecules highlight the challenge of installing enantiomerically pure tertiary benzylic stereocentres; commercial syntheses have required lengthy sequences that rely on chiral auxiliary control or chiral resolution.[5]

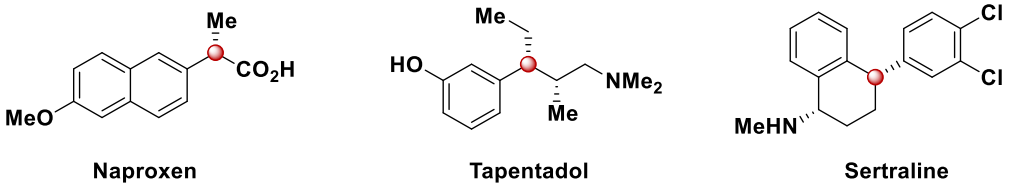
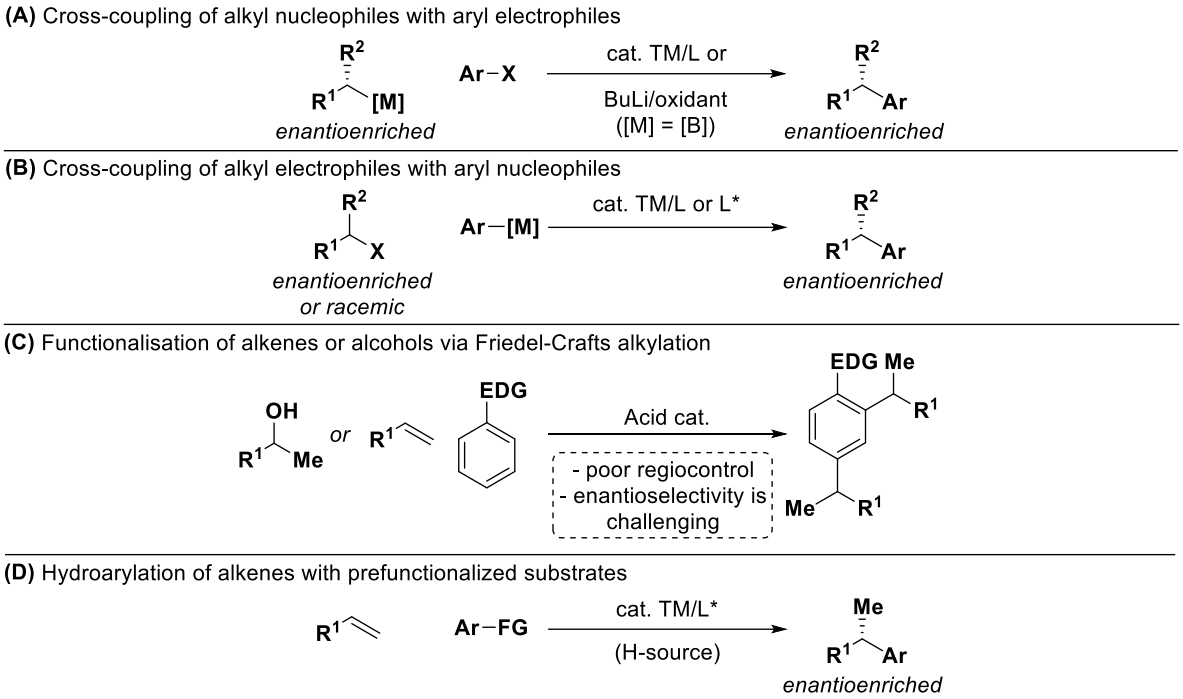


Figure 1: *Examples of pharmaceutical drugs containing tertiary benzylic stereocentres.*

A convergent solution to the problem of accessing enantioenriched tertiary benzylic stereocentres lies in methods that can install the key C(sp^3)-Ar(sp^2) bond in a direct and stereocontrolled manner. Whilst the Suzuki-Miyaura cross-coupling reaction is widely used for the construction of C(sp^2)-C(sp^2) bonds, it has not generally found application to the formation of tertiary-C(sp^3)-C(sp^2) bonds, and therefore tertiary benzylic stereocentres, because isomerisation of the alkyl-Pd(II) intermediate often leads to isomeric side products.[6–9] Methodological advances have emerged that address this issue, and numerous alternate cross-coupling strategies have also been developed. Pd-catalysed methods that tolerate enantioenriched alkyl nucleophiles, including powerful enantiodivergent processes, have been reported by the groups of Sigman and Biscoe (**Scheme 1A**),[10,11] while transition metal-free cross-couplings of enantioenriched alkyl-boronic esters with aryl-lithium reagents have been developed by Aggarwal and co-workers.[12–17] Pd-catalysed processes, in which enantioenriched alkyl nucleophiles are formed *in situ*, have been disclosed by Buchwald[18] and Liao.[19] Lu and co-workers have developed enantioselective benzylic C-H arylations that deliver tertiary benzylic stereocentres with moderate to high enantiomer ratios.[20] It was shown that aryl nucleophiles can be cross-coupled with enantioenriched or racemic alkyl electrophiles to give enantioenriched products, as reported by the groups of Jarvo,[21] Watson,[22,23] Tang[24] and Fu[25] (**Scheme 1B**). Additionally, effective methods that harness two electrophiles have been reported.[26]

The aforementioned strategies to form tertiary benzylic stereocentres require pre-functionalisation of, in some cases, one or, more commonly, both cross-coupling partners. From an atom and step economy perspective, it would be more desirable to reduce the degree of pre-

functionalisation. In principle, this can be achieved by the enantioselective addition of aryl C-H bonds across alkenes. Friedel-Crafts alkylation offers one approach to this, but, despite advances,[27–31] stereocontrolled processes are still rare,[32–35] particularly with respect to minimally polarised alkenes (**Scheme 1C**). Additionally, well established problems associated with regiocontrol, polyalkylation and the scope of the arene limit applicability. Recent metal-catalysed strategies address some, but not all of these issues.[36,37] Indeed, prevailing enantioselective methods for the hydroarylation of minimally polarised alkenes do not use aryl C-H bonds and instead employ a combination of a pre-functionalised arene and an exogenous or internal reductant (**Scheme 1D**).[18,38–41]



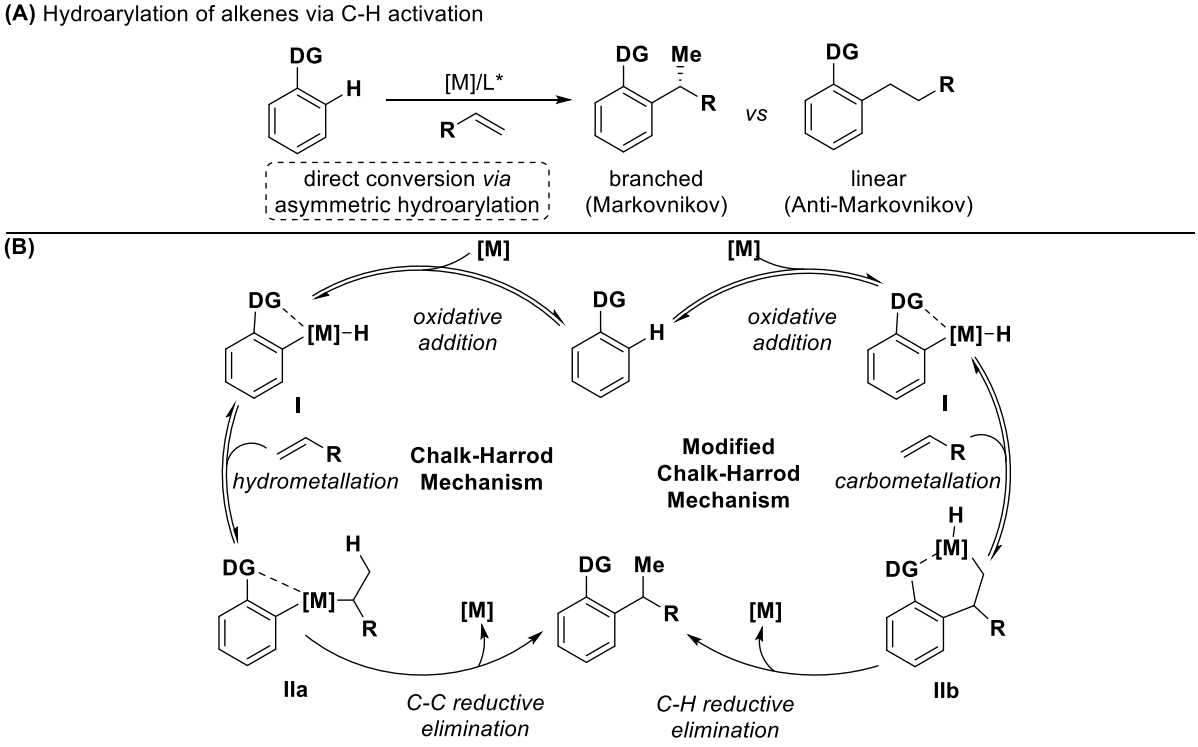
Scheme 1: *Representative methods to construct tertiary stereocentres.*

1.2 Branch selective hydroarylation strategies

Regiocontrol issues associated with Friedel-Crafts reactions can be circumvented by directing group controlled C-H activation of the arene partner (**Scheme 2A**).[42–44] This strategy directs the catalyst into the proximal C-H bond of the aromatic system, thereby providing *ortho*-selectivity for the ensuing alkylation process. For reactions involving mono-substituted alkenes, recent advances have shown that the catalyst can be tuned to enforce the formation of branched (Markovnikov) products over more conventional linear (anti-Markovnikov) products (*vide infra*). Further, by employing a chiral ligand, products bearing enantioenriched tertiary benzylic stereocentres can be formed. Accordingly, this Murai-type approach can exert three-fold control over (a) aryl C-H bond selectivity, (b) alkene hydrofunctionalisation regioselectivity, and (c) enantioselectivity; importantly, this is all achieved within a step and atom economic framework.

In general, branch selective hydroarylation reactions are proposed to proceed through one of two mechanisms shown in **Scheme 2B**. In both, a directing group reversibly initiates insertion of a metal

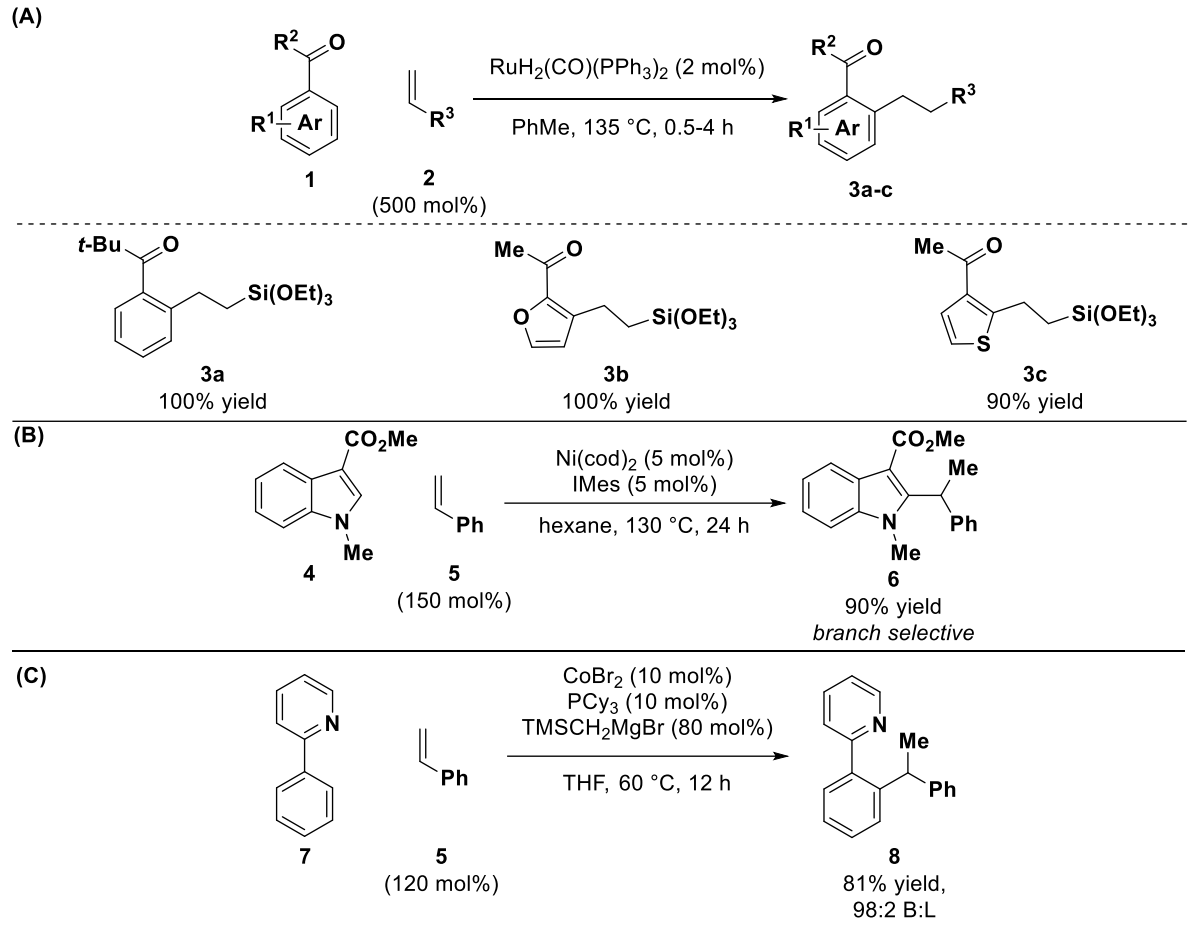
catalyst into the *ortho*-C-H bond to form **I**. This is followed by either hydrometallation (**I** to **IIa**, left, *Chalk-Harrod*) or carbometallation (**I** to **IIb**, right, *Modified Chalk-Harrod*) of the alkene reactant.[45] In certain cases, these pathways have been probed through computational[46–49] and experimental studies;[50,51] however, a Modified Chalk-Harrod mechanism has been invoked less commonly (*vide infra*) due to the generally higher activation barrier of alkene migratory insertion into the metal-carbon bond versus the metal-hydride bond of **I**. The final irreversible reductive elimination step gives the desired product and closes the catalytic cycle.



Scheme 2: *(A) Hydroarylation of alkenes via C-H activation can generate branched or linear products; (B) Common mechanisms by which these hydroarylation reactions proceed.*

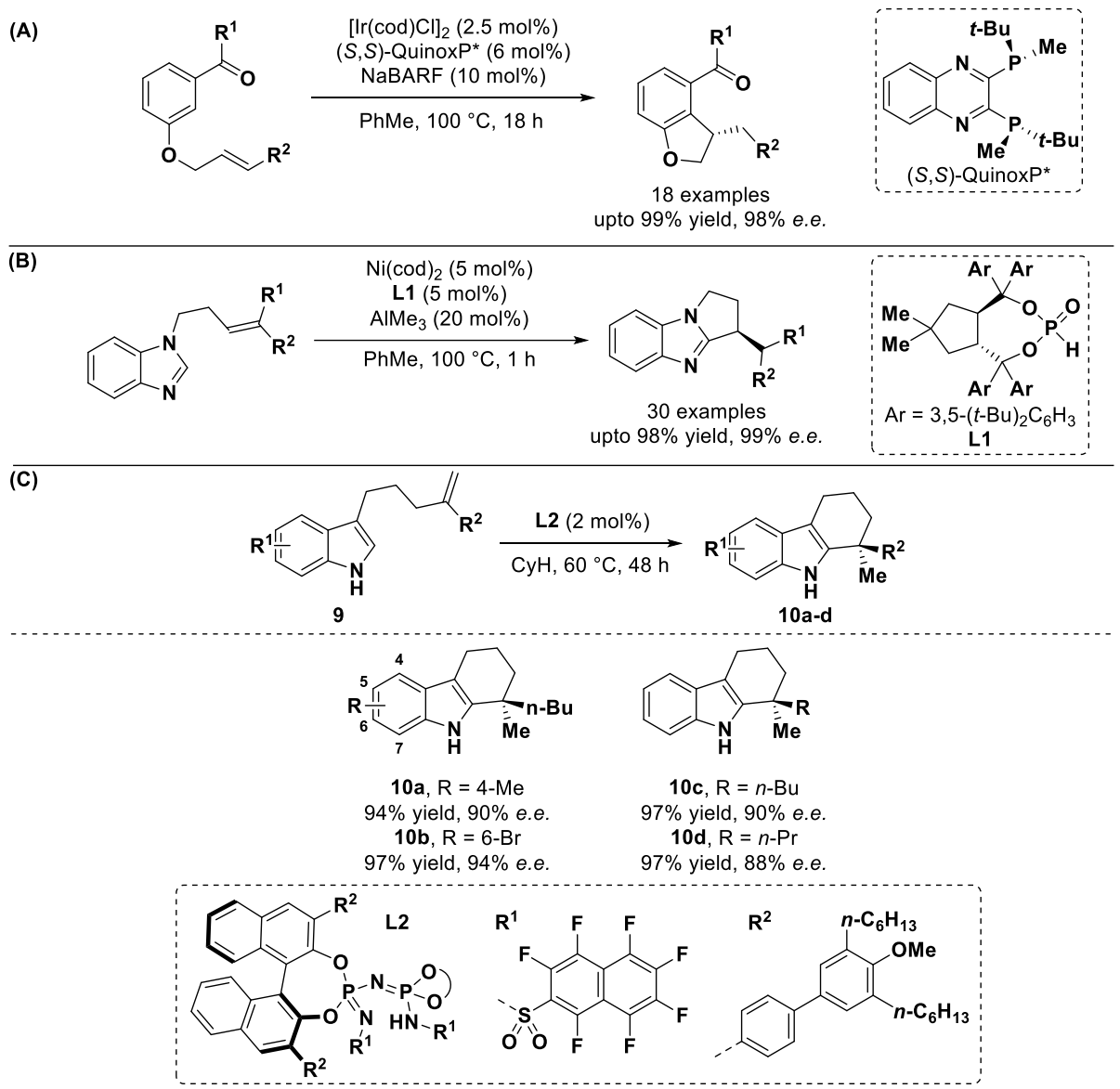
The key steps of Murai-type processes were realised in 1986 when Lewis and Smith reported an *ortho*-selective alkylation of phenols *via* directed Ru-catalysed C-H activation.[52] A phosphite directing group and a high pressure of ethylene were employed to afford alkylated phenols in moderate yield. Building upon this work, Murai and co-workers described Ru-catalysed linear-selective hydroarylations of mono-substituted alkenes, **2** with (hetero)aryl ketones **1** (**Scheme 3A**).[53] For ketone-based systems **1**, it was postulated that the carbonyl group coordinates the metal and directs C-H activation at the *ortho*-position, thereby enforcing exquisite regioselectivity with respect to the arene. For example, hydroarylation of triethoxyvinylsilane with 2,2-dimethylpropiophenone gave solely **3a** in quantitative yield**.** Similarly, furan and thiophene substrates gave **3b** and **3c** in 100% and 90% yield, respectively. The key advance in Murai's report was the discovery that "native" functional groups can be used to enforce very high levels of efficiency in these C-H activation-based processes.

In 2010, Nakao, Hiyama and co-workers established the first general methodology that overrides the usual linear selectivity of Murai hydroarylations to give more sterically-demanding branched products. This was achieved through the development of a Ni-catalysed hydro*hetero*arylation of vinylarenes with indoles (**Scheme 3B**).[54] Prior to this, branch selective Murai-type hydroarylation processes were limited to isolated examples.[55] In Nakao and Hiyama's study, complete branch selectivity was achieved using $Ni(cod)_2$ with IMes as the ligand; to illustrate, hydroheteroarylation of styrene **5** with indole **4** provided **6** in 90% yield and as solely the branched product. Following this, Yoshikai and co-workers developed a branch selective hydroarylation protocol.[56] This was achieved by employing a PCy_3-ligated Co catalyst for the coupling of 2-arylpyridines (e.g. **7**) with styrene derivatives (**Scheme 3C**). For example, hydroarylation of styrene with 2-phenylpyridine gave **8** in 81% yield and 98:2 branched to linear selectivity. Branch selective Murai hydroarylation reactions set a new stereocentre, and this has stimulated the development of intermolecular enantioselective variants (*vide infra*). Cross-couplings of this type are becoming increasingly sophisticated, such that benzylic stereocentres can now be accessed in a direct and by-product free manner.



Scheme 3: *(A) Murai's hydroarylation protocol; (B) Nakao and Hiyama's branch selective hydroheteroarylation of styrene with an indole; (C) Yoshikai's branch selective hydroarylation of styrene with 2-phenylpyridine.*

It is important to note that C-H activation triggered alkene hydroarylation and hydroheteroarylation reactions have also been developed in intramolecular settings.[57] These processes are relatively well suited to enantioselective processes; this is because regioselectivity with respect to the alkene is usually (although not always)[58] under substrate control, and so the development of chiral catalyst systems is simplified. The groups of Ellman and Bergman,[59–62] Cramer[63] and others[64–69] have reported enantioselective intramolecular processes that proceed *via* C-H activation (**Scheme 4A–B**). Enantioselective organocatalytic[70] and Friedel-Crafts-type[71,72] processes have also been disclosed. Reductive processes, in which a pre-functionalised aryl substrate is used, have been pursued as an alternative approach.[73–75] List and co-workers have disclosed intramolecular hydroheteroarylations of non-polarised alkenes with indole moieties (**Scheme 4C**).[76] This method uses a chiral Brønsted-acid catalyst (**L2**) to produce tertiary carbocations from alkenes *in situ*, and provides a broad range of tetrahydrocarbazoles possessing quaternary stereocentres.



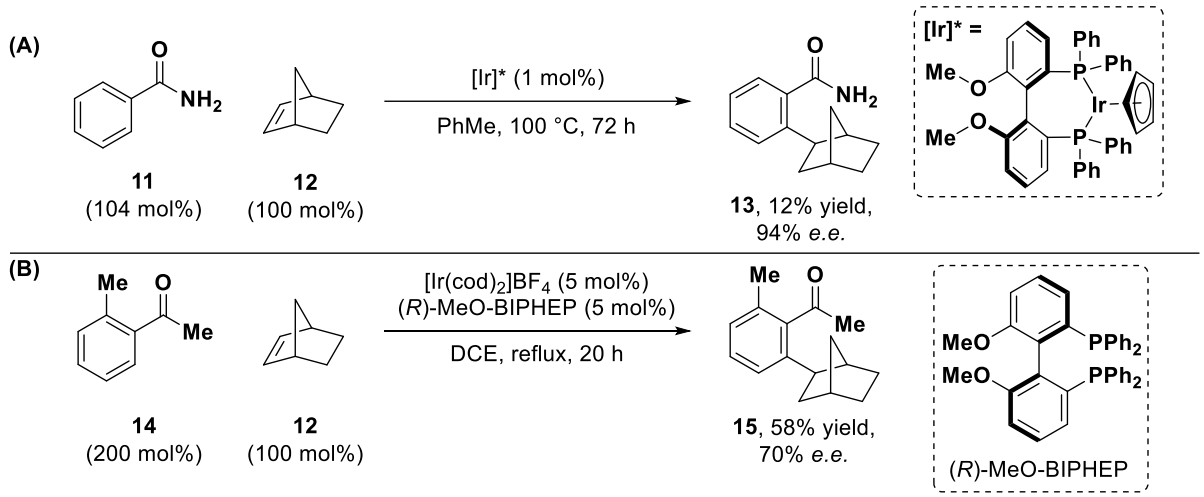
Scheme 4: *(A) Ketone directed enantioselective intramolecular hydroarylations; (B) enantioselective intramolecular hydroheteroarylations using benzimidazoles; (C) enantioselective intramolecular hydroheteroarylations of non-polarised alkenes using a chiral acid.*

1.3 Branch and enantioselective hydroarylation reactions of strained bicyclic alkenes

Early developments into intermolecular enantioselective Murai hydroarylations exploited strained and symmetrical bicyclic alkenes. The symmetry of these systems removes the issue of regiocontrol with respect to the alkene partner (*vide supra*). Additionally, their high steric bulk facilitates high enantioinduction, while their high reactivity enhances C-C bond forming efficiency.

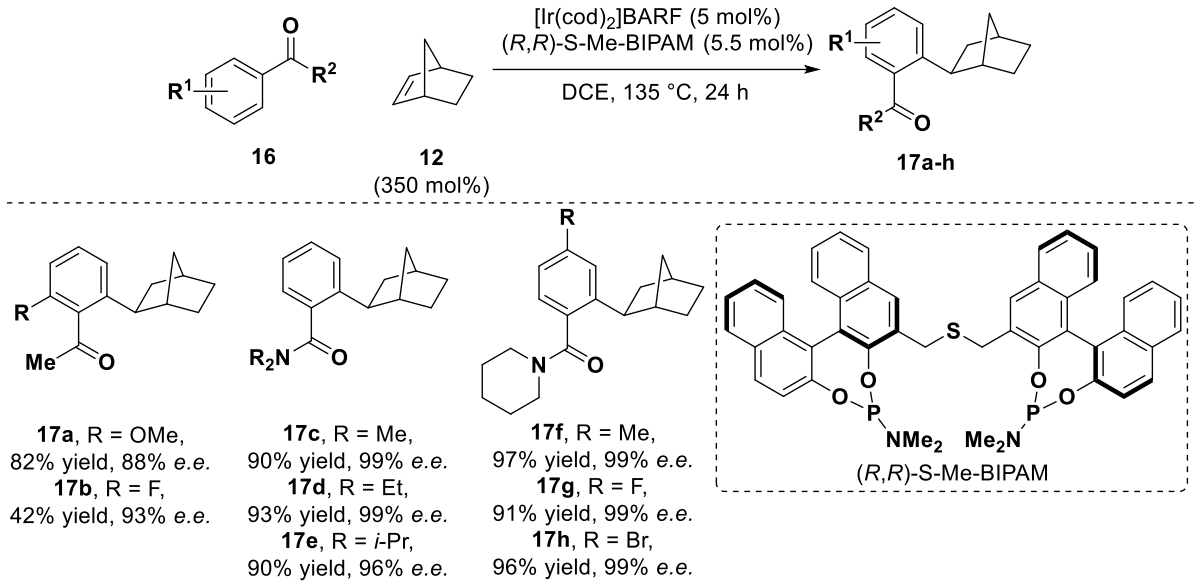
The first reported example of a highly enantioselective Murai hydroarylation process involving a strained bicyclic alkene was demonstrated in 2000 by Togni and co-workers (**Scheme 5A**).[77] Here, a CpIr(I) complex, modified with a chiral bisphosphine ligand, promoted enantioselective intermolecular hydroarylation of norbornene **12** with benzamide **11** to afford **13** in 12% yield and 94% *e.e.* The process was extended further by Shibata and co-workers in 2008 (**Scheme 5B**).[78] In this study, the combination

of a cationic Ir(I) precatalyst and (*R*)-MeO-BIPHEP promoted the reaction between aromatic ketone **14** and norbornene to provide **15** in 58% yield and 70% *e.e.* Note that, compared to the process in **Scheme 5A**, the Shibata protocol offers a higher yield and shorter reaction time, while using a more weakly-coordinating ketone directing group.



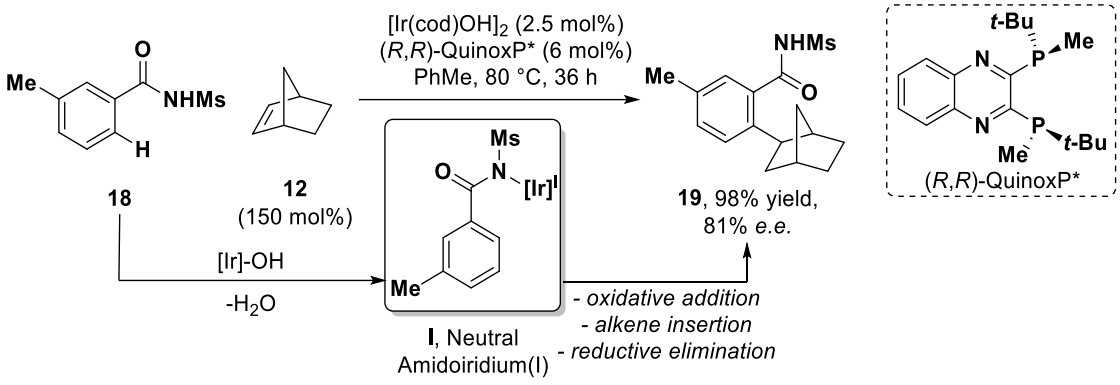
Scheme 5: *(A) Togni's and (B) Shibata's enantioselective hydroarylations of norbornene.*

Building upon the proof-of-concept studies described above, Yamamoto and Shirai developed, and thoroughly exemplified, a highly enantioselective protocol for the hydroarylation of norbornene (**Scheme 6**).[79] As with Shibata's study, a cationic Ir(I) pre-catalyst was used, but this time modified with (*R*,*R*)-S-Me-BIPAM, a sulfide-linked bis(phosphoramidite) ligand. Under these conditions, various aromatic ketones and *N*,*N*-disubstituted benzamides (**16**) participate to provide the targets with invariably high levels of enantioinduction (**17a–h**). For ketone-based systems, *ortho*-substitution on the starting arene (**17a–b**) is required to prevent uncontrollable formation of bis-*ortho*-alkylated products. Conversely, only mono-*ortho*-alkylated adducts were observed when *N*,*N*-disubstituted amide directing groups were employed (**17c–h**). For these substrates, it was postulated that initial mono-*ortho*-alkylation restricts rotation about the acyl-aryl bond, such that subsequent directed C-H bond activation of the remaining *ortho*-site is prevented.



Scheme 6: *Enantioselective hydroarylations of norbornene using (R,R)-S-Me-BIPAM.*

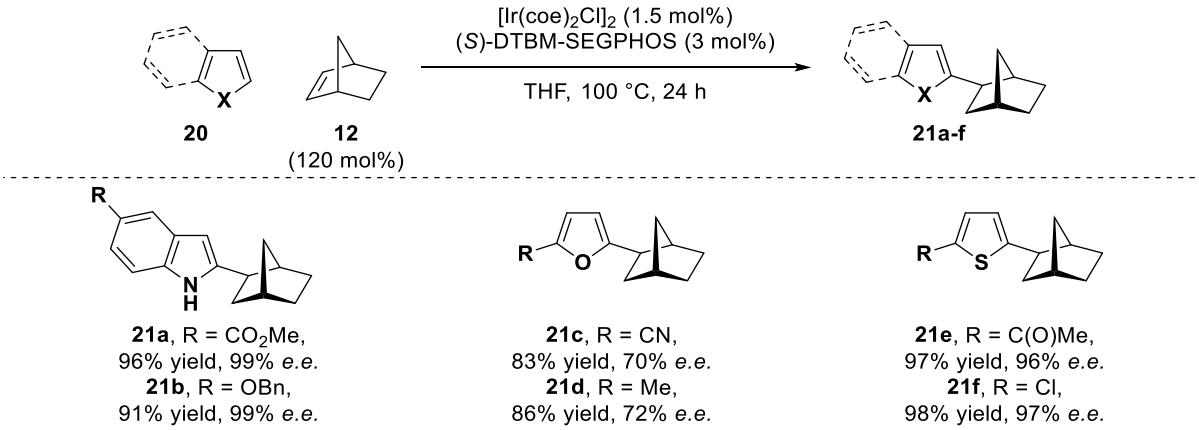
The processes described so far are postulated to proceed *via* carbonyl directed C-H bond activation. An alternative directing approach was reported in 2017 by Nishimura and co-workers, who demonstrated enantioselective hydroarylations of norbornene using an *N*-sulfonylbenzamide directing group (**Scheme 7**).[80] The process employs an Ir(I) pre-catalyst that can function as a base to deprotonate the *N*-sulfonylamide directing group with concomitant loss of water. This generates a neutral amidoiridium(I) intermediate (**I**) that undergoes C-H activation and alkylation. Deprotonation of another equivalent of starting amide by the *N*-Ir moiety enables turnover, such that exogenous base is not required. The use of (*R,R*)-QuinoxP* as the chiral ligand provided **19** with 81% *e.e.* and in excellent yield.



Scheme 7: *Nishimura's amidoridium(I) directed enantioselective hydroarylation of norbornene.*

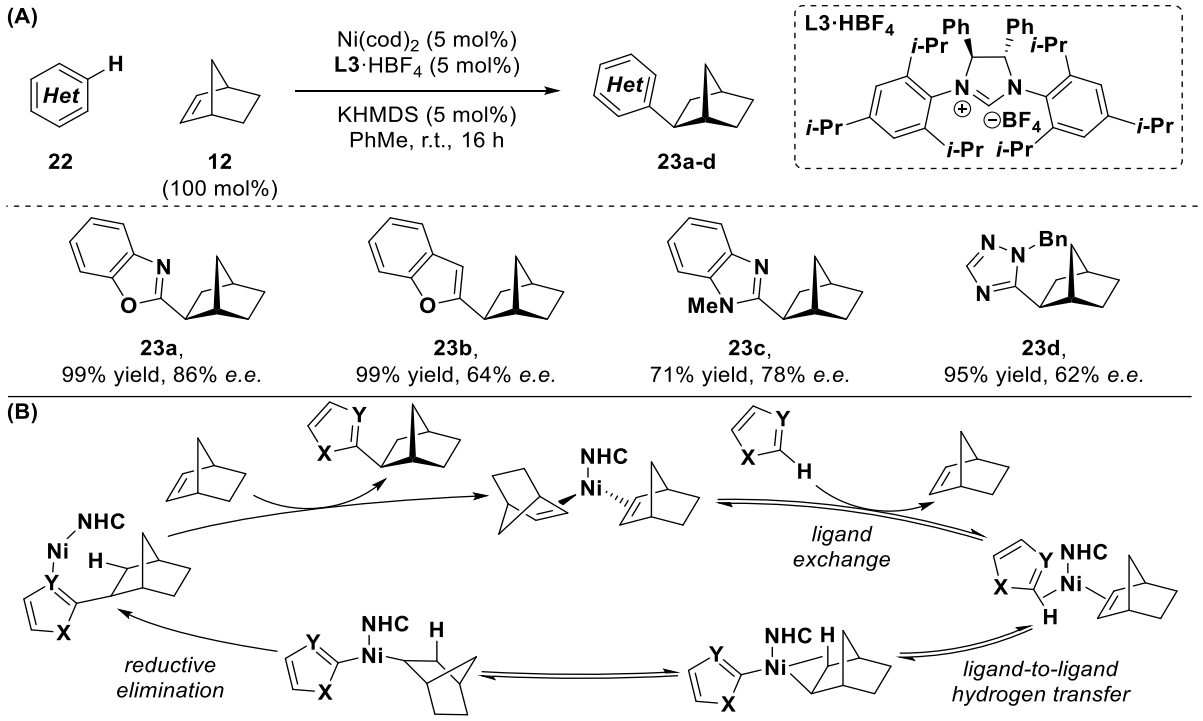
Enantioselective Murai-type hydro*hetero*arylations of strained bicycloalkenes were first realised by Hartwig and Sevov in 2013 (**Scheme 8**).[81] Here, it was shown that the C2-H bond of indoles, thiophenes, pyrroles and furans will add across norbornene **12** using an Ir(I) pre-catalyst modified with DTBM-SEGPHOS. The protocol demonstrates good functional group tolerance and provides the targets with

generally high levels of enantioinduction. For example, reaction of methyl indole-5-carboxylate with norbornene gave **21a** in 96% yield and 99% *e.e.* The most notable feature of these processes is that a directing group is not required; this demonstrates that electronically controlled C-H activation is feasible if the aromatic partner is sufficiently electron-rich.



Scheme 8: *Enantioselective hydroheteroarylations of norbornene developed by Hartwig and Sevov.*

This concept was further illustrated by Montgomery in 2022 (**Scheme 9A**) who used Ni-catalysis in conjunction with NHC ligand **L3** to promote hydroheterorylations of strained bicycloalkenes with electron-rich heteroaromatic substrates.[82] A variety of benzoxazoles, benzofurans, benzimidazoles and 1,2,4-triazoles could be employed to afford corresponding branched products in high yield and *e.e.* Mechanistic investigations were consistent with a ligand-to-ligand hydrogen transfer (LLHT) pathway in which C−H bond activation precedes a rate-determining reductive elimination step (**Scheme 9B**).

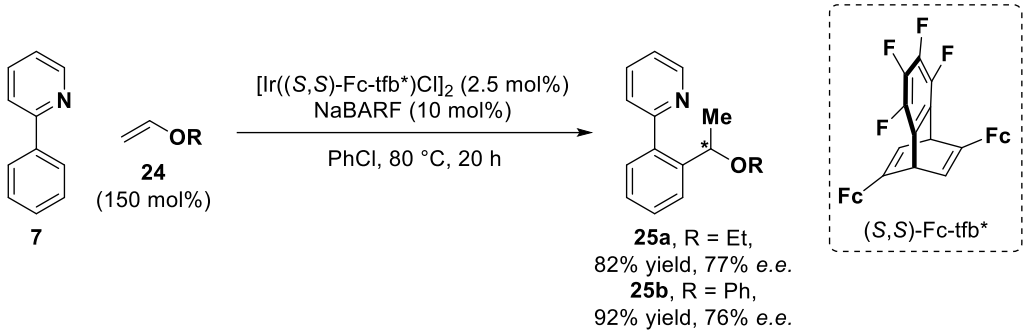


Scheme 9: *(A) Ni-catalysed enantioselective hydroheteroarylations developed by Montgomery; (B) Proposed mechanism.*

1.4 Branch and enantioselective hydroarylation reactions of electron-rich acyclic alkenes

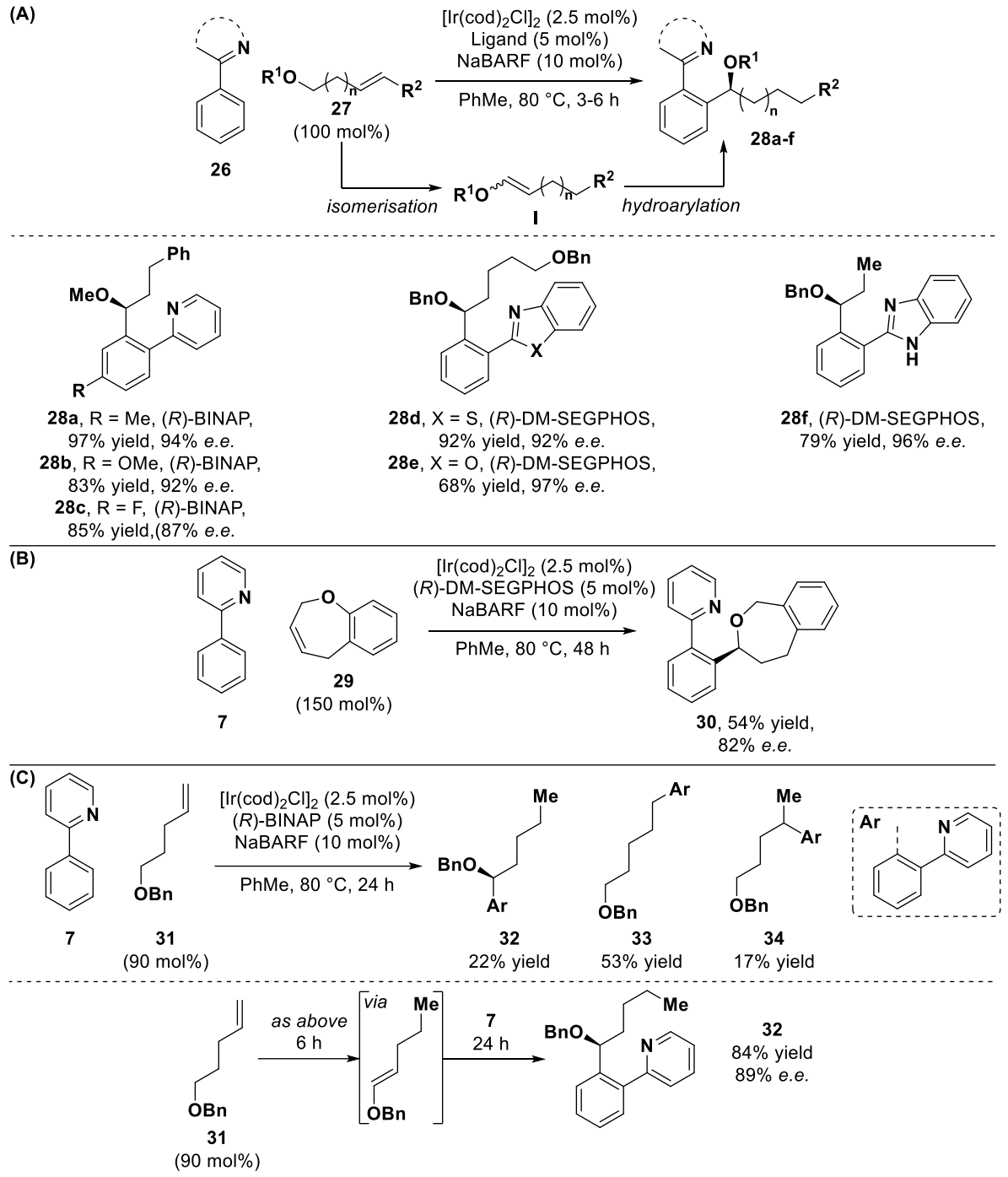
Enantioselective hydroarylation reactions of acyclic, non-strained alkenes are more challenging. A particular issue is that processes of this type must usually address the additional element of Markovnikov versus anti-Markovnikov regioselectivity. Most advances in enantioselective Murai-type hydroarylations of acyclic alkenes have exploited strongly polarised variants, in which there is a natural bias for the regioselectivity of C-C bond formation. More recently, processes that exploit minimally polarised alkenes have emerged, and these are described later.

In 2015, Nishimura and Ebe disclosed Ir(I)-catalysed enantioselective and branch selective hydroarylations of vinyl ethers **24** with 2-phenylpyridine **7** (**Scheme 10**).[83] The group employed a cationic Ir(I) catalyst (formed *in situ*) modified with (*S,S*)-Fc-tfb*, a chiral diene ligand based on the barrelene framework (Fc = ferrocene). Under these conditions, hydroarylation of ethyl and phenyl vinyl ethers occurred in high yields and promising enantioselectivities. For example, **25a** and **25b** were generated in 77% and 76% *e.e.*, respectively. Importantly, the process offers very high regioselectivity with respect to the alkene, likely due to the strong electron donating properties of the ether oxygen (*vide infra*). Although this process does not generate demanding tertiary stereocentres (i.e. those bearing 3-carbon-based substituents), it does demonstrate that enantioselective hydroarylation of acyclic alkenes is feasible, and it also provides an interesting approach to benzylic alcohol derivatives.



Scheme 10: *Nishimura and Ebe's enantioselective hydroarylation of vinyl ethers.*

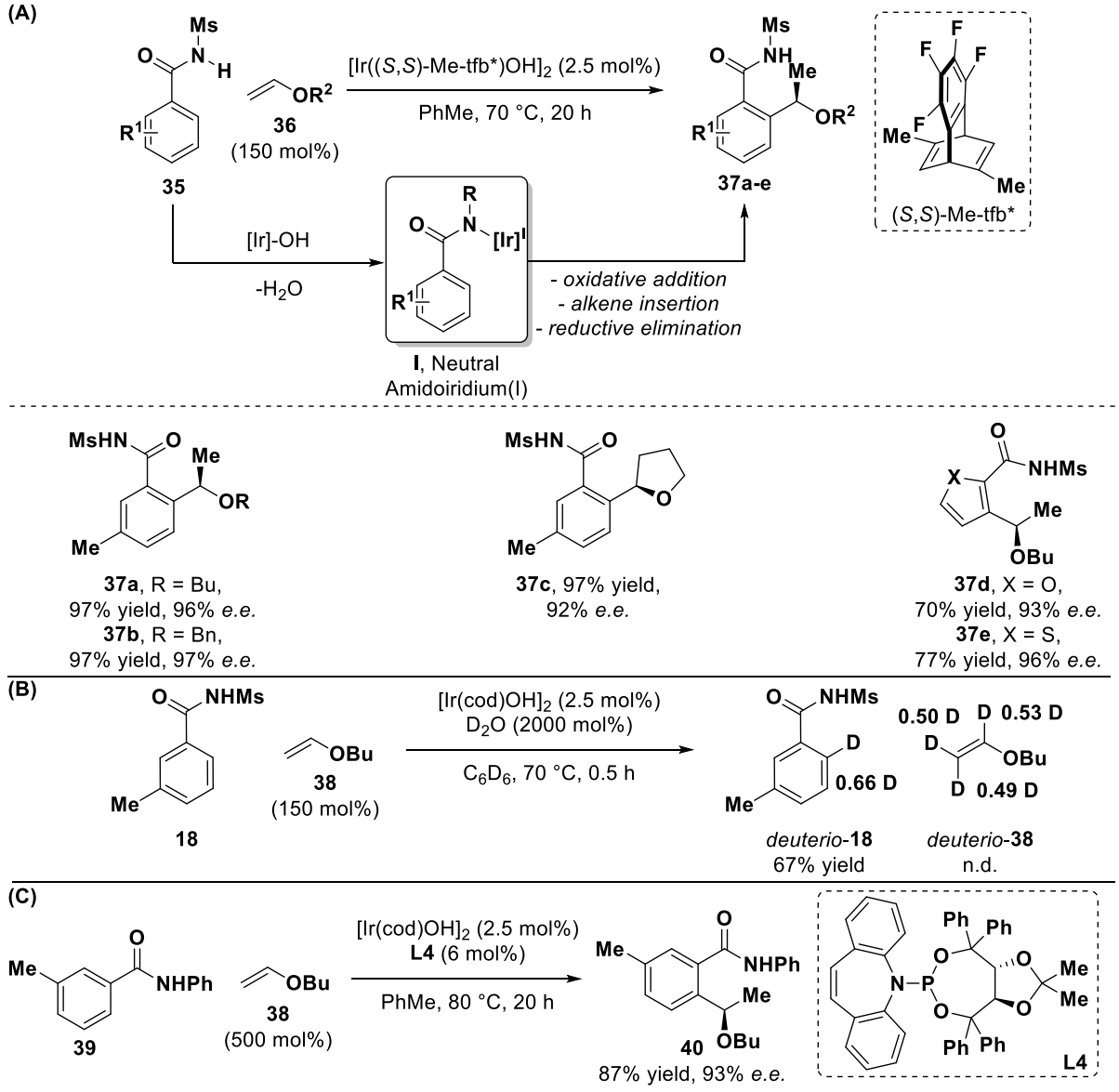
Deuterium labelling studies showed that reversible hydrometallation occurs in the process shown in **Scheme 10**. This observation stimulated cross-couplings of vinyl ethers that are generated *in situ via* olefin isomerisation of alkenyl ethers **25** (**Scheme 11A**).[84] Optimised conditions employ an *in situ* generated cationic Ir(I) catalyst modified with (*R*)-BINAP or (*R*)-DM-SEGPHOS. Under these conditions a range of arenes possessing heterocyclic directing groups are tolerated, and this allows access to alkylated 2-phenyl-pyridines (**28a–c**), -benzothiazoles (**28d**), -benzoxazoles (**28e**) and -benzimidazoles (**28f**). Thorough scope studies revealed that substitution is tolerated at all positions of the aromatic ring. Notably, the methodology was also used to synthesize flavan derivatives by reaction of acetophenone with 2*H*-chromene; this demonstrates that weaker carbonyl-based directing groups are effective. The group later expanded the methodology to a broader range of aromatic ketones, in addition to seven- and eight-membered cyclic alkenes. For example, the isomerisation-hydroarylation reaction of seven-membered alkene **29** with 2-phenylpyridine **7** gave **30** in 54% yield and 82% *e.e.* (**Scheme 11B**).[85] For the processes in **Scheme 11**, hydroarylation occurs after isomerisation to the enol ether and direct coupling of **27** is usually not observed. However, when terminal alkene **31** was used, linear and branched products **33** and **34** were formed in a 3:1 ratio, in addition to target product **32** (**Scheme 11C**). This selectivity issue was resolved by exposing alkene **31** to the Ir(I) catalyst for 6 h prior to addition of 2-phenylpyridine **7**. This modification allowed isomerisation to occur fully before hydroarylation, such that **32** could be isolated in 84% yield and 89% *e.e.*



Scheme 11: *(A) Isomerisation-hydroarylation reactions of (A) acyclic and (B) cyclic alkenyl ethers, and (C) key regioselectivity observations.*

In 2016, Nishimura and co-workers reported Ir(I)-catalysed asymmetric alkylations of *N*-sulfonylbenzamides **35** with vinyl ethers **36** that employ the chiral diene ligand (*S*,*S*)-Me-tfb* (**Scheme 12A**).[86] Here, a hydroxyiridium(I) complex was used, which, as outlined earlier (*cf.* **Scheme 7**), likely forms a catalytically-active neutral amidoiridium(I)-complex *in situ*. The protocol tolerates a variety of vinyl ethers (**37a–b**), as well as a cyclic variants such as **37c**. Certain heteroaromatic substrates are effective, and this allowed access to **37d** and **37e**. Deuterium-exchange studies using D_2O and butyl vinyl ether are consistent with a sequence of reversible oxidative addition of the *ortho*-C-H to the Ir(I)

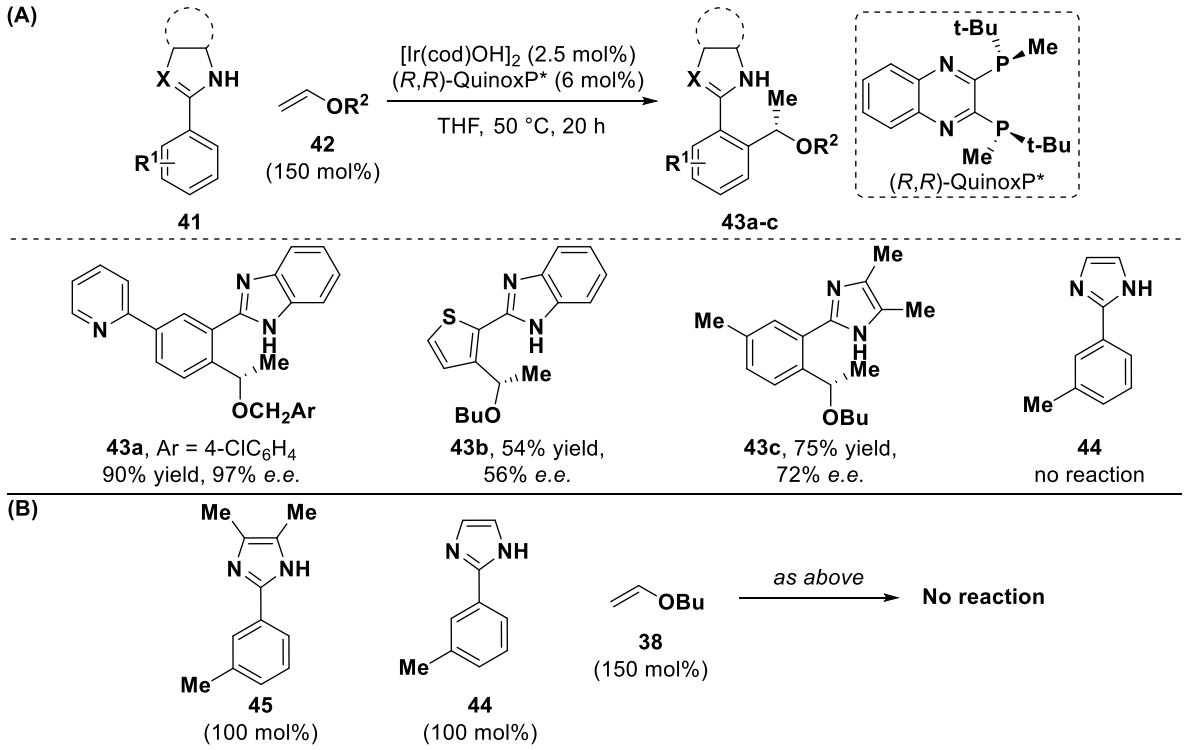
catalyst, followed by reversible and non-selective alkene hydrometallation (**Scheme 11B**). Based on further control experiments, it was proposed that, in fact, alkene hydrometallation is non-productive and C-C bond formation instead proceeds *via* carbometallation (i.e. a modified Chalk-Harrod mechanism). This scenario would nicely rationalise regioselectivity with respect to the alkene – the more electron rich carbon-centre of the enol ether interacts with the more electropositive Ir-centre during migratory insertion. The group later expanded this work to include *N*-arylbenzamide substrates by use of chiral phosphoramidite ligand **L4**, as shown by **40** which was generated in 87% yield and 93% *e.e.* (**Scheme 12C**).[87]



Scheme 12: *(A) Benzamide directed enantioselective hydroarylations of vinyl ethers; (B) Associated deuterium-exchange studies.*

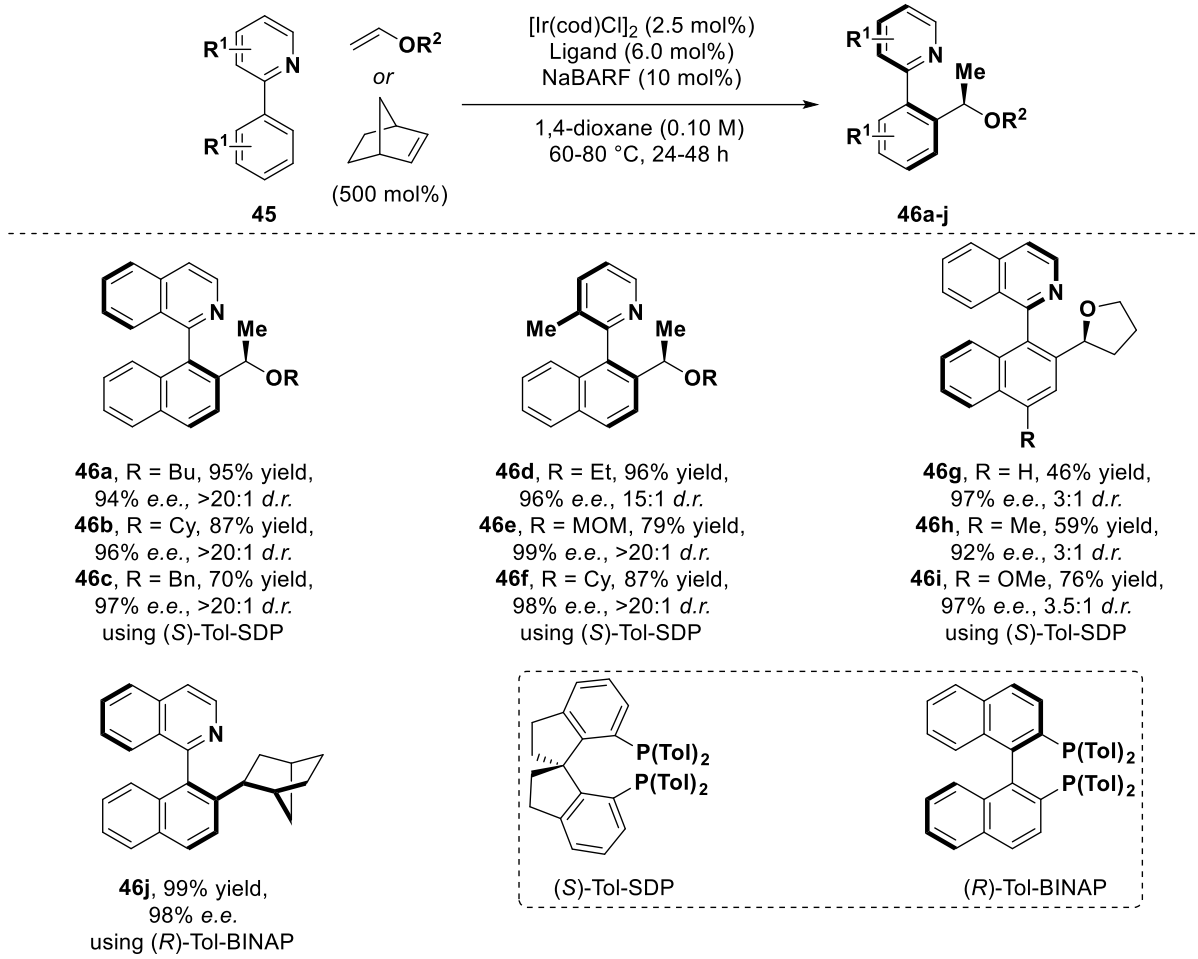
Subsequently, the scope of the directing group was expanded to include pyrroles, imidazoles, indoles and benzimidazoles, this time using (*R,R*)-QuinoxP* as the chiral ligand (**Scheme 13A**).[88] The azole *N*-

H unit is essential for the formation of the amidoiridium(I) species, such that *ortho*-alkylation to give **43a** could be achieved even in the presence of a potentially competing 2-pyridyl group. This result shows how careful tuning of properties of the catalyst and directing group can be used to enforce the desired C-H functionalisation selectivity. Interestingly, C-C bond formation was not observed when 2-(*m*-tolyl)imidazole **44** was used. A competition experiment showed that **44** inhibits the hydroarylation reaction (**Scheme 13B**), perhaps because it coordinates too strongly to the Ir catalyst.



Scheme 13: *(A) Heteroarene directed enantioselective hydroarylations of vinyl ethers; (B) Competition experiment to probe reaction inhibition.*

In 2020, Lassaletta and co-workers reported a method for the installation of axial chirality by Ir(I)-catalysed enantioselective hydroarylations with naphthylisoquinolines of type **45** (**Scheme 14**).[89] Here, using (*S*)-Tol-SDP or (*R*)-Tol-BINAP as the chiral ligand, hydroarylation of enol ethers or bicycloalkenes gave a range of demanding targets in high enantioselectivity and diastereopurity. For example, hydroarylation of acyclic vinyl ethers provided **46a–f** in 70–96% yield and 94–99% *e.e.*, whereas cyclic systems generated **46g–i** in 46–76% yield, and 92–97% *e.e.* Hydroarylation of norbornene provided **46j** in 99% yield and 98% *e.e.* Computational studies suggested that the reaction proceeds *via* a modified Chalk-Harrod mechanism, and that the carbometallation step is stereodetermining.



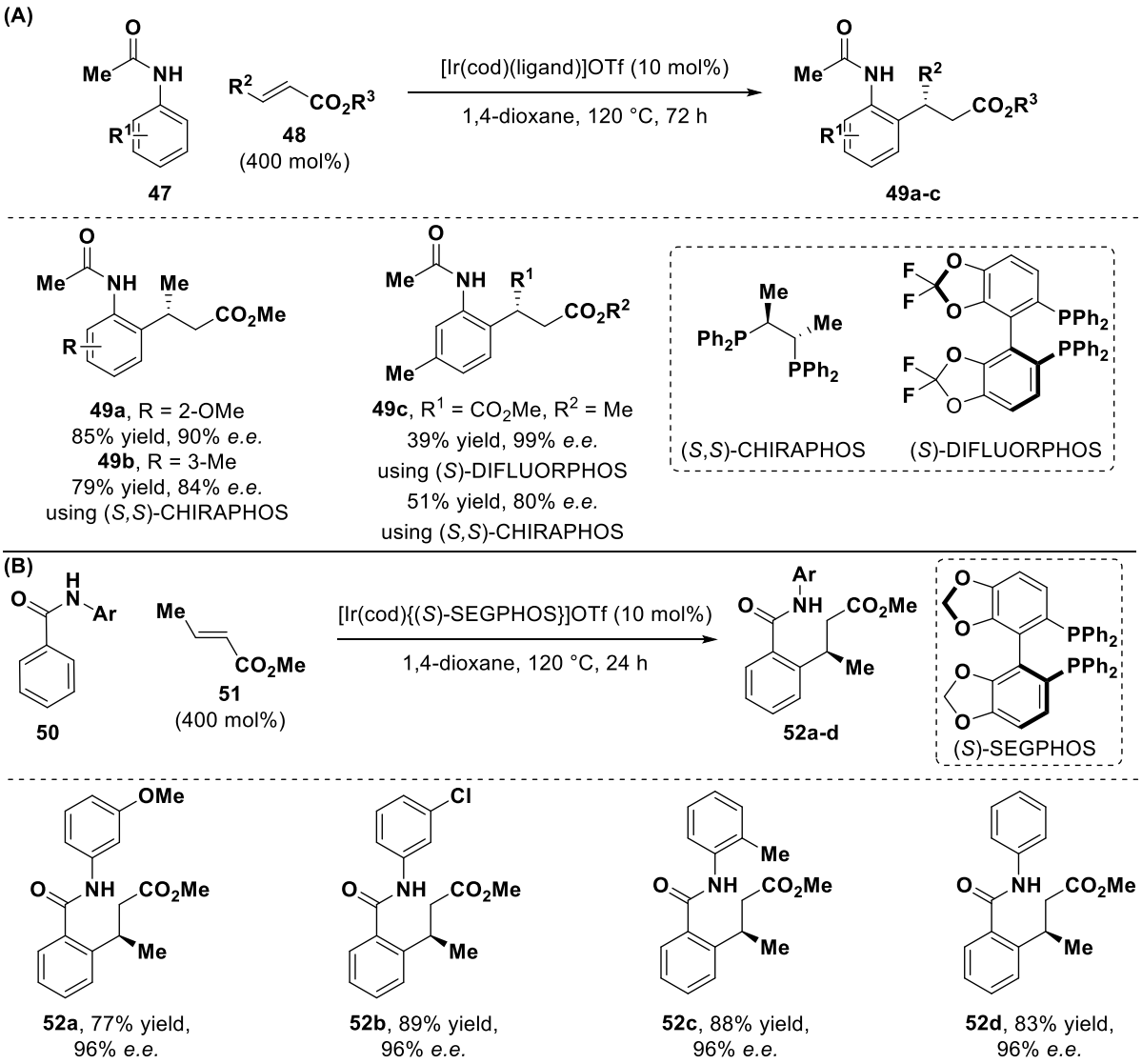
Scheme 14: *Enantioselective and diastereoselective hydroarylations of enol ethers and bicycloalkenes to generate axial chirality.*

1.5 Branch and enantioselective hydroarylation reactions of electron-poor acyclic alkenes

The processes described in the previous section use electron-rich enol ethers where there is a natural preference for C-C bond formation to occur at the α-position. Electron-deficient alkenes are also predisposed to regioselective hydroarylation and this offers an alternative to conventional conjugate addition chemistry.

Shibata and co-workers used acetanilides as directing groups to develop enantioselective hydroarylations of β-substituted acrylates (**Scheme 15A**).[90] Optimised conditions used a cationic Ir(I) pre-catalyst modified with (*S,S*)-CHIRAPHOS or (*S*)-DIFLUORPHOS, to give a range of *ortho*-alkylated products in excellent yield and enantioselectivity. Substitution is tolerated at all positions on the acetanilide, and hydroarylations of (*E*)-methyl crotonate gave **49a, b** in 79–85% yield and 84–90% *e.e.* Variations of the β-substituent (R^2) and the acrylate ester group (R^3) were also explored and uniformly high enantioselectivities were obtained. Mechanistically, it was proposed that reversible and non-selective hydrometallation occurs in advance of irreversible and regioselectivity determining C-C reductive elimination. In contrast to studies described in the previous section, it is noteworthy that the processes in **Scheme 15** generate demanding tertiary benzylic stereocentres in a by-product free

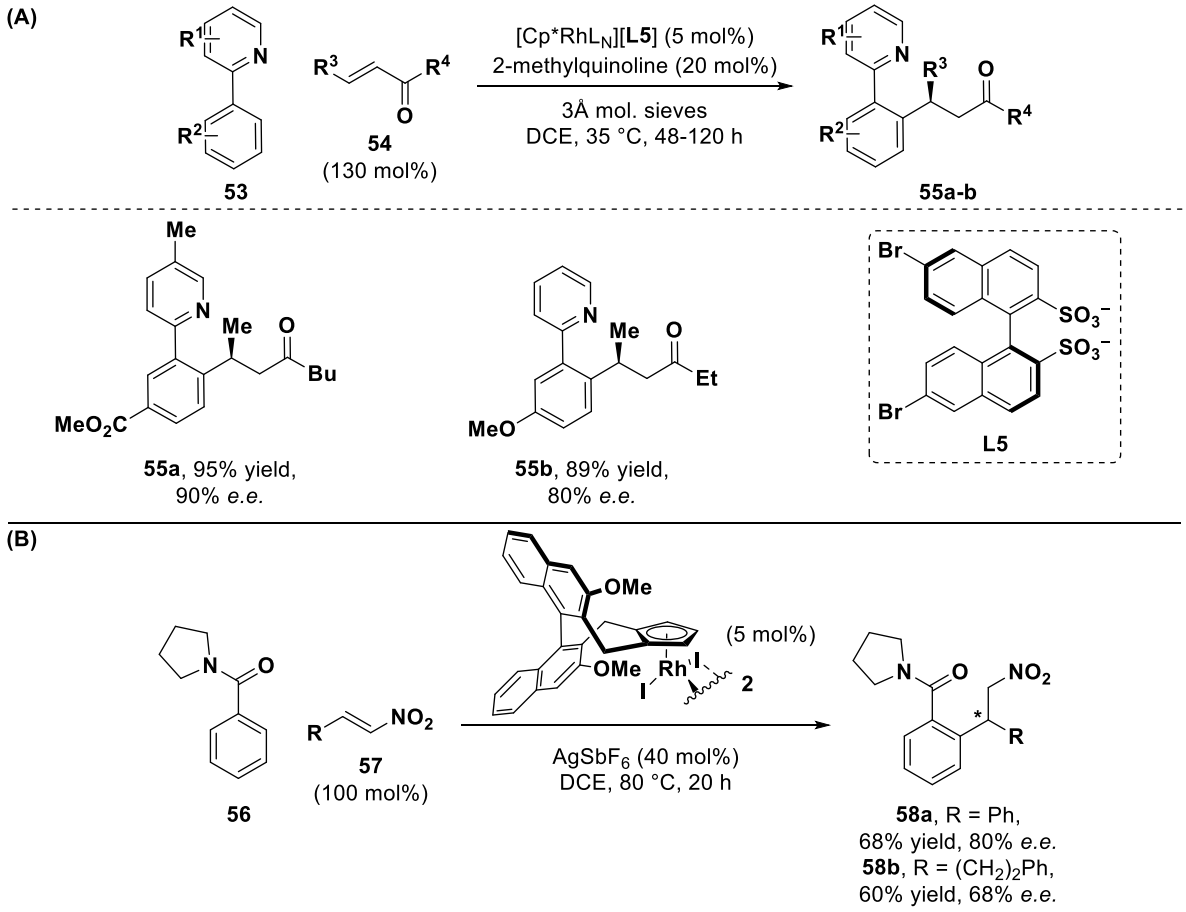
manner. The group extended the methodology to include *N*-arylated benzamide substrates **50** (**Scheme 15B**).[91] Here, a pre-formed, cationic Ir(I) catalyst, modified with (*S*)-SEGPHOS, was employed. Although scope studies were limited, it was shown using β-methyl acrylate, **51**, that the protocol is insensitive to the electronics of the *N*-aryl substituent.



Scheme 15: *Enantioselective hydroarylations of β-substituted acrylates with (A) acetanilides and (B) N-arylated benzamides.*

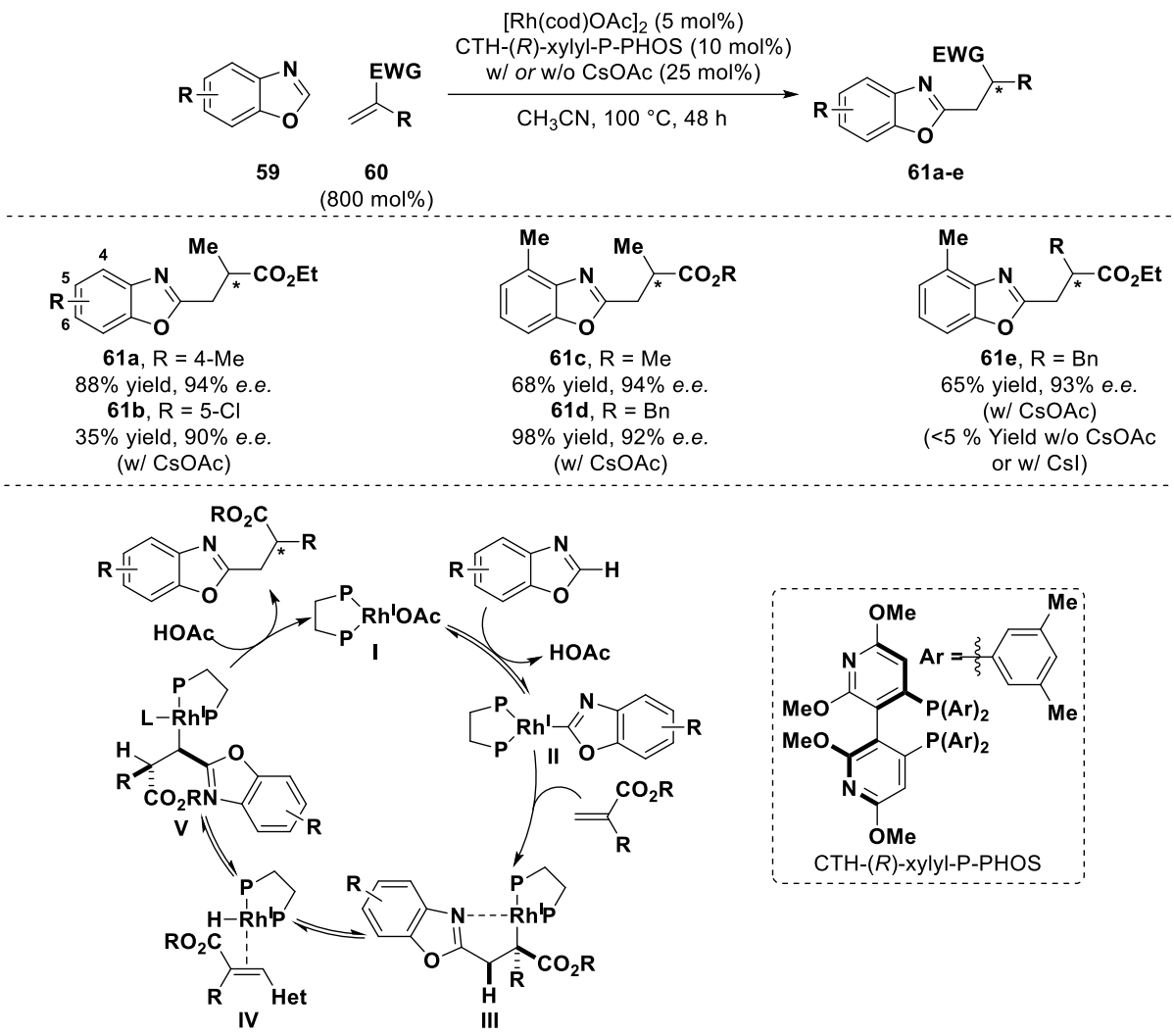
Yoshino, Matsunaga and co-workers have reported mechanistically distinct β-selective and enantioselective hydroarylations of β-substituted enones (**Scheme 16A**).[92] Here, an *N*-heteroarene directing group was employed in combination with a Rh(III)Cp* complex modified with a chiral counterion (**L5**). Under these conditions, **55a** and **55b** were obtained in 90% *e.e.* and 80% *e.e.*, respectively. The mechanism is distinct from the options outlined in **Scheme 2** because it is isohypsic with respect to the Rh-catalyst. Directed *ortho*-C-H-metallation is proposed to occur *via* either concerted metallation-deprotonation or electrophilic aromatic substitution (rather than by C-H oxidative addition). This generates an aryl-Rh(III) species, which carbometallates the enone, in advance of

protodemetallation. By employing a Rh(III) catalyst modified with a chiral Cp unit, Ellman has developed amide directed branch selective and enantioselective hydroarylations of nitroalkenes to generate addition products such as **58a** and **58b** (**Scheme 16B**).[93] The group exemplified this methodology in the total synthesis of (+)-pancratistatin.[94]



Scheme 16: *Enantioselective hydroarylations of (A) β-substituted enones and (B) nitroalkenes.*

Enantioselective hydro(hetero)arylations of electron poor alkenes can also be used to install tertiary stereocentres at the alkene α-position. Rovis and co-workers have reported Rh(I)-catalysed processes of this type using acrylates **60** and benzoxazoles **59** (**Scheme 17**).[95] The methodology is mediated by a Rh(I)-acetate complex modified with CTH-(*R*)-xylyl-P-Phos. Through deuterium labelling and competition experiments, a mechanism was proposed where reversible acetate-assisted C-H activation of the benzoxazole gives Rh(I) species **II**. Migratory insertion of the acrylate gives complex **III**, which undergoes β-hydride elimination (to **IV**) and hydrorhodation to provide **V**. Protonation by acetic acid releases the product and regenerates the active Rh-acetate complex. The protocol offers good scope with respect to the acrylate and benzoxazole partner. In many cases, addition of 25 mol% CsOAc was necessary to achieve optimal efficiencies, possibly because this additional acetate source helps to facilitate conversion of **I** to **II**.

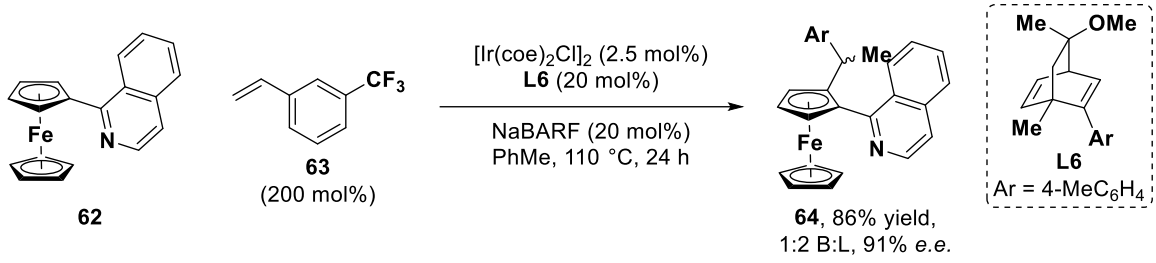


Scheme 17: *Enantioselective hydroheteroarylations of α-substituted acrylates; w/ = with, w/o = without.*

1.6 Branch and enantioselective hydroarylation reactions of minimally-polarised acyclic alkenes

Enantioselective Murai-type hydroarylations of minimally polarised monosubstituted alkenes (i.e. styrenes and α-olefins) are especially challenging because the catalyst system must be designed to enforce both branch selectivity and enantioselectivity. Additionally, minimally polarised alkenes are not electronically predisposed to C-C bond formation, which, in turn, means that bond forming efficiency can be problematic.

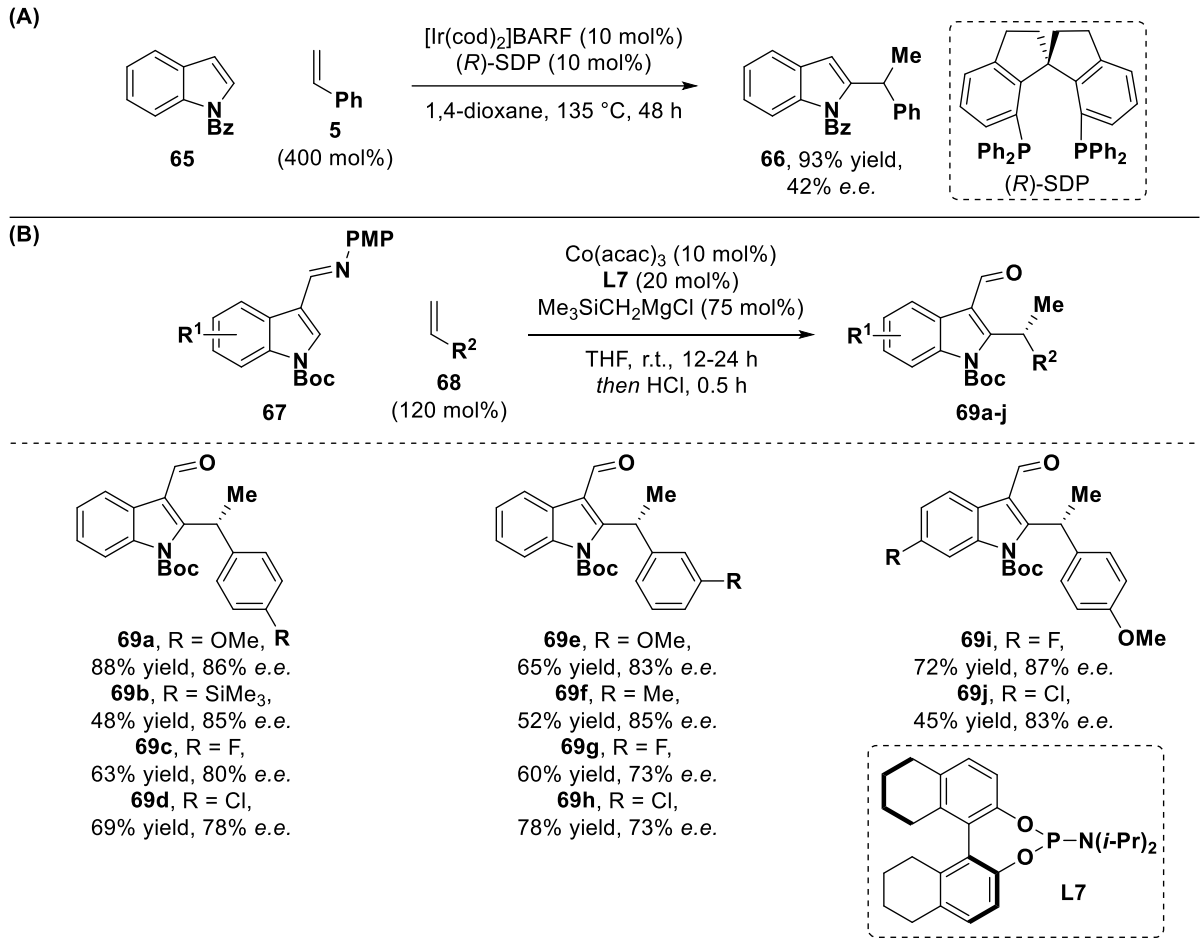
The issues outlined above do not preclude using enantioselective Murai hydroarylation of minimally-polarised alkenes in certain specialised contexts. For example, Shibata and Shizuno disclosed *N*-directed enantioselective alkylations of (isoquinolin-1-yl)ferrocene with alkenes (**Scheme 18**).[96] Under Ir-catalysed conditions, reaction of **62** with **63** gave **64** in 86% yield and 91% *e.e.* (B:L 1:2). In this desymmetrisation process, the site of C-H functionalisation establishes the planar chirality of the product, whereas branched:linear selectivity is a secondary issue. A range of other alkenes were shown to be suitable and these predominantly offered high linear selectivity.



Scheme 18: *Ir-catalysed N-directed enantioselective alkylation of a ferrocene derivative with a styrene.*

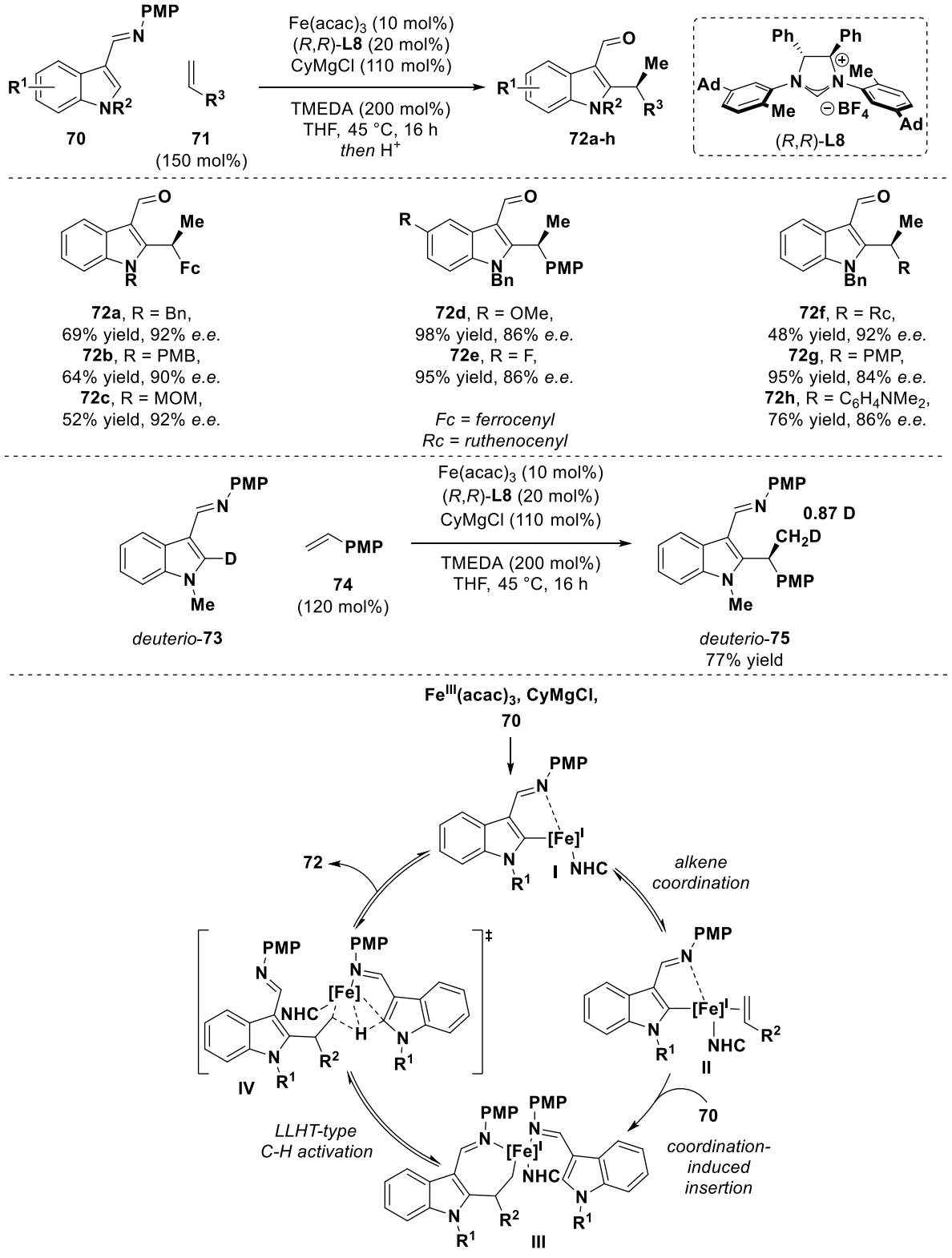
In recent years, there have been significant developments towards generalising Murai-type hydro(hetero)arylations of monosubstituted alkenes as an enantioselective method for the construction of tertiary benzylic stereocentres. Typically, reaction development has harnessed electron-rich heteroarenes bearing relatively strong directing groups. These features likely stabilise the cyclometallated intermediate that arises upon C-H activation, thereby facilitating its engagement with the alkene reaction partner.

In 2012, Shibata and co-workers disclosed a protocol for the C2-selective and branch selective alkylation of *N*-acyl indole derivatives with various alkenes (**Scheme 19A**).[97] Under Ir-catalysed conditions, using (*R*)-SDP as the chiral ligand, hydroarylation of styrene **5** with indole **65** provided **66** in 93% yield and 42% *e.e.* Interestingly, the preference for the linear or branched product could be controlled by employing either an acetyl or benzoyl directing group, respectively. Further, under conditions analogous to those shown in **Scheme 19A**, but using (*rac*)-BINAP as the ligand, branch selective hydroheteroarylation of non-1-ene occurred in 83% yield, but took 7 days, thereby highlighting the diminished reactivity of α-olefins. In 2015, Yoshikai and Lee reported a complementary C2-selective alkylation of indoles related to **65** that offers broad scope for styrene derivatives (**Scheme 19B**).[98] Here, by using a PMP-imine directing group at C3, a cobalt/phosphoramidite (**L7**) catalyst system was shown to promote the C2-alkylation of *N*-Boc-protected indoles **67** with promising enantioselectivities. Me_3SiCH_2MgCl was used to reduce a Co(III) precatalyst to an active Co(I) species *in situ*. Using these conditions, a range of *meta*- and *para*-substituted styrene derivatives participated to provide the corresponding aldehydes **69a–j** after *in situ* imine hydrolysis. For example, hydroheteroarylation of 4-methoxystyrene with *N*-Boc indole-3-carbaldehyde gave **69a** in 88% yield and 86% *e.e.* whereas a 6-fluoroindole-derived substrate gave **69i** in 72% yield and 87% *e.e.* Through deuterium labelling experiments, the authors proposed a Chalk-Harrod-type mechanism. The process is notable for using a relatively abundant metal as the catalyst, which also provides mild, room temperature reaction conditions. However, the process is limited to styrenes and the requirement for installation of an imine directing group detracts from step efficiency.



Scheme 19: *(A) N-Benzoyl directed enantioselective Ir-catalysed hydroheteroarylation of styrene with an indole; (B) Co-catalysed enantioselective hydroheteroarylations of styrene derivatives with indoles.*

In 2017, Ackermann and co-workers showed that a similar transformation could be achieved using Fe(I)-catalysis (**Scheme 20**).[99] Key to the reaction was the use of novel *meta*-substituted *N*,*N*'-diaryl NHC ligand, **L8**. Similar to the examples in **Scheme 19B**, a stoichiometric equivalent of CyMgCl, as well as TMEDA, were required to form the active Fe(I) catalyst *in situ*. The process is limited to styrene-like alkenes, but a variety of protecting groups are tolerated on the indole. For example, hydroheteroarylation of vinylferrocene with a benzyl protected indole gave **72a** in 69% yield and 92% *e.e.*

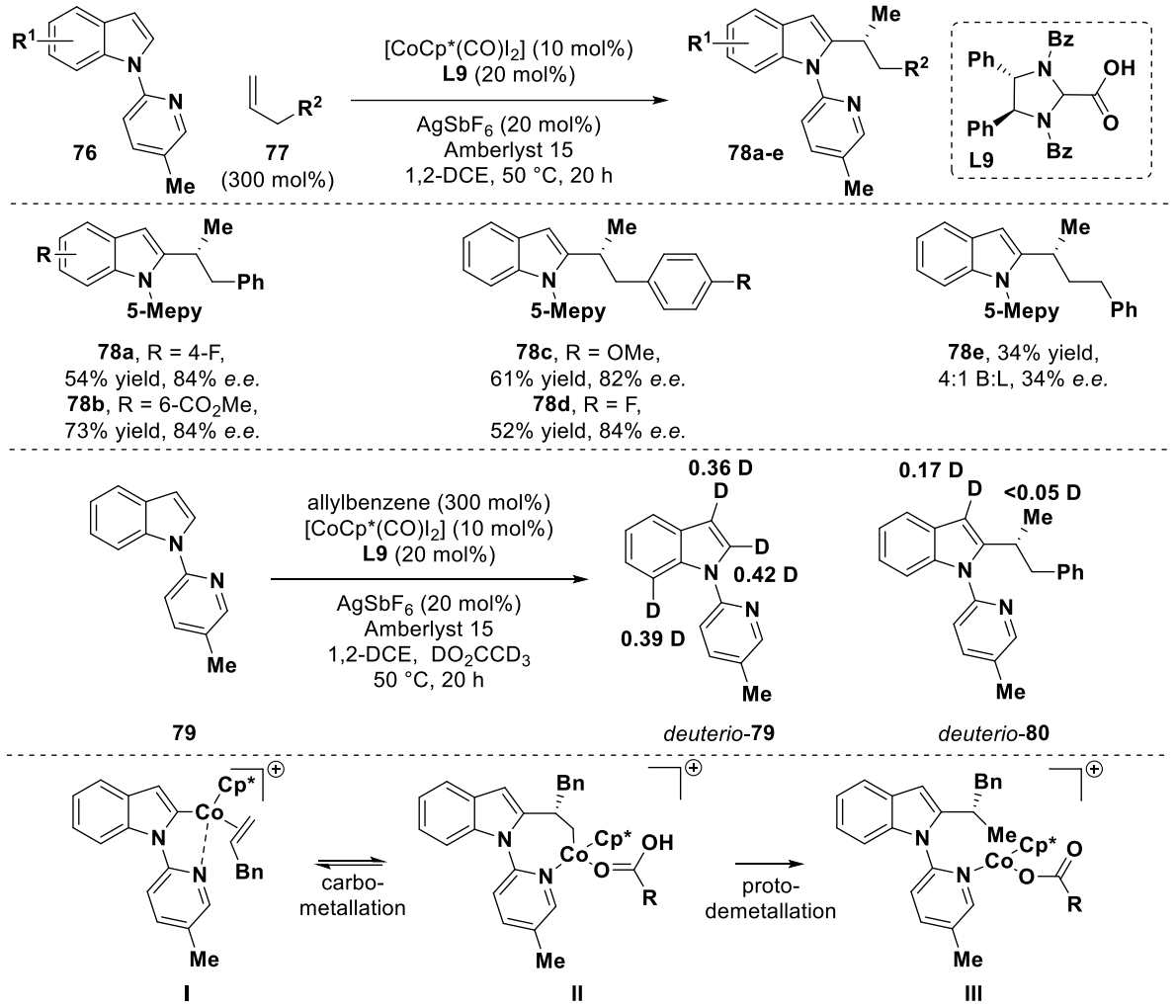


Scheme 20: *Ackermann's Fe-catalysed hydroheteroarylations of styrene-like alkenes via a LLHT mechanism.*

A deuterium labelling study showed very high levels of deuterium transfer from the indole C2 position (*deuterio*-**73**) to the methyl group of the product, *deuterio*-**75** (**Scheme 20**). Based on this, and with the support of computation, it was proposed the C-H cleavage occurs through an inner-sphere, ligand-to-ligand-hydrogen-atom-transfer (LLHT) mechanism. Following imine-directed insertion into the C-H

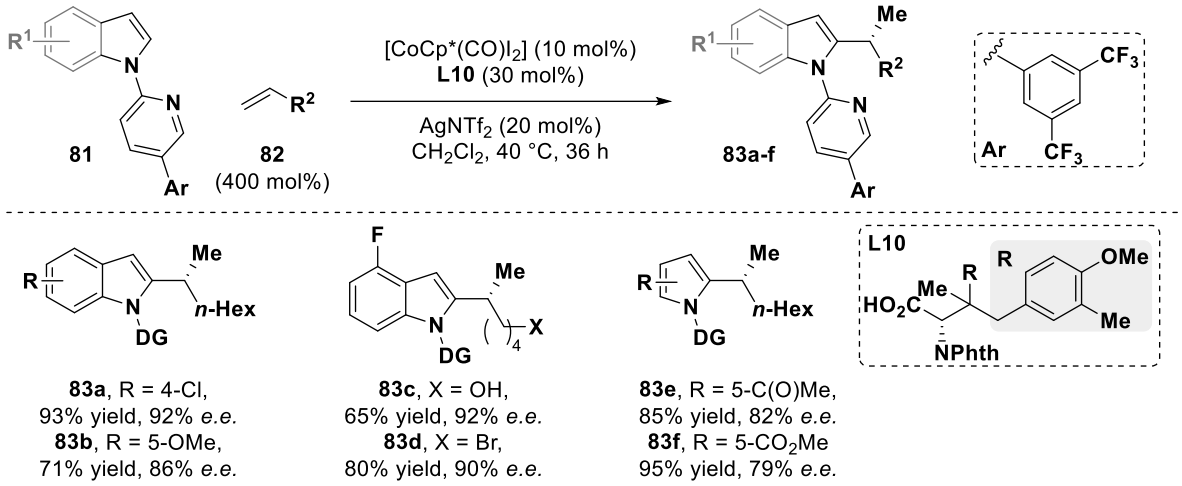
bond of **70** and alkene coordination (**I** to **II**), irreversible carbometallation is induced by ligation of a second equivalent of substrate (**III**). The Fe(I) species then transfers the C2-hydrogen atom from the second equivalent of **70** by a reversible LLHT mechanism (**III** to **IV**).

In a significant advance, Ackermann and co-workers subsequently developed a Co-catalysed protocol for the C2-selective and enantioselective alkylation of indoles using allylarenes (**Scheme 21**).[100] In this work, a chiral carboxylic acid **L9** was used to induce asymmetry and an *N*-pyridyl-based directing group was employed on the indole. The protocol offers good scope with respect to the indole and alkene components. Notably, as opposed to other Co-catalysed processes (*cf.* **Scheme 19B**), the developed "Grignard-free" conditions tolerate substrates featuring electrophilic functional groups, such as esters (**78b**, 73% yield, 84% *e.e.*). Reaction efficiency and branch selectivity are reduced when the R^2 substituent is moved further from the alkene; for example, **78e** was formed in 34% yield, 34% *e.e.*, and with 4:1 branched:linear selectivity. Deuterium exchange studies using DO_2CCD_3 revealed deuterium incorporation at the 2-, 3- and 7-positions of the indole substrate (*deuterio*-**79**), and minimal deuterium incorporation at the methyl group of the product, *deuterio*-**80**. With the support of computational studies, it was proposed that **L9** mediates enantiodetermining protodemetallation (**II** to **III**). This mechanism contrasts the Co-catalysed hydroheteroarylations in **Scheme 19B**, where a reductive elimination step completes the catalytic cycle.



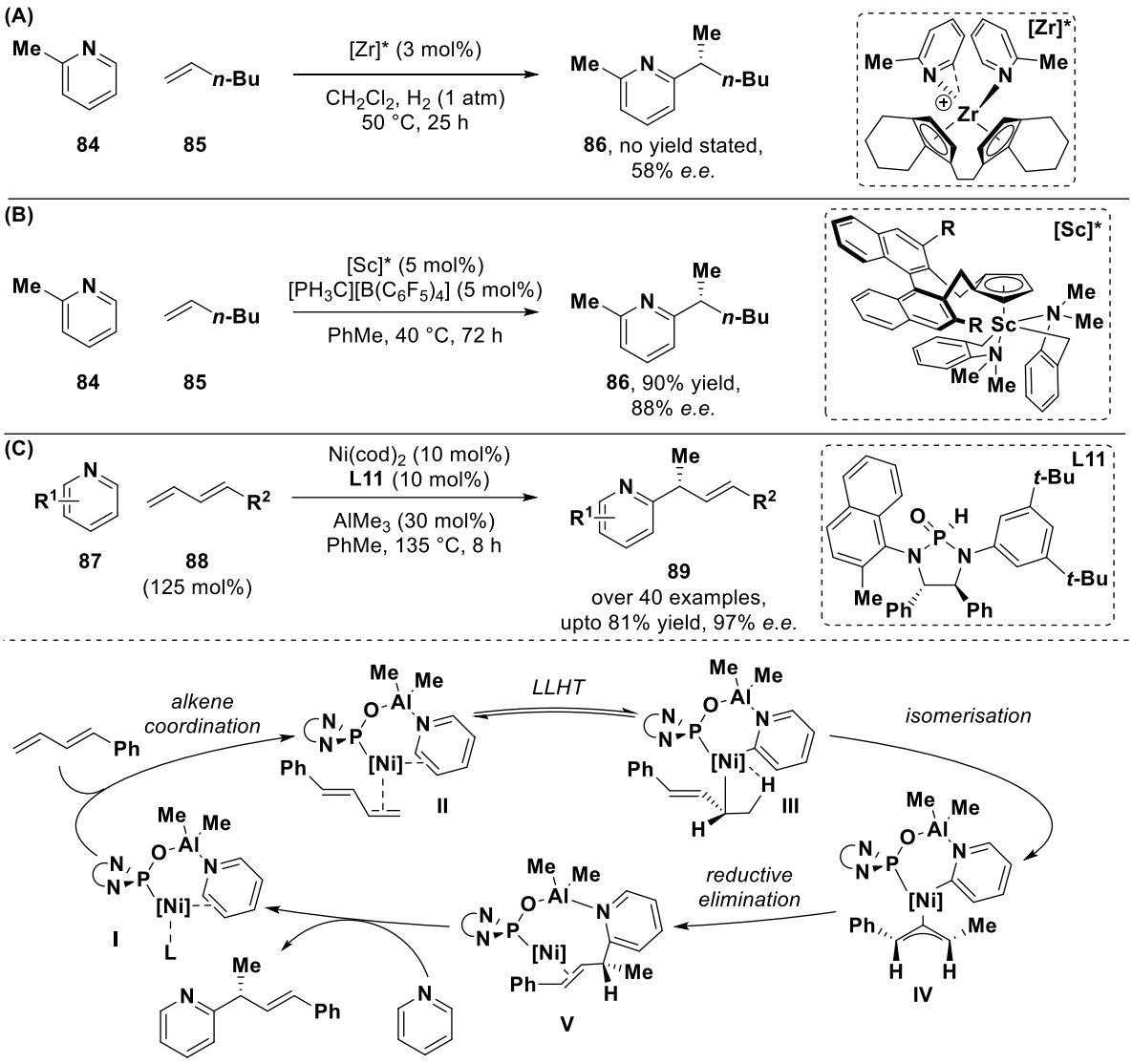
Scheme 21: *Co-catalysed C2-selective and enantioselective alkylations of indoles using allylarenes.*

This approach was furthered in 2021 by Hong and Shi to include aliphatic alkenes, by harnessing non-covalent interactions.[101] Under Co-catalysed conditions in conjunction with chiral amino acid-derived ligand **L10**, a range of indoles and pyrroles were selectivity alkylated at the C-2 position to afford enantioenriched branched products (**Scheme 22**). Indoles bearing electron-deficient (**83a**) or electron-rich (**83b**) groups were tolerated. Likewise, employment a range of aliphatic alkenes, including those with synthetically useful functional groups (**83c**, **83d**), could be used to afford the desired products in high yield, alkene regiospeicficity (B:L 11:1 – >20:1) and with good enantiocontrol. Extension of the substrate scope to include C-3 functionalised indoles was unsuccessful, and only linear products were obtained, preseumably due to steric hindrance. Use of unsubstituted pyrrole under standard conditions was unyielding; however, pyrrole substrates bearing electron-withrawing groups were found to be suitable (**83e**, **83f**). From supporting DFT calculations, it was proposed that π-π stacking occurs between aryl substituents associated with the directing group and ligand, respectively. This generates a chiral pocket which facilitates rate- and enantiodetermining alkene carbometallation. This contrasts to Ackermann's studies, in which enantiodetermining protodemetallation is proposed (*cf.* **Scheme 21**).



Scheme 22: *Hong and Shi's Co-catalysed C-2 alkylation of indoles and pyrroles using aliphatic alkenes.*

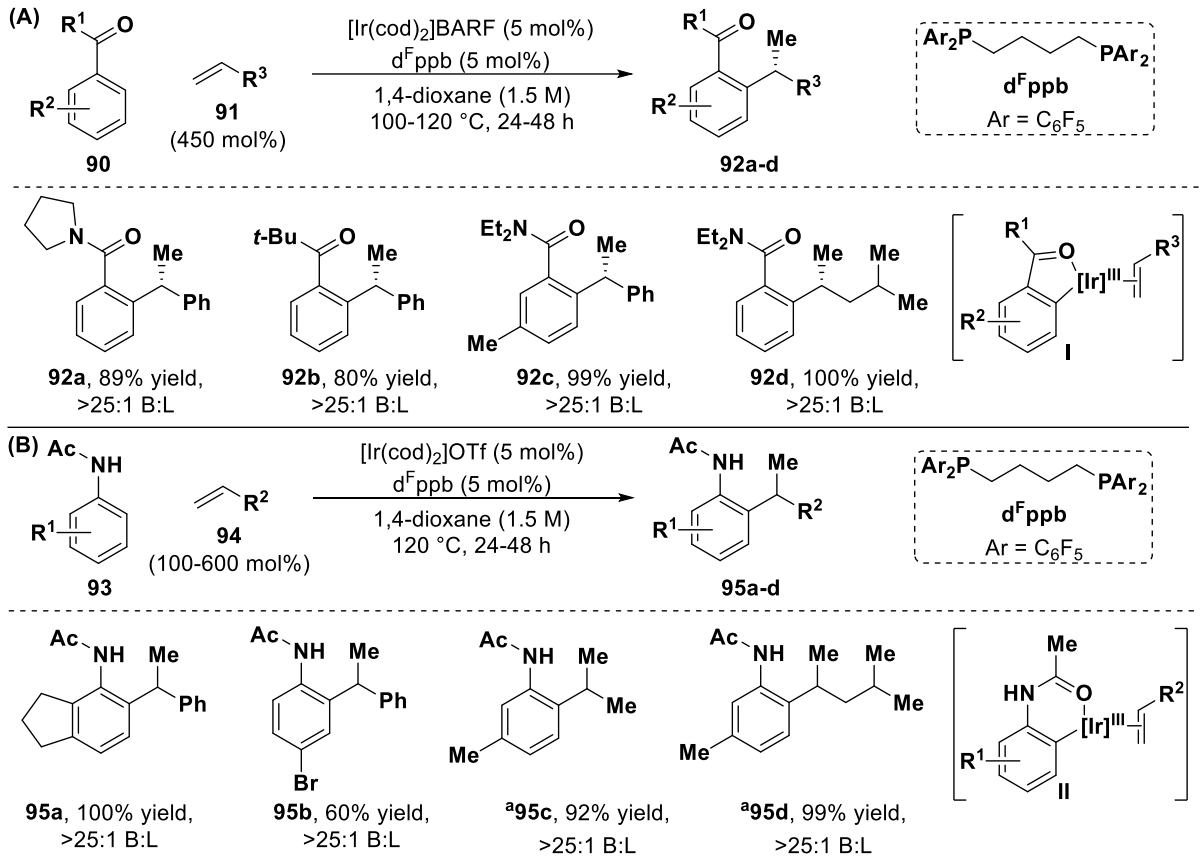
Several important reports exist in which a directing group is not required to promote branch and enantioselective hydroarylation of minimally-polarised aliphatic alkenes. As described in **Scheme 8**, non-directed C-H activation is feasible if the aromatic partner is sufficiently electron-rich. In 1994, Jordan reported an enantioselective alkylation of picoline with 1-hexene, catalysed by a zirconocene complex (**Scheme 23A**).[102] Promisingly, this generated **86** in 58% *e.e.* An improved process was reported by Hou which generated **86** in 88% *e.e.* using a cationic half-sandwich Sc(IV) alkyl complex (**Scheme 23B**).[103] A variety of substrates were suitable under the reaction conditions; however, the scope was limited to C-2 functionalised pyridines to prevent catalyst deactivation. This limitation to C-2 functionalised pyridines was overcome by Huang and Ye who disclosed enantioselective C-2 alkylations of non-functionalised pyridines using 1,3-dienes by employing a Ni-Al bimetallic catalyst in conjunction with phosphine oxide ligand, **L11** (**Scheme 23C**).[104] Resultantly, a broad array of 1,3-dienes could be employed to afford branched products of type **89** (over 40 examples, upto 81% yield, 97% *e.e.*). From stoichiometric experiments, it was proposed that phosphine oxide **L11** acts as a linker between the pyridine-bound Al-centre and the Ni-complex to direct reactivity towards the pyridine C-2 position. It was postulated from deuterium labelling studies and supporting DFT calculations that C-H activation proceeds *via* a reversible LLHT mechanism (**II** to **III**). Subsequent isomerisation of η^1 to η^3 allylic Ni-complex gives **IV** before reductive elimination affords **V**. It is thought that this final step is both rate- and enantiodetermining.



Scheme 23: *Non-directed, branch selective and enatioselective hydroarylations of minimally polarised alkenes using pyridine substrates by (A) Jordan, (B) Hou and (C) Huang and Ye.*

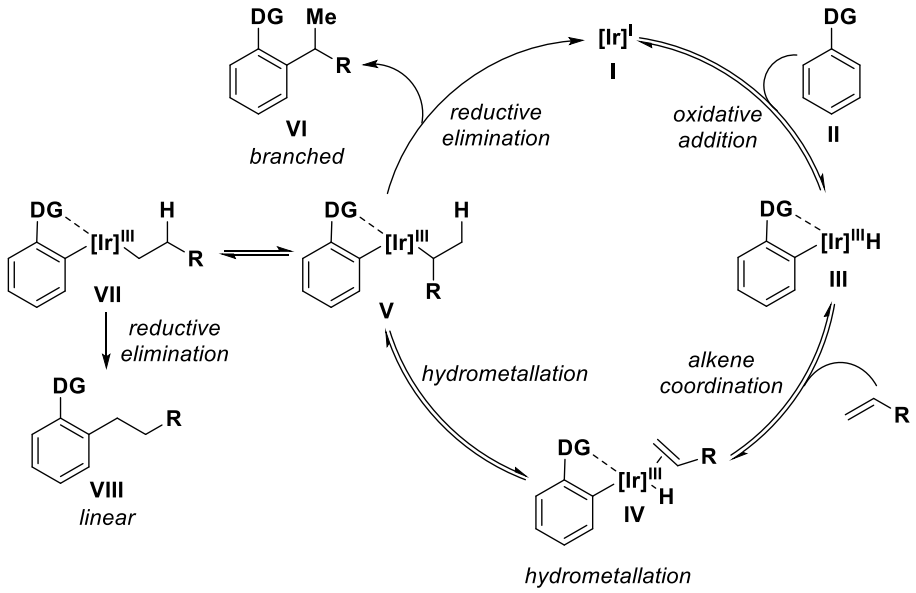
1.7 Hydroarylation processes developed by the Bower group

In 2014, Dr Giacomo Crisenza developed a protocol for the branch selective hydroarylation of styrenes and aliphatic alkenes with aromatic coupling partners of type **90** (**Scheme 24A**).[105] This chemistry relies on a cationic Ir(I) catalyst used in conjunction with electron-deficient, wide bite angle bisphosphine ligand, 1,4-bis(di(pentafluorophenyl)-phosphino)butane (d^Fppb). Under these conditions, substrates bearing amide- or ketone-derived directing groups were employed to deliver the corresponding branched products in high yield and site-selectivity *via* a 5-membered chelate, **I**. By altering the reaction conditions, acetanilides **93** were also found to be suitable substrates; in this manifold, it is proposed the reaction proceeds *via* a 6-membered chelate, **II** (**Scheme 24B**).[106]



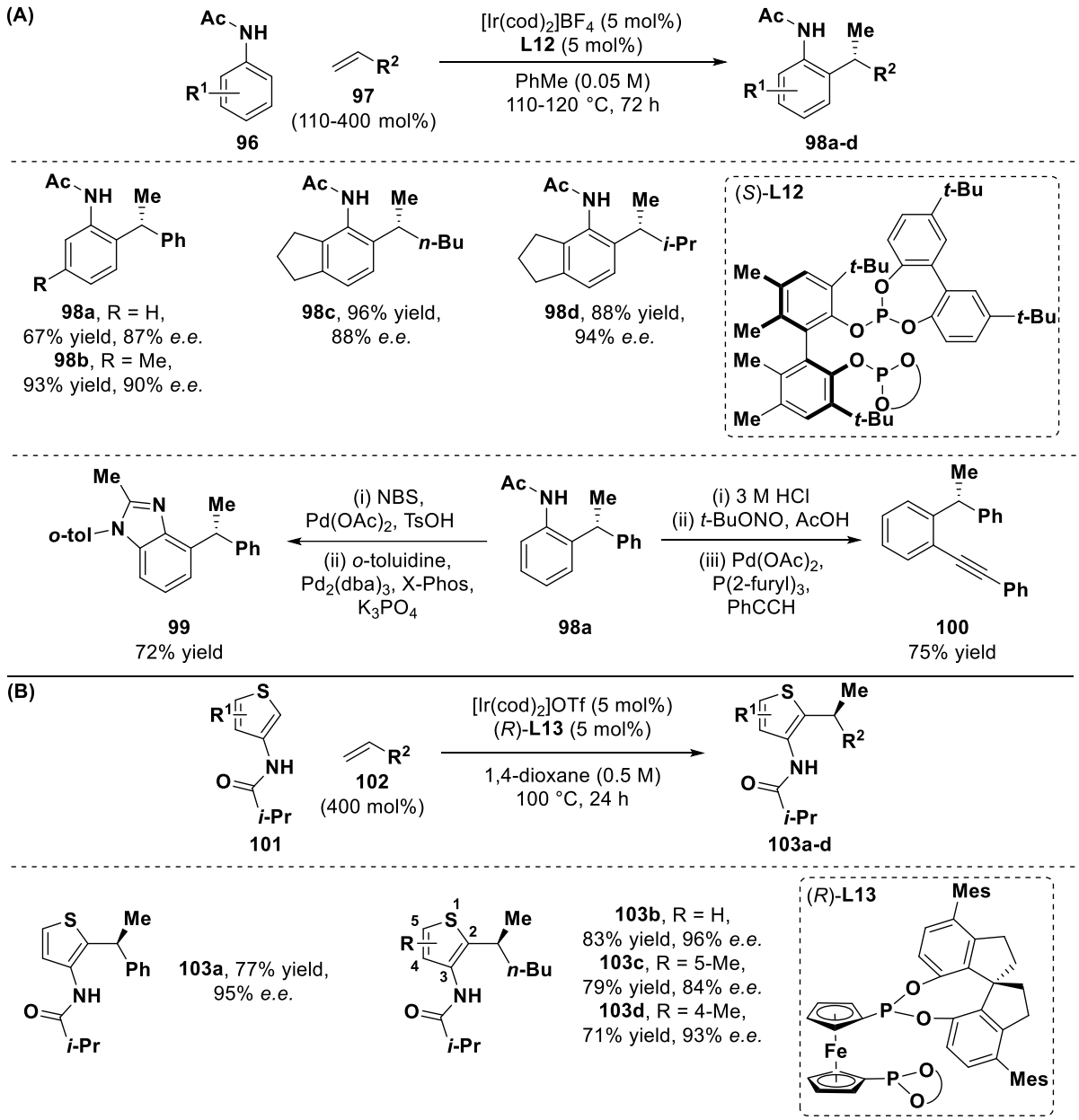
Scheme 24: *Branch selective Ir(I)-catalysed hydroarylation reactions developed by the Bower group. [a][Ir(cod)2]BARF, 1,2-DCB used.*

From ^{13}C kinetic isotope effect (KIE) studies and deuterium labelling and exchange experiments, it was proposed that *ortho*-C-H oxidative addition of the Ir-catalyst into the *ortho*-C-H bond (**I→III**) precedes reversible hydrometallation of the coordinated alkene (**IV→V**) (**Scheme 25**). From **V**, irreversible C-C reductive elimination affords **VI** and completes the catalytic cycle. It is thought that electron-deficient and wide bite angle ligand d^Fppb destabilizes **V** to a greater extent than **VII** (due to a more hindered steric environment) thus increasing its propensity to undergo C-C reductive elimination.



Scheme 25: *Proposed mechanism for branch selective hydroarylations using d^{F}ppb.*

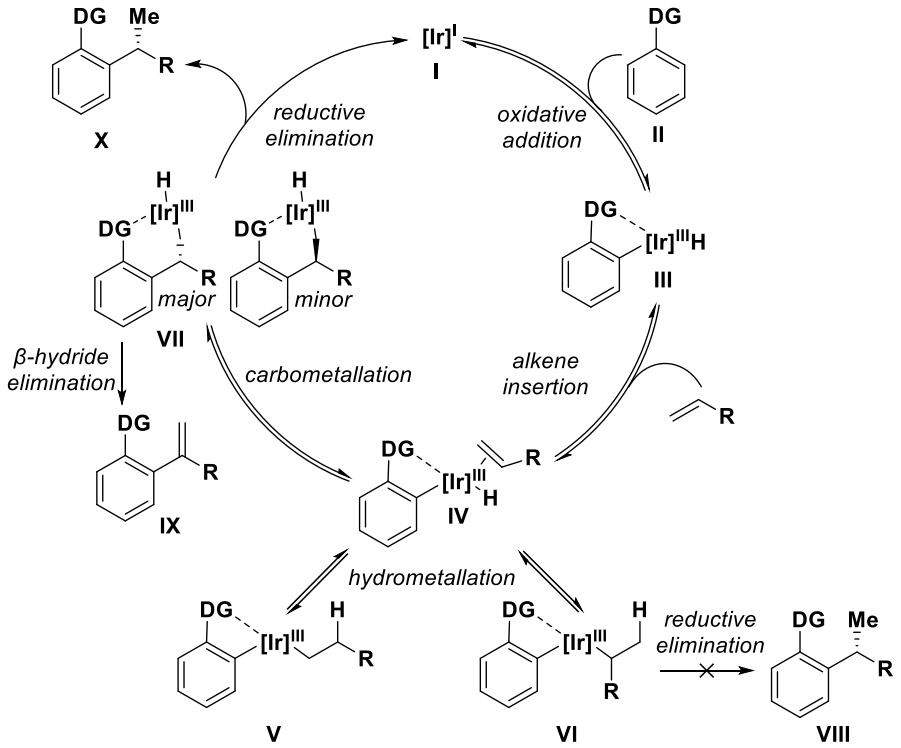
With a non-enantioselective methodology in hand, investigations into developing an asymmetric analogue were pursued by Dr Simon Grélaud and Dr Phillippa Cooper through modular ligand design.[107] With desirable ligand specifications known (electron-deficiant and wide-bite angle), bisphosphonite ligand **L12** was developed and used in conjunction with $[Ir(cod)_2]BF_4$ for the enantioselective and branch selective hydroarylation of styrene and aliphatic alkenes using anilide derivatives **96**, (**Scheme 26A**). Under these conditions a broad range of substrates were tolerated and even challenging aliphatic alkenes participated efficiently; for example, hydroarylation of 1-hexene gave **98c** in 96% yield and 88% *e.e.* Further, the anilide unit of the product could easily be derivatised, either by incorporation into an eventual heterocycle (**99**), or *via* the intermediacy of an aryl diazonium (**100**). Enantioselective hydro*hetero*arylations of styrenes and aliphatic alkenes were also developed, this time using modular SPINOL-derived bisphosphonite ligand **L13**, which was developed to meet the required ligand specifications discussed previously (**Scheme 26B**). As such, thiophene **101**, bearing an amide-derived directing group at C-3, could be employed with styrene (**103a**, 77% yield, 95% *e.e.*) or aliphatic alkenes (**103b-d**, up to 83% yield, 96% *e.e.*) to deliver the corresponding branched products.



Scheme 26: *(A) Ir(I)-catalysed enantioselective and branch selective hydroarylations of styrenes and α-olefins using anilide derivatives; (B) Related enantioselective hydroheteroarylation reactions.*

The mechanism of the process in **Scheme 26A** was probed by in-depth experimental studies, leading to the working hypothesis shown in **Scheme 27**. Following formation of active catalyst, **I**, reversible directed C-H oxidative addition of **II** forms **III**. Reversible alkene coordination (**III** to **IV**) and reversible alkene hydrometallation generates linear and branched intermediates **V** and **VI**. These are non-productive, and instead, natural abundance ^{13}C KIE experiments indicated that reversible carbometallation from **IV** generates **VII** in advance of irreversible and turnover limiting C-H reductive elimination. A key feature of both of the ligands shown in **Scheme 26** is that their wide bite angle enhances both reaction efficiency and branch selectivity. Overall, the protocol offers a viable alternative

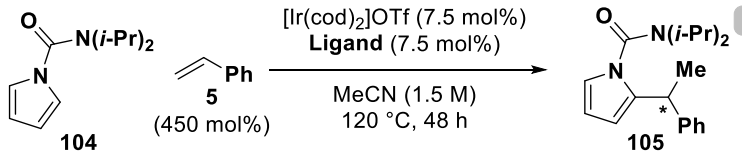
to problematic Friedel-Crafts reactions and sets the stage for the development of related by-product free functionalisations of benzenoid systems.



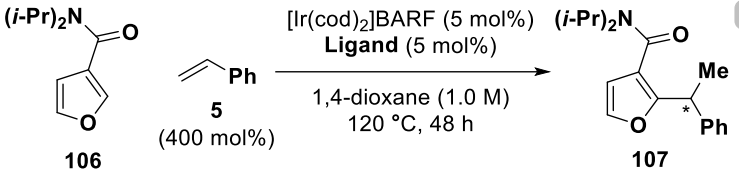
Scheme 27: *Proposed mechanism for the Ir(I)-catalysed enantioselective and branch selective hydroarylations of styrenes.*

1.8 Cooper's investigations into enantioselective hydroheteroarylations of styrene

As shown above, SPINOL-derived bisphosphonite ligands of type **L13** facilitate the branch- and enantioselective hydroheteroarylation of styrene and aliphatic alkenes with thiophene substrates. Development of analogous hydroheteroarylation reactions using corresponding pyrrole and furan substrates would significantly increase the utility of the methodology. As such, initial studies into expanding the substrate scope were conducted by Dr Phillippa Cooper (**Table 1**).[108] Under Ir(I)-catalysed conditions using **L14**, it was demonstrated that styrene undergoes efficient reaction with pyrrole **104** to give C-2 alkylated **105** (75% yield, 76% *e.e.*) with high branch selectivity. In attempts to optimise this process, C-4 functionalised SPINOL ligands **L13** and **L15** were synthesised and screened. Although employment of these ligands gave **105** in high yields (upto 95% yield using **L13**), no improvement in *e.e.* was obtained. Pleasingly, when ligands **L13–15** were subsequently trialled in the corresponding reaction using furan substrate **106**, it was found that ligand C-4 functionalisation proved beneficial, as shown by the formation of **107** in 72% yield and 80% *e.e.* using mesityl-**L13** (an increase from 59% yield, 69% *e.e.* using **L14**).



Entry	Ligand	R^1	Yield	*e.e.*
1	(*R*)-**L14**	H	75%	76%
2	(*R*)-**L15**	Ph	84%	61%
3	(*R*)-**L13**	Mes	95%	24%



Entry	Ligand	R^1	Yield	*e.e.*
1	(*R*)-**L14**	H	59%	69%
2	(*R*)-**L15**	Ph	59%	74%
3	(*R*)-**L13**	Mes	72%	80%

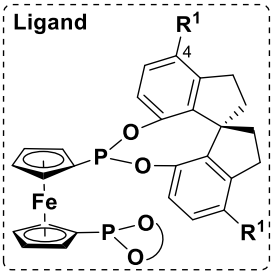
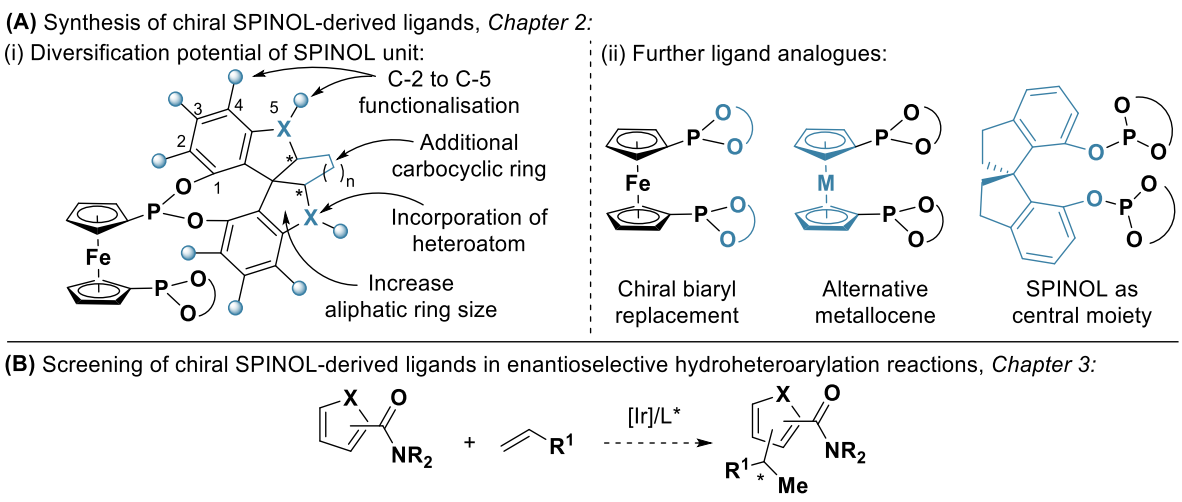


Table 1: *Previous investigations into C-4 functionalised SPINOL ligands for the hydroheteroarylation of styrene. Conducted by Dr. Phillippa Cooper.*

1.9 Project aims

1.9.1 Proposed optimisation of hydroheteroarylation through ligand design

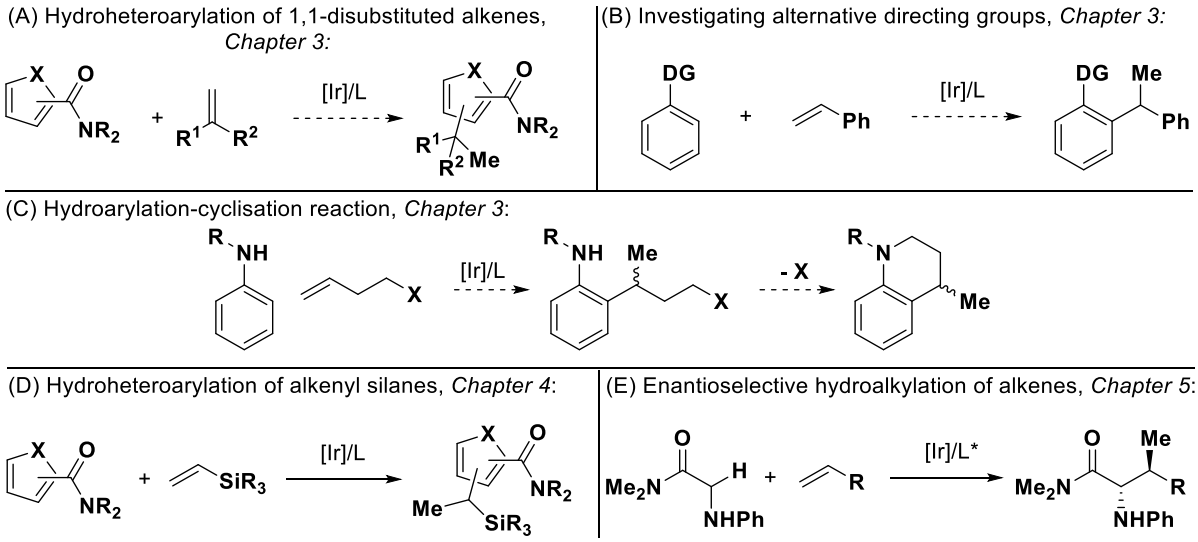
From these results, and owing to the high modularity of the SPINOL moiety, it was envisaged that further reaction optimisation could be attained through variation of the ligand structure (**Scheme 28Ai**). Since C-4 functionalised SPINOL ligands performed well, it was proposed that this position, as well as C-2, C-3 and C-5, be further investigated by appendage of electron-rich, electron-deficient and sterically bulky aryl groups. Further optimisation of the ligand structure could be realised by: (i) incorporation of a heteroatom or (ii) increasing the ring size of the aliphatic portion of the SPINOL backbone. Investigations into an additional carbocylic ring could also prove beneficial. Further ligand analogues can also be obtained by employing alternative chiral biaryl components, as opposed to SPINOL, or by replacing the central metallocene (**Scheme 28Aii**). Finally, given the success of SPINOL-derived ligands, it seemed relevant to utilise a chiral SPINOL component as the central moiety of the ligand. Accordingly, **Chapter 2** describes the synthesis of a library of chiral bisphosphonite and bisphosphite ligands in collaboration with Dr Andrew Dalling and Dr Raymond Chung for the optimisation of hydroheteroarylation reactions developed by Cooper.[109] Subsequent screening of these ligands is discussed in the opening sections of **Chapter 3 (Scheme 28B)**.



Scheme 28: *Summary of hydroheteroarylation optimisation through ligand design.*

1.9.2 Exploration of additional substrates and alkenes in hydrofunctionalisation processes

A second project aim was to augment the scope of substrates and alkenes used in hydrofunctionalisation processes (**Scheme 29**). The latter sections of **Chapter 3** focus on the use of: (i) 1,1-disubstituted alkenes in hydroheteroarylation reactions to install challenging quaternary stereocentres, (ii) alternative directing groups in hydroarylation reactions and (iii) alkenes bearing suitable functional groups to promote a hydroarylation-cyclisation sequence. Building upon this, **Chapter 4** demonstrates the use of alkenyl silanes in hydroheteroarylation reactions, while **Chapter 5** transitions to an enantioselective hydro*alkyl*ation proccess, which can be used to generate amino acid derivatives.



Scheme 29: *Summary of additional project aims.*

Chapter 2

Synthesis of Chiral SPINOL-derived Ligands

Chapter 2 – Synthesis of Chiral SPINOL-derived Ligands

2.1 Ligand synthesis plan

As described in **Chapter 1**, it was envisaged that hydroheteroarylation processes developed by Dr Phillippa Cooper could be optimised through modular ligand design (**Figure 2**). As such, the proceeding sections describe the synthesis of a library of chiral bisphosphonite and bisphosphite ligands in collaboration with Dr Andrew Dalling and Dr Raymond Chung.

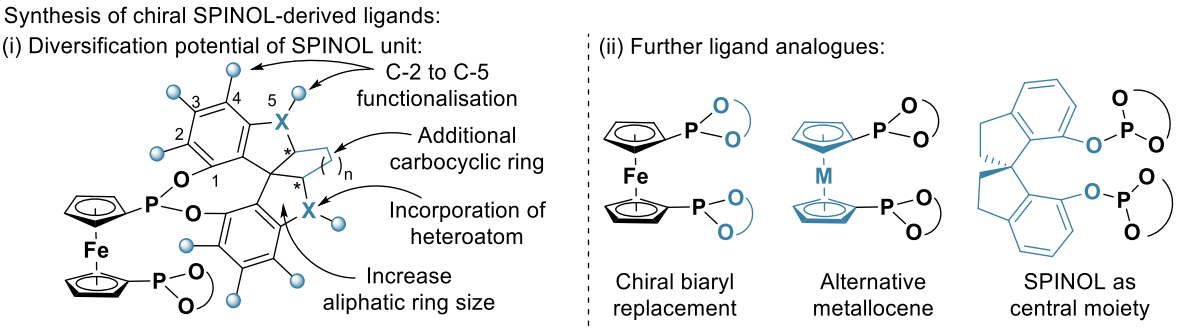
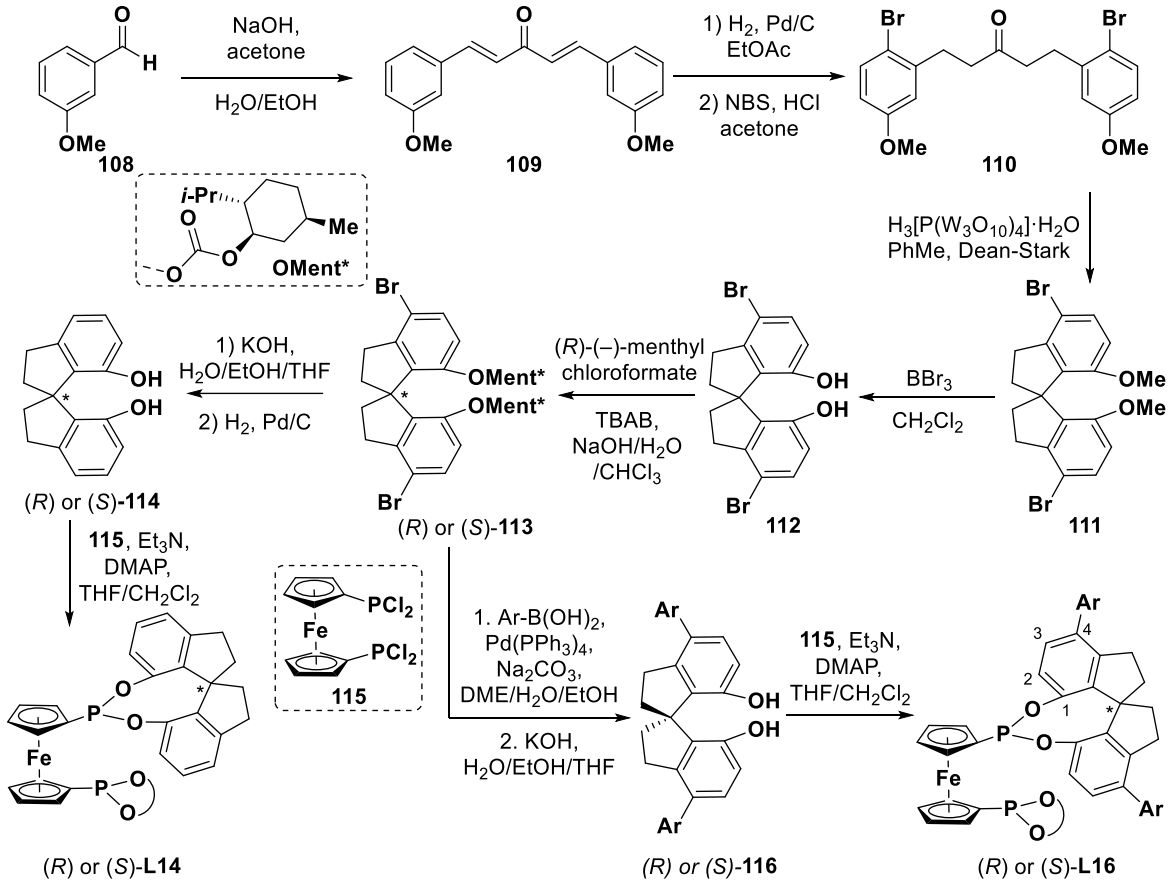


Figure 2: *Plan for modular ligand design approach.*

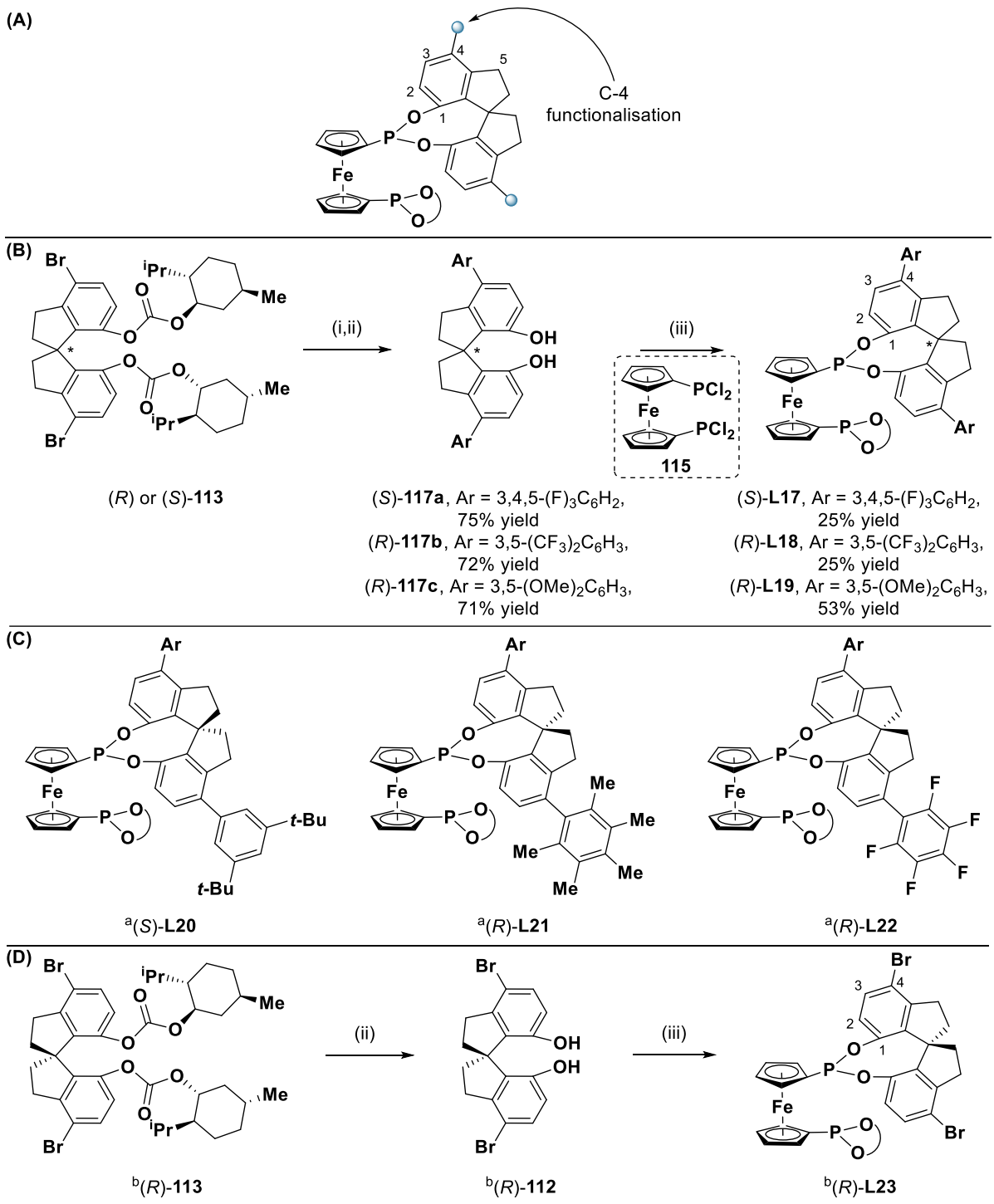
2.2 Synthesis of C-4 functionalised SPINOL-derived ligands

The synthesis of SPINOL ligands of type **L13–15** has been previously developed by the group and is based on a report by Birman and co-workers (**Scheme 30**).[110,111] Aldol condensation of 3-methoxybenzaldehyde **108** with acetone under basic conditions affords enone **109**. Reduction of the alkene components is accomplished using Pd/C under an atmosphere of hydrogen before *para*-selective bromination proceeds using NBS to provide **110**.[112] Spirocyclisation of **110** is achieved using tungstophosphoric acid hydrate ($H_3[P(W_3O_{10})]_4 \cdot H_2O$) and reaction with BBr_3 unveils the diol **112**.[113] Exposure to (*R*)-(–)-menthyl chloroformate generates two diastereomers, (*R*) or (*S*)-**113**, which can be separated by recrystallisation and flash column chromatography.[114] In terms of structure diversification, **113** is a valuable scaffold as either (i) enantiopure SPINOL **114** can be accessed by hydrolysis then hydrogenolysis or (ii) Pd-catalysed Suzuki-Miyaura cross-coupling between the SPINOL bromo-substituent and suitable boronic acids can generate C-4 functionalised motifs before hydrolysis affords the corresponding diol.[107] To complete the synthesis, reaction with ferrocene-derived chlorophosphine **115** provides bisphosphonite ligands of type **L14** and **L16**.[115]



Scheme 30: *Previously developed synthetic route towards SPINOL ligands of type **L14** and C-4 functionalised SPINOL ligands **L16**.*

Given the success of C-4 functionalised SPINOL ligands of type **L16** for the hydroheteroarylation of styrene using pyrrole and furan substrates, it seemed appropriate to investigate the effect of electron-rich, electron-poor and bulky aryl groups at the C-4 position (**Scheme 31A**). As such, the synthesis of these ligands began using (*R*)- or (*S*)-**113**, which were subjected to Pd-catalysed Suzuki-Miyaura cross-coupling with the appropriate aryl boronic acid (**Scheme 31B**). Synthesis of a tri-fluorophenyl-substituted SPINOL proceeded in 75% yield from (*S*)-**113** before coupling to chlorophosphine **115** afforded (*S*)-**L17** in 25% yield. Likewise, (*R*)-**L18** was obtained in 25% yield from di-trifluoromethylphenyl-(*R*)-**117b**. Coupling to **115** proceeded in higher yield using electron-rich (*R*)-**117c** (53% yield), presumably due to an increased stability of (*R*)-**117c** towards hydrolysis or oxidation during purification by column chromatography. Using the same protocol, ligands **L20**, **L21** and **L22** featuring bulky or electron-deficient aryl groups were synthesised by Dalling (**Scheme 31C**). To investigate the effect of the bromo-substituents at the C-4 position, (*R*)-**L23** was synthesised by Dr Raymond Chung in two steps from (*R*)-**113** (**Scheme 31D**).

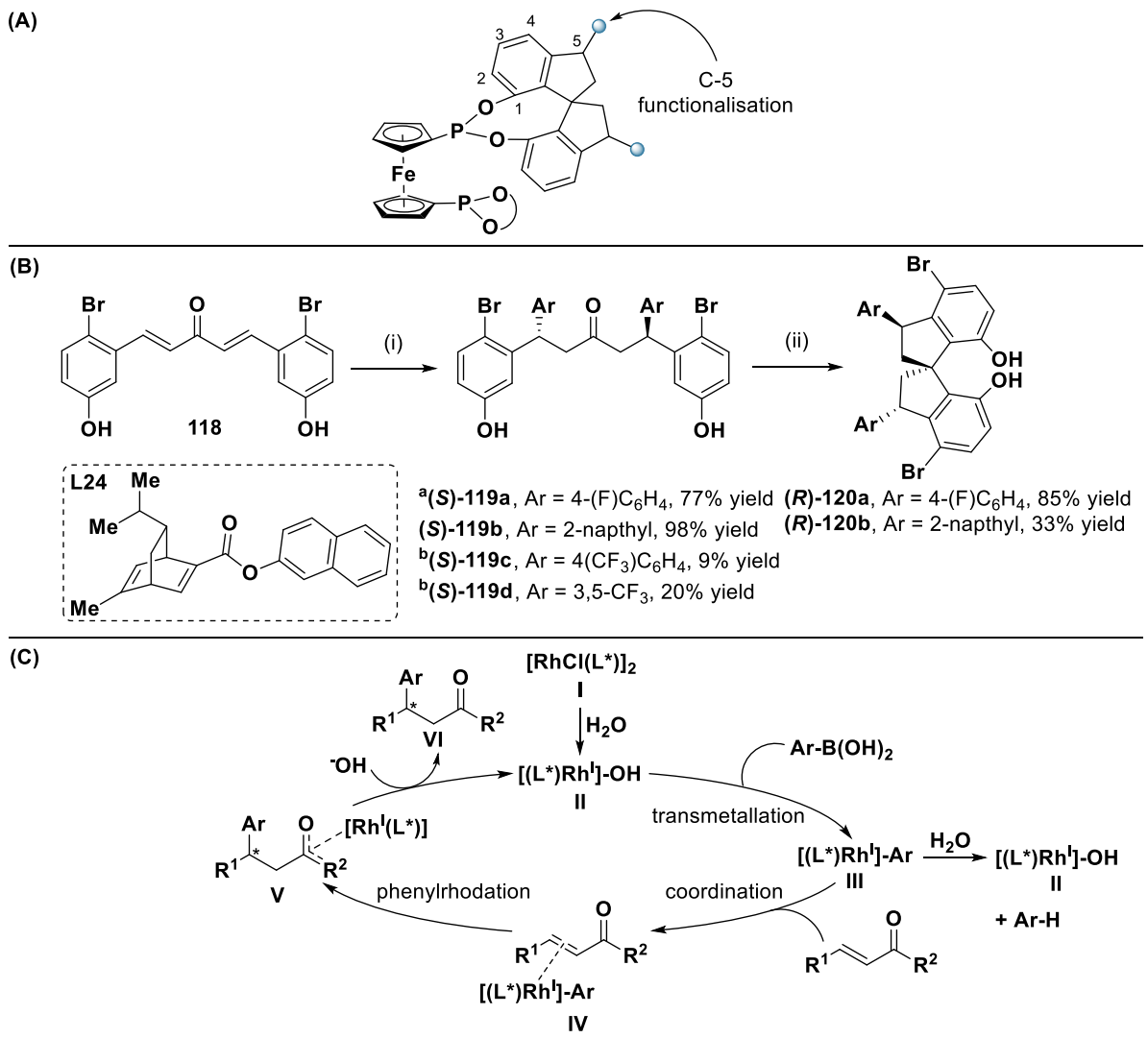


Scheme 31: *(A) General structure of C-4 functionalised ligands; (B) Reagents and conditions: (i) $Pd(PPh_3)_4$, aryl boronic acid, Na_2CO_3, DME:H_2O:EtOH (5:2:1), 100 °C, 16 h; (ii) KOH, H_2O:EtOH:THF (1:1:1), 80 °C, 1 h; (iii)* ***115****, Et_3N, DMAP, THF:CH_2Cl_2 (2:1), 0 °C– r.t., 16 h; (C) [a]Synthesised by Dr Andrew Dalling; (D) [b]Synthesised by Dr Raymond Chung.*

2.3 Synthesis of C-5 functionalised SPINOL-derived ligands

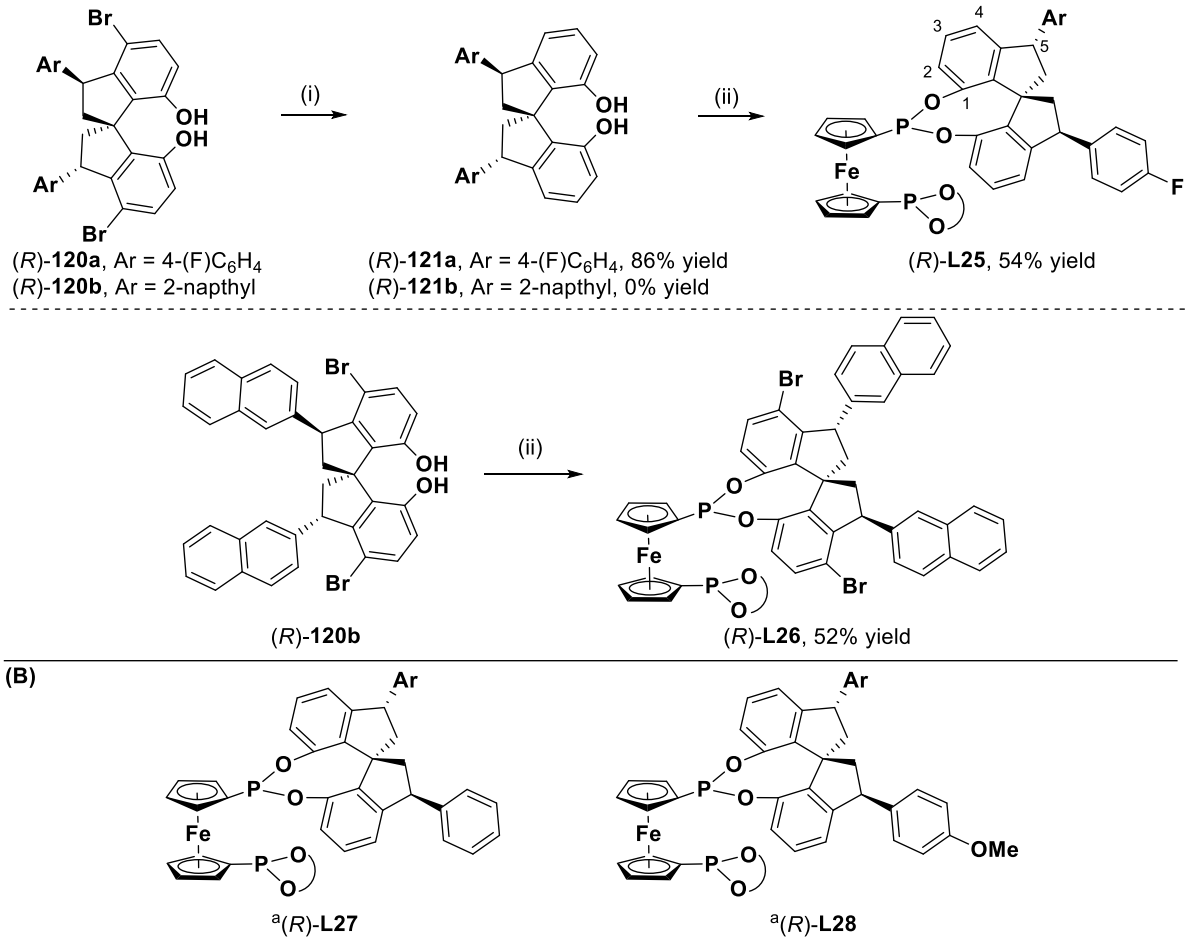
With a library of C-4 functionalised SPINOL ligands in hand, attention turned to the synthesis of ligands bearing C-5 functionalisation using a procedure reported by Lu, Hayashi and Dou (**Scheme 32A**).[116] The key step in this work is a Rh-catalysed asymmetric 1,4-addition of aryl boronic acids to enones to afford enantioenriched ketones in excellent yields and enantiocontrol as single diastereomers.

Ultimately, this negates the requirement for additional chiral resolution steps. Accordingly, enone **118** (synthesised by Dalling from reaction of **110** with BBr_3) was subjected to Rh-catalysed conditions in the presence of chiral diene ligand **L24** (**Scheme 32B).** Using 4-fluorophenylboronic acid, (*S*)-**119a** was obtained in 77% yield, while employment of 2-naphthylboronic acid afforded (*S*)-**119b** in 98% yield. The reaction was assumed to proceed with high enantioselectivity for the major isomer as per the Horeau principle.[117] This was confirmed as the optical value for (*S*)-**119b** matched literature values. Using 4-fluorophenylboronic acid, an increased yield, from 7% to 77%, was observed upon the addition of 5 mol% of KOH. This is postulated to assist the formation of the active catalyst, **II** (which i**s** assumed to be more reactive towards transmetallation) from either the pre-catalyst, **I**, or Rh(I)-*oxo*-π-allyl intermediate, **V** (**Scheme 32C**).[118,119] Addition of KOH proved detrimental when 2-naphthylphenylboronic acid was employed, potentially due to promoting hydrolytic B-C or Rh-Ar bond cleavage (**III** to **II**); these effects can be subdued by using surplus (usually 6 equivalents) of boronic acid.[120] Trifluoromethyl analogues **119c** and **119d** were obtained in low yields, with or without KOH, and so were not carried through to the next steps. Spirocyclisation of (*S*)-**119a** and (*S*)-**119b** using $BF_3{\cdot}OEt_2$ gave SPINOL derivatives (*R*)-**120a** and (*R*)-**120b** in 85% and 33% yields, respectively. It was assumed that the sterically demanding naphthyl groups of **120b** prevented efficient spirocyclisation from occurring, resulting in a diminished yield; also, the naphthyl groups could outcompete the phenol moiety in C-C bond formation, due to their more electron-rich nature.



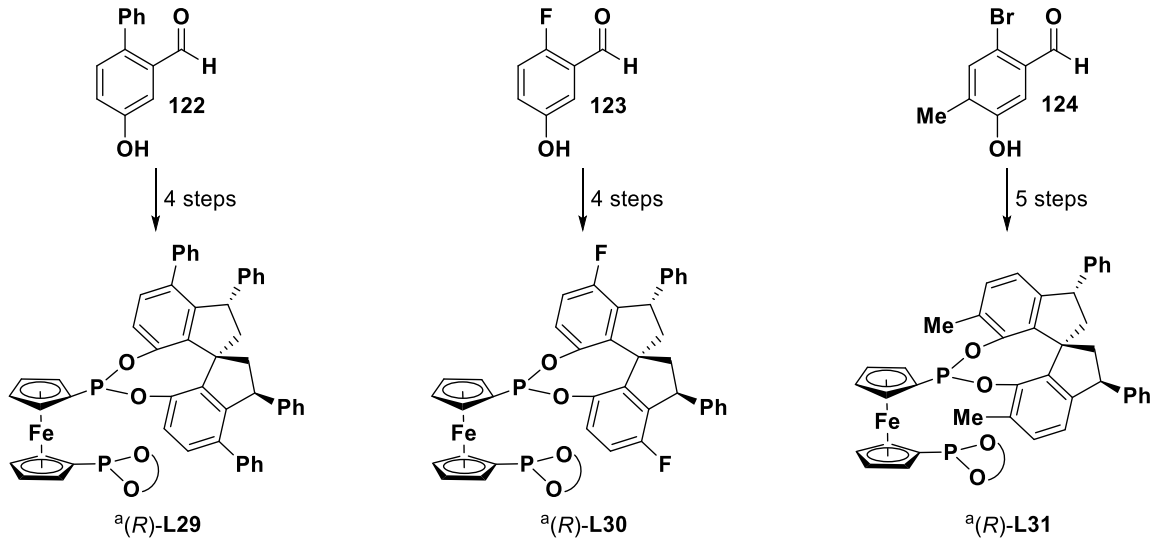
Scheme 32: *(A) General structure of C-5 functionalised ligands; (B) Reagents and conditions: (i) [RhCl(**L24**)]$_2$, Ar-B(OH)$_2$, KOH, PhMe/H$_2$O, 60–80 °C, 16 h; (ii) BF$_3$·OEt$_2$, PhMe, 60–70 °C, 48–72 h; (C) Proposed mechanism for the Rh(I)-catalysed asymmetric conjugate arylation; [a]KOH not used; [b]Yields determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.*

Hydrogenolysis of (*R*)-**120a** using Pd/C gave (*R*)-**121a** in 86% yield, before reaction with **115** gave (*R*)-**L25** in 54% yield (**Scheme 33**). The analogous hydrogenolysis using naphthyl-(*R*)-**120b** was slower and (*R*)-**121b** degraded upon extended reaction times. Instead, (*R*)-**120b** was directly reacted with **115** to give (*R*)-**L26** in a 52% yield. By employing phenylboronic acid and 4-methoxyphenylboronic acid in the synthetic route, ligands (*R*)-**L27** and (*R*)-**L28** were synthesised by Dalling (**Scheme 33B**).



Scheme 33*: (A) Reagents and conditions: (i) Pd/C, H_2 (1 atm), THF/H_2O, r.t., 16 h; (ii)* ***115****, Et_3N, DMAP, THF.CH_2Cl_2 (2:1), r.t., 16 h; (B) [a]Synthesised by Dr Andrew Dalling.*

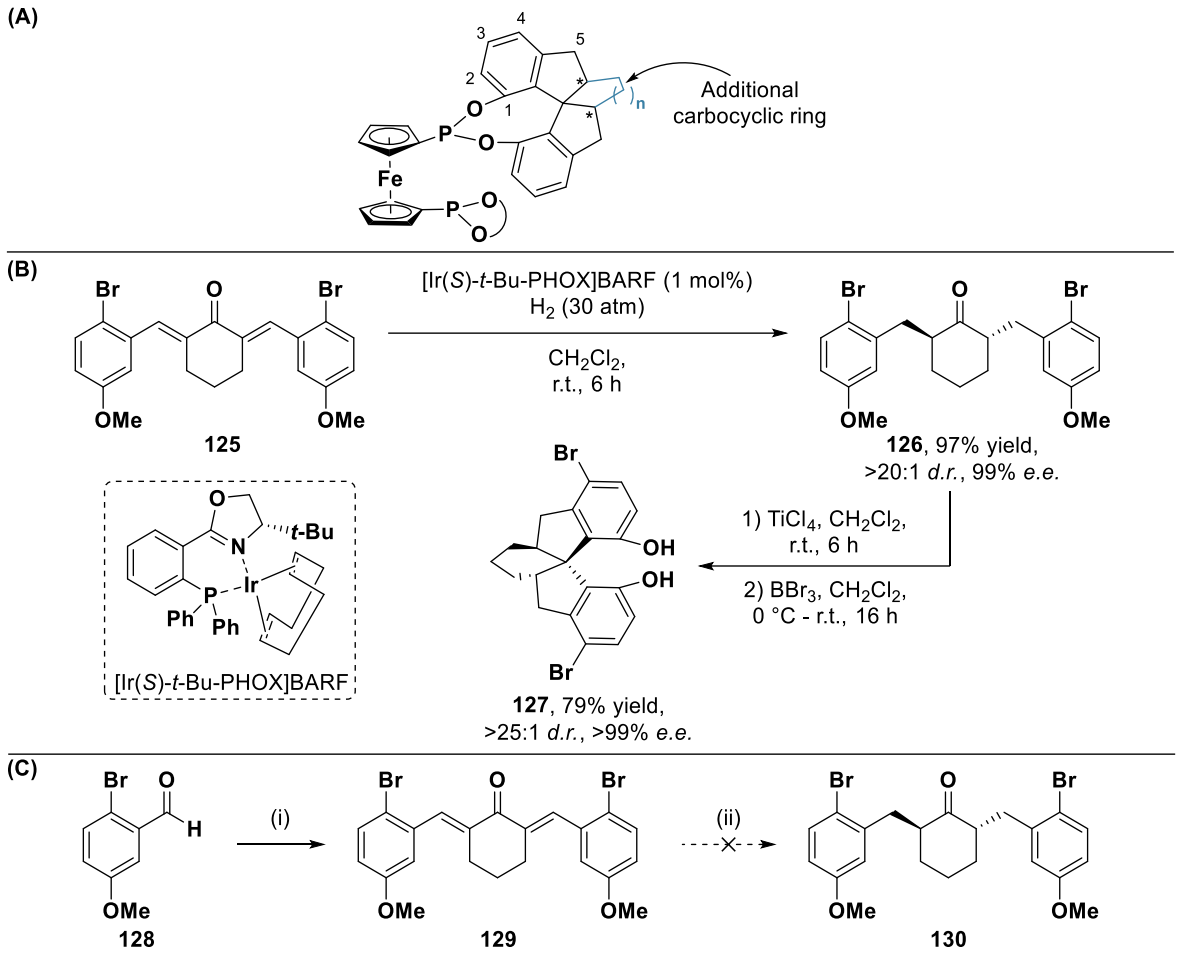
Through combination of Lu, Hayashi, and Dou's asymmetric 1,4-addition methodology and judicious choice of starting aldehyde, a library of di-functionalised SPINOL-derived ligands were also synthesised by Dalling. Accordingly, (*R*)-**L29**, featuring phenyl groups at both C-4 and C-5 was obtained in four steps from aldehyde **122**; similarly, (*R*)-**L30** was obtained from aldehyde **123**. Thus far, modifications of the SPINOL structure had been limited to C-4 and C-5. To address this, aldehyde **124** was employed to afford C-2/C-5 difunctionalised (*R*)-**L31**, featuring a methyl group at C-2.



Scheme 34: *Library of di-functionalised SPINOL-derived ligands.* [a]*Synthesised by Dr Andrew Dalling.*

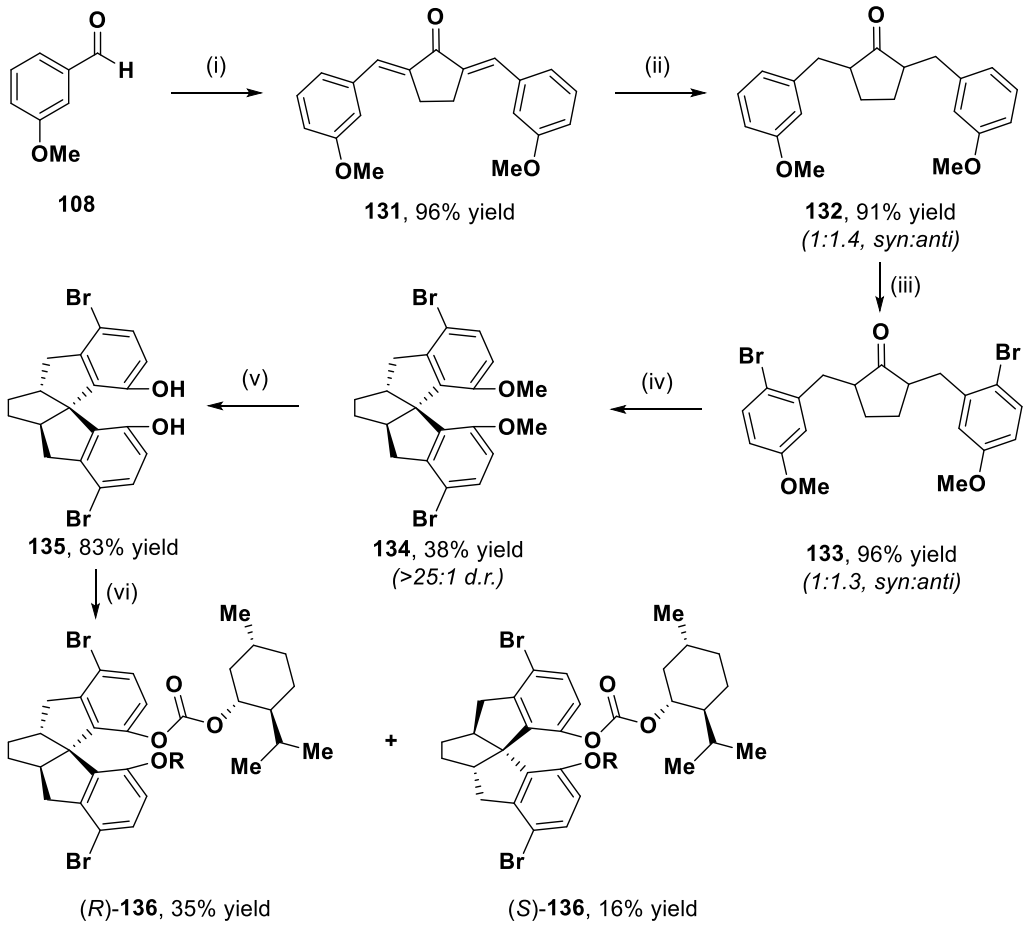
2.4 Synthesis of cyclopentyl-fused SPINOL-derived ligands

Having synthesised C-4 and/or C-5 functionalised SPINOL-derived ligands, attention turned to incorporating an additional carbocyclic ring into the SPINOL backbone (**Scheme 35A**). As such, we were drawn to a recent publication by Ding which described the synthesis of cyclohexyl-fused spirobiindane diols in which the key step was an [Ir(*S*)*t*-Bu-PHOX]BARF-catalysed asymmetric hydrogenation of enone **125** using a high pressure of hydrogen (**Scheme 35B**).[121] This affords ketones of type **126** in high enantioselectivity and as single diastereoisomers. Spirocyclisation using $TiCl_4$ and reaction with BBr_3 unveils chiral cyclohexyl-fused spirobiindane diols of type **127**. In an attempt to reproduce this methodology, Dalling employed enone **129** under the reported conditions; however, ketone **130** was not observed and starting enone **129** was recovered (**Scheme 35C**).



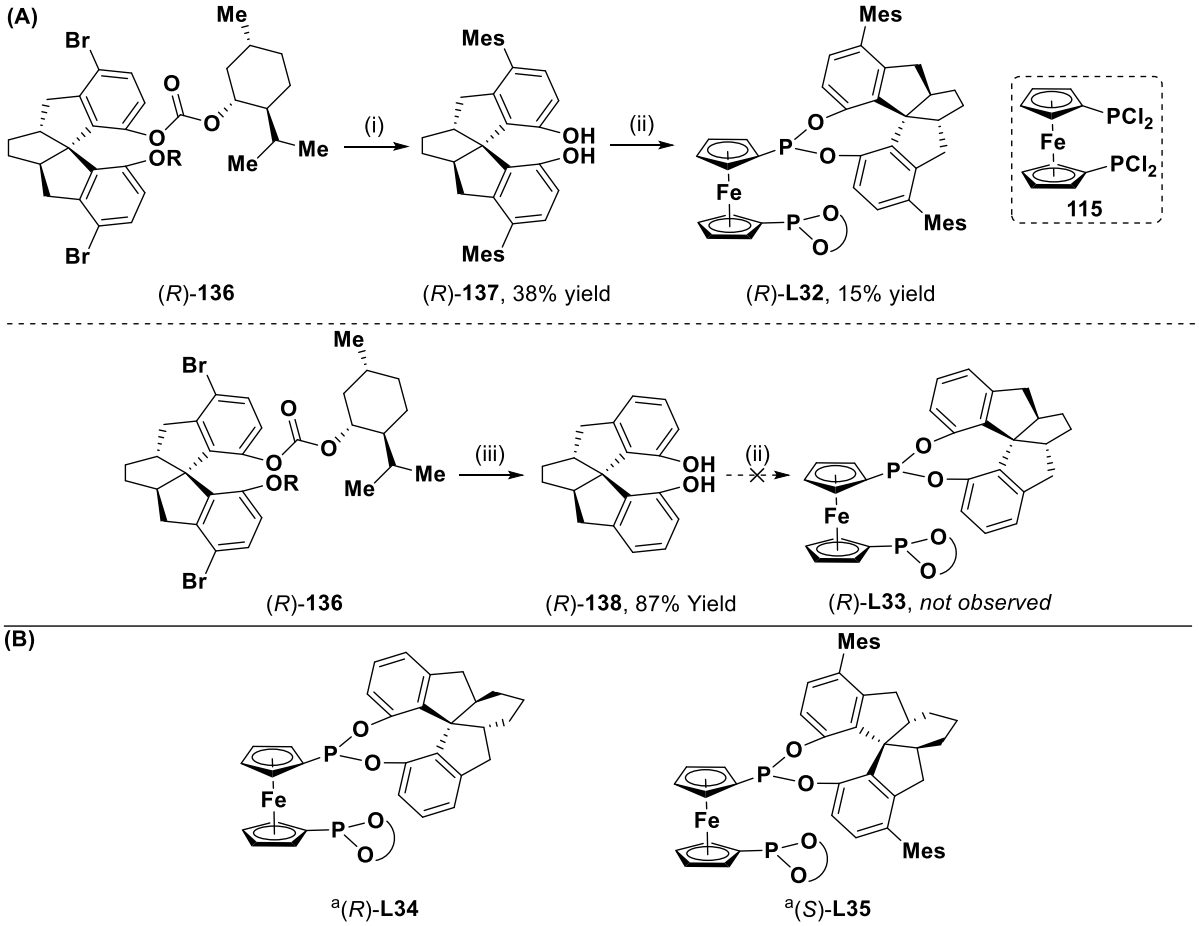
Scheme 35: *(A) General structure of ligands bearing an additional carbocyclic ring; (B) Synthesis of cyclohexyl-fused SPINOL systems; (C) Reagents and conditions: (i) cyclohexanone, NaOH, EtOH:H₂O (1:1), 0 °C–r.t., 16 h; (ii) [Ir(S)-t-Bu-PHOX]BARF (1 mol%), H₂ (50 atm), CH₂Cl₂, r.t., 6 h. Reactions conducted by Dr Andrew Dalling.*

To circumvent this issue, it was proposed that cyclopentyl- and cyclohexyl-fused structures could be obtained by employing cyclopentanone or cyclohexanone in a conventional SPINOL synthesis as described above in **Scheme 35**.[122] Accordingly, synthesis of a cyclopentyl-fused structure began with aldol condensation of *m*-anisaldehyde **108** with cyclopentanone to afford enone **131** in 96% yield (**Scheme 36**). Reduction with Raney®-nickel gave ketone **132** in an inseparable 1.4:1 mixture of *anti*- to *syn*-diastereomers. Subsequent bromination using *N*-bromosuccinimide (NBS) and catalytic HCl generated dibrominated product **133** in 96% yield. Spirocyclisation of **133** was reported to give **134** in 81% yield; however, only a 38% yield was obtained when these conditions were reproduced. In a study by Dalling, a range of Lewis and Brønsted acids ($BF_3{\cdot}OEt_2$, $H_3[P(W_3O_{10})_4]{\cdot}H_2O$, Eaton's reagent[123]) were screened for this transformation, but all failed to deliver the desired product. Demethylation using BBr_3 provided racemic **135** in 83% yield, before reaction with (*R*)-(–)-menthyl chloroformate generated (*R*)-**136** and (*S*)-**136** in 35% and 16% yields respectively, after recrystallisation and flash column chromatography.



Scheme 36: *Reagents and conditions: (i) Cyclopentanone, NaOH, H_2O/EtOH (1:1), r.t., 4 h; (ii) Raney®-Nickel, H_2 (1 atm), acetone, r.t., 2 h; (iii) NBS, 1 M aq. HCl (cat.), acetone, 0 °C, 10 min; (iv) Polyphosphoric acid, 105 °C, 16 h; (v) BBr_3, CH_2Cl_2, -78 °C to r.t., 16 h; (vi) NaOH, TBAB, (R)-(–)-menthyl chloroformate, H_2O:$CHCl_3$ (1:1), 0 °C–r.t., 10 mins.*

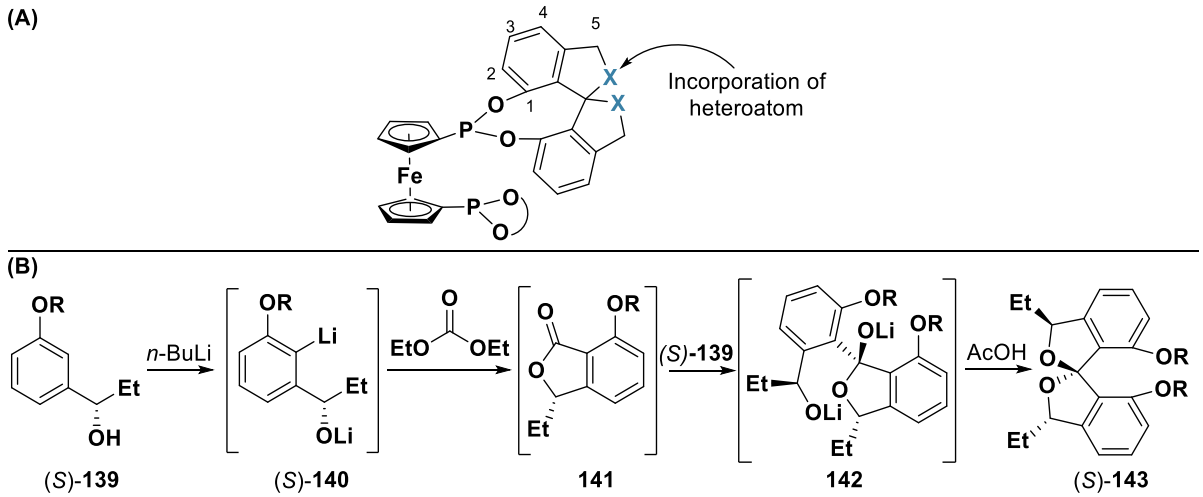
Functionalisation of (*R*)-**136** was achieved by Pd-catalysed Suzuki-Miyaura cross-coupling with 2,4,6-trimethylphenylboronic acid before hydrolysis of the menthyl group gave (*R*)-**137** in 38% yield (**Scheme 37A**). Reaction with chlorophosphine **115** afforded (*R*)-**L32** in 15% yield. (*R*)-**138** was then obtained in 87% yield by hydrogenolysis using Pd/C and acetic acid (**Scheme 37B**). Interestingly, reaction of (*R*)-**138** with **115** using the standard procedure did not afford desired (*R*)-**L33**. Analysis of purified reaction material by ^{31}P NMR spectroscopy gave signals at approximately δ 30 ppm, indicative of a phosphonate by-product.[124] Using the same procedure, analogous cyclohexyl-fused ligands (*R*)-**L34** and (*S*)-**L35** were synthesised by Dalling from cyclohexanone (**Scheme 37C**).



Scheme 37: *(A) Reagents and conditions: (i) (a) Pd(PPh₃)₄, 2,4,6-trimethylphenylboronic acid, Na₂CO₃, DME:H₂O:EtOH (5:2:1), 100 °C, 16 h. (b) KOH, H₂O:EtOH:THF (1:1:1), 80 °C, 1 h (ii)* ***115****, Et₃N, DMAP, THF:CH₂Cl₂ (2:1), 0 °C–r.t., 16 h (iii): (a) KOH, H₂O:EtOH:THF (1:1:1), 80 °C, 1 h; (b) Pd/C, AcOH, MeOH, H₂ (1 atm), r.t., 4 h.; (B) [a]Synthesised by Dr Andrew Dalling.*

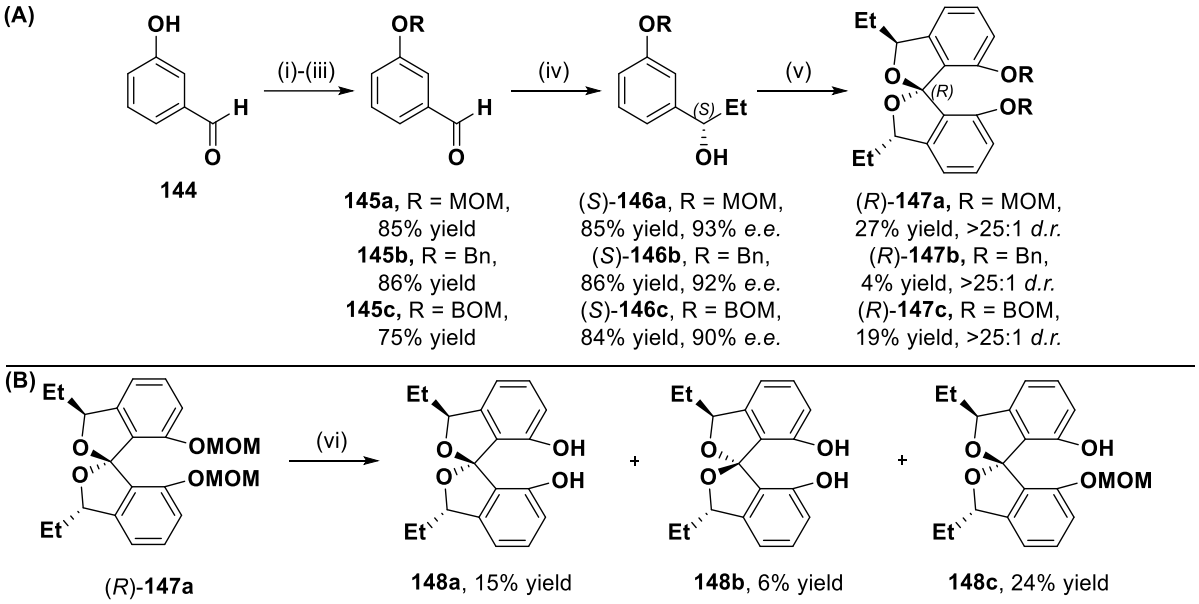
2.5 Synthesis of SPINOL-derived ligands with a saturated heterocyclic backbone

After the successful synthesis of cyclopentyl-(*R*)-**L32**, efforts were focused on synthesising a SPINOL-derived ligand bearing a saturated heterocyclic backbone (**Scheme 38A**). As such, attention turned to a recent report by Nagorny *et al.* which described the synthesis of spiroketal-derived SPINOL ligands for the hydroarylation of vinyl enol ethers (**Scheme 38B**).[125] In this work, treatment of a chiral benzylic alcohol (of type (*S*)-**139**) with *n*-BuLi and trapping with diethyl carbonate affords spiroketal (*S*)-**143** in high diastereoselectivity through the intermediacy of an isobenzofuranone **141**. This route was particularly appealing due to its low step count and an asymmetric alkylation step negates the need for a chiral resolution.



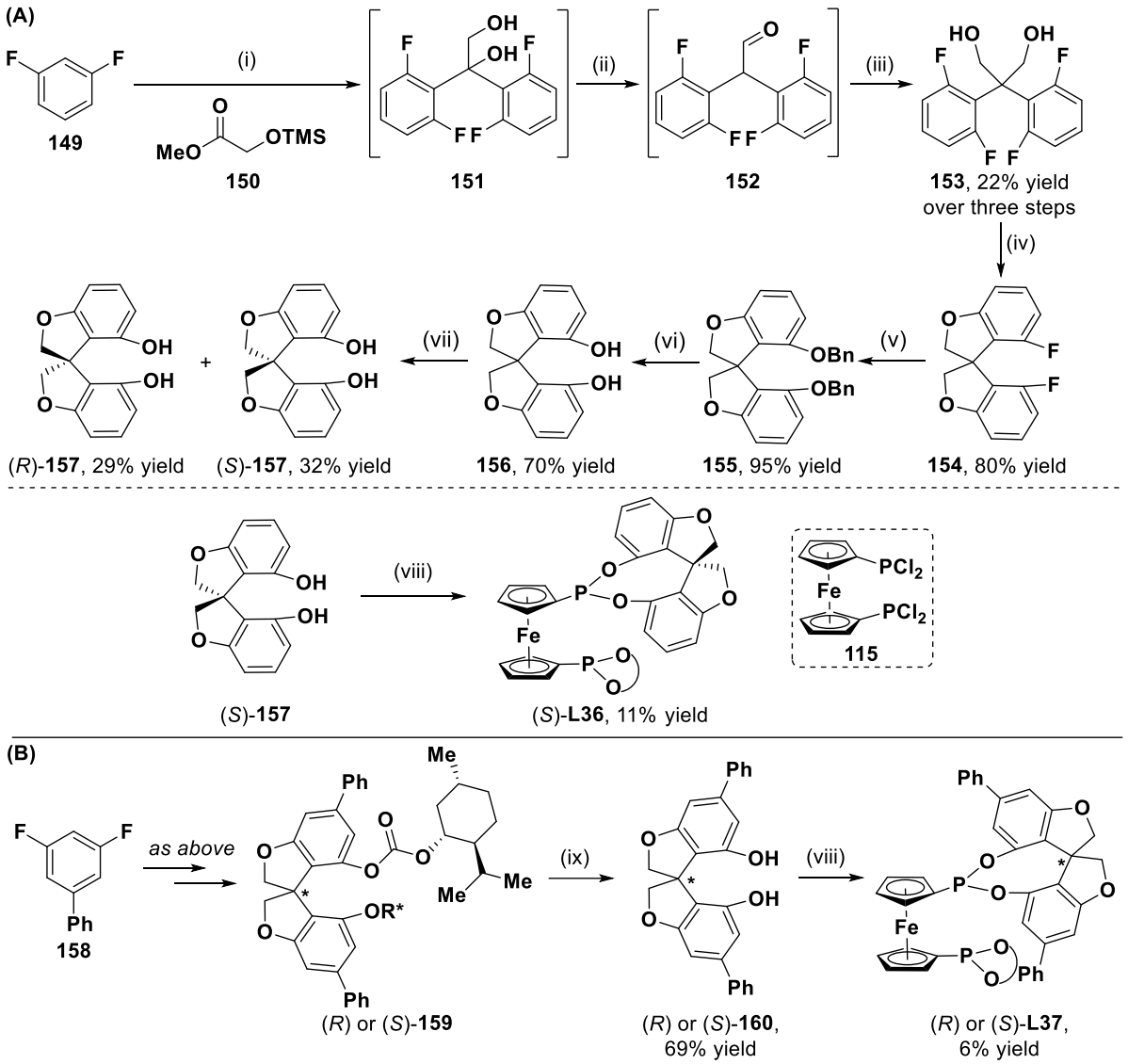
Scheme 38: *(A) General structure of ligands bearing a saturated heterocyclic backbone; (B) Synthesis of spiro-ketal SPINOL structures.*

To determine the most suitable directing group for asymmetric alkylation, the synthesis began with protection of 3-hydroxybenzaldehyde **144** with a variety of groups reported by Nagorny to afford **145a** (85% yield, R = MOM), **145b** (86% yield, R = Bn) and **145c** (75% yield, R = BOM, **Scheme 39A**). Reactions of **145a–c** with diethylzinc in the presence of (1*S*,2*R*)-(−)-2-(dibutylamino)-1-phenyl-1-propanol ((–)-DBNE), proceeded smoothly. The optimal substrate was MOM-protected **145a** which gave (*S*)-**146a** in 85% yield and 93% *e.e.* Subsequent spirocyclisation of chiral benzylic alcohols **146a–c** did not proceed as efficiently as reported. The highest yield was obtained from **146a**: treatment with *n*-BuLi and diethylcarbonate afforded (*R*)-**147a** in 27% yield, compared to the reported 67% yield. Nevertheless, the reaction proceeded with excellent diastereoselectivity (>25:1 *d.r.*). (*R*)-**147b** and (*R*)-**147c** were obtained in only 4% yield and 19% yield, respectively, so were not carried through to later steps. Deprotection of (*R*)-**147a** using acetyl chloride in methanol afforded **148a** in 15% yield (compared to 93% yield reported) as an inseparable mixture of **148a** and diastereomer **148b** (**Scheme 39B**). Additionally, mono-deprotected **148c** was produced in 24% yield. It is unclear whether epimerisation occurred under the acidic reaction conditions or upon purification by flash column chromatography. Due to the low stability towards epimerisation, an alternative ligand system was pursued.



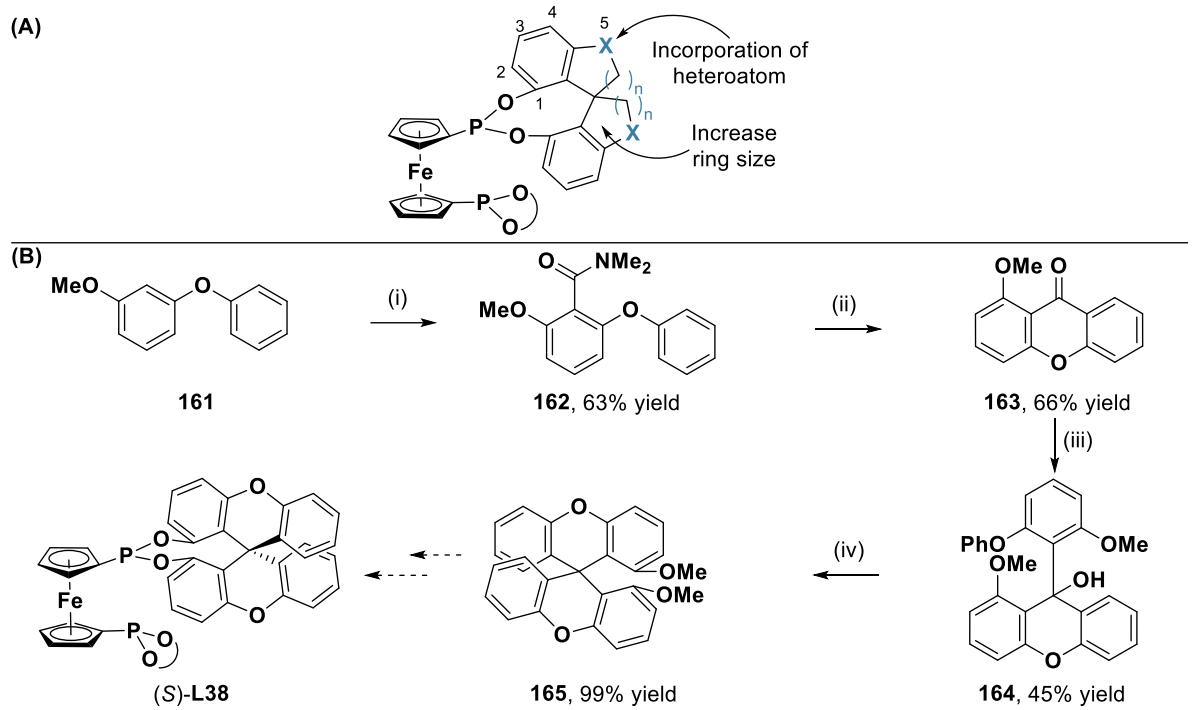
Scheme 39: *Reagents and conditions: (i) MOMCl, DIPEA, CH_2Cl_2, 0 °C–r.t., 16 h; (ii) BnCl, K_2CO_3, EtOH, 80 °C, 24 h; (iii) NaH, DMF, 0 °C, 15 mins then BOMCl, DMF, 0°C–r.t., 3 h; (iv) Et_2Zn, (1S,2R)-(−)-2-(dibutylamino)-1-phenyl-1-propanol, hexane, 0 °C, 4 h; (v) n-BuLi, PhMe, 0 °C, 2 h then diethyl carbonate, PhMe, 0 °C–r.t., 16 h, then AcOH, PhMe, r.t., 4h. (vi) AcCl, MeOH, 0 °C–r.t., 6 h.*

As spiro-ketal based structures were unstable towards epimerisation, we turned to a recent report by Zhang and co-workers for the synthesis of *O*-SPINOL, a structure that bears oxygen atoms at the benzylic positions of the aliphatic backbone.[126] Accordingly, synthesis of *O*-SPINOL was replicated by Chung and used for the synthesis of (*S*)-**L36** (**Scheme 40A**). Starting from commercially available **149**, treatment with *n*-BuLi and quenching with **150** gave diol **151**. Heating in strong acid forces a pinacol rearrangement to generate aldehyde **152** before reaction with paraformaldehyde furnished diol **153** *via* an aldol/Cannizzaro cascade. Overall, **153** was obtained in 22% yield over three steps from **149**. From here, spirocyclisation by intramolecular S_NAr proceeded using KO*t*-Bu to afford **154** (80% yield) and subsequent S_NAr with BnOH provided **155** in 95% yield. Hydrogenation of the benzyl units generated diol **156** in 70% yield which was resolved by heating with L-proline before recrystallisation gave (*R*)-**157** (29% yield) and (*S*)-**157** (32% yield). Finally, (*S*)-**157** was reacted with **115** under standard conditions to provide (*S*)-**L36** in 11% yield. Thus far, ligands synthesised in the group were limited to functionalisation at the C-2, C-4 and C-5 positions. Accordingly, Chung utilised the above procedure for the synthesis of C-3 functionalised **159** from 3,5-difluorobiphenyl **158** (**Scheme 40B**). Due to solubility issues, chiral resolution was conducted using (1*R*)-(−)-menthyl chloroformate to give **158**. Hydrolysis of **159** (69% yield) and reaction with chlorophosphine **115** afforded **L37** in 6% yield. In future work, the absolute configuration of **160** should be obtained by X-ray crystallography.



Scheme 40: *Reagents and conditions: (i) (a) n-BuLi, THF, -78 °C, 1 h (b)* ***150****, r.t., 1 h; (ii) 25% H_2SO_4, 100 °C, 16 h (iii) LiOH, paraformaldehyde, 1,4-dioxane, 100 °C, 16 h; (iv) KOt-Bu, THF, 60 °C, 16 h; (v) BnOH, KOt-Bu, DMF, 100 °C, 30 h; (vi) Pd/C, H_2 (1 atm), THF/AcOH (1:1), r.t., 24 h; (vii) L-Proline, EtOAc, 70 °C, 16 h; Reactions conducted by Dr Raymond Chung; (B)(viii)* ***115****, Et_3N, DMAP, THF:CH_2Cl_2 (2:1), 0 °C–r.t., 16 h; (ix) KOH, EtOH:H_2O:THF (1:1:1), 80 °C, 1h.*

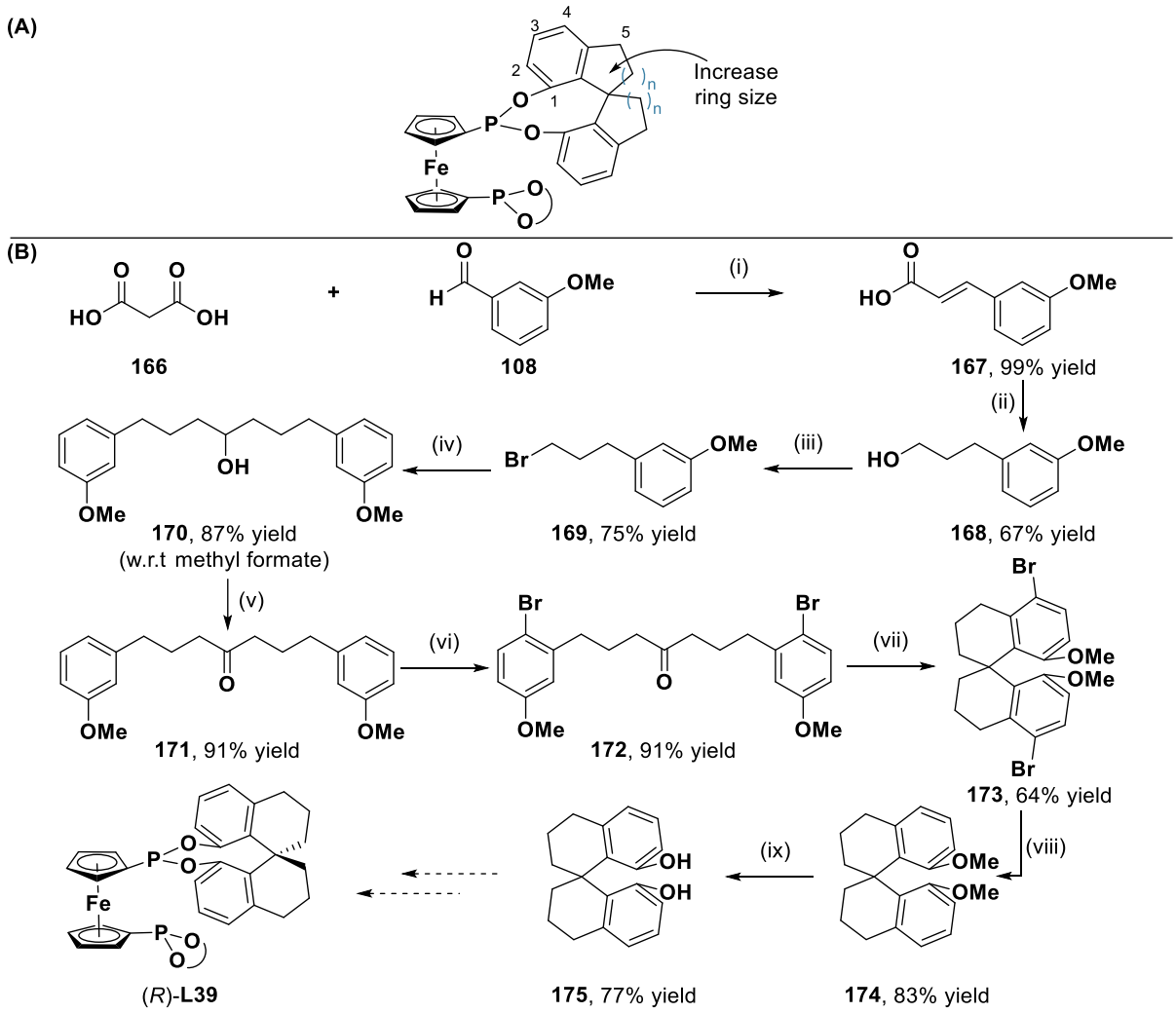
Once the synthesis of *O*-SPINOL-derived ligands was complete, investigations progressed towards exploring the ring size of the saturated heterocycle backbone (**Scheme 41A**). A recent report by Zhang described the synthesis of a spirocyclic bi-xanthene diol structure which features a six-membered saturated heterocyclic backbone.[127] An appealing aspect of this work was that the product could be obtained in seven steps from commercial 3-phenoxyanisole **161**. To replicate this work, synthesis commenced with *ortho*-lithiation of **161** with *n*-BuLi before quenching with *N*,*N*-dimethylcarbamoyl chloride to afford **162** in 63% yield (**Scheme 41B**). A second *ortho*-lithiation was conducted, this time with LDA, and subsequent quenching with 2M HCl gave cyclic ketone **163** in 66% yield. Addition of lithiated **161** to **163** generated tertiary alcohol **164** in 45% yield, before spirocyclisation using acetic acid and concentrated HCl produced **165** in 99% yield. To complete the synthesis, deprotection of the methyl groups with BBr_3, before chiral resolution and appendage to **115** should give access to **L38**.



Scheme 41: *(A) General structure of ligands bearing a larger saturated heterocyclic backbone; Reagents and conditions: (i) (a) n-BuLi, THF, -78 °C–r.t., 3 h; (b) N,N-dimethylcarbamoyl chloride, -78 °C–r.t., 16 h; (ii) (a) LDA, -78 °C–0 °C, 2 h; (b) 2M HCl, 0 °C, 1 h (iii) (a)* ***161****, n-BuLi, THF, -78 °C–r.t., 3 h; (b)* ***163****, -78 °C–r.t., 16 h; (iv) AcOH, 12 M HCl, 100 °C, 16 h.*

2.6 Studies towards the synthesis of tetralin-derived spirocyclic ligands

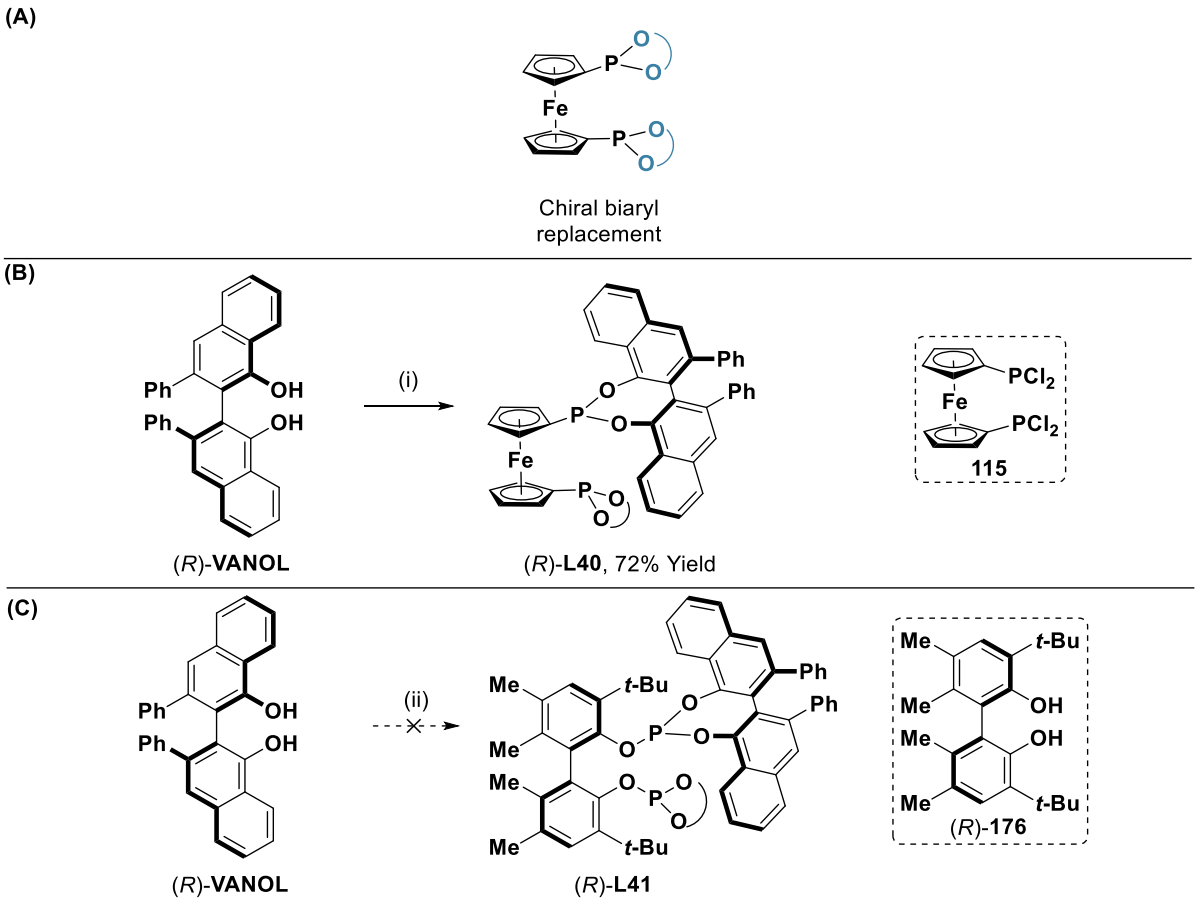
Investigations were also undertaken increase the size of the carbocyclic backbone (**Scheme 42A**). Recently, Zhou and co-workers described the synthesis of a spirocyclic bi-tetralin motif.[128] To reproduce this methodology, synthesis began with Knoevenagel condensation of malonic acid with *m*-anisaldehyde to give **167** in 99% yield (**Scheme 42B**). Reduction with $LiAlH_4$ generated **168** in 67% yield, before **169** was obtained in 75% yield from an Appel reaction using NBS. From here, **169** was converted into the corresponding Grignard reagent before exposure to methyl formate gave **170** in 87% yield. Swern oxidation proceeded smoothly (**171**, 91% yield) and subsequent bromination afforded **172** in 91% yield. Spirocyclisation was conducted using methanesulfonic acid (**173**, 64% yield) before hydrogenolysis using Pd/C (**174**, 83% yield) and methyl deprotection with BBr_3 gave **175** in 77% yield. To complete the ligand synthesis, **175** should be resolved by chiral resolution using menthyl chloroformate before reaction with chlorophosphine **115** to afford **L39**. To generate further analogues, the C-4 position could be functionalised by Pd-catalysed cross-coupling of **173** with a range of aryl boronic acids.



Scheme 42: *(A): General structure of ligands bearing a larger carbocyclic backbone; (B) Reagents and conditions: (i) piperidine, pyridine, 90 °C, 48 h; (ii) $LiAlH_4$, THF, 0–50 °C, 72 h (iii) PPh_3, CBr_4, Et_2O (0.25 M), 0 °C–r.t., 16 h; (iv) (a) Mg, I_2, THF, 70 °C, 16 h; (b) methyl formate, 0 °C–r.t., 16 h; (v) NEt_3, DMSO, $(COCl)_2$, CH_2Cl_2, -70 °C–r.t., 4 h; (vi) NBS, 2M HCl, acetone, 0 °C, 0.5 h (vii) MsOH, r.t., 16 h; (viii) 10% Pd/C, AcOH, MeOH, H_2 (1 atm), r.t., 16 h; (ix) BBr_3, CH_2Cl_2, 0 °C–r.t., 16 h.*

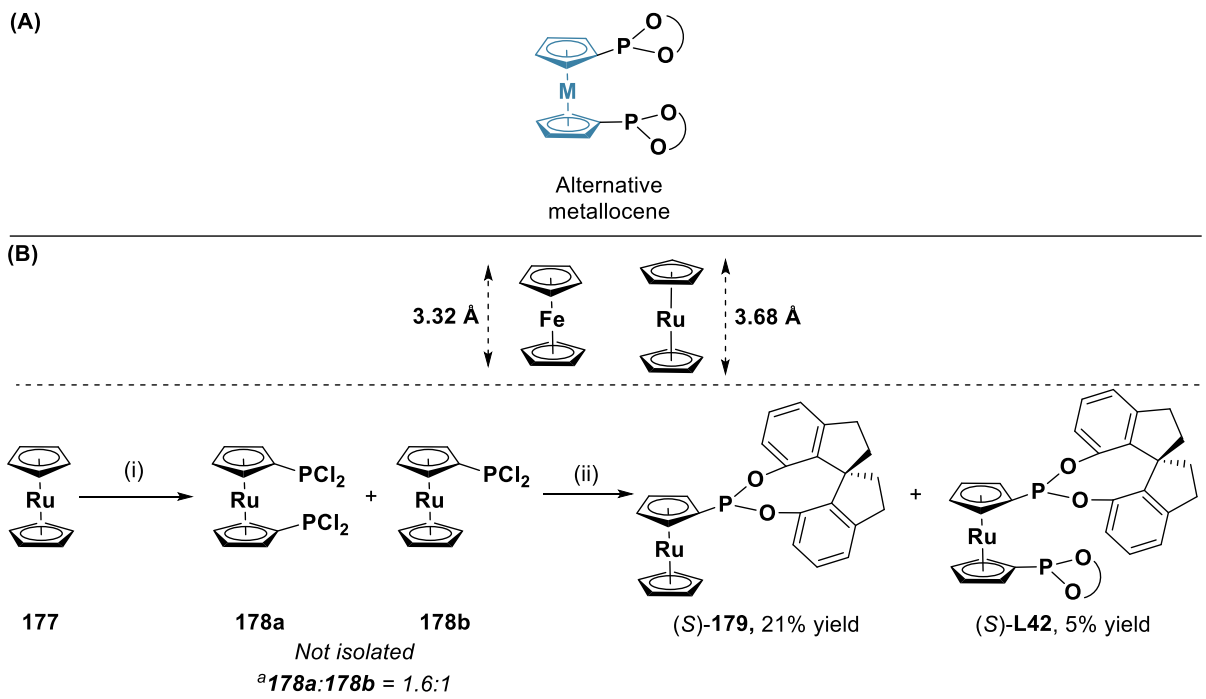
2.7 Synthesis of additional chiral ligands

To investigate other chiral biaryl units as depicted in **Scheme 43A**, commercial (*R*)-VANOL was employed to generate (*R*)-**L40** in 72% yield by reaction with chlorophosphine **115** (**Scheme 43B**).[129] Efforts towards the corresponding phosphite ligand **L41** were unsuccessful using (*R*)-VANOL and diphenol (*R*)-**176**, a moiety which featured in previous work in the group, and **L41** was not formed (**Scheme 43C**).[107] Analysis of purified reaction material by ^{1}H NMR spectroscopy revealed a 1:1 ratio of (*R*)-VANOL to (*R*)-**176**, and ^{31}P NMR spectroscopy showed two distinct peaks at δ 126 ppm and 136 ppm. These data suggest that addition of the second (*R*)-VANOL unit does not occur, presumably due to the steric hindrance of the mono-addition product.



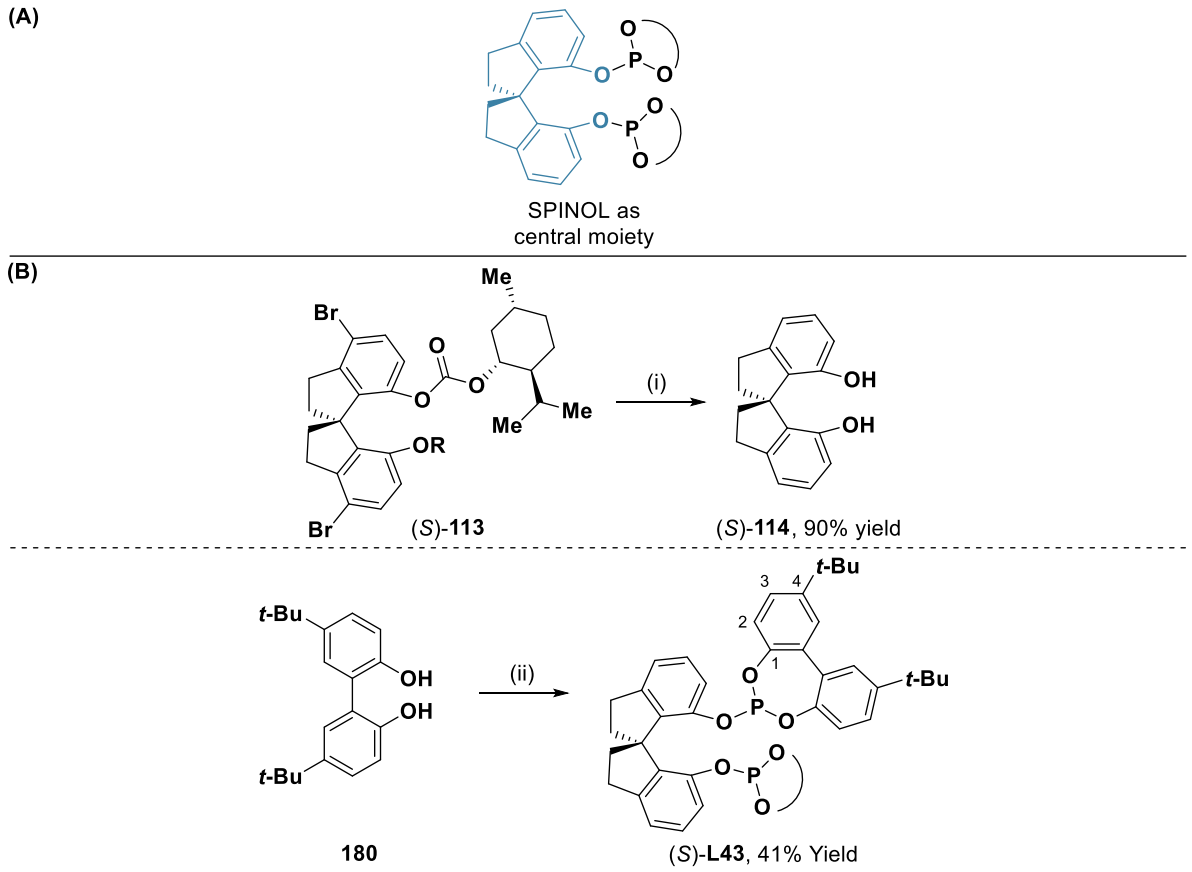
Scheme 43: *(A) General structure of ligands bearing alternative chiral biaryl groups; (B) Reagents and conditions: (i)* ***115****, Et_3N, DMAP, THF:CH_2Cl_2 (2:1), 0 °C–r.t., 16 h; (ii) (a) PCl_3, 85 °C, 2 h (b) (R)-****176****, Et_3N, DMAP, THF, 0 °C–r.t., 16 h.*

Since the majority of research had focused on modifying the chiral biaryl unit, efforts shifted towards modifying the central portion of the ligand (**Scheme 44A**). We postulated whether use of ruthenocene in place of ferrocene could affect the ligand bite angle due to the increased distance between cyclopentyl rings (**Scheme 44B**, ruthenocene = 3.68 Å *vs.* ferrocene = 3.32 Å).[130–134] Synthesis of **178a** proved to be challenging. Treatment of ruthenocene **177** with *n*-BuLi before quenching with bis(diethylamino)chlorophosphine afforded a mixture of *di*-**178a** and *mono*-**178b** (1.6:1). Subsequent reaction of this mixture with (*S*)-SPINOL afforded *mono*-(*S*)-**179** (21% yield) and desired (*S*)-**L42** (5% yield) which were separated by flash column chromatography.



Scheme 44: *(A) General structure of ligands bearing an alternative metallocene; (B) Reagents and conditions: (i) (a) TMEDA, n-BuLi, THF, r.t., 16 h; (b) $PCl(NEt_2)_2$, THF, -78 °C–r.t., 96 h; (ii) (S)-SPINOL, Et_3N, DMAP, THF:CH_2Cl_2 (2:1), 0 °C–r.t., 72 h; [a]Determined by ^1H NMR spectroscopy of the crude reaction mixture.*

Given the success of SPINOL-derived ligands, it seemed relevant to utilise a chiral SPINOL component as the central moiety of the ligand (**Scheme 45A**). As steric bulk at the C-4 position seemed beneficial, biphenol **180**, which has featured in ligands used for previous work in the group, was employed as the outer unit. Accordingly, (*S*)-**114** was obtained after hydrolysis and reduction from (*S*)-**113** (90% yield over two steps), and subsequent reaction with **180** afforded bisphosphite (*S*)-**L43** in 41% yield (**Scheme 45B**).

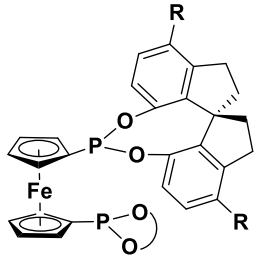


Scheme 45: *Reagents and conditions: (i) (a) KOH, H_2O:EtOH:THF (1:1:1), 80 °C, 1 h; (b) Pd/C, AcOH, MeOH, H_2 (1 atm), r.t., 16 h; (ii) (a) PCl_3, 85 °C, 2 h; (b) (S)-SPINOL, Et_3N, DMAP, THF, 0 °C–r.t., 16 h.*

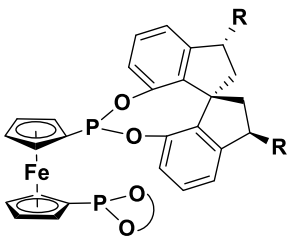
2.8 Summary and conclusions

In collaboration with Dr Andrew Dalling and Dr Raymond Chung, a library of chiral bisphosphonite and bisphosphite ligands were synthesised following the initial diversification plan outlined in **Section 2.1**. By utilising the synthetic route towards SPINOL derivatives previously developed in the group, functionalisation at the C-4 position was achieved with a multitude of aryl groups by Pd-catalysed Suzuki-Miyaura coupling. C-5 functionalised ligands were obtained *via* enantioselective 1,4-conjugate addition of arylboronic acids to enones, as reported by Lu, Hayashi and Dou; this route was also implemented to afford C-4/C-5 and C-2/C-5 di-functionalised SPINOL ligands. Cyclopentyl- and cyclohexyl-fused SPINOL ligands were obtained following a report by Ding, and C-4 functionalised analogues of these were also synthesised. The ligand library was diversified by inclusion of a heteroatom in the aliphatic backbone using Zhang's report for the synthesis of *O*-SPINOL. This process was used the generate a C-3 functionalised SPINOL ligand. A further bisphosphonite ligand was obtained by employing (*R*)-VANOL instead of (*R*)-SPINOL. Finally, to modify the central component, ruthenocene was used in place of ferrocene to generate (*S*)-**L42**, while (*S*)-SPINOL was used with biaryl **180** to afford (*S*)-**L43**. Ongoing work involves completion of bi-xanthene **L38** and bi-tetralin **L39**. To conclude, over 20 chiral bisphosphonite and bisphosphite ligands were synthesised for optimisation of the hydroheteroarylation reactions (**Figure 3**).

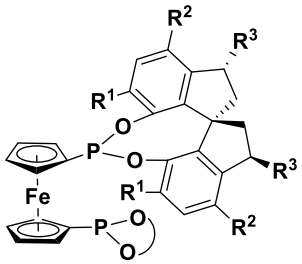
Summary of synthesised ligands:



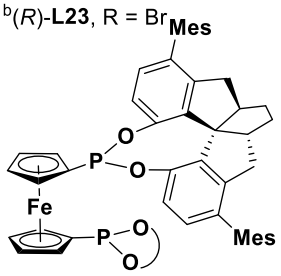
(*S*)-**L17**, R = 3,4,5-$(F)_3C_6H_2$
(*R*)-**L18**, R = 3,5-$(CF_3)_2C_6H_3$
(*R*)-**L19**, R = 3,5-$(OMe)_2C_6H_3$
[a](*S*)-**L20**, R = 3,5-(*t*-Bu)$_2C_6H_3$
[a](*R*)-**L21**, R = C_6Me_5
[a](*R*)-**L22**, R = C_6F_5
[b](*R*)-**L23**, R = Br



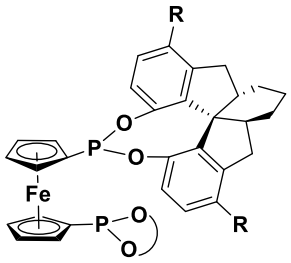
(*R*)-**L25**, R = 4-$(F)C_6H_4$
[a](*R*)-**L27**, R = Ph
[a](*R*)-**L28**, R = 4-$(OMe)C_6H_4$



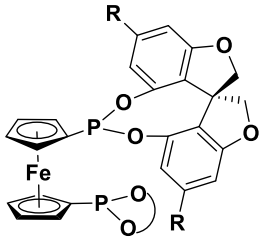
(*R*)-**L26**, R^1 = H, R^2 = Br, R^3 = 2-naphth
[a](*R*)-**L29**, R^1 = H, R^2 = Ph, R^3 = Ph
[a](*R*)-**L30**, R^1 = H, R^2 = F, R^3 = Ph
[a](*R*)-**L31**, R^1 = Me, R^2 = H, R^3 = Ph



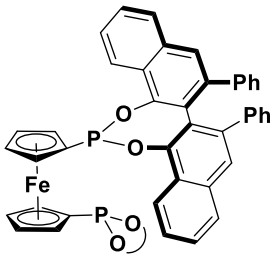
(*R*)-**L32**



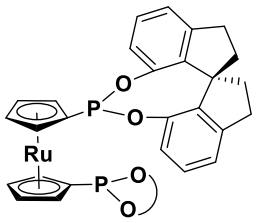
[a](*R*)-**L34**, R = H
[a](*S*)-**L35**, R = Mes



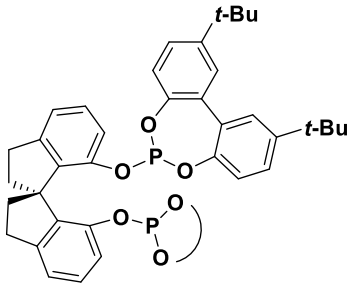
[b](*S*)-**L36**, R = H
(*R*) or (*S*)-**L37**, R = Ph



(*R*)-**L40**

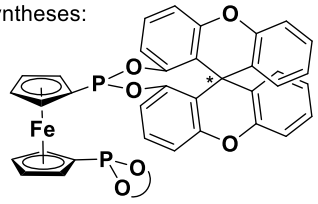


(*S*)-**L42**

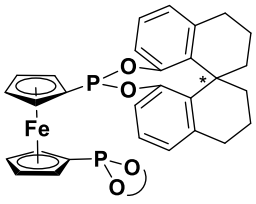


(*S*)-**L43**

Ongoing ligand syntheses:



(*R*) or (*S*)-**L38**



(*R*) or (*S*)-**L39**

Figure 3: *Summary of synthesised ligands and ongoing ligand targets. Ligands synthesised by: [a]Andrew Dalling or [b]Raymond Chung.*

Chapter 3

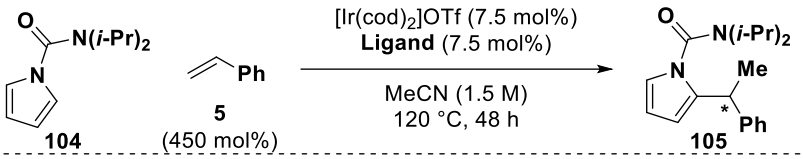
Investigations into Ir(I)-catalysed Alkene Hydro(hetero)arylation Reactions

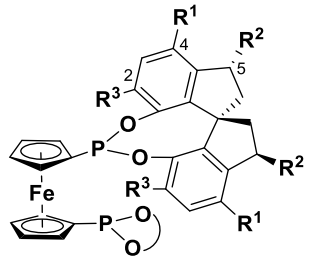
Chapter 3 – Investigations into Ir(I)-catalysed Alkene Hydro(hetero)arylation Reactions

3.1 Evaluation of ligands for enantioselective hydroheteroarylation using pyrrole substrates

As described in **Chapter 1**, it was proposed that hydroheteroarylation reactions using pyrrole and furan substrates could be optimised through judicious modification of the ligand structure. As such, over 20 chiral bisphosphonite and bisphosphite ligands were synthesised in collaboration with Dr Andrew Dalling and Dr Raymond Chung, as described in **Chapter 2**. Alongside Dalling, the ligands were trialled in Ir(I)-catalysed hydroheteroarylation reactions of styrene using heterocyclic substrates.[109]

Investigations commenced using pyrrole substrate **104** (**Table 2**). It had been shown previously by Dr Phillippa Cooper that employment of unfunctionalised SPINOL ligand **L14** gave **105** in 75% and 76% *e.e.* (**Entry 1**).[108] Functionalisation at C-4 of the SPINOL unit with either a phenyl (**Entry 2**) or mesityl group (**Entry 3**) provided **105** in higher yields. From here, it seemed pertinent to investigate additional ligands with C-4 functionality. As such, ligands with either bulky (**Entries 4** & **5**), electron-deficient (**Entries 6–8**) or electron-rich substituents (**Entry 9**) at C-4 were screened and showed good reactivity (yields up to 94%) but struggled to control enantioselectivity. Next, ligands featuring substituents at C-5 were trialled (**Entries 11–13**). Of these, 4-fluorophenyl **L25** performed well (**Entry 12**), generating **105** in 85% yield 75% *e.e.* Further increases were not found using difunctionalised SPINOL ligands (**Entries 14–17**). Notably, C-5 functionalisation was shown generally to be detrimental to reaction yield as seen by comparing **Entries 10** & **14**. In all cases, only branched product was observed from ^{1}H NMR spectroscopy of the crude reaction mixture. From these results, it was clear that functionalisation at different positions of the SPINOL moiety was having a profound effect upon the reaction outcome. This validated our ligand design approach and hence, we were optimistic further reaction optimisation could be achieved through additional ligand screening.

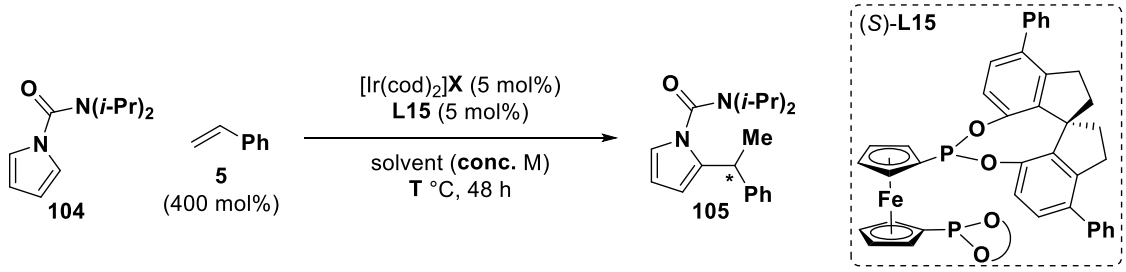




Entry	Ligand	R^1	R^2	R^3	Yield	*e.e.*
1[a]	(*R*)-**L14**	H	H	H	75%	76%
2[a]	(*R*)-**L15**	Ph	H	H	84%	61%
3[a]	(*R*)-**L13**	Mes	H	H	95%	24%
4[b]	(*S*)-**L20**	3,5-(*t*-Bu)$_2$C$_6$H$_3$	H	H	77%	70%
5[b]	(*R*)-**L21**	C$_6$(Me)$_5$	H	H	94%	41%
6[b]	(*R*)-**L22**	C$_6$F$_5$	H	H	94%	55%
7	(*S*)-**L17**	3,4,5-(F)$_3$C$_6$H$_2$	H	H	94%	52%
8	(*R*)-**L18**	3,5-(CF$_3$)$_2$C$_6$H$_3$	H	H	94%	59%
9	(*R*)-**L19**	3,5-(OMe)$_2$C$_6$H$_3$	H	H	70%	54%
10[c]	(*R*)-**L23**	Br	H	H	99%	34%
11[b]	(*R*)-**L27**	H	Ph	H	71%	75%
12	(*R*)-**L25**	H	4-(F)C$_6$H$_4$	H	85%	75%
13[b]	(*R*)-**L28**	H	4-(OMe)C$_6$H$_4$	H	74%	74%
14	(*R*)-**L26**	Br	2-naphth	H	65%	36%
15[b]	(*R*)-**L29**	Ph	Ph	H	52%	56%
16[b]	(*R*)-**L30**	F	Ph	H	80%	68%
17[b]	(*R*)-**L31**	H	Ph	Me	0%	N/A

Table 2: *Chiral ligand evaluation for the enantioselective hydroheteroarylation of styrene with pyrrole **104**. [a]Reaction conducted by Dr Phillippa Cooper; [b]Reaction conducted by Dr Andrew Dalling; [c]Reaction conditions: [Ir(cod)$_2$]BARF (5 mol%), Ligand (5 mol%), 1,4-dioxane (1.5 M), 90 °C, 48 h; Enantiomeric ratios determined by chiral SFC analysis.*

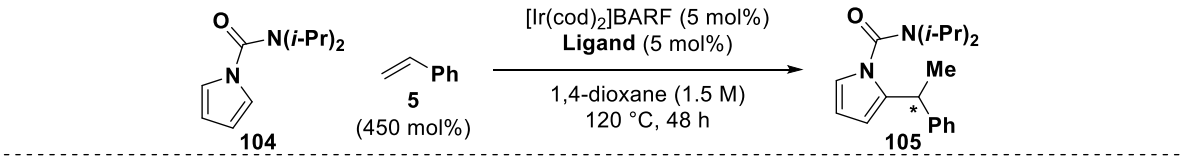
Before additional ligands were trialled, optimisation efforts continued through alteration of reaction conditions (**Table 3**). Using **L15**, pyrrole **105** can be obtained in 84% yield, 61% *e.e.* by employment of [Ir(cod)$_2$]OTf in MeCN (1.5 M) at 130 °C (**Entry 1**). It was found that changing the solvent to 1,4-dioxane had minimal impact on reaction outcome, as did lowering the reaction temperature to 120 °C (**Entries 2** & **3**). A slight increase in enantioselectivity was achieved through use of [Ir(cod)$_2$]BARF, giving **105** in 84% yield, 63% *e.e.* (**Entry 4**) but further optimisation by screening several solvents was unsuccessful (**Entries 5–8**).

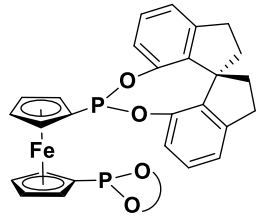


Entry	X	Solvent	Conc. /M	T /°C	Yield	*e.e.*
1[a]	OTf	MeCN	1.5	130	84%	61%
2	OTf	1,4-dioxane	1.5	120	84%	58%
3	OTf	1,4-dioxane	0.5	120	78%	59%
4	**BARF**	**1,4-dioxane**	**1.5**	**120**	**84%**	**63%**
5	BARF	1,2-DCB	1.5	120	77%	60%
6	BARF	THF	1.5	120	81%	60%
7	BARF	DME	1.5	120	84%	62%
8	BARF	Diglyme	1.5	120	85%	62%

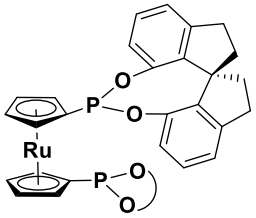
Table 3: *Optimisation of reaction conditions for the enantioselective hydroheteroarylation reaction of styrene with pyrrole **104**; [a]7.5 mol% [Ir] was used; Enantiomeric ratios were determined by chiral SFC analysis.*

Since only marginal gains were made from revisiting reaction conditions, optimisation continued with screening of additional bisphosphonite and bisphosphite ligands (**Table 4**). As seen previously, use of unfunctionalised SPINOL **L14** gave pyrrole **105** in 75% yield and 76% *e.e.* (**Entry 1**). Higher reactivity was observed using ruthenocene-derived **L42**, producing **105** in 91% yield, but in 46% *e.e.* (**Entry 2**). Incorporation of oxygen atoms into the SPINOL aliphatic backbone proved detrimental to the reaction outcome, affording **105** in 65% yield, 45% *e.e.* (**Entry 3**). It was found that the reaction was unaffected by inclusion of a cyclohexyl moiety (**Entry 4**), while appendage of mesityl groups increased yield, but lowered enantioselectivity (**Entry 5**). Similar results were obtained using cyclopentyl-fused**,** or VANOL-derived ligands (**Entries 6** & **7**). Bisphosphite ligands were also found to be unsuitable for the process; for instance, by employing **L44**, **105** was obtained in 82% yield, 37% *e.e.* (**Entry 9**). As no improvements were made through ligand screening or re-optimisation of reaction conditions, investigations turned to the use of furan substrates in this process.

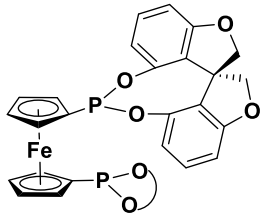




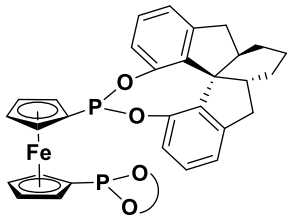
Entry 1[a,c], (*R*)-**L14**,
75% yield, 76% *e.e.*



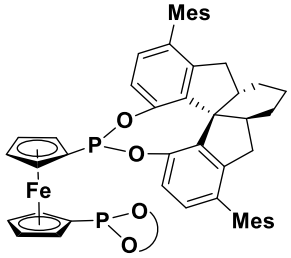
Entry 2, (*S*)-**L42,**
91% yield, 46% *e.e.*



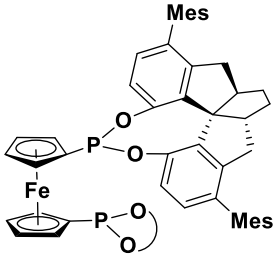
Entry 3, (*S*)-**L36**,
65% yield, 45% *e.e.*



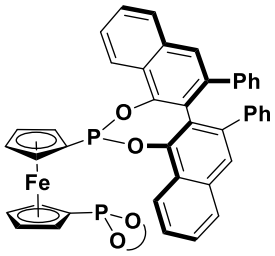
Entry 4[b,c], (*R*)-**L34**,
78% yield, 78% *e.e.*



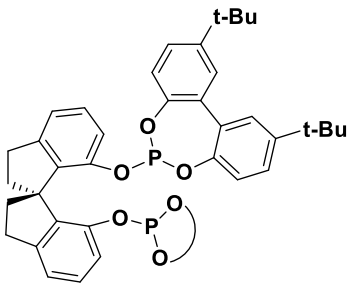
Entry 5[b,c], (*S*)-**L35**,
86% yield, 30% *e.e.*



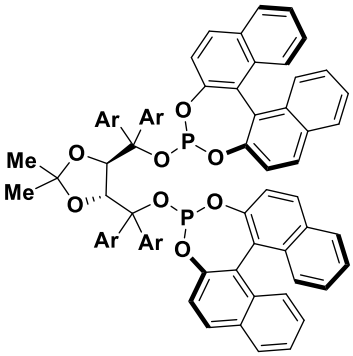
Entry 6, (*R*)-**L32**,
83% yield, 57% *e.e.*



Entry 7, (*R*)-**L40**,
80% yield, 45% *e.e.*



Entry 8, (*S*)-**L43**,
0% yield

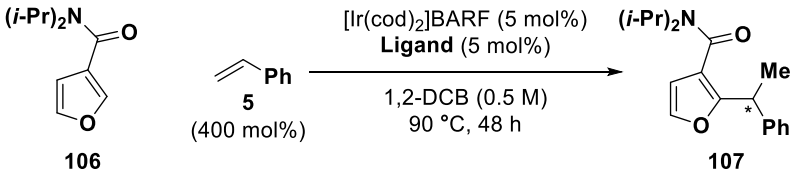


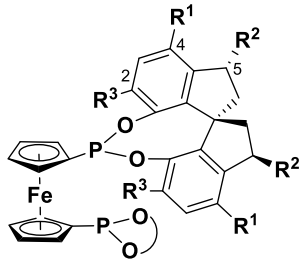
Entry 9, (*R*)-**L44**, Ar = 3,5-$(Me)_2C_6H_3$,
82% yield, 37% *e.e.*
Entry 10, (*R*)-**L45**, Ar = 4-$(F)C_6H_4$,
65% yield, 17% *e.e.*

Table 4: *Chiral ligand evaluation for the enantioselective alkene hydroarylation of styrene with pyrrole* ***104****;* [a]*Reaction conducted by Dr Phillippa Cooper;* [b]*Reaction conducted by Dr Andrew Dalling;* [c]*Reaction conditions: [Ir(cod)2]OTf (7.5 mol%), Ligand (7.5 mol%), MeCN (1.5 M), 130 °C, 48 h; Enantiomeric ratios determined by chiral SFC analysis.*

3.2 Evaluation of ligands for enantioselective hydroheteroarylation using furan substrates

The newly synthesised bisphosphonite ligands were then screened for the hydroheteroarylation of styrene using furan **106**. Initial investigations by Cooper into C-4 functionalisation of the SPINOL unit gave promising results (**Table 5**).[108] For instance, comparison of **L14** (**Entry 1**) with **L13** (**Entry 3**) showed addition of a mesityl group at C-4 gave a drastic increase in both the yield and enantioselectivity of **107** (83% yield, 88% *e.e. vs.* 59% yield, 69% *e.e.*). Accordingly, a variety of ligands with C-4 functionalisation were screened in the hydroheteroarylation process. Pleasingly, pentafluorophenyl-**L22** provided **107** in high yield and enantioselectivity (**Entry 6**, 82% yield, 90% *e.e.*). Screening of additional ligands featuring electron-deficient aryl groups failed to improve upon this result (**Entries 7** & **8**). Finally, functionalisation at C-5 (**Entries 11** & **12**) or di-functionalisation (**Entries 13–16**) failed to deliver **107** in higher yield and enantioselectivity than by employment of **L22**. Compared to the pyrrole reaction, it is notable that C-5 functionalised ligands gave high yields of product (*cf.* **Table 2**). In all cases, only branched product was observed by ^{1}H NMR spectroscopy of the crude reaction mixture.



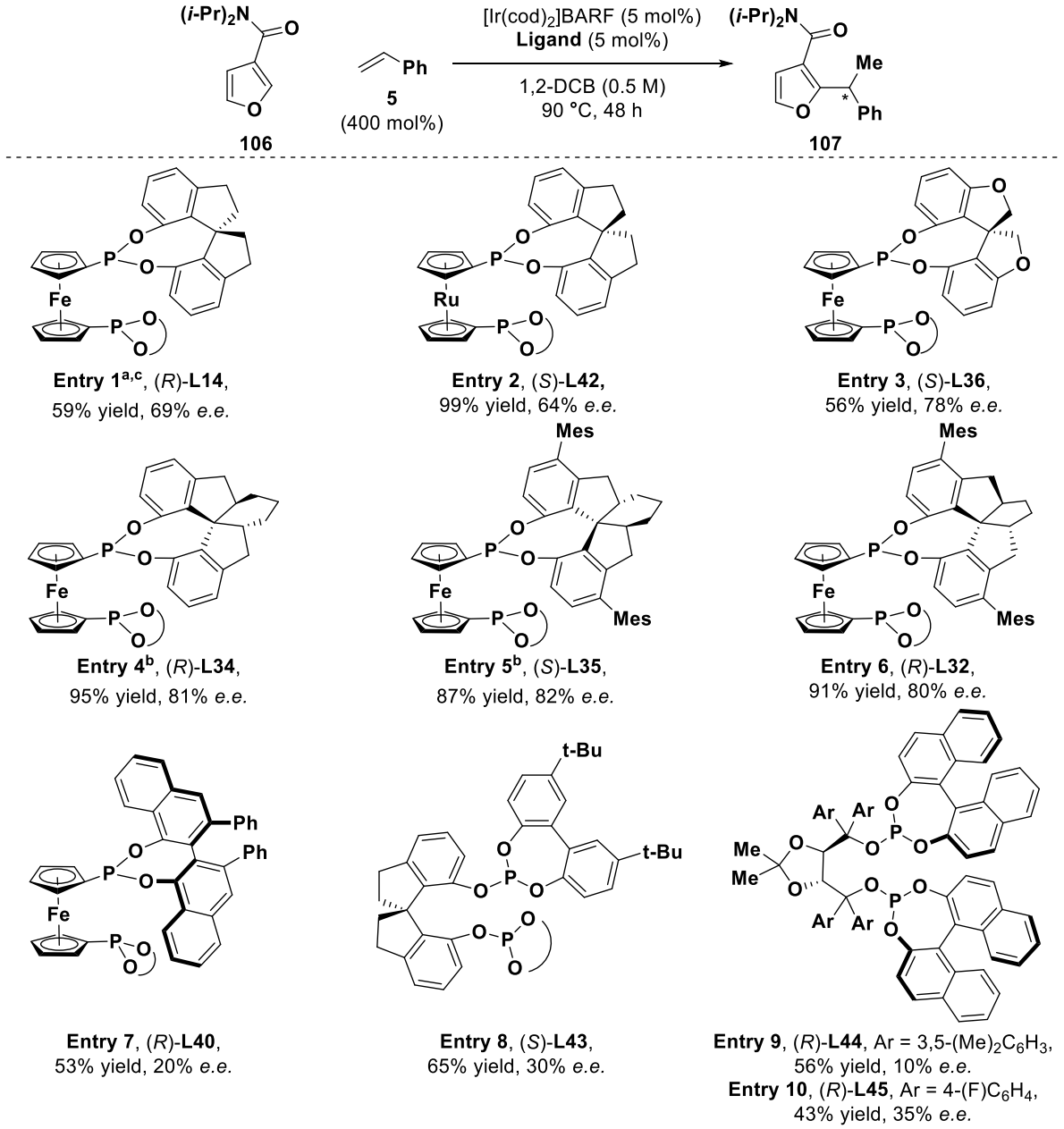


Entry	Ligand	R^1	R^2	R^3	Yield	e.e.
1[a,c]	(*R*)-**L14**	H	H	H	59%	69%
2[a,c]	(*R*)-**L15**	Ph	H	H	59%	74%
3[b]	(*R*)-**L13**	Mes	H	H	83%	88%
4[b]	(*S*)-**L20**	3,5-(*t*-Bu)$_2$C$_6$H$_3$	H	H	88%	87%
5[b]	(*R*)-**L21**	C$_6$(Me)$_5$	H	H	87%	88%
6[b]	(*R*)-**L22**	C$_6$F$_5$	H	H	82%	90%
7	(*S*)-**L17**	3,4,5-(F)$_3$C$_6$H$_2$	H	H	68%	77%
8	(*R*)-**L18**	3,5-(CF$_3$)$_2$C$_6$H$_3$	H	H	77%	86%
9	(*R*)-**L19**	3,5-(OMe)$_2$C$_6$H$_3$	H	H	86%	86%
10	(*R*)-**L23**	Br	H	H	89%	71%
11[b]	(*R*)-**L27**	H	Ph	H	86%	68%
12	(*R*)-**L25**	H	4-(F)C$_6$H$_4$	H	95%	67%
13	(*R*)-**L26**	Br	2-naphth	H	96%	52%
14[b]	(*R*)-**L29**	Ph	Ph	H	83%	64%
15[b]	(*R*)-**L30**	F	Ph	H	93%	64%
16[b]	(*R*)-**L31**	H	Ph	Me	47%	4%

Table 5: *Chiral ligand evaluation for the enantioselective hydroheteroarylation of styrene with furan **106**; [a]Reaction conducted by Dr Phillippa Cooper; [b]Reaction conducted by Dr Andrew Dalling; [c]Reaction conducted in 1,4-dioxane (1.0 M) at 120 °C; Enantiomeric ratios determined by chiral SFC analysis.*

To improve further the yield and enantioselectivity for the hydroheteroarylation of styrene with furan **106**, additional bisphosphonite and bisphosphite ligands were screened in the process (**Table 6**). Firstly,

use of ruthenocene-derived **L42** gave **107** in quantitative yield but in 64% *e.e.* (**Entry 2**). A minor improvement was made using *O*-SPINOL-derived **L36**, which provided **107** in 56% yield, 78% *e.e.* (**Entry 3**). Cyclohexyl- and cyclopentyl-fused SPINOL ligands performed similarly – the best outcome was attained using **L34** which gave **107** in 95% yield, 81% *e.e.* (**Entry 4**). Addition of steric bulk at C-4 positions in the cyclohexyl-fused system led to a less efficient ligand (**Entry 5**, 87% yield, 82% *e.e.*) while (*R*)-VANOL-derived ligand **L40**, as well as bisphosphite ligands proved to be unsuitable in the reaction (**Entries 7–10**).



Entry 1[a,c], (*R*)-**L14**, 59% yield, 69% *e.e.*

Entry 2, (*S*)-**L42,** 99% yield, 64% *e.e.*

Entry 3, (*S*)-**L36**, 56% yield, 78% *e.e.*

Entry 4[b], (*R*)-**L34**, 95% yield, 81% *e.e.*

Entry 5[b], (*S*)-**L35**, 87% yield, 82% *e.e.*

Entry 6, (*R*)-**L32**, 91% yield, 80% *e.e.*

Entry 7, (*R*)-**L40**, 53% yield, 20% *e.e.*

Entry 8, (*S*)-**L43**, 65% yield, 30% *e.e.*

Entry 9, (*R*)-**L44**, Ar = 3,5-$(Me)_2C_6H_3$, 56% yield, 10% *e.e.*
Entry 10, (*R*)-**L45**, Ar = 4-$(F)C_6H_4$, 43% yield, 35% *e.e.*

Table 6: *Chiral ligand evaluation for the enantioselective hydroheteroarylation of styrene with furan **106**. [a]Reaction conducted by Dr Phillippa Cooper; [b]Reaction conducted by Dr Andrew Dalling; [c]Reaction conducted in 1,4-dioxane (1.0 M) at 120 °C; Enantiomeric ratios determined by chiral SFC analysis.*

3.3 Investigating the effect of SPINOL structures upon hydroheteroarylation reactions

3.3.1 Previous computational approaches to ligand design

With minimal improvement in reaction outcome through ligand screening, it was postulated that a computational approach could help elucidate desirable ligand properties to guide future synthesis efforts. The key role of ligands in transition metal catalysis has prompted many attempts to quantify their steric and electronic contributions. Two of the most prominent descriptors of P-donor ligands were reported by Tolman, who compiled data from infrared (IR) spectroscopic measurements of CO ligands on a tetrahedral Ni-complex, [Ni(CO)$_3$L], in which the measured carbonyl stretching frequency (ν) indicates the strength of the M-L bond; this is now commonly referred to as the Tolman electronic parameter (**Figure 4**).[135] A complimentary steric descriptor, which details the angle between the metal centre and the outermost atoms of the ligand, θ, was also disclosed and is known as the Tolman cone angle.

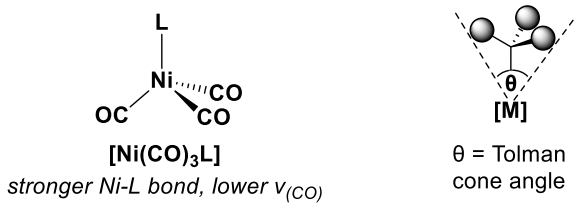
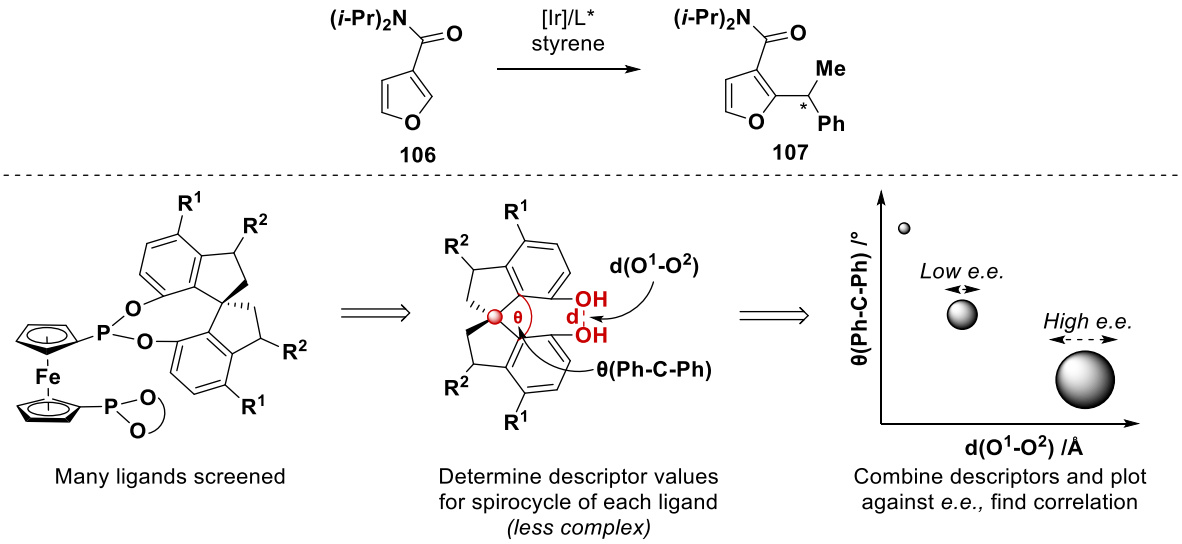


Figure 4: *Visualisation of Tolman's electronic parameter and cone angle.*

These descriptors, amongst others, have been utilised in rational ligand design approaches to provide a powerful means to tune transition metal reactivity and reaction selectivity.[136] While this is a useful approach, a truly rational design of novel catalysts can rarely be achieved due to the multivariate nature of catalytic manifolds. With the rise of computational power, a more desirable approach was reported by Harvey and Orpen[137,138] who implemented density functional theory (DFT) to calculate multiple electronic and steric descriptors of a range of ligands.[139] By using principal component analysis, which reduces a multidimensional set of descriptors to a few derived variables that capture a large proportion of the variation in the data set, ligands can be plotted into ligand maps. This "Ligand Knowledge Base" approach has been implemented to display monodentate *P*-ligands (28 descriptors, 366 ligands),[138] *C*-ligands (26 descriptors, 113 ligands),[140] bidentate *P*,*P*- and *P*,*N*-ligands (28 descriptors, 324 ligands)[141] in addition to further ligand types. By selecting ligands from different clusters, a chemist can screen ligands which possess diverse properties to optimise a reaction. Inspired by this work, it was envisaged that two simple descriptors of our SPINOL-derived ligands could be calculated; to limit required computational power, we proposed that descriptors should only be determined for the spirocyclic component of the ligand (**Scheme 46**). By combining these descriptors and plotting against *e.e.* values obtained for the hydroheteroarylation of furan **106**, desirable ligand properties could be determined, which would guide future ligand synthesis efforts. In an attempt to explore the steric properties of the ligands, two descriptors were proposed to be calculated: (i) d(O^1-

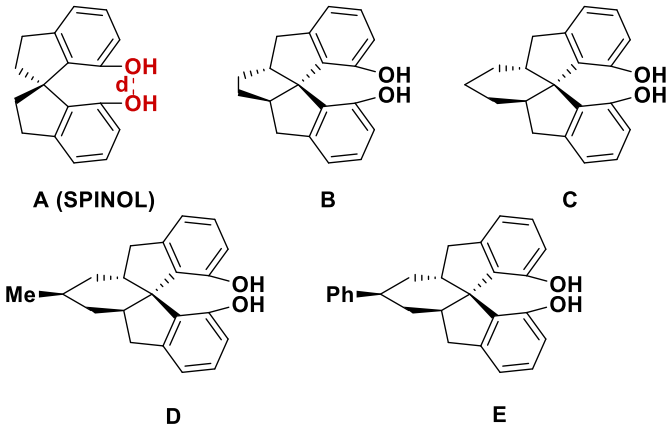
O^2), the distance between the two chelating oxygen atoms, and (ii) θ(Ph-C-Ph), the angle about the central quaternary carbon atom.



Scheme 46: *Visual representation of investigating the effect of SPINOL structures upon hydroheteroarylation using furan **106**.*

3.3.2 Validation of the method

Firstly, we were interested in validating calculated descriptor values against those reported in the literature. Accordingly, geometry optimisation calculations (see *Experimental* for computational details) of five SPINOL-derived molecules **A**–**E** were undertaken, and [d(O^1-O^2)] values were obtained for each. These values were then compared with experimental data, reported by Ding and co-workers, obtained from X-ray analyses of **A**–**E**.[122] From **Table 7**, some correlation was observed between calculated and literature d(O^1-O^2) values for simple spirocycles. For example, SPINOL (A) has a lit. d(O^1-O^2) = 4.1004 Å which correlated with calc. d(O^1-O^2) = 4.39423 Å. Likewise, near-identical values were also obtained from analysis of cyclopentyl-**B** (Lit. = 4.7013 Å, Calc. = 4.70541 Å). For more complex structures, however, large discrepancies were found between literature and calculated d(O^1-O^2) values. For example, a large deviation was discovered between calculated and literature values for both **C** (Lit. = 4.0909 Å, Calc. = 5.0865 Å) and **D** (Lit. = 4.2590 Å, Calc. = 5.0915 Å). Overall, this investigation suggested that calculated structural analyses were valid for simple spirocycles, but were less reliable for more complex molecules.

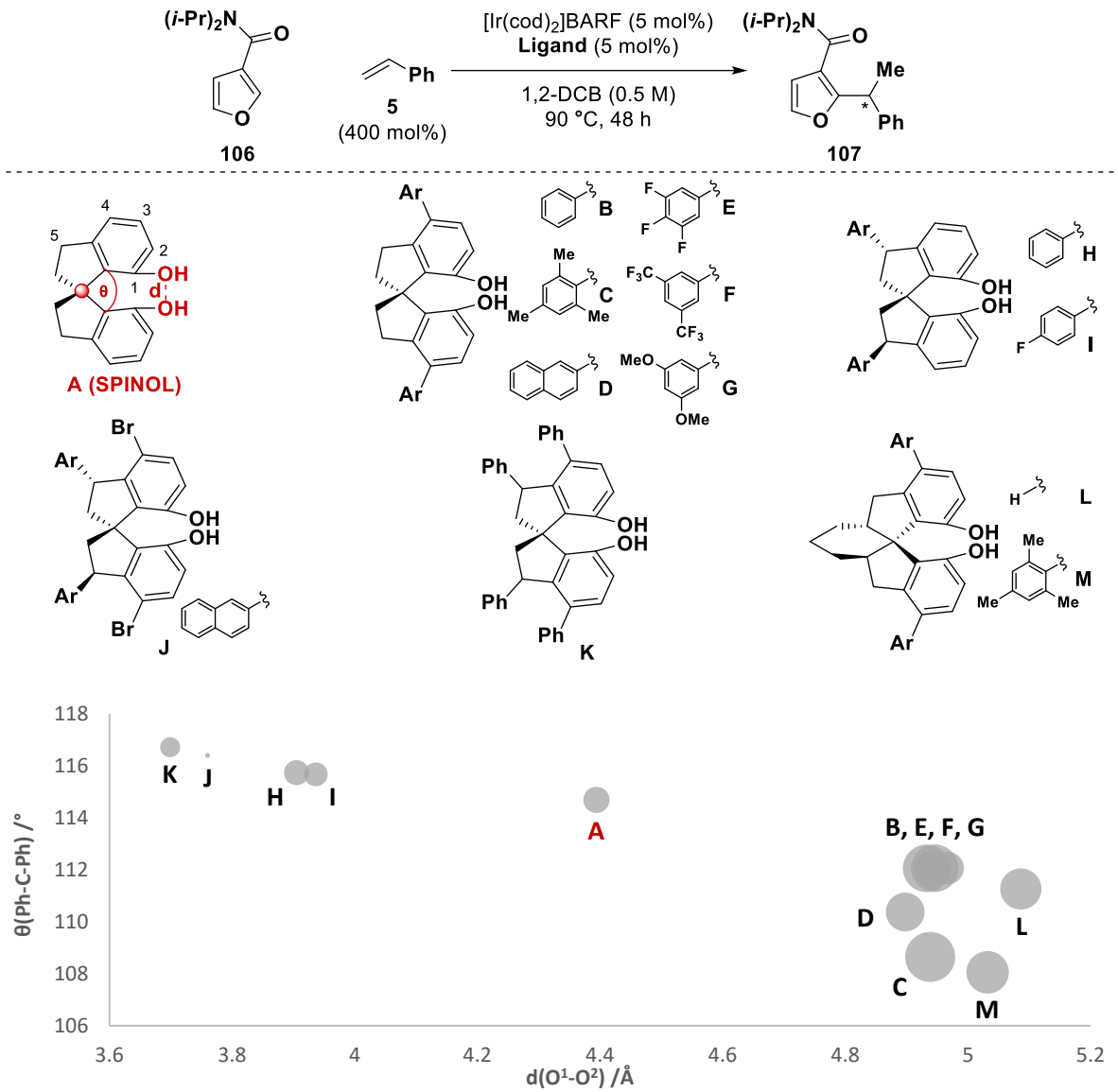


Structure	Lit. $d(O^1\text{-}O^2)$ /Å	Calc. $d(O^1\text{-}O^2)$ /Å
A	4.1004	4.3942
B	4.7013	4.7054
C	4.0909	5.0865
D	4.2590	5.0915
E	3.9665	4.4216

Table 7: *Comparison of literature and calculated $d(O^1\text{-}O^2)$ values; Calculations conducted using B3LYP functional and 3-21G basis set.*

3.3.3 Comparison of calculated parameters *vs.* enantioselectivity

Investigations proceeded by calculating the ground-state geometries of spirocycles **A**–**M** and obtaining the corresponding $d(O^1\text{-}O^2)$ and θ(Ph-C-Ph) values (see **Section 7.7** for details). To illustrate for SPINOL (**A**): $d(O^1\text{-}O^2)$ = 4.1004 Å and θ(Ph-C-Ph) = 114.68°. The ligands were then plotted in the ligand map shown in **Graph 1**. From the map, it can be seen that ligands possessing similar steric properties reside in two distinct clusters: an Eastern cluster (**A**–**G**, **L**, **M**) and a Western cluster (**H**–**K**). Importantly, these two clusters are sterically diverse compared to parent structure **A**. **Graph 1** shows that C-5 functionalisation (**H**–**K**) results in a reduced $d(O^1\text{-}O^2)$ compared to **A**. Conversely, C-4 functionalisation (**B**-**G**) or inclusion of a cyclohexyl moiety (**L, M**) increases $d(O^1\text{-}O^2)$. On the other hand, C-5 functionalisation (**H**–**K**) increases θ(Ph-C-Ph) compared to **A**, while other modifications decrease θ(Ph-C-Ph) (**B**–**G, L, M**). The two descriptors, $d(O^1\text{-}O^2)$ and θ(Ph-C-Ph), were then compared with the *e.e.* values obtained using the corresponding bisphosphonite ligands of structures **A**–**M** – a larger plot indicates a higher *e.e.* value. In general, it can be seen that ligands that reside in the Western cluster afford lower *e.e.* values while higher enantiocontrol is observed using ligands in the Eastern cluster. Overall, ligands with large $d(O^1\text{-}O^2)$ and small θ(Ph-C-Ph) are desirable, suggesting that a "puckered" ground state geometry of the spirocyclic structure is beneficial to induce high enantioselectivity.

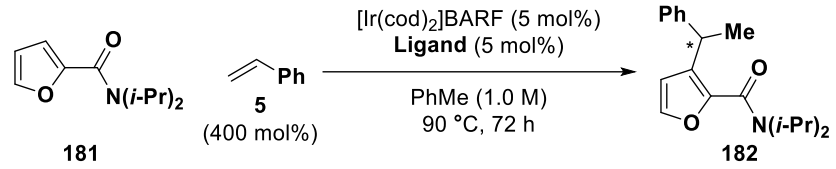


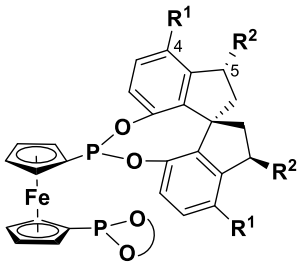
Graph 1: *Correlation between d(O¹-O²) and θ(Ph-C-Ph) vs. e.e. for hydroheteroarylation using furan **106**. Larger plot indicates higher e.e.. Enantiomeric ratios determined by chiral SFC analysis. Calculations conducted using B3LYP functional and 3-21G basis set.*

While still in its infancy, it is envisaged that this approach could be used to optimise reaction outcomes further by screening ligands in unexplored areas of the ligand map. Fey reported the use of 28 descriptors, while only 2 were used in this work. As such, the methodology should be furthered by calculating additional descriptors, including electronic parameters. Additionally, the current approach does not take into account the full bisphosphonite ligand and only considers the spirocyclic component. Accordingly, future work should calculate descriptors of the whole ligand system at a higher level of theory to produce more robust and reliable data.

3.4 Investigations into the directing group for hydroheteroarylation using furan substrates

As C-3 substituted furan **106** was proving to be a suitable substrate for the hydroheteroarylation of styrene, it seemed pertinent to assess the effect of employing the *N*,*N*-diisopropylamide directing group at the C-2 position. Accordingly, efforts were made to investigate the effect of C-4 or C-5 functionalisation of the SPINOL moiety upon hydroheteroarylations using furan **181** (**Table 8**). It has been demonstrated previously that **182** could be obtained in good yield and enantioselectivity by use of **L14** (**Entry 1**, 82% yield, 79% *e.e.*) or **L15** (**Entry 2**, 85% yield, 73% *e.e.*).[108] Unfortunately, employment of **L17** or **L18**, featuring electron-withdrawing substituents, gave **182** with moderate enantiocontrol but in low yields (**Entries 4** & **5**). Use of **L19** featuring electron-donating substituents proved beneficial to enantioselectivity, but **182** was formed in low yield (**Entry 5**, 44% yield, 78% *e.e.*). Use of C-5 functionalised ligands provided **182** in high yields, but addition of substituents at this position resulted in decreases in *e.e.* (**Entries 7** & **8**). This effect is similar to that observed using furan substrate **106** bearing a C-3 directing group (*cf.* **Table 5**).





Entry	Ligand	R^1	R^2	Yield	e.e.
1[a,b]	(*R*)-**L14**	H	H	82%	79%
2[a,b]	(*R*)-**L15**	Ph	H	85%	73%
3	(*S*)-**L17**	3,4,5-$(F)_3C_6H_2$	H	64%	66%
4	(*R*)-**L18**	3,5-$(CF_3)_2C_6H_3$	H	30%	67%
5	(*R*)-**L19**	3,5-$(OMe)_2C_6H_3$	H	44%	78%
6[c]	(*R*)-**L23**	Br	H	74%	80%
7	(*R*)-**L25**	H	4-$(F)C_6H_4$	87%	74%
8	(*R*)-**L26**	Br	2-naphth	94%	63%

Table 8: *Chiral ligand evaluation for the enantioselective hydrohetreroarylation of styrene with furan **181**; [a]Reaction conducted by Dr Phillippa Cooper; [b]Reaction conducted in 1,4-dioxane (1.0 M) at 120 °C; [c]Reaction conducted for 48 h; Enantiomeric ratios determined by chiral SFC analysis.*

Moving the directing group to the C-2 position did not optimise the reaction outcome and so attention turned to investigating alternative amide-derived directing groups. It was reported by Cooper that hydroheteroarylation of styrene could be achieved using pyrrole substrate **104** bearing an isopropyl-amide directing group (**Table 9**).[108] In initial optimisation studies, Cooper showed by employing (*R*)-H_8-BINAP as the chiral ligand (**Entry 1**), **105** was formed in 74% yield but in 2% *e.e.* Interestingly, under the same reaction conditions using pyrrole **184** with a *N*,*N*-dicyclohexylamide directing group, both reactivity and enantioselectivity were improved and **186** was formed in 83% yield and in 6% *e.e.*; control over branched selectivity also increased. Understandably, as only a minimal enhancement was obtained using *N*,*N*-dicyclohexylamide **184**, subsequent reaction optimisation by Cooper involved heterocycles which possessed an *N*,*N*-diisopropylamide directing group.

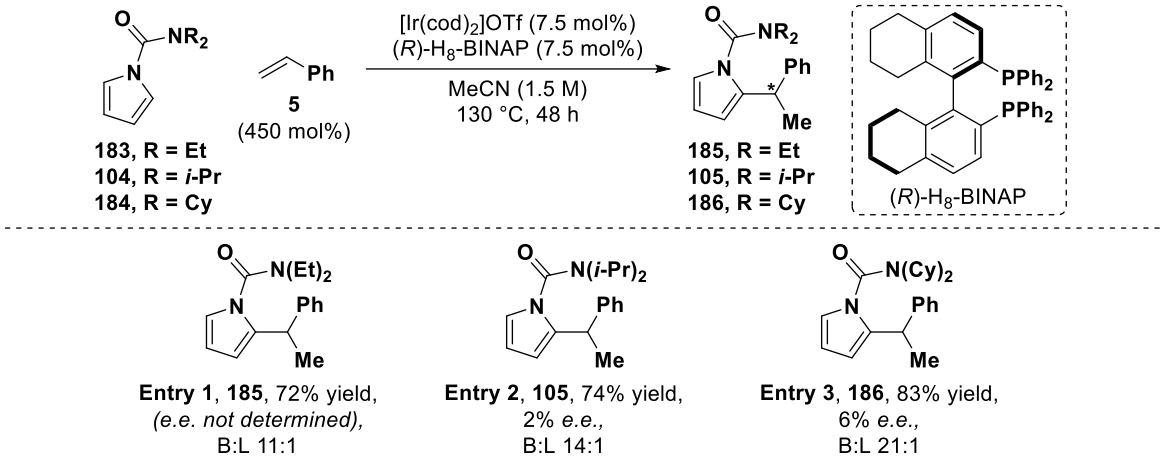
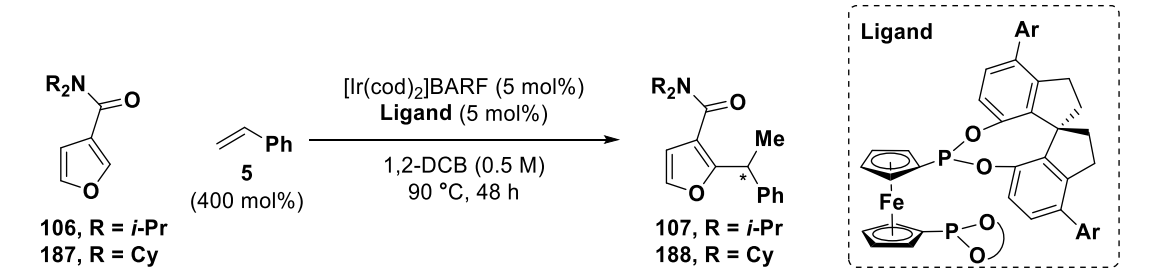


Table 9: *Investigations into amide directing groups on hydroheteroarylation of styrene with pyrrole substrates, conducted by Dr Phillippa Cooper.*

As a result of the work described above, *N*,*N*-dicyclohexylamide furan **187** was synthesised and evaluated in the catalytic protocol using **L13**. Pleasingly, employment of **187** generated **188** in 93% yield and in 92% *e.e.* (**Table 10**, **Entry 2**). Likewise, increases in yield and enantiocontrol were also observed using pentafluoro-**L22** (**Entries 3** & **4**) or pentamethyl-**L21** (**Entries 5** & **6**); however due to a higher yielding synthetic route, **L13** was used in subsequent scope studies.



Entry	R	Ligand	Ar	Yield	*e.e.*
1[a]	*i*-Pr	(*R*)-**L13**	Mes	83%	88%
2	**Cy**	(*R*)-**L13**	**Mes**	**93%**	**92%**
3[a]	*i*-Pr	(*R*)-**L22**	C_6F_5	82%	90%
4	Cy	(*R*)-**L22**	C_6F_5	82%	93%
5[a]	*i*-Pr	(*R*)-**L21**	C_6Me_5	87%	88%
6	Cy	(*R*)-**L21**	C_6Me_5	90%	92%

Table 10: *Investigations into amide directing groups with bisphosphonite ligands; Enantiomeric ratios determined by chiral SFC analysis.*

3.5 Scope of enantioselective hydro(hetero)arylation reactions

With optimal Ir(I)-catalysed conditions in hand for the hydroheteroarylation of styrene with furan **187**, investigations into the scope of the alkene component ensued using ligand **L13** (**Table 11**). Pleasingly, a broad range of styrenes with functionalisation at C-2 (**193a–d**), C-3 (**193e**, **f**) or C-4 (**193g–j**) positions were tolerated. The efficiency of the reaction was demonstrated by employment of 4-*tert*-butylstyene, which afforded **193h** in 95% yield and high enantiocontrol (86% *e.e.*). Styrenes bearing potentially sensitive groups such as 3-chlorostyrene (**193f**, 83% yield, 90% *e.e.*) and 4-bromostyrene (**193i**, 74%

yield, 87% *e.e.*) were also well-tolerated. A limitation of the reaction was observed by using either 2-chloro or 2-bromostyrene, which led to the formation of **193c** (82% yield, 54% *e.e.*) and **193d** (78% yield, 38% *e.e.*) in high yield but with low enantiocontrol, presumably owing to steric bulk of *ortho*-substituents. Pleasingly, aliphatic alkenes also performed well in the reaction as shown by production of **193k** (85% yield, 85% *e.e.*) and **193l** (56% yield, 80% *e.e.*) from 3,3-dimethyl-1-butene and 4-methyl-1-pentene, respectively. Substitution was tolerated at the C-5 position of the furan with either 4-fluorophenyl (**193p**, 75% yield, 79% *e.e.*) or 4-methoxyphenyl (**193q**, 70% yield, 86% *e.e.*) groups. The directing group could be employed at the C-2 position to afford C-3 alkylated product **193r** in 92% yield, 65% *e.e.* To demonstrate the applicability of the *N*,*N*-dicyclohexylamide group to other heterocycles, thiophene product **193s** was generated in 83% yield and 81% *e.e.*; however attempts to further augment the substrate scope benzofuran, benzothiophene and pyrrole substrates were unsuccessful. In all cases, only branched product was observed by ^{1}H NMR spectroscopy of the crude reaction mixture. Additionally, the reaction produced exclusively C-2 alkylated products as opposed to other regioisomeric outcomes. A further aspect of control is demonstrated by the generation of tertiary benzylic stereocentres with high enantiocontrol. Control over these three factors demonstrates the utility of the reaction manifold – this is particularly notable considering the use of minimally-polarised alkenes, which have low electronic and steric bias to form branched products. Current work in this area is focused on determining absolute configuration of the formed products by X-ray analysis of a crystalline product or corresponding salt. Investigations into post-catalysis functionalisation of these products is also ongoing. This work is complimentary to enantioselective hydroarylation reactions using benzamide substrates, optimised by Dr Raymond Chung (*vide infra*, **Table 19**).

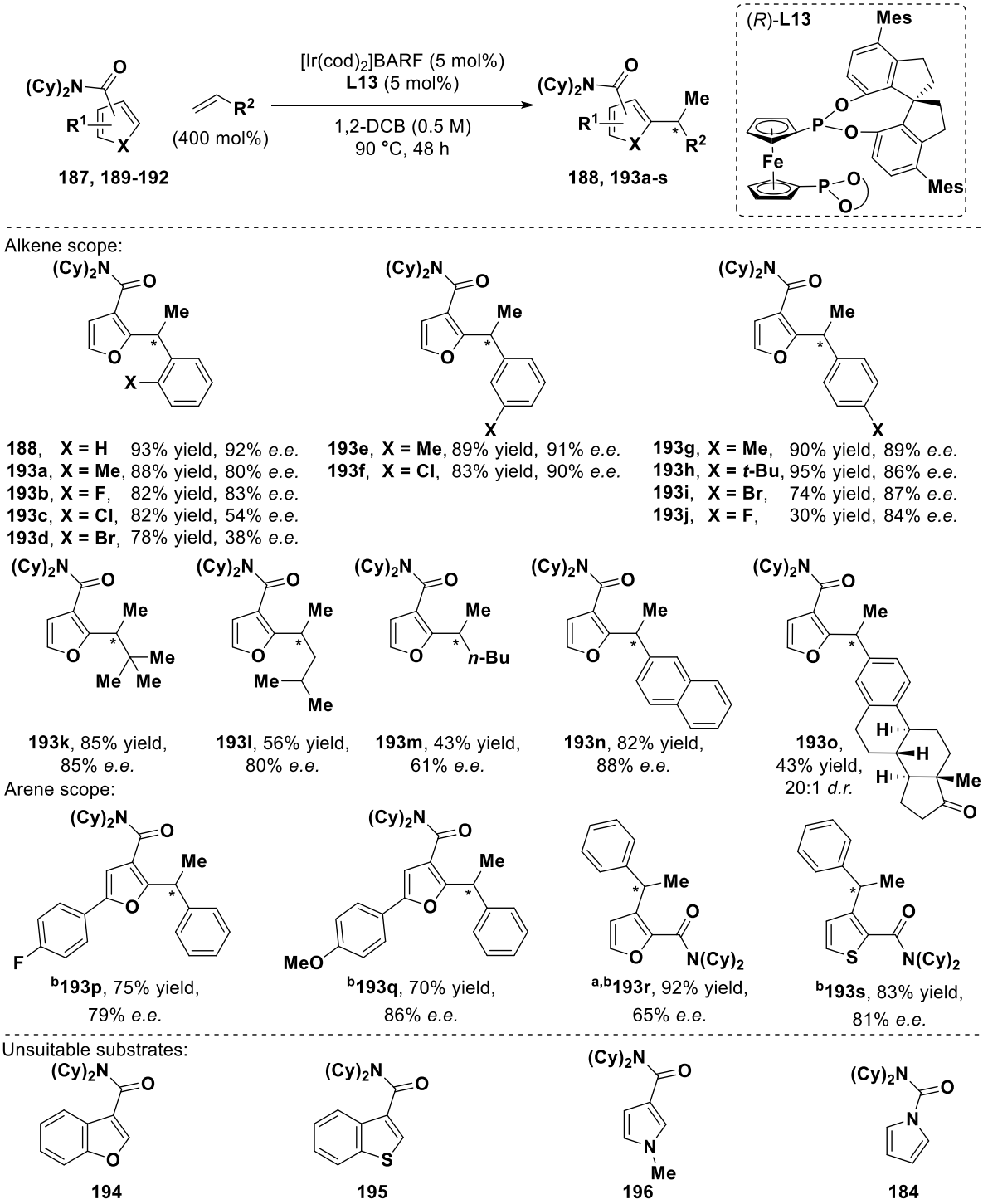


Table 11: *Scope of a hydroheteroarylation reaction with furan substrates; [a]Reaction conducted at 120 °C; [b]**(S)-L13** used; Enantiomeric ratios determined by chiral SFC analysis.*

3.6 Catalyst-controlled diastereoselective hydroheteroarylation of alkenes

Methodologies that enable access to complex stereochemical motifs, such as contiguous stereocentres, are of high value to medicinal and synthetic chemists. This is shown by the prevalence of such structural features in the pharmaceutical compounds, for example voriconazol[142,143] (fungicide) and mixanpril[144] (reduces hypertension, **Figure 5**).

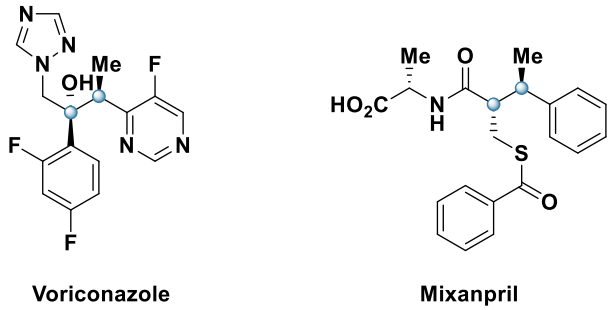
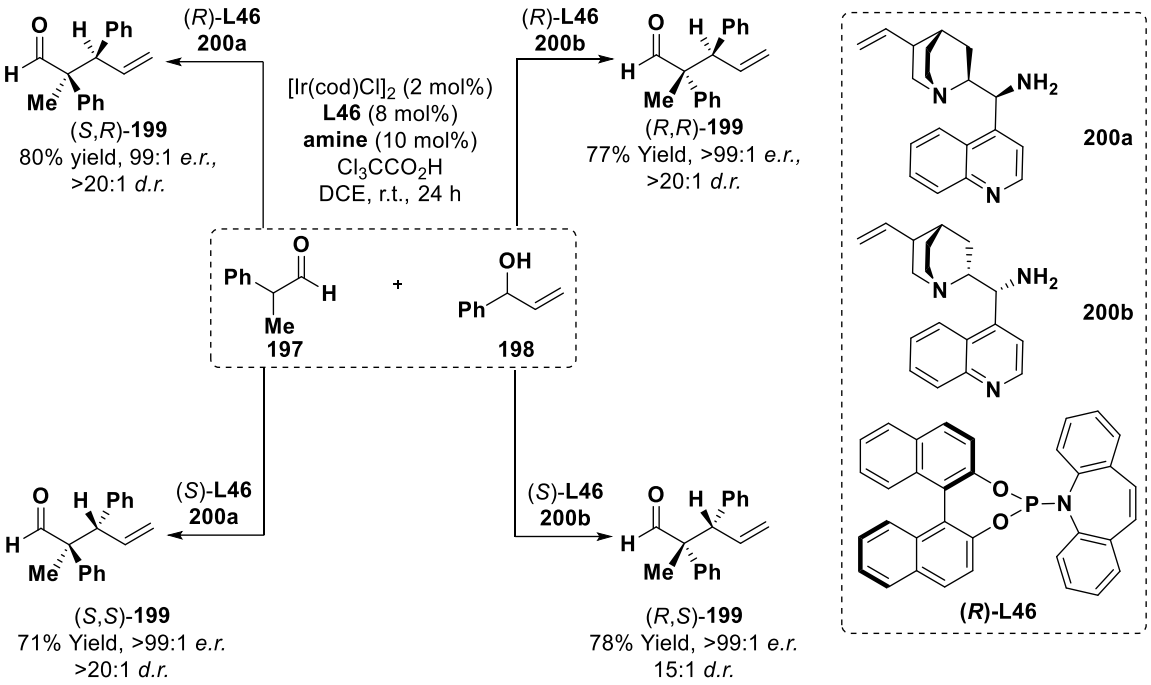


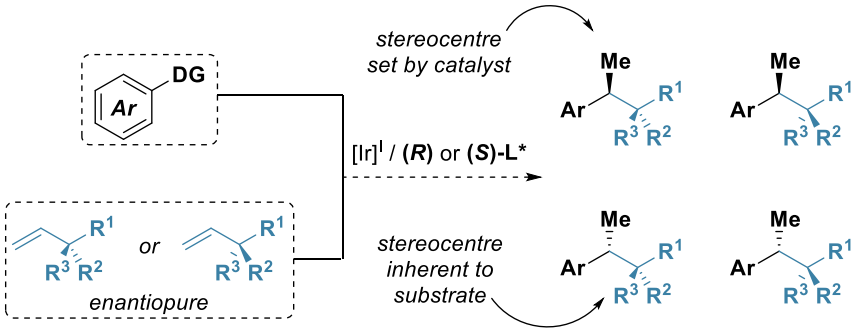
Figure 5: *Pharmaceutical compounds featuring contiguous stereocentres.*

Existing protocols that allow installation of contiguous stereocentres can proceed under chiral auxiliary control or substrate control. Many research groups have developed chiral auxiliary approaches which have since been applied to asymmetric alkylations, condensations, aldol reactions and Diels-Alder cycloadditions amongst others (*vide infra*, **Chapter 5**). The major drawback from these approaches is the need for pre-functionalised substrates, which leads to reduced step economy. Carreira and co-workers demonstrated how this can be overcome by utilising a dual catalysis strategy. This work featured a catalytic stereodivergent approach whereby racemic α-branched aldehydes **197** and racemic alcohol **198** can be combined to access all possible stereoisomers of γ,δ-unsaturated aldehyde **199** with excellent diastereocontrol (**Scheme 47**).[145] This was achieved using a mixture of Ir/**L46** and amine catalyst **200**. This process is particularly notable as it allows for the catalytic preparation of acyclic contiguous stereocentres.



Scheme 47: *Enantiodivergent and diastereodivergent dual catalysis.*

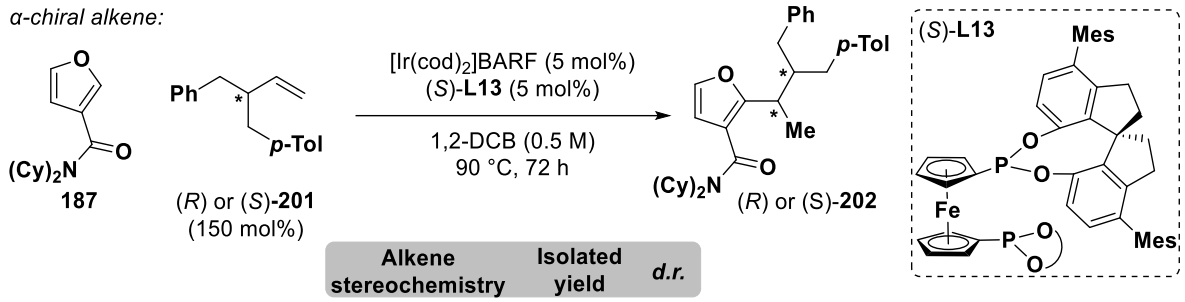
Rather than using a dual catalysis approach, we were interested in addressing a similar synthetic challenge through a combination of substrate and catalyst control; employing an enantiopure substrate with a chiral catalyst would reduce the possible number of stereochemical outcomes. In theory, this could be realised by an Ir(I)-catalysed hydroarylation reaction, in which the stereochemistry at the benzylic position can be controlled by the chiral catalyst, while changing the enantiomer of the alkene can allow access to all possible stereoisomers (**Scheme 48**). The caveat of this methodology, however, is the requirement to synthesise both enantiomers of the alkene substrate or the chiral ligand.



Scheme 48: *Proposed cross-coupling of enantiopure substrates with a chiral catalyst.*[109]

Studies began by using furan **187**, which exhibited high reactivity and enantiocontrol in the enantioselective hydroheteroarylation of styrenes and α-olefins with chiral alkenes synthesised by Dalling (**Table 12**).[109] Under standard Ir(I)-catalysed conditions, hydroarylation of α-chiral alkene (*R*)-**201** delivered (*R*)-**202** in 68% yield (3:1 *d.r.*). Conversely, employing (*S*)-**201** enabled a switch in the diastereoselective outcome – (*S*)-**202** was obtained in 72% yield (1:3 *d.r.*). This demonstrates the

absence of a matched-mismatched effect.[146] Although not assigned, the relative stereochemistry of the diastereomers could be determined by X-ray analysis, if crystalline.

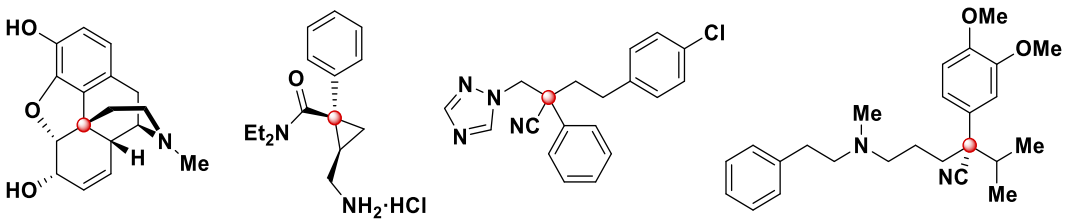


Alkene stereochemistry	Isolated yield	*d.r.*
(*R*)	68%	3:1
(*S*)	72%	1:3

Table 12: *Diastereoselective hydroarylation of an α-chiral alkene.*

3.7 Ir(I)-catalysed hydroarylation of 1,1-disubstituted alkenes to access quaternary stereocentres

3.7.1 Significance of quaternary stereocentres



Morphine *analgesic* | **Levomilnacipran** *anti-depressant* | **Fenbuconazole** *fungicide (racemate)* | **Verapamil** *treatment for high blood pressure*

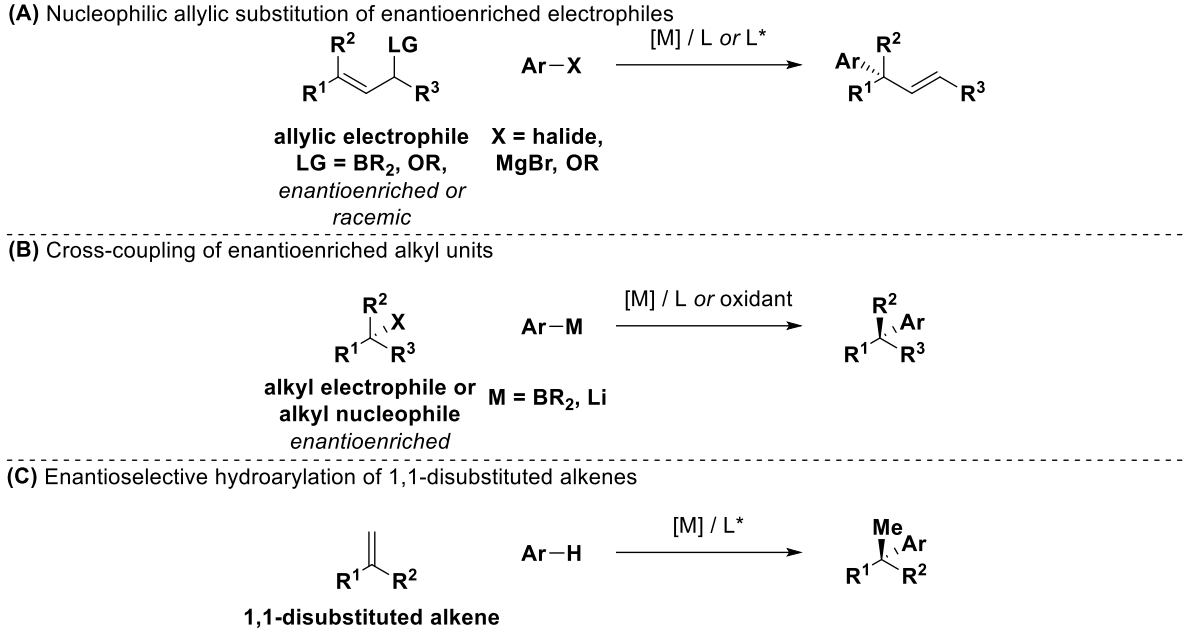
Figure 6: *Bio-active molecules featuring quaternary stereocentres.*

Quaternary benzylic stereocentres are prevalent in a broad array of bioactive molecules including natural products such as Morphine, and those developed by the pharmaceutical and agrochemical industries, namely Levomilnacipran, Fenbuconazole and Verapamil (**Figure 6**). Currently, a large majority of chemical products which feature a non-racemic quaternary centre are derived from the chiral pool.[147] Hence, there is high demand for methodologies which facilitate *de novo* asymmetric syntheses of quaternary stereocentres. One key challenge is presented by the congested structure which may cause poor orbital overlap between reacting partners. While numerous reports disclose approaches to access quaternary stereocentred products in cyclic systems[148–153] analogous methods to provide corresponding acyclic products remain limited, owing to increased conformational flexibility.[154,155]

3.7.2 Existing metal-catalysed strategies to prepare quaternary benzylic centres

Methodologies which facilitate access to cyclic quaternary stereocentres are known,[147] but only a handful of examples exist in which the aryl-alkyl C-C bond is formed during the stereocentre-determining step. One example involves nucleophilic allylic substitution using aryl nucleophiles (**Scheme 49A**)[156,157] which was demonstrated by Aggarwal and Crudden.[158] This work involves a Pd-catalysed enantiospecific cross-coupling reaction of chiral secondary allylic boronic esters with aryl iodides. Similarly, Watson reported the use of chiral allylic pivalates in Ni-catalysed coupling with arylboroxines.[159] In an alternative approach, pre-functionalised aryl units can be directly coupled with alkyl nucleophiles or electrophiles (**Scheme 49B**)[13,14,23] as shown by Aggarwal and co-workers, who reported an enantio-specific coupling between metallated-furan substrates and enantioenriched boronic esters.[12] Methods which employ 1,1-disubstituted alkenes as coupling partners are known, but usually require pre-functionalised substrates and/or additives which detracts from atom-economy.[40,160,161] To address this, Sigman and co-workers reported an elegant Ni-catalysed dehydrogenative redox-relay Heck arylation of trisubstituted alkenols with indoles; while powerful, the scope was limited to inherently nucleophilic indole substrates.[41] Accordingly, formation of quaternary stereocentred

products from unactivated 1,1-disubstituted alkenes using a range of non-privileged aryl and heteroaryl substrates presents a more ideal process in terms of atom-economy (**Scheme 49C**).



Scheme 49: *Methodologies for the construction of quaternary benzylic stereocentres.*[2]

3.7.3 Ir(I)-catalysed hydroarylation of 1,1-disubstituted alkenes

Chapter 1 described previous research into the branch selective hydroarylation of styrenes and aliphatic alkenes with acetanilide and benzamide substrates, and subsequent development of asymmetric protocols for the enantioselective hydro(hetero)arylation using acetanilides, benzamides, furans and thiophenes to afford tertiary benzylic stereocentred products. Considering the significance of quaternary benzylic centres as described above, previous group members Dr Phillippa Cooper and Dr Andrew Dalling further augmented the hydro(hetero)arylation protocol by use of 1,1-disbustitued alkenes of type **204** (**Table 13**).[108,109] Accordingly, benzamide, pyrrole and thiophene substrates were employed under optimised Ir(I)-catalysed conditions with bisphosphite ligand **L12** to afford quaternary benzylic products in excellent yield and branch selectivity.[162]

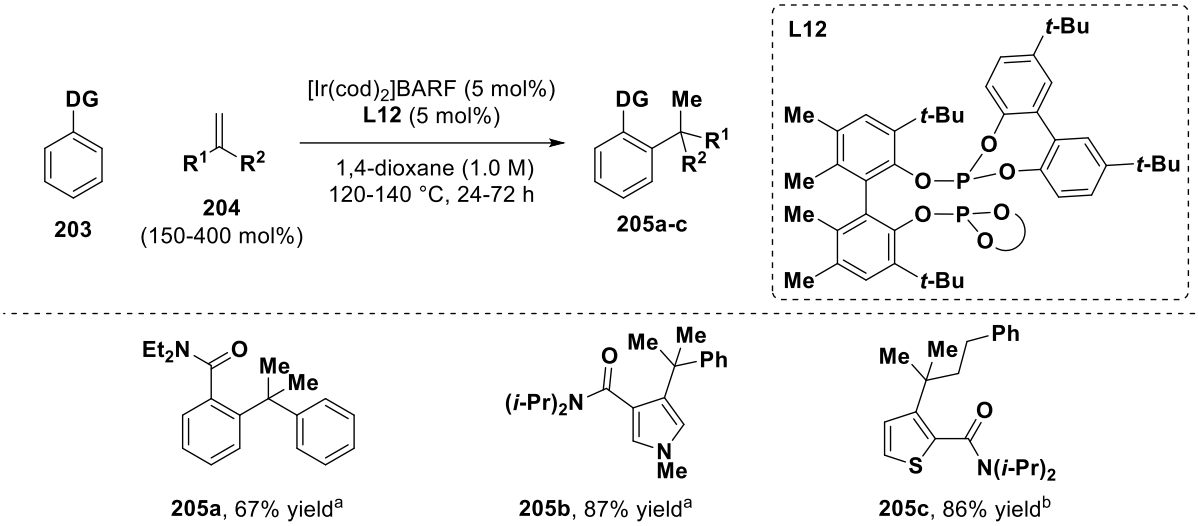


Table 13: *Selected scope for the hydro(hetero)arylation of 1,1-disubstituted alkenes with benzamides, pyrrole and thiophene substrates; [a]Reaction conducted by Dr Phillippa Cooper; [b]Reaction conducted by Dr Andrew Dalling.*

From here, attention focused on the use of furan substrate **106** in this process (**Table 14**). It was found that a range of 1,1-disubstituted styrenes bearing cyclic and acyclic alkyl substituents were tolerated as shown by **207a–c**. 1,1-Disubstituted alkenes bearing heteroatoms were also suitable coupling partners as demonstrated by formation of **207d**. Notably, styrenes with excessive steric bulk at the β-position or bearing additional functionality were unsuitable (**208a**, **b**). Under the reaction conditions, alkenes bearing ethers (**208c**, **d**) isomerised to give a more stable internal alkene products, presumably *via* sequential Ir catalyst insertion and elimination steps.[41]

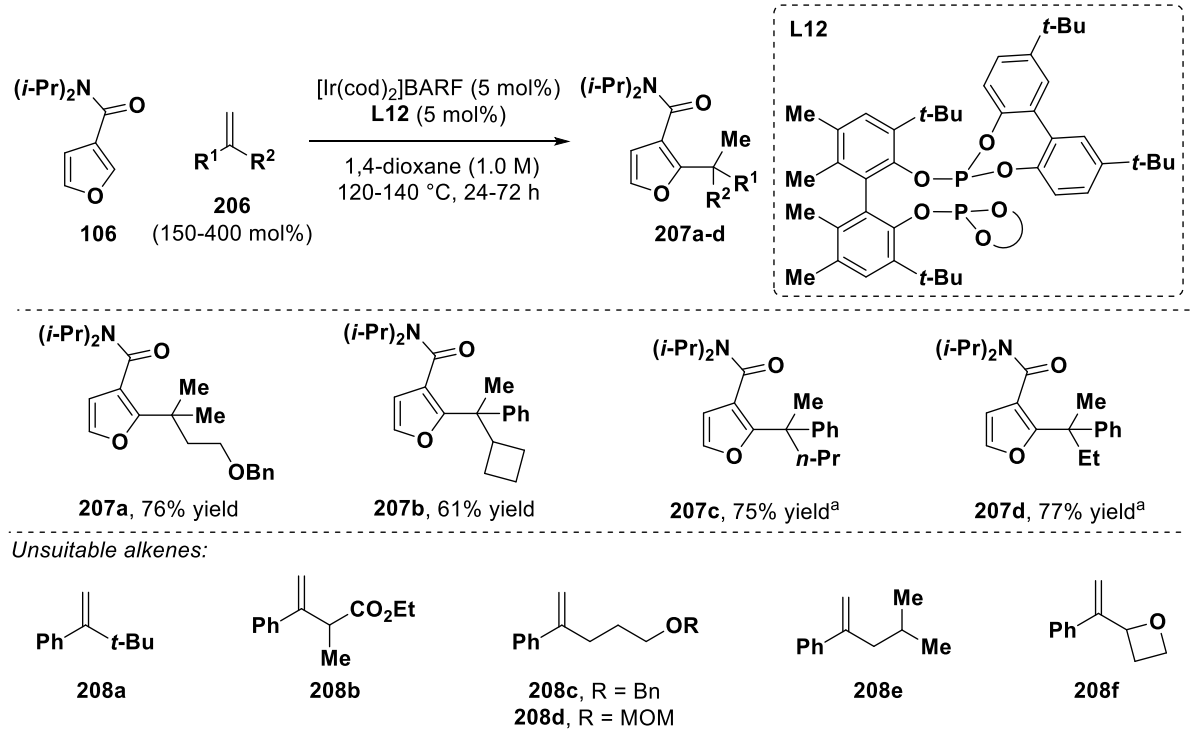
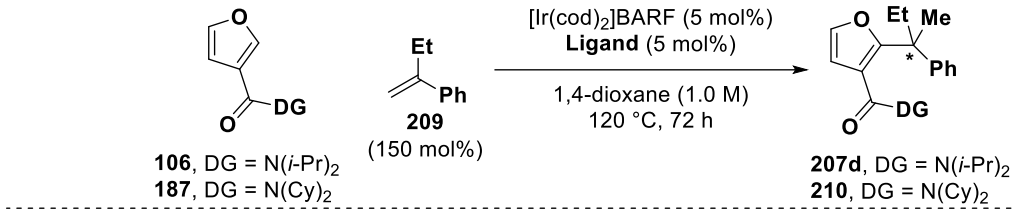
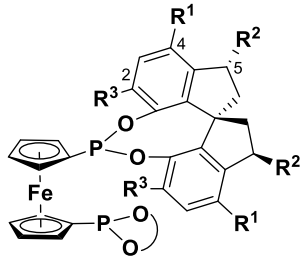


Table 14: *Selected scope for the hydro(hetero)arylation of 1,1-disubstituted alkenes using furan substrates; [a]Reaction conducted by Dr Phillippa Cooper.*

3.7.4 Studies towards enantioselective hydroarylation of 1,1-disubstituted alkenes

With an established protocol for the hydro(hetero)arylation of 1,1-disubstituted alkenes, an asymmetric variant of the reaction was sought to install challenging quaternary benzylic stereocentres. Previous investigations by Dalling indicated that bisphosphonite ligands were suitable for the coupling of furan **106** with alkene **209** as shown by using **L14** which provided **207d** in 72% yield, 80% *e.e.* (**Entry 1, Table 15**).[108] Minimal improvements were made through using C-4 mesityl **L13** (**Entry 2**), alteration of reaction conditions (**Entry 3**) or by changing the directing group (**Entry 4**). Consequently, ligands bearing functionalisation at either C-2, C-4 or C-5 positions of the SPINOL moiety were assessed with Dalling to further optimise the catalytic protocol. No improvement was found using sterically bulky (**Entries 5** & **6**), electron-withdrawing (**Entries 7** & **8**) or electron-donating groups (**Entry 9**) at the C-4 position. Presumably, the low yields highlight the increased steric bulk using 1,1-disubtitued styrenes compared to monosubstituted styrenes. Compared to previously discussed hydroheteroarylation reactions, ligands bearing C-5 functionalisation gave products in higher *e.e.* than unfunctionalised ligands. Pleasingly, it was found that **L27** provided **207d** in 60% yield and 84% *e.e.* (**Entry 10**). Further exploration at the C-5 position was unsuccessful using electron-donating or -withdrawing substituents (**Entries 11** & **12**). Di-functionalisation did not provide further increases in yield or enantioselectivity (**Entries 13–15**). Notably **L31**, featuring a methyl group at C-2, severely affected both yield and enantioselectivity (31% yield, 28% *e.e.*).





Entry	Ligand	DG	R^1	R^2	R^3	Yield	e.e.
1[b]	(*R*)-**L14**	N(*i*-Pr)$_2$	H	H	H	72%	80%
2[a]	(*R*)-**L13**	N(*i*-Pr)$_2$	Mes	H	H	71%	78%
3[b,c]	(*R*)-**L13**	N(*i*-Pr)$_2$	Mes	H	H	52%	83%
4[d]	(*S*)-**L13**	N(Cy)$_2$	Mes	H	H	59%	73%
5[b]	(*S*)-**L20**	N(*i*-Pr)$_2$	3,5-(*t*-Bu)$_2$C$_6$H$_3$	H	H	7%	84%
6[b]	(*R*)-**L21**	N(*i*-Pr)$_2$	C$_6$(Me)$_5$	H	H	46%	80%
7	(*S*)-**L17**	N(*i*-Pr)$_2$	3,4,5-(F)$_3$C$_6$H$_2$	H	H	8%	51%
8	(*R*)-**L18**	N(*i*-Pr)$_2$	3,5-(CF$_3$)$_2$C$_6$H$_3$	H	H	3%	67%
9	(*R*)-**L19**	N(*i*-Pr)$_2$	3,5-(OMe)$_2$C$_6$H$_3$	H	H	31%	76%
10[b]	(*R*)-**L27**	N(*i*-Pr)$_2$	**H**	**Ph**	**H**	**60%**	**84%**
11	(*R*)-**L25**	N(*i*-Pr)$_2$	H	4-(F)C$_6$H$_4$	H	31%	75%
12[b]	(*R*)-**L28**	N(*i*-Pr)$_2$	H	4-(OMe)C$_6$H$_4$	H	67%	81%
13[b]	(*R*)-**L30**	N(*i*-Pr)$_2$	F	Ph	H	46%	70%
14[b]	(*R*)-**L29**	N(*i*-Pr)$_2$	Ph	Ph	H	33%	70%
15[b]	(*R*)-**L31**	N(*i*-Pr)$_2$	H	Ph	Me	31%	28%

Table 15: *Chiral bisphosphonite ligand evaluation for the enantioselective alkene hydroarylation of **209** with furan substrates; [a]Reaction conducted by Dr Phillippa Cooper; [b]Reaction conducted by Dr Andrew Dalling; [c]Reaction conducted at 85 °C; [d]Reaction conducated for 48 h; Enantiomeric ratios determined by chiral SFC analysis.*

While use of **L27** provided **207d** in 60% yield and 84% *e.e.*, it was envisaged further optimisation could be achieved through screening of additional bisphosphonite and bisphosphite ligands (**Table 16**). It was observed that use of cyclopentyl or VANOL-derived ligands proved detrimental to both yield and enantioselectivity (**Entries 1** & **2**). The reaction outcome was unaffected by incorporation of an oxygen atom into the aliphatic unit of the SPINOL structure (**Entry 3**), while functionalisation at the C-3 position of the ligand completely shut down reactivity (**Entry 4**). Similarly, minimal reactivity was observed when screening bisphosphite ligands **L43–45** (**Entries 5**–**7**). To conclude, **L27** was found to be the optimal ligand for this process, generating **207d** in 60% yield, 84% *e.e.* (**Entry 10**). While this result is impressive, higher values of yield and enantiocontrol were desired in order to develop a synthetically useful methodology. As no further improvements were obtained through ligand screening, investigations turned to other promising research areas.

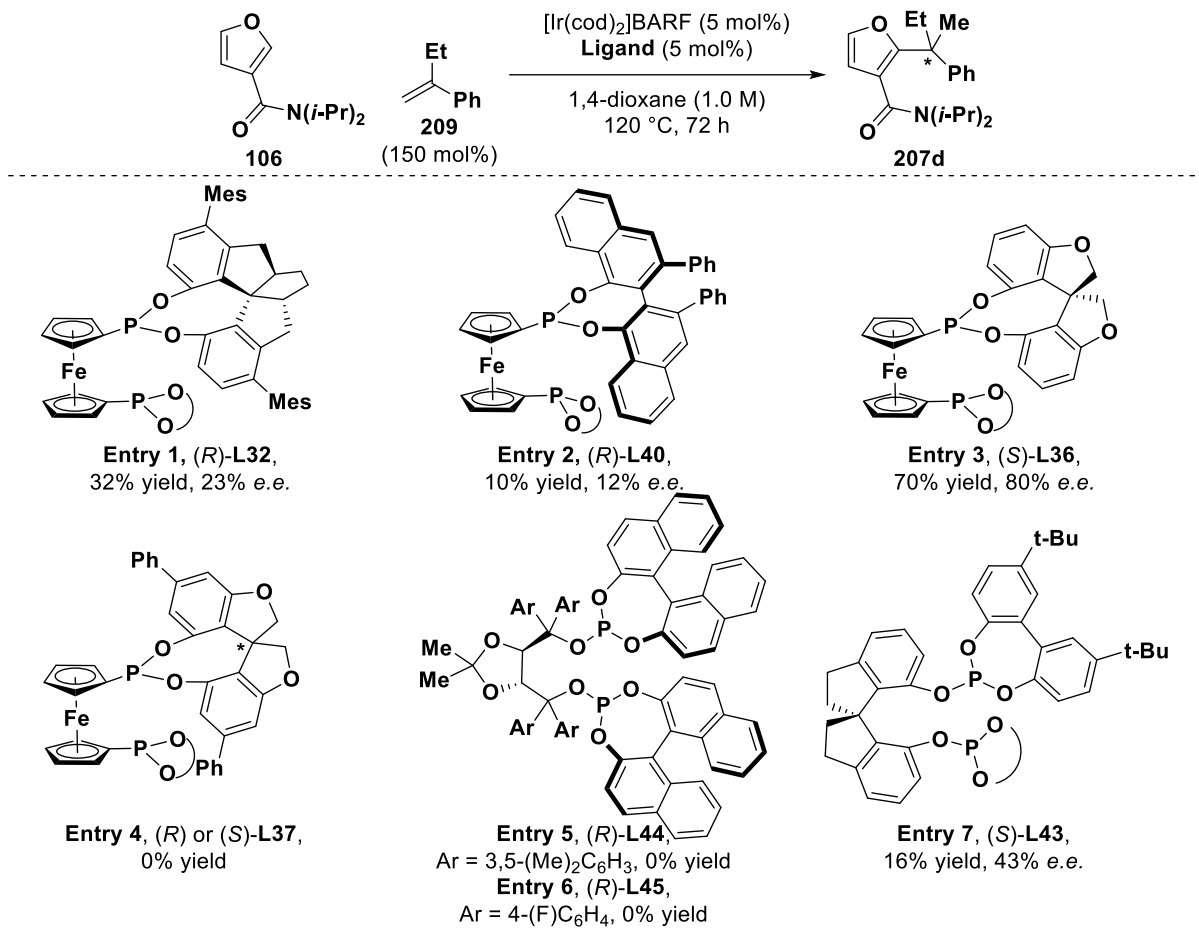


Table 16: *Chiral ligand evaluation for the enantioselective alkene hydroarylation of **209** with **106**; Enantiomeric ratios determined by chiral SFC analysis.*

3.8 Investigations into alternative directing groups for branch-selective hydroarylation

At this point, the branch selective hydro(hetero)arylation processes that had been developed thus far were limited to ketone or amide-derived directing groups. Inspired by the seminal work of Chatani for the Ru-catalysed hydrofunctionalisation of alkenes[53] and more recently, Pd-catalysed procedures from Yu[163] and related studies from Norrby,[164] we were committed to augment the directing group scope to include other weakly-coordinating moieties. Equally, extension of the methodology to include phenol-derived substrates would further increase its applicability towards the synthesis of natural product targets.[165] As such, phenol and aryl substrates bearing either weakly coordinating directing groups (carbonyl and sulfonyl-derived) or more strongly-coordinating directing groups (imidazolyl and pyridyl-derived) were synthesised and subjected to optimal Ir(I)-catalysed conditions in the absence of alkene but in the presence of D_2O using either **L47** or d^Fppb as ligands – these substrates had precedence as directing groups in related studies (**Table 17**).[166,167] As a control experiment, acetanilide **211** was first employed with **L47** and selective deuterium incorporation was observed at less hindered C-2 (0.52 D) over more hindered C-6 (<0.05 D). These results corroborate with the observed regiochemical outcome for the hydroarylation of styrene with **211** and indicate a regioselective oxidative addition was operational. Using **L47**, it was found that use of an imidazolyl directing group (**212**) effected deuterium incorporation (0.25 D) at both *ortho*-positions; this value increased by using d^Fppb (0.90 D). Using this ligand, phenol-derived pyridyl-**213** also facilitated deuterium incorporation into the *ortho*-positions (0.18 D). Carbonyl and sulfonyl directing groups were found to be unsuitable using either **L47** or d^Fppb for functionalisation of both phenol (**214** and **215**) or aryl (**216**) substrates.

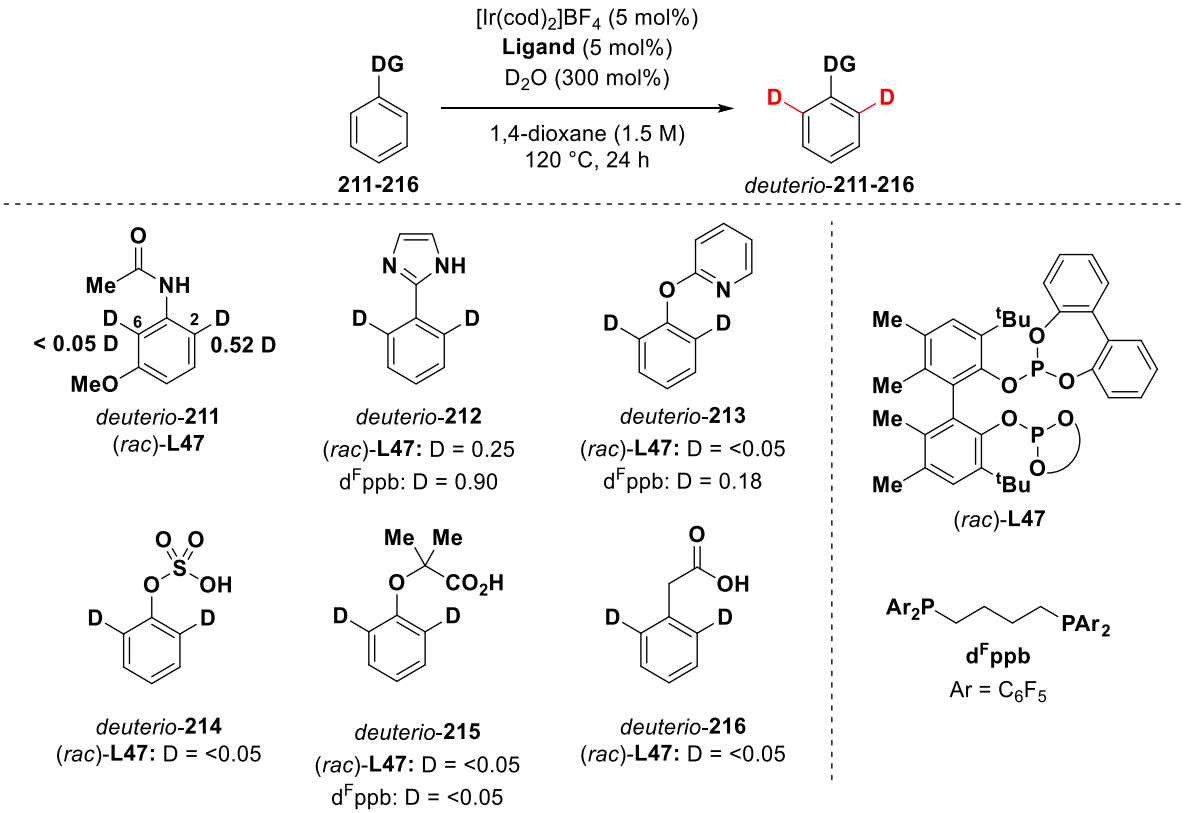


Table 17: *Deuterium labelling experiment using substrates **211-216.***

With promising deuterium-labelling results in hand, particularly using **212** and **213**, investigations into use of alternative directing groups proceeded by evaluating **212–216** for the Ir(I)-catalysed hydroarylation of styrene. Additionally, substrates **217–220**, which had been reported as suitable directing groups in other C-H activation manifolds but were unsuitable for deuterium exchange studies, were also investigated (**Table 18**).[168–171] Despite successful deuterium incorporation, **212** and **213** were found to be unreactive when subjected to Ir(I)-catalysed conditions with styrene (See *Experimental* for details). It was postulated that the resulting metallacycles are too thermodynamically stable (i.e. the directing group binds too strongly to the cationic Ir-catalyst) thus preventing successful alkene insertion. It has been shown by Nishimura that **212** is a suitable substrate for the hydroarylation of vinyl ethers[88] by use of a neutral Ir(I)-catalyst. Based on this, it was postulated that a neutral Ir(I)-catalyst such as $[Ir(cod)_2(OH)_2]$ and $[Ir(cod)_2Cl_2]$ would form a less stable (and more reactive) metallacycle to facilitate alkene insertion; however, no reaction was observed for the hydroarylation of styrene with **212** or **213** using neutral Ir(I)-catalysts. No reactivity was observed using carbonate, ester and carbamate directing groups **217**–**220,** which were assumed to be too weakly coordinating to promote reaction.

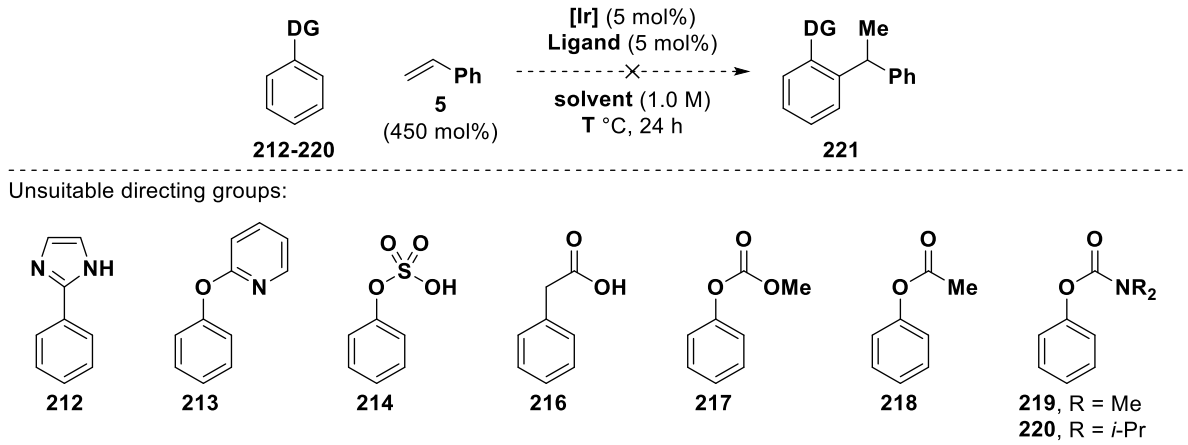


Table 18: *Screening of substrates **212–220.***

3.9 Development of an enantioselective hydroarylation methodology using benzamide substrates

As a result of directing group investigations, Dr Raymond Chung optimised a protocol for the hydroarylation of styrenes and aliphatic alkenes using benzamide substrates of type **222**. This process used [Ir(cod)$_2$]BARF with bromo-functionalised ligand **L23** to deliver C-2 alkylated branched products in excellent yield and with high enantiocontrol. As shown in **Table 19**, styrenes with functionalisation at C-3 or C-4 were tolerated. For example, use of 3-chlorostyrene generated **224b** in 80% yield and with 90% enantiomeric excess while 4-phenylstyrene was employed to give **224g** (92% yield, 90% *e.e.*). Difunctionalised styrenes such as 2-vinylnaphthalene performed well to afford **224h** (88% yield, 92% *e.e.*). Likewise, aliphatic alkenes were also suitable as shown by formation of **224j** (40% yield, 80% *e.e.*) from allylbenzene and **224k** (46% yield, 72% *e.e.*) from 1-decene. Functionalisation of the benzamide component was tolerated at C-3 as shown by **224l** (67% yield, 81% *e.e.*) used for the hydroarylation of 2-vinylnaphthalene. While functionalisation at the C-4 position was suitable, as shown by **224p** (64% yield, 90% *e.e.*), employment of 4-bromo-derived benzamide substrate gave **224q** in low yield and diminished enantiocontrol (23% yield, 70% *e.e.*) potentially due to competing insertion of the Ir-catalyst into the C-Br bond.

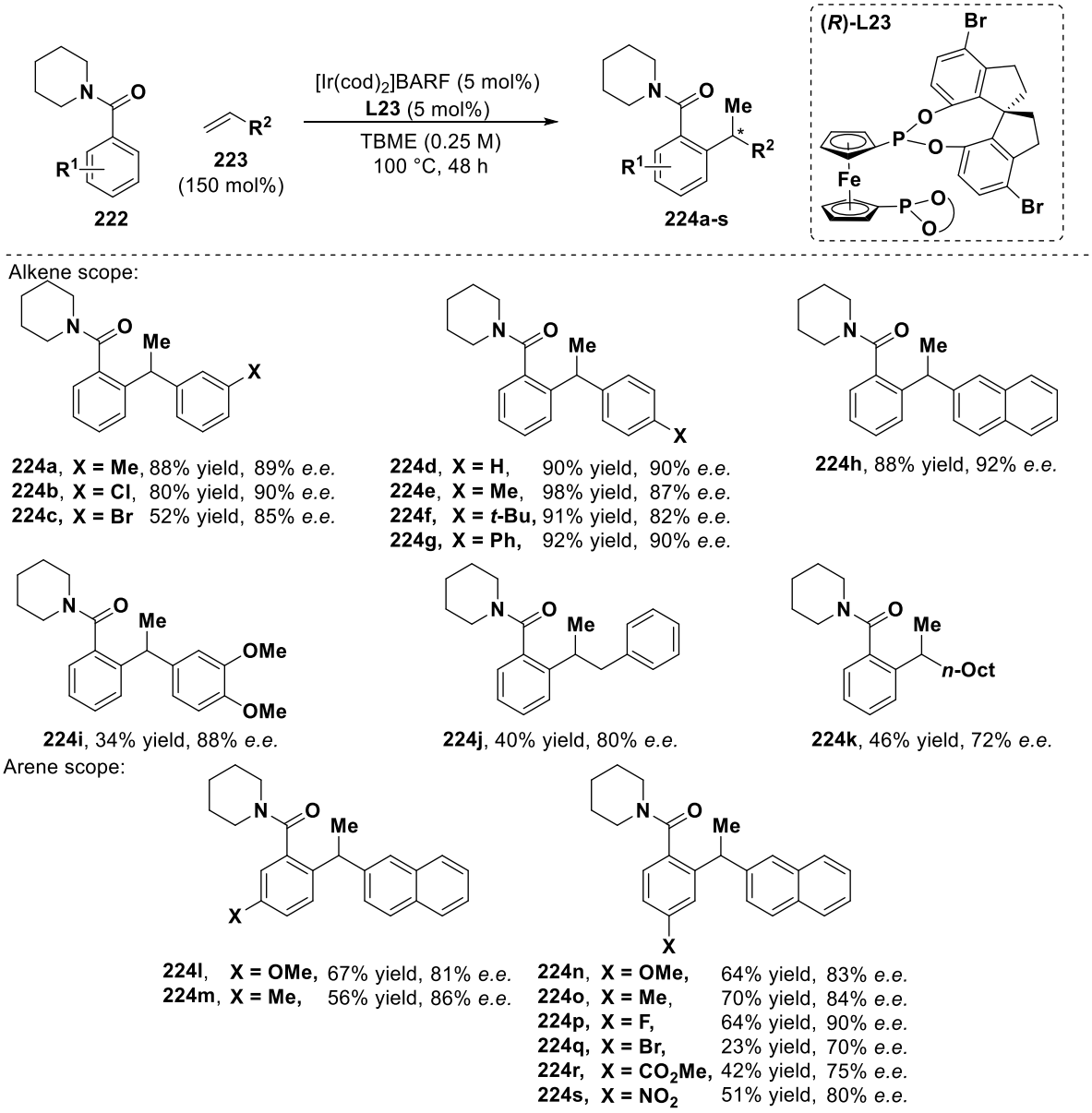
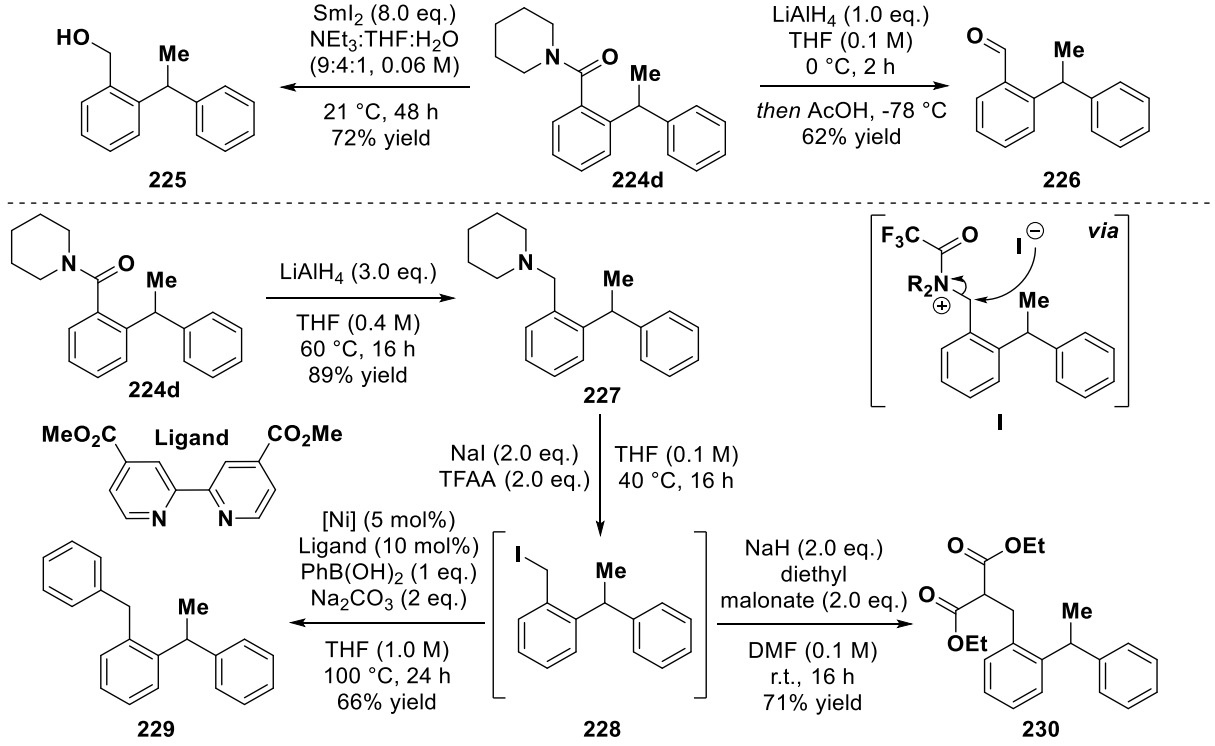


Table 19: *Scope of a hydroarylation reaction with benzamide substrates, conducted by Dr Raymond Chung; Enantiomeric ratios determined by chiral SFC analysis.*

Elaboration of the catalysis products was investigated by Chung to demonstrate their synthetic utility (**Scheme 50**). Accordingly, **224d** was subjected to Proctor's SmI_2-catalysed reduction conditions to afford benzylic alcohol **225** in 72% yield.[172] Likewise, aldehyde **226** was obtained in 62% yield by reaction of **224d** with $LiAlH_4$ before quenching with AcOH at low temperature. Alternatively, by subsequent quenching at room temperature, **224d** can be reduced to amine **227** in 89% yield by reaction with excess $LiAlH_4$. From here, a mild C-N activation procedure can be used, in which quaternisation of the amine moiety by reaction with trifluoroacetic anhydride (TFAA) generates an electrophilic *N*-acyl ammonium salt.[173] This acts as a leaving group in a proposed S_N2 displacement by iodide (from NaI, as illustrated in **I**), to afford highly electrophilic benzylic iodide **228** *in situ*. From here, further functionalisation can be attained by Ni-catalysed cross-coupling with phenylboronic acid to generate

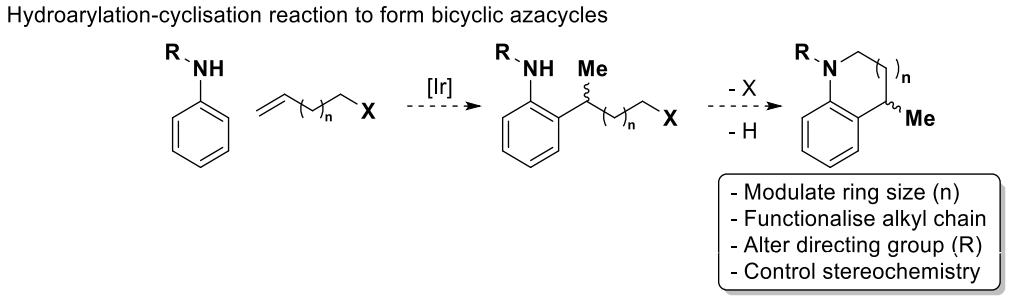
229 in 66% yield, or by substitution of the iodide with a suitable nucleophile such as diethyl malonate to give **230** in 71% yield.



Scheme 50: *Post-catalysis functionalisation of benzamide hydroarylation products, conducted by Dr Raymond Chung; [Ni] = Ni(II)hexafluoroacetylacetonate hydrate.*

3.10 Investigations into alternative alkenes for branch-selective hydroarylation

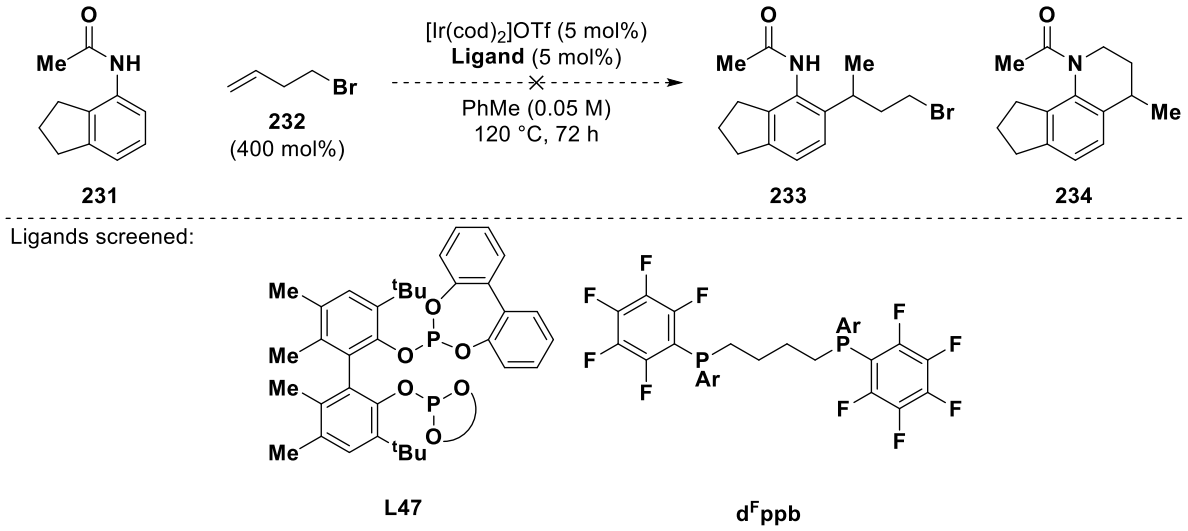
With the successful development of a hydroarylation protocol by investigation of the directing group, attention turned to probing the use of alternative alkenes in the hydroarylation process. As described in **Chapter 1**, acetanilides were found to be suitable substrates for the Ir(I)-catalysed enantioselective hydroarylation of styrenes and aliphatic alkenes using bisphosphite ligand **L12** (*vide supra*, **Scheme 26A**). One current limitation of this methodology is the requirement of a directing group, and while post-catalysis removal is possible, we considered whether the aniline functionality could be utilised to form valuable enantioenriched azabicyclic scaffolds. Hence, it was postulated that if the alkene was tethered to a suitable leaving group, the anilide directing group could function as a nucleophile (after hydroarylation) to form a new ring with several modes of derivatisation, leading to a library of novel azacycles – such as tetrahydroquinolines (**Scheme 51**). If these structures could be furnished with substituents in a stereoselective manner, they would serve as valuable building blocks for pharmaceutical purposes.[174–176]



Scheme 51: *Proposed hydroarylation-cyclisation reaction to form bicyclic azacycles.*

3.10.1 Development of a hydroarylation-cyclisation reaction

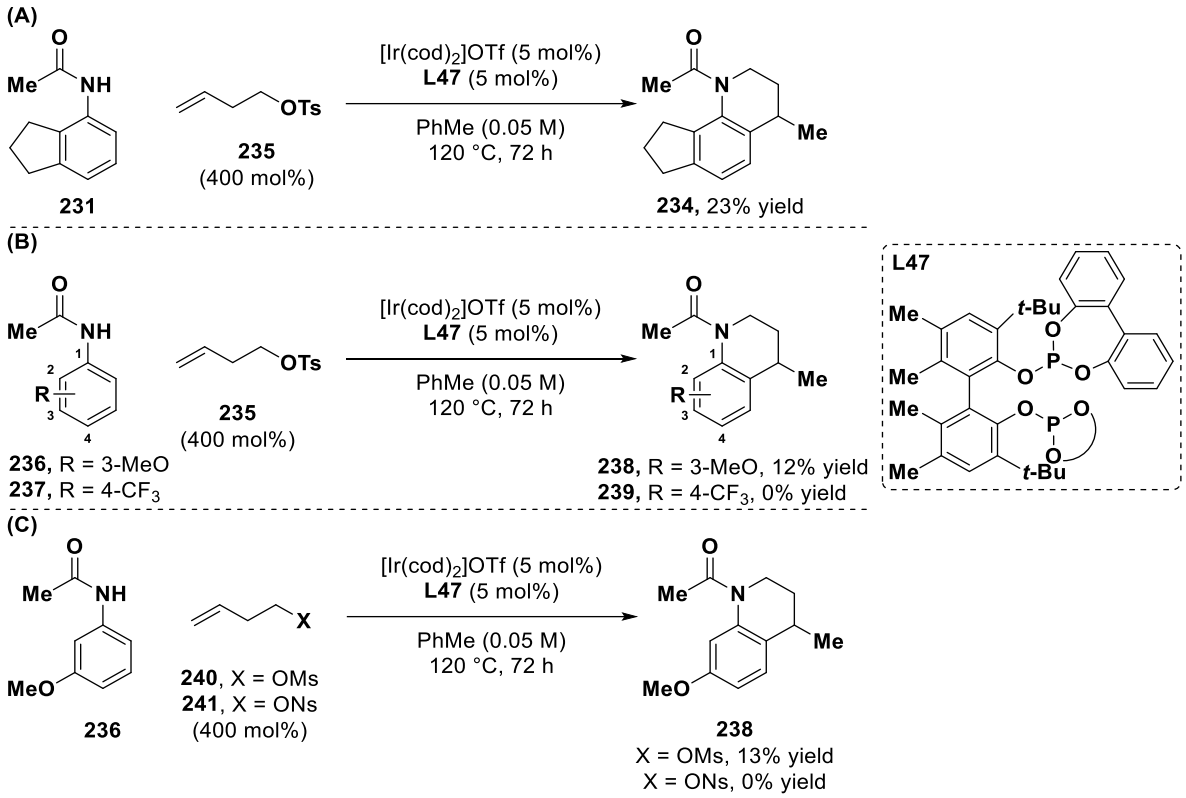
Investigations began by employment of bromoalkene **232** with acetanilide **231**, which had been shown to undergo successful hydroarylation reactions (**Scheme 52**).[107] Unfortunately, under previously reported conditions using either bisphosphite ligand **L47** or d^{F}ppb, only starting material was recovered and no product was detected. Additionally, **232** was not present in the crude reaction mixture. It was postulated that an Ir(I)-species could insert into the C-Br bond of **232** which could cause degradation and/or inhibit hydroarylation.



Scheme 52: *Hydroarylation using bromoalkene **232**; d^{F}ppb = 1,4-bis(di(pentafluorophenyl)-phosphino)butane.*

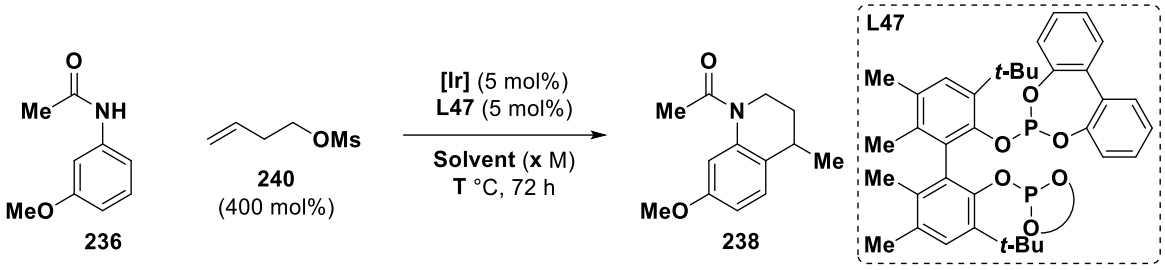
To limit unwanted C-X insertion, *pseudo*-halides were screened under the same Ir(I) conditions using bisphosphite ligand **L47** as they have been shown to undergo slower oxidative addition onto metal complexes than the corresponding halides.[177] Initial success was found using tosyl-alkene **235,** which gave tetrahydroquinoline derivative **234** in 23% yield (**Scheme 53A**). To simplify the determination of NMR yields, acetanilide substrates **236** and **237** were screened to provide more distinct peaks in the ^{1}H and ^{19}F NMR spectra (**Scheme 53B**). While only starting material was recovered using trifluoromethyl-**237** (79% recovered), using 3-methoxy-**236,** novel tetrahydroquinoline derivative **238** was obtained in modest 12% yield. To seek further increases in yield, efforts were focused on the role of the sulfonyl leaving group on the alkene (**Scheme 53C**). It was found that a comparable yield was obtained when

using mesyl-alkene **240**, providing **238** in a 13% yield. However, nosyl-alkene **241** was unsuitable in the reaction, possibly due to its propensity to bind to the Ir-centre.[178]



Scheme 53: *(A) Hydroarylation of tosyl-alkene **235**; (B) Substrate screening; (C) Investigations of sulfonyl groups.*

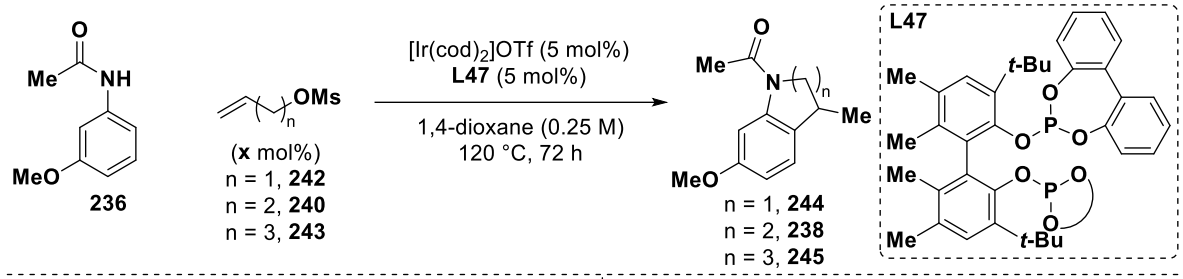
As stated previously, the methoxy unit on acetanilide **236** allowed for easier determination of analytical yields compared to **231**. With **240** proven to be the optimal sulfonyl alkene for the process, further optimisation for the formation of **238** continued through investigation of the reaction conditions (**Table 20**). Changing the solvent from PhMe to 1,4-dioxane proved beneficial, forming **238** in 28% yield (**Entry 1**). 1,2-DCB was also suitable, albeit to a lesser extent, giving **238** in 16% yield (**Entry 2**), however use of THF or MeCN proved inapposite (**Entries 3** & **4**). It was found that neutral Ir sources did not catalyse the reaction; use of $[Ir(cod)_2Cl]_2$ or $[Ir(cod)_2OMe]_2$ gave no yield of **238** (**Entries 5** & **6**). The optimal concentration was found to be 0.25 M; moving to more dilute (**Entry 7**, 0.10 M, 5% yield) or more concentrated (**Entry 10**, 2.0 M, 13% yield) systems saw decreases in yield. Finally, lowering the reaction temperature to 100 or 110 °C or raising to 130 °C proved deleterious to the reaction (**Entries 11–13**). No uncyclised products were observed in any of the crude reaction mixtures by ^{1}H NMR spectroscopy.



Entry	[Ir]	Solvent	x /M	Temp /°C	Yield
1	$[Ir(cod)_2]OTf$	1,4-dioxane	0.25	120	28%
2	$[Ir(cod)_2]OTf$	1,2-DCB	0.25	120	16%
3	$[Ir(cod)_2]OTf$	THF	0.25	120	trace[a]
4	$[Ir(cod)_2]OTf$	MeCN	0.25	120	trace[a]
5	$[Ir(cod)Cl]_2$	1,4-dioxane	0.25	120	trace[a,b]
6	$[Ir(cod)OMe]_2$	1,4-dioxane	0.25	120	trace[a,b]
7	$[Ir(cod)_2]OTf$	1,4-dioxane	0.10	120	5%[a]
8	$[Ir(cod)_2]OTf$	1,4-dioxane	0.50	120	11%[a]
9	$[Ir(cod)_2]OTf$	1,4-dioxane	1.0	120	14%[a]
10	$[Ir(cod)_2]OTf$	1,4-dioxane	2.0	120	13%[a]
11	$[Ir(cod)_2]OTf$	1,4-dioxane	0.25	100	trace[a]
12	$[Ir(cod)_2]OTf$	1,4-dioxane	0.25	110	trace[a]
13	$[Ir(cod)_2]OTf$	1,4-dioxane	0.25	130	trace[a,c]

Table 20: *Optimisation studies for the hydroarylation-cyclisation of **236**; [a]Yields determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard; [b]24 h; [c]**240** = 315 mol%, 7.5 mol% [Ir] & ligand used.*

With minimal further increase in yield, we endeavoured to further optimise the hydroarylation-cyclisation sequence through investigation of **240** (**Table 21**). Lowering the loading of **240** from 400 mol% to 100-300 mol% (**Entries 1–3**) saw a decrease in the yield of **238** obtained. In the interest of finding a more suitable alkene, efforts were focused on altering the length of the carbon chain. This resultantly would provide access to a range of bicyclic azacycles of type **238**; however, no yield of the corresponding products was obtained by shortening (**Entry 4**) or lengthening (**Entry 5**) the chain. It was postulated that functionalisation of the sulfonyl alkene chain could prevent its degradation through steric hindrance. Furthermore, employing functionalise alkenes would give rise to azacycles bearing groups on the saturated moiety. As such mesyl-alkenes **246** and **247** were screened in the reaction manifold, however in both cases, starting material was recovered and no reactivity was observed.



Entry	x /mol%	n	Yield[a]
1	100	2	7%
2	200	2	14%
3	300	2	14%
4	400	1	trace[b]
5	400	3	trace[b]

Unreactive alkenes:

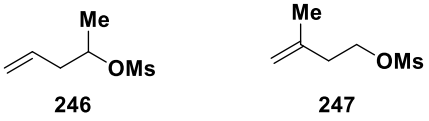
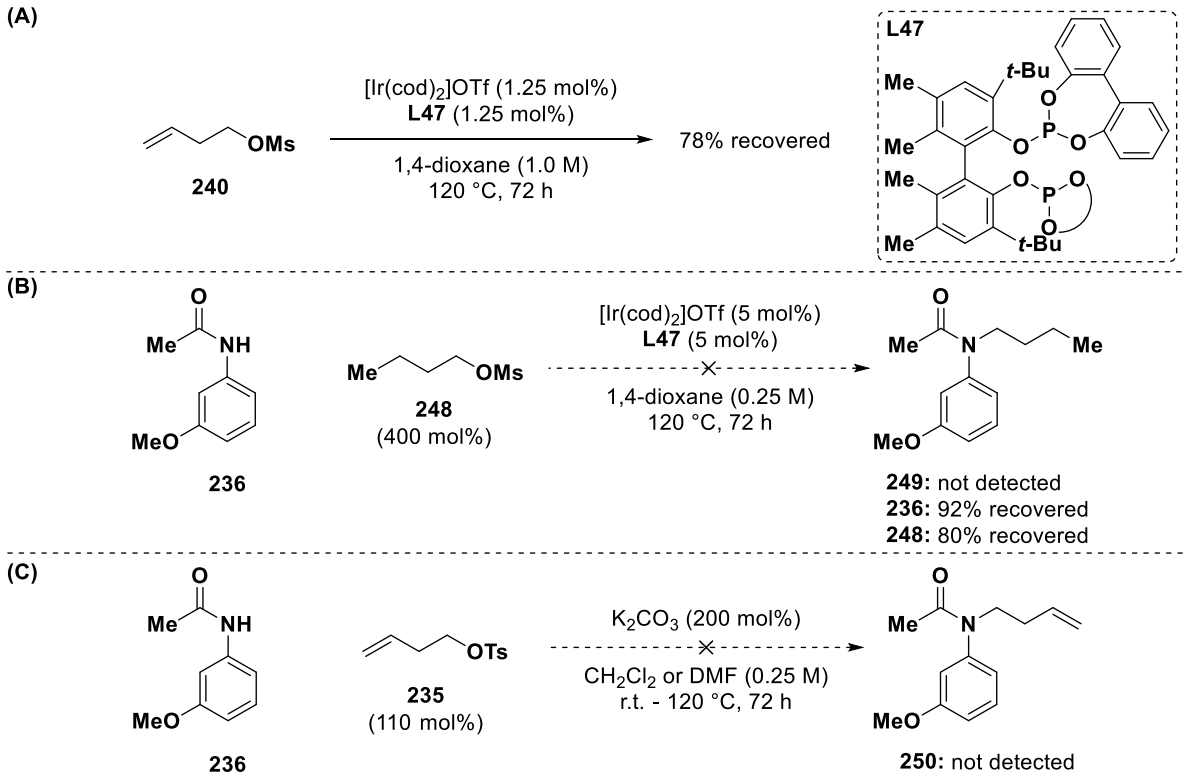


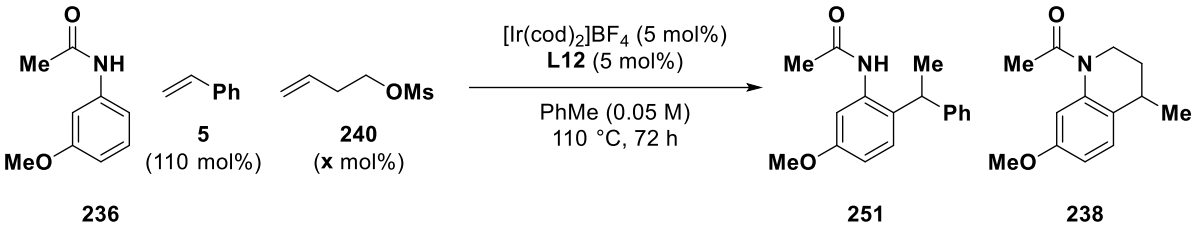
Table 21: *Screening of sulfonyl alkenes; [a]Yields determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard; [b]PhMe used.*

With little flexibility in yield and scope, a series of experiments ensued to investigate the reaction mechanism. More specifically, we were interested to establish the fate of the alkene under Ir(I)-catalysed conditions. Hence, **240** was subjected to optimised catalytic conditions in the absence of acetanilide **236** and was recovered in a 78% yield (**Scheme 54A**). Mesyl-**248**, without alkene functionality, was subjected to Ir(I)-catalysed conditions with **236** (**Scheme 54B**). Once more, no reaction occurred and **236** and **248** were both recovered. To try and force S_N2 reactivity, **236** was reacted with **235** under basic conditions (**Scheme 54C**). Again, no reaction occurred and only starting material and alkene were detected by ^{1}H NMR spectroscopy. A stronger base was not used in order to avoid degradation of mesylate by elimination. From these three experiments, it was determined that: (i) the alkene was stable under reaction conditions, (ii) the reaction probably proceeds by hydroarylation followed by cyclisation and (iii) the cyclisation could potentially occur either *via* Ir(I)-insertion into the C-O bond of the mesylate or *via* an intramolecular S_N2 mechanism.[179]



Scheme 54: *Control experiments to determine reaction mechanism.*

To probe the mechanism further, a competition experiment was set-up to investigate the effect of **240**, upon a working hydroarylation reaction reported previously by the group (**Table 22**).[107] As such, acetanilide **236** was subjected to Ir(I) conditions with both styrene and **240** in the same reaction mixture. It was found that increasing equivalents of **240** had a detrimental effect upon the yield of styrene hydroarylation product **251** obtained. For instance, increasing equivalents of **240** from 0 mol% to 50 mol% (**Entries 1** & **2**) decreased the yield of **251** from 76% to 35% yield. This observation was coupled with a simultaneous increase in starting acetanilide **236** recovered from 23% to 65%. Further increasing the loading of **240** to 110 mol% (**Entry 3**) yielded no appreciable amount of **238** or **251** resulting in an 85% recovery of **236**. As only low amounts of **240** were recovered from the reaction mixtures (**Entries 2** & **3**), it was suggested that **240** could degrade either by reaction with either styrene or a putative Ir-species. Notably, no cyclisation product **238** was observed in any of the reactions with **240** suggesting styrene inhibited hydroarylation of **240** with acetanilide **236** from occurring. Further work could investigate the use of different directing groups and leaving groups, or the effect of different ligands upon the system.



Entry	240 x /mol%	Recovered 236[a]	Recovered 240[a]	Yield 251[a]	Yield 238
1	0	23%	-	76%	0%
2	50	65%	9%	35%	0%
3	110	85%	49%	0%	0%

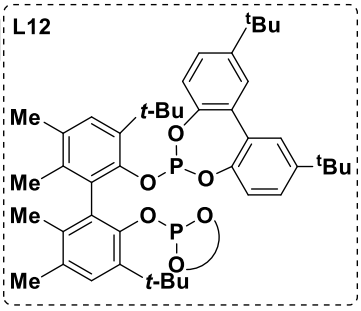


Table 22: *Competition experiment to determine the hydroarylation-cyclisation mechanism; [a]Yields determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.*

3.11 Summary and conclusions

Using novel bisphosphonite and bisphosphite ligands described in **Chapter 2**, significant investigations were undertaken to optimise the branch and enantioselective hydroheteroarylation of alkenes with heterocyclic substrates. While no further increase in yield or *e.e.* was achieved from ligand screening, by exploring different amide-derived directing groups it was determined that employment of an *N*,*N*-dicyclohexylamide group was optimal for furan substrates. Accordingly, it was found that a broad array of styrenes and aliphatic alkenes were suitable reactants. Further research demonstrated the applicability of this process towards a catalyst-controlled diastereoselective hydroarylation of alkenes. An analogous procedure for the branch and enantioselective hydroarylation using benzamide substrates was also described; the catalysis products were further elaborated to demonstrate their synthetic utility. Research progressed into employment of 1,1-disubstituted alkenes to generate quaternary stereocentred products. While this was successful for the formation of racemic products, a related enantioselective protocol remains elusive. Future work in this area should look to optimise (i) the enantioselective hydroheteroarylation of alkenes with additional heterocycles such as pyrroles (currently 78% yield, 78% *e.e.* using **L34**) and (ii) the enantioselective hydro(hetero)arylation of 1,1-disubstituted alkenes (currently 60% yield, 84% *e.e.* using **L27** with furan **106**). The chapter also described research into augmenting the scope of directing groups used in the hydroarylation process and development of a hydroarylation-cyclisation sequence.

Chapter 4

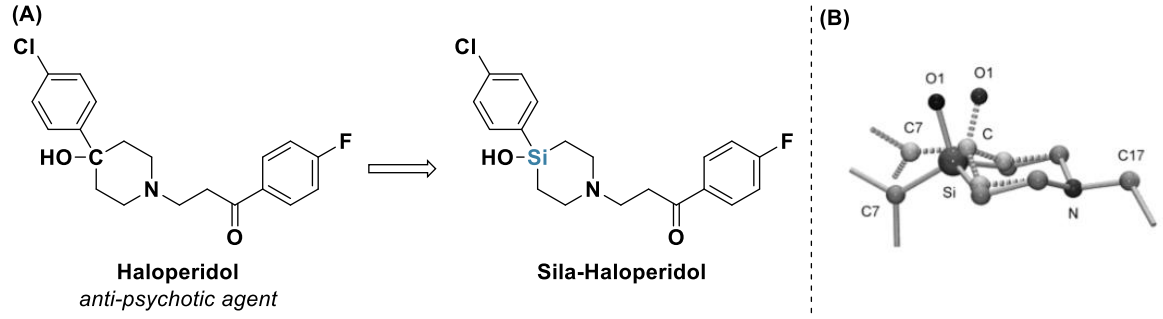
Development of Hydroheteroarylation Reactions using Alkenyl Silanes

Chapter 4 – Development of Hydroheteroarylation Reactions using Alkenyl Silanes

4.1 Importance of molecules bearing silicon-based functional groups

4.1.1 In drug design

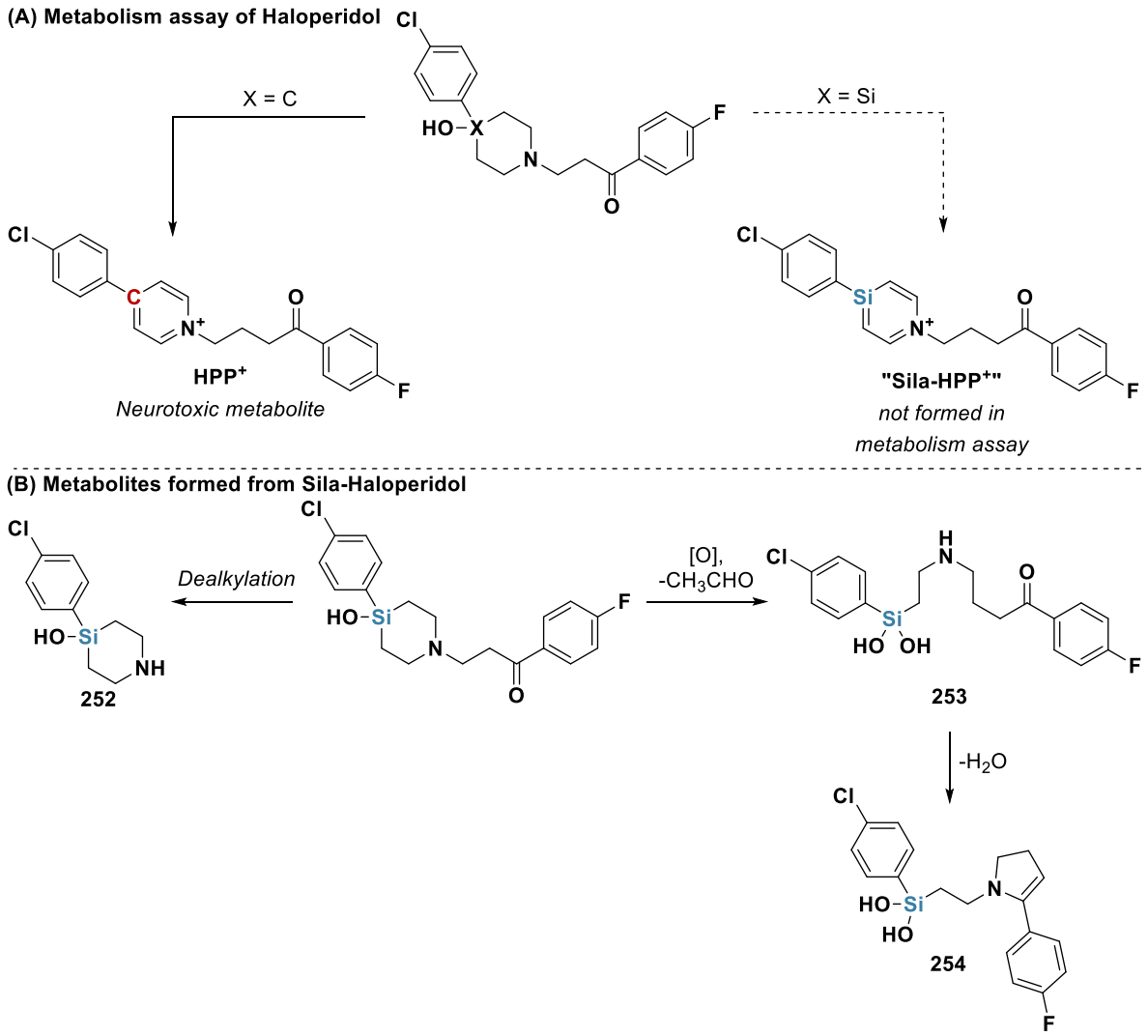
Recently, there has been considerable interest in the synthesis of organosilicon molecules and subsequent comparisons with their carbon analogues.[180–185] Incorporation of silicon atoms into drug-like molecules can solve problems associated with medicinal chemistry. The diverse steric geometries and substitution patterns available to organosilicon compounds give rise to opportunity to alter pharmacokinetic, stability and solubility properties. Silicon is a carbon isostere with unique physicochemical properties. The C-Si bond is longer than a C-C bond (C-Si = 1.87 Å, C-C = 1.54 Å), and this leads to changes in geometry of a drug-like molecule, which in turn alters interactions with desired targets. Additionally, silicon exhibits different bonding preferences compared to carbon; double and triple bonds with silicon are disfavoured. This is shown in the preference to form stable silane-diols which can mimic the structure of unstable carbon-derived hydrated carbonyl groups.[1] An illustration of these two differences in chemical properties was shown by Tacke and co-workers in the synthesis of sila-haloperidol, the silicon-containing analogue of haloperidol, a widely-used anti-psychotic used to treat schizophrenia (**Scheme 55**).[186,187] Superimposition of the corresponding crystal structures of the two analogues revealed a change in geometry of the piperidine ring due to the differing C-C *vs* C-Si bond lengths (*vide infra*). In turn, this altered the vectors of the hydroxyl (O1) and 4-chlorophenyl groups (C7). It was speculated that the different geometries between analogues was responsible for the lower affinity observed for the σ_2-receptor using sila-haloperidol compared to haloperidol. Interestingly, it was found that sila-haloperidol showed a significantly different dopamine receptor subtype selectivity profile than its carbon analogue, including a five-fold higher affinity for hD_2 receptors than haloperidol.



Scheme 55: *(A) Structures of haloperidol and sila-haloperidol; (B) Superimposed crystal structures of haloperidol (dashed lines) and sila-haloperidol (solid lines)*[187]

While differences in receptor selectivity profiles between the two analogues had been speculated to result from different C-C *vs.* C-Si bond lengths, it was found that the inherent ability of organosilicon molecules to form stable silane diols significantly altered the metabolic fate of sila-haloperidol (**Scheme 56**). It is known that one of the metabolites formed using haloperidol is HPP^+, a neurotoxic molecule which has been suspected to cause Parkinsonism-type effects in patients. Notably, instead of formation

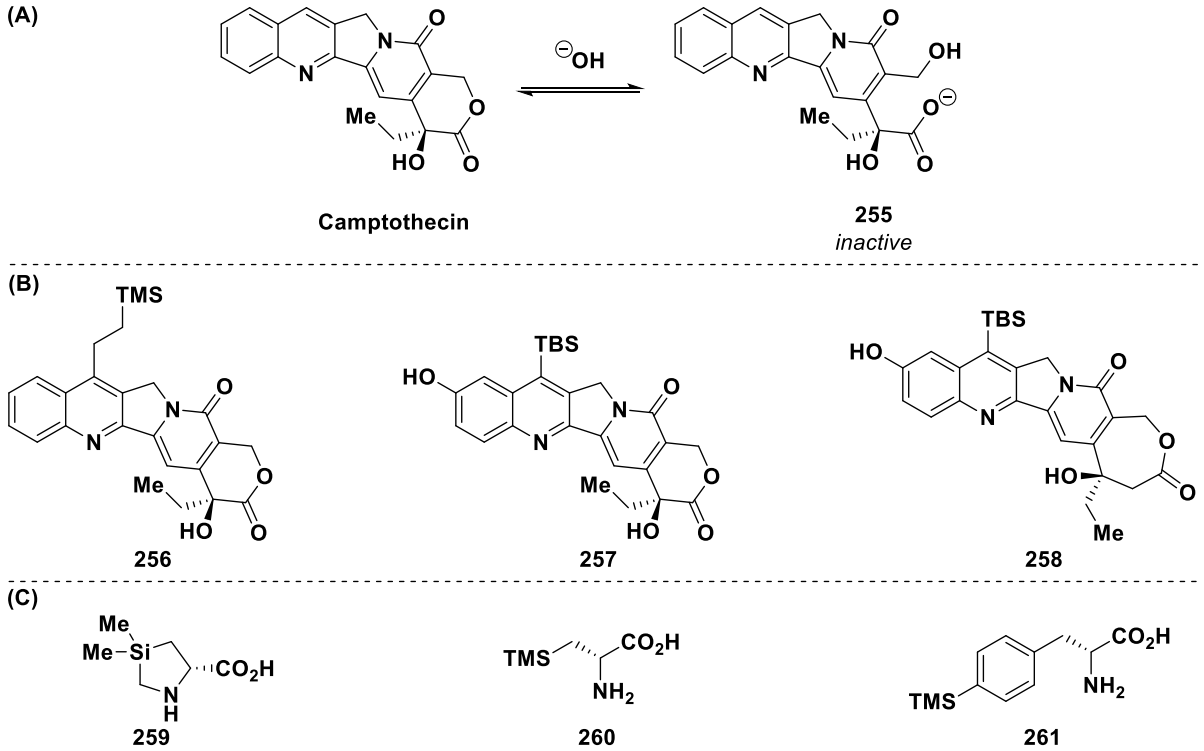
of "sila-HPP$^+$", sila-haloperidol undergoes either oxidative *N*-dealkylation to form metabolite **252**, or follows an oxidation/ring-opening pathway to afford **253** with concomitant loss of acetaldehyde, which gives **254** after dehydration. This outcome can be attributed to the thermodynamic instability and reactivity of the Si=C bond, thus preventing formation of a silylpyridinium metabolite. Due to their similar structural geometries, silane diols can be used instead of hydrated carbonyl species as transition state analogues in protease inhibitors. Further to silicon-analogues as isosteres for hydrated carbonyl species, Nakamura and co-workers demonstrated the use of a tetrasubstituted silicon linker as a bioisostere of a *cis*-C=C bond.[188] Fujii has also shown that a *cis*-amide structure found in phenanthridinone can be replaced with an alkylsilyl group such as dibenzosilole.[189] As intellectual property (IP) space often omits silicon analogues, silicon bioisosteres can be utilised in medicinal chemistry to avoid patent infringements.[181]



Scheme 56: *(A) Formation of HPP$^+$ from haloperidol; (B) Metabolites formed from sila-haloperidol.*

In addition to the property differences described above, silicon-containing analogues can lead to increased cell penetration and potency as they are usually more lipophilic than their carbon analogues.

This was demonstrated in studies of silicon analogues of the natural product camptothecin, which possesses anti-cancer properties and inhibits the enzyme DNA topoisomerase I (**Scheme 57**). A decrease in bioactivity results upon *in vivo* hydrolysis of the α-hydroxy-γ-lactone component of camptothecin, forming a biologically inactive carboxylate compound **255**. In the blood, **255** binds to albumin, a predominant blood serum protein, which further shifts the equilibrium towards the hydrolysis of camptothecin. To combat this, Burke and co-workers synthesised a range of silicon analogues of camptothecin (**256**–**258**) and these were found to possess increased blood-stability, likely due to their higher lipophilicity.[190] **257** also exhibited high potency for DNA topoisomerase I with a unique DNA cleavage profile. The increased lipophilicity of silicon analogues has also led to the incorporation of silicon atoms in unnatural amino acids. This can increase resistance to proteolytic degradation[191] and increase cellular uptake.[192] Various silicon analogues of amino acids are known such as γ- (dimethylsila)proline **259**, β-TMS-alanine **260**, and β-TMS-phenylalanine **261**,[193–196] and many of these can be employed in standard peptide coupling protocols to provide peptides with improved physiochemical properties and *in vivo* activity.[191] In general, however, increased lipophilicity can be detrimental in drug design, as it can lead to poor solubility and metabolic clearance.



Scheme 57: *(A) Structure of camptothecin and hydrolysis product **255**; (B) Silicon analogues of camptothecin **256–258**; (C) Structures of silicon analogues of amino acids.*

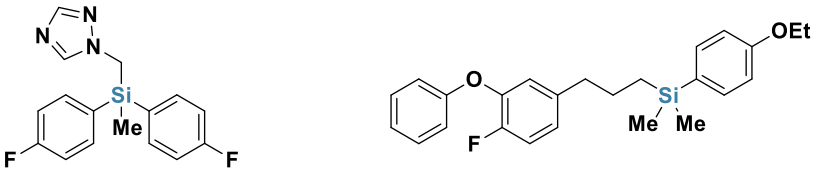
The reversal of polarity of C-H *vs.* Si-H bonds provides another property difference that can be exploited in drug design. This is demonstrated in the synthesis of Zifrosilone (**Scheme 58**), a silicon compound that was synthesised to inhibit the enzyme acetylcholine-esterase (AChE) for treating Alzheimer's disease.[197] It was found that switching the ammonium cation portion of **262**, a known inhibitor of AChE, for a trimethylsilyl group gave Zifrosilone which possessed greater lipophilicity than **262** and showed

lower toxicity compared to other AChE inhibitors. It is postulated that the electropositivity of the silicon centre mimics an ammonium cation and as such, allowed **262** to interact with the cation binding site of the target enzyme.

262 **Zifrosilone**

Scheme 58: *Structure of acetylcholine-esterase inhibitor **262** and silicon analogue Zifrosilone.*

In addition to the illustrated examples above, the distinct properties of organosilanes have seen applications of these molecules in drug delivery systems as well as fluoride acceptors for imaging.[180] Further, there is no known elemental-specific toxicity associated with silicon atoms in small molecules. Despite these advantages and application potential, silicon has only been successfully applied in the agrochemical industry, as seen by flusilazole (fungicide) and silafluofen (insecticide, **Figure 7**). Although there has been significant interest, no silicon-containing pharmaceuticals have been approved in the US or Western Europe. This lack of success has been attributed to a dearth of general synthetic methodologies to construct suitable silicon-containing structures.[184] Hence, methodologies in which silicon can be installed from feedstock sources would have significant value in medicinal chemistry.



Flusilazole
fungicide

Silafluofen
insecticide

Figure 7: *Structures of silicon-containing flusilazole (fungicide) and silafluofen (insecticide).*

4.2 Current protocols for hydroarylation of alkenyl silanes

As described in the previous section, synthetic methodologies that allow the efficient incorporation of silicon atoms into small molecules are still under developed. In terms of alkene hydroarylation reactions, the use of silyl alkenes was first reported by Murai *et al.* who disclosed a linear selective Ru(I)-catalysed methodology for the addition of phenyl ketones and heterocycles across triethoxyvinylsilane (**Table 23A,** *cf.* **Scheme 3**).[53] For example, hydroarylation of triethoxyvinylsilane with 2,2-dimethylpropiophenone gave solely **3a** in quantitative yield. Similarly, using a thiophene-derived substrate, **3c** was obtained in 90% yield. Whilst linear selective alkylation of vinylsilanes has been widely explored, only one example exists of a complimentary branched selective methodology. In 2020, Chatani reported the Rh(II)-catalysed branched selective C-H alkylation of aryl sulfonamides with vinylsilanes (**Table 23B**).[198] This procedure uses $[Rh(OAc)_2]_2$ with benzoic acid to deliver alkylated sulfonamides in good yield and branched selectivity. The benzoic acid is required to promote protodemetallation of a reaction intermediate in the proposed catalytic cycle. For example, **268a** was obtained by hydroarylation of trimethylvinylsilane in 80% yield (B:L 92:8). A range of vinylsilanes could be employed, as demonstrated by formation of **268c** which was produced in 41% yield (B:L 94:6).

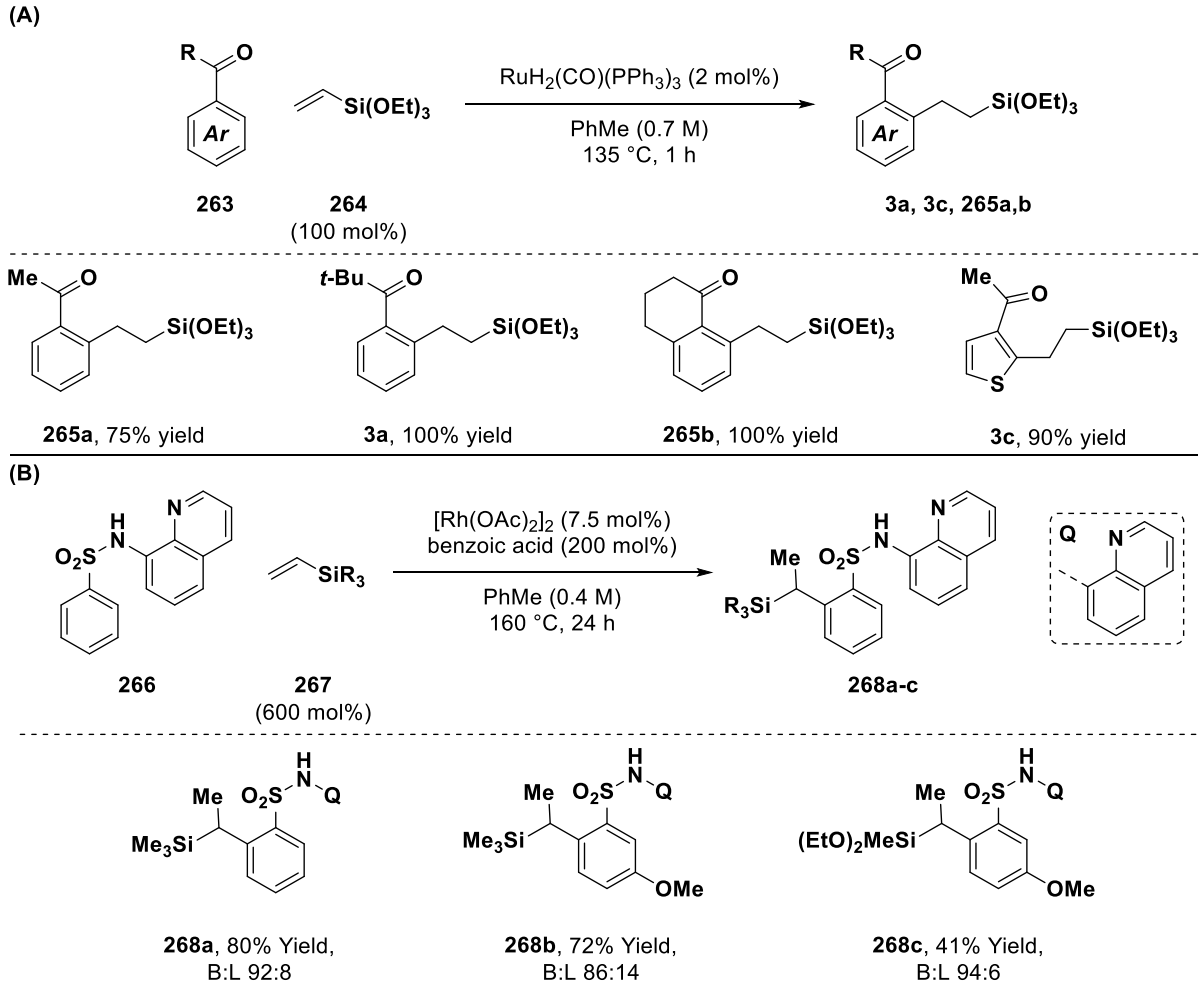
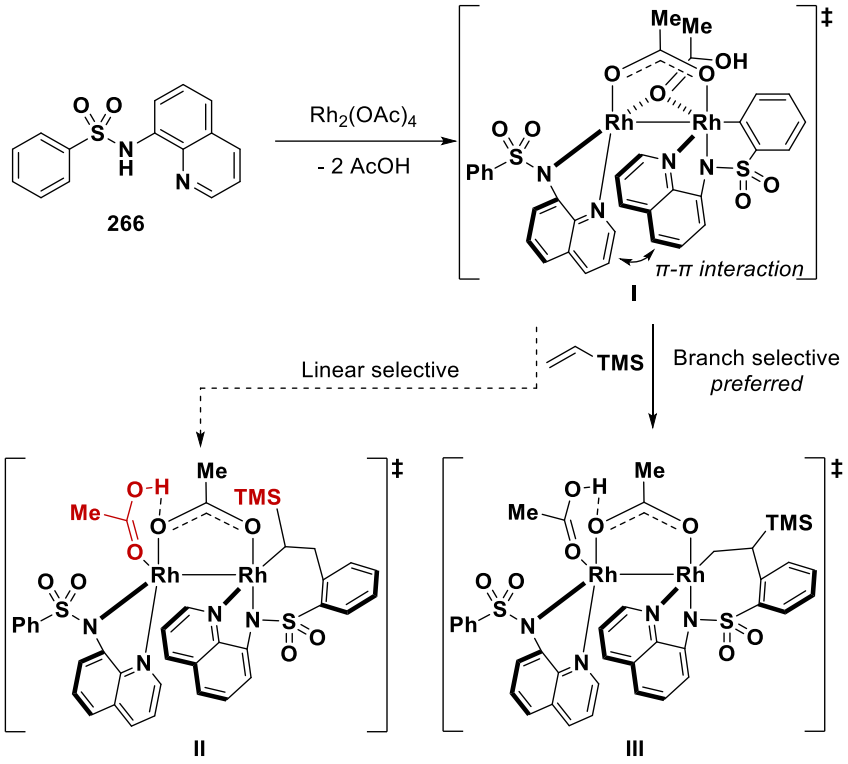


Table 23: *(A) Murai's linear selective hydroarylation using triethoxyvinylsilane; (B) Chatani's branch-selective using aryl sulfonamides.*

Computational studies provided mechanistic insight into the branch selective outcome (**Scheme 59**).[199] Based on complimentary X-ray crystallography data, it was proposed that a twisted paddlewheel Rh-complex is formed upon reaction with sulfonamide **266** and is stabilised by a *π*-*π* interaction between aminoquinoline units. A strained perpendicular metallacycle **I** is then established upon C-H activation of **266** (*via* a CMD mechanism), which favours the development of branch selective transition state **III** over linear transition state **II**. The latter is disfavoured due to steric repulsion between the newly incorporated silyl group and an equatorial acetate ligand (shown in red).



Scheme 59: *Transition states calculated by DFT for the hydroarylation of trimethylvinylsilane with sulfonamide **266**.*

To the best of our knowledge, the process in **Table 23** is the first example of a methodology for the branch selective hydroarylation of vinylsilanes. Although the targets can be obtained in good yield, the associated branch selectivity can be improved. Further, use of a large directing group and excess benzoic acid is undesirable from an atom-economy viewpoint. We envisioned that an improved enantioselective protocol could be developed by adaptation of our previously reported Ir(I)-catalysed methodology. If successfully applied in a regio-, enantio- and branch selective process, this would allow access to a library of heterocyclic and carbocyclic chiral benzylic organosilicon structures.

4.3 Development of a hydroheteroarylation methodology

As described in **Chapter 3**, efficient branched and enantioselective hydroarylation of styrenes and aliphatic alkenes could be achieved by employing heteroaromatic substrates. For example, reaction of furan **187** with styrene under Ir(I)-catalysed conditions afforded **188** in 93% yield and 92% *e.e.* Key to this transformation was the application of chiral bisphosphonite ligand **L13**, which was designed and synthesised within the Bower group to meet the steric and electronic requirements described in **Chapter 1**. These results prompted investigations into use of alkenyl silanes as coupling partners in an enantioselective hydroarylation protocol. Development of such a methodology would allow for step-economical synthesis of small molecules (i) suitable for drug development studies and/or (ii) possessing a functional handle from which further reactivity can ensue.

Reaction development began by extensive ligand screening for the coupling of furan **106** with dimethylphenylvinylsilane **269** under standard Ir(I)-catalysed conditions. Over 20 commercially available bidentate phosphine ligands were screened in the reaction; the key results are shown in **Table 24**. It was found that no reactivity was observed using achiral bisphosphine ligands such as xantphos and dppf, or by employment of achiral bisphosphite or bisphosphonite ligands (**Entries 1–4**). Employing BINAP (**Entry 5**) gave hydroarylation product **270** in 7% yield and with minimal alkene regiocontrol (B:L 1:1). Based upon this result, we anticipated we could obtain enantioenriched **270** by use of a chiral ligand. Pleasingly, chiral bisphosphine ligands such as (*R*)-MeO-BIPHEP (**Entry 6**, 22% yield, B:L 2:1, 38% *e.e.*) or the more electron-deficient analogue CTH-(*R*)-P-Phos (**Entry 7**, 8% yield, B:L 6:1, 37% *e.e.*) gave promising results. Increased reactivity and branch selectivity were observed in these cases compared to BINAP. Complete branch selectivity was achieved using narrow bite angle chiral ligand (*R*,*R*)-Me-DuPHOS, but in low yield (**Entry 8**, 13% yield, B:L 25:1, 40% *e.e.*).

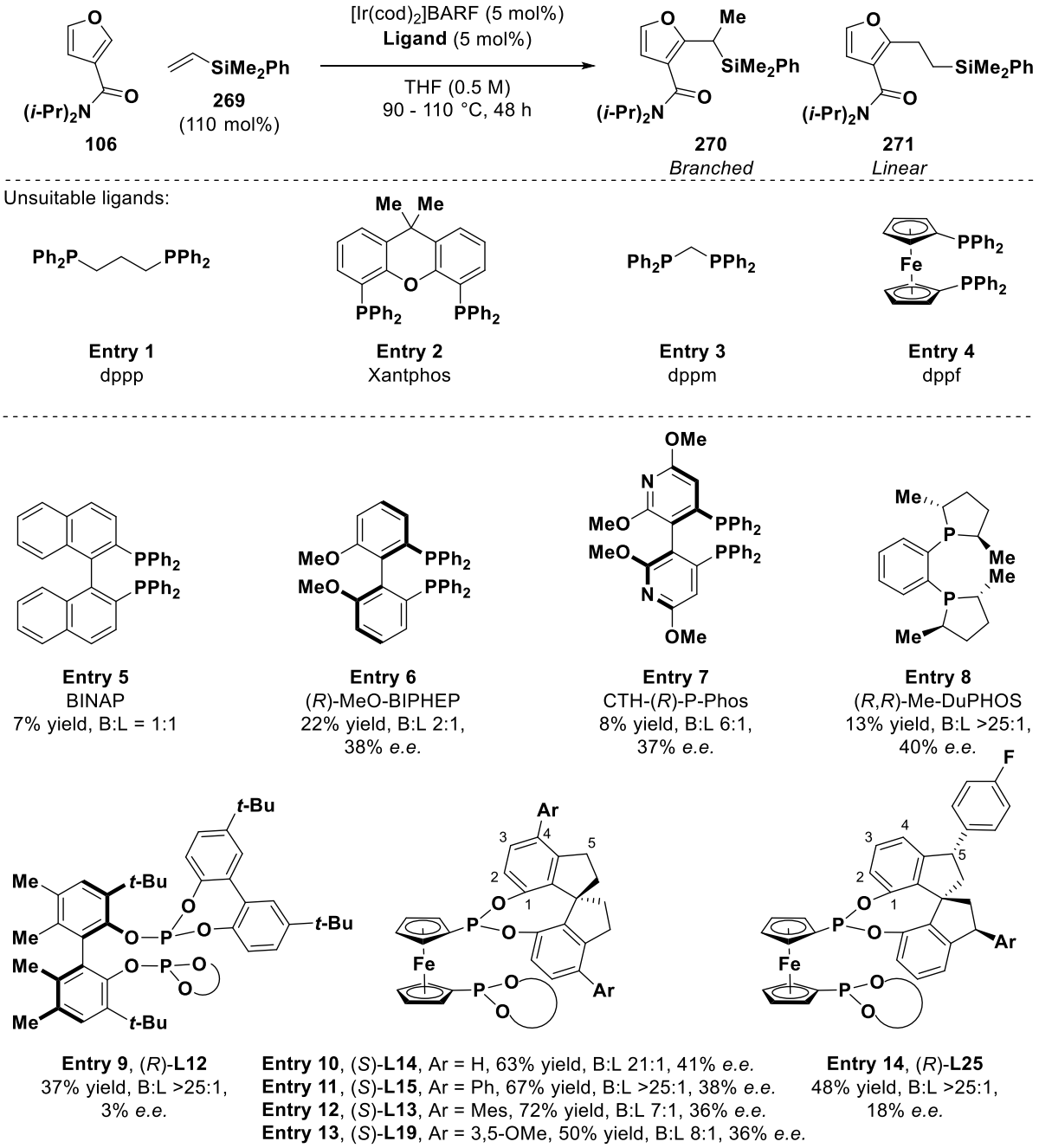
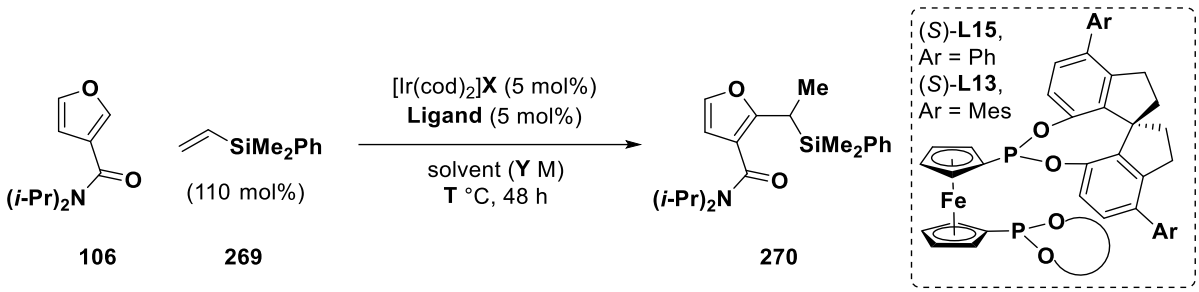


Table 24: *Selected results for the hydroarylation of vinylsilane **269** with furan **106** under Ir(I)-catalysed conditions; B:L selectivities obtained by ^1H analysis of the crude material against an internal standard.*

A commercially available ligand suitable for the hydroarylation of dimethylphenylvinylsilane with **106** was not identified. However, it was noted that use of an electron-deficient ligand CTH-(*R*)-P-Phos (**Entry 7**) afforded **270** in modest yield and in higher branch selectivity than the more electron-rich analogue (**Entry 6**). As a result, we evaluated electron-deficient ligands used in previous hydroarylation methodologies. Pleasingly, use of chiral bisphosphite ligand **L12** afforded **270** in 37% yield and complete branch selectivity, albeit in low *e.e.* (**Entry 9**). Further increases in reactivity and branch selectivity were found from screening bisphosphonite ligands (**Entries 10–14**). One advantage of using ligands of this type is in their highly modular synthesis which allows for structural optimisation of the

ligand. Use of C-4 functionalised **L15** provided **270** in 67% yield, B:L >25:1 and 38% *e.e.* (**Entry 11**) compared to the unfunctionalised **L14** which afforded **270** in 63% yield, B:L 21:1 and 41% *e.e.* (**Entry 10**). Use of a more sterically demanding mesityl **L13** group saw a small increase in yield at the expense of branch selectivity (**Entry 12**, 72% yield, B:L 7:1, 36% *e.e.*) while functionalisation using an electron-rich 3,5-dimethoxyphenyl, **L19**, group saw decreases in all values (**Entry 13**, 50% yield, B:L 8:1, 36% *e.e.*). As noted previously, higher branch selectivities were observed during screening of electron-deficient commercial ligands. As such **L25,** functionalised with an electron-deficient 4-fluorophenyl group at C-5, was screened for the coupling of dimethylphenylvinylsilane with **106**. While the product was formed with excellent alkene regiocontrol, it was isolated in 48% yield, roughly 20% lower yield than when **L15** was used (**Entry 14**). Despite extensive ligand screening and further optimisation, **270** could only be obtained in a maximum of 41% *e.e.* Consequently, efforts from this point were focused on development of an efficient, non-enantioselective, branch selective hydroarylation process.

With **L15** identified as the optimal ligand for the hydroarylation of dimethylphenylvinylsilane **106** with **269**, optimisation of the reaction conditions commenced (**Table 25**). It was ascertained that $[Ir(cod)_2]BARF$ was the optimal Ir(I) source. Changing the counterion to more strongly coordinating species such as ^{-}OTf or $^{-}BF_4$ (**Entries 1–4**) led to a decrease in isolated yield of **270**. Conducting the reaction in 1,4-dioxane or 1,2-DCB (**Entries 5** & **6**) also proved detrimental to the reaction outcome giving **270** in 22% and 18% yields, respectively. Due to ligand availability, **L13** bearing a mesityl group was used for further optimisation. It was shown in ligand screening studies (**Table 24**) that only branched selectivity differed significantly when comparing reaction outcomes using **L13** and **L15** (Ar = Ph, B:L >25:1, Ar = Mes, B:L 7:1); the yield of **270** obtained was also comparable (Ar = Ph, 67% yield, Ar = Mes, 72% yield). Increasing the reaction temperature to 110 °C using **L13** delivered **270** in 77% yield (**Entries 7–9**). Finally, changing the concentration (**Entries 10–14**) from 0.5 M to 0.1 M afforded **270** in 85% yield and with excellent regiocontrol (B:L 14:1). Pleasingly, throughout ligand screening and reaction optimisation, only C-2 alkylated products were obtained. This demonstrates a further aspect of regiocontrol that is achieved in the reaction manifold.



Entry	Ar	X	Y	T /°C	Solvent	Yield	B:L
1	Ph	BARF	0.5	90	THF	67%	>25:1
2	Ph	OTf	0.5	90	THF	23%	>25:1
3	Ph	BF_4	0.5	90	THF	9%	>25:1
4	Ph	SbF_6	0.5	90	THF	23%	>25:1
5	Ph	BARF	0.5	90	1,4-dioxane	22%	>25:1
6	Ph	BARF	0.5	90	1,2-DCB	18%	>25:1
7	Mes	BARF	0.5	90	THF	72%	7:1
8	Mes	BARF	0.5	110	THF	77%	9:1
9	Mes	BARF	0.5	120	THF	69%	8:1
10	Mes	BARF	0.05	110	THF	49%	6:1
11	**Mes**	**BARF**	**0.1**	**110**	**THF**	**85%**	**14:1**
12	Mes	BARF	1.0	110	THF	75%	13:1
13	Mes	BARF	1.5	110	THF	49%	16:1
14	Mes	BARF	2.0	110	THF	43%	14:1

Table 25: *Selected optimisation results for the hydroarylation of vinylsilane **269** with furan **106** under Ir(I)-catalysed conditions; B:L selectivities obtained by ^1H analysis of the crude material against an internal standard.*

Unfortunately, although **270** could be isolated in 85% yield and high branch selectivity, the reproducibility of this result was poor. Only side-product **275**, presumably formed from protodesilylation of the catalysis product, was observed (**Table 26**).[200] We hypothesised that formation of **275** was caused by adventitious H_2O or trace acidic impurities in the reaction mixture. However, screening of basic additives (e.g. $NaHCO_3$ or the Proton Sponge) did not alleviate these reproducibility issues. Taking precautionary measures to remove traces of H_2O or air, such as sparging the reaction mixture with argon or running the reaction in the glovebox, were also unsuccessful.

As a result, we sought to investigate the robustness of a series of catalysis products (**Table 26**). Branched products **270**, **272** and **273**, bearing either an *N*,*N*-diethyl, -diisopropyl or -dicyclohexylamide directing group were synthesised and re-subjected to Ir(I)-catalysed conditions. When **272**, featuring *N*,*N*-diethylamide was employed, only 11% of **272** was recovered after 72 hours and 29% of the desilylated **274** was observed. The identity of the other side-products of this decomposition are currently unknown. Interestingly, when the steric bulk of the directing group was increased to *N*,*N*-diisopropylamide, 40% of **270** was recovered and only 11% of desilylated **275** was observed. Finally, it was found that 77% **273** was recovered by using an *N*,*N*-dicyclohexylamide directing group and the remaining mass balance could be attributed to desilylated **276**. It appeared that the steric bulk of the *N*,*N*-dicyclohexylamide directing group reduced the rate of protonation and/or hydrolysis pathways,

presumably by shielding the silyl functional group. Re-subjecting **273** under standard catalysis conditions gave similar results even in the absence of either (i) vinyl silane or (ii) vinyl silane and [Ir(cod)$_2$]BARF. This suggests that any acidic impurity in the reaction mixture is not the result of reaction between alkene and Ir(I) source.

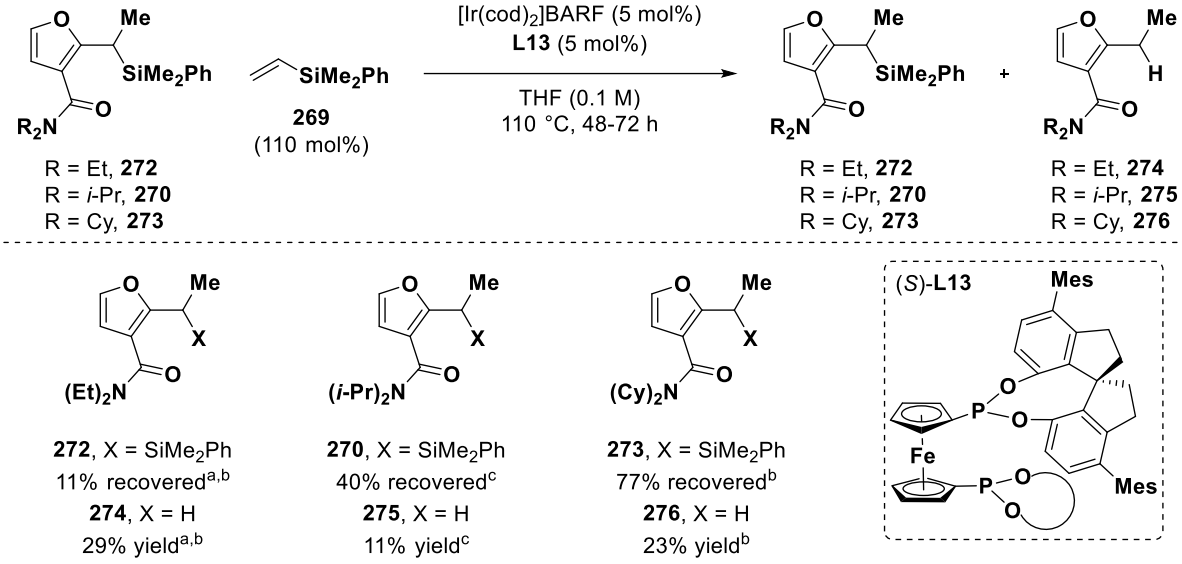
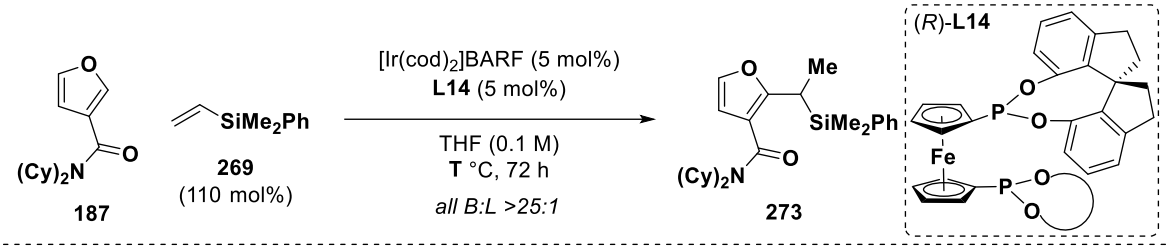


Table 26: *Robustness screening results for the hydroarylation of vinylsilane **269** with furan substrates under Ir(I)-catalysed conditions; [a]Yields calculated by ^{1}H analysis of the crude material against an internal standard; [b]Reaction conducted for 72 h; [c]Reaction conducted for 48 h.*

With the results of the robustness screening in hand, further optimisation for the coupling of dimethylphenylvinylsilane **269** was carried out with furan **187** bearing an *N*,*N*-dicyclohexylamide directing group (**Table 27**). Due to the commercial availability of (*R*)-SPINOL and to negate any further reproducibility issues, **L14** was employed as large quantities could be synthesised in fewer steps; this minimised potential discrepancies between ligand batches. As some desilylated product was observed in the robustness screening using **273**, we hypothesised that lowering the reaction temperature, but running the reaction for a longer reaction time would provide a balance between reactivity of the substrates and decomposition of the product (**Entries 1–3**). Unfortunately, no reactivity was observed by running the reaction at 60 °C and likewise only 41% of **273** was isolated with the reaction at 80 °C for 72 hours. At 90 °C, 68% of **273** was isolated after 72 hours (**Entry 3**). Pleasingly, a further increase in yield was found by carrying out the reaction at elevated temperatures over a shorter reaction time. Hence at 120 °C, **273** was obtained in 73% yield in just 24 hours (**Entry 5**). Once more, a balance between temperature and time was sought by performing the reaction at 100 °C for 48 hours, however this delivered **273** in only 53% yield (**Entry 4**). Branch selectivity was attained in all cases (B:L >25:1).



Entry	T / °C	Yield
1	60	0%
2	80	41%
3	90	68%
4	100	53%[a]
5	**120**	**73%[b]**

Table 27: *Selected optimisation results for the hydroarylation of vinylsilane **269** with furan **273** under Ir(I)-catalysed conditions; B:L selectivities obtained by ^{1}H analysis of the crude material against an internal standard; [a]Reaction conducted for 48 h; [b]Reaction conducted for 24 h.*

4.4 Reaction scope using vinyl silanes

With optimised conditions in hand for the hydroarylation of dimethylphenylvinylsilane **269** with furan **187** using **L14**, we were eager to investigate the reaction scope in terms of suitable vinyl silanes (**Table 28**). Pleasingly, a range of vinyl silanes were tolerated, affording the corresponding branched products in good to excellent yields. Trimethyl- and triethylvinylsilane were found to be suitable coupling partners in the reaction with furan **187**, affording products **278a** and **278b** in 77% and 99% yields, respectively. Furan substrates with functionalisation at the C-5 position were also tolerated. For example, inputting a furan substrate with C-5 functionalisation of a 4-fluorophenyl group under the reaction conditions with triethylvinylsilane afforded **278f** in 84% yield. Furan substrates bearing a directing group at the C-2 position could also be used. For instance, reacting **191** with dimethylvinylsilane afforded **278c** in 65% yield. As seen in the robustness screening in **Table 26** a variety of amide-based directing groups could be used in the methodology. In general, higher yields were obtained when bulkier directing groups were used. Reacting furan **280**, appended with a piperidine-amide directing group (as seen in the hydroarylation using benzamide substrates, **Chapter 3**), with triethylvinylsilane afforded **278j** in 55% yield. It was postulated that **278k**, which was obtained in 75% yield, would be more amenable to post-catalysis functionalisation of the amide owing to the presence of a less sterically hindered secondary amide directing group (as opposed to a tertiary amide).

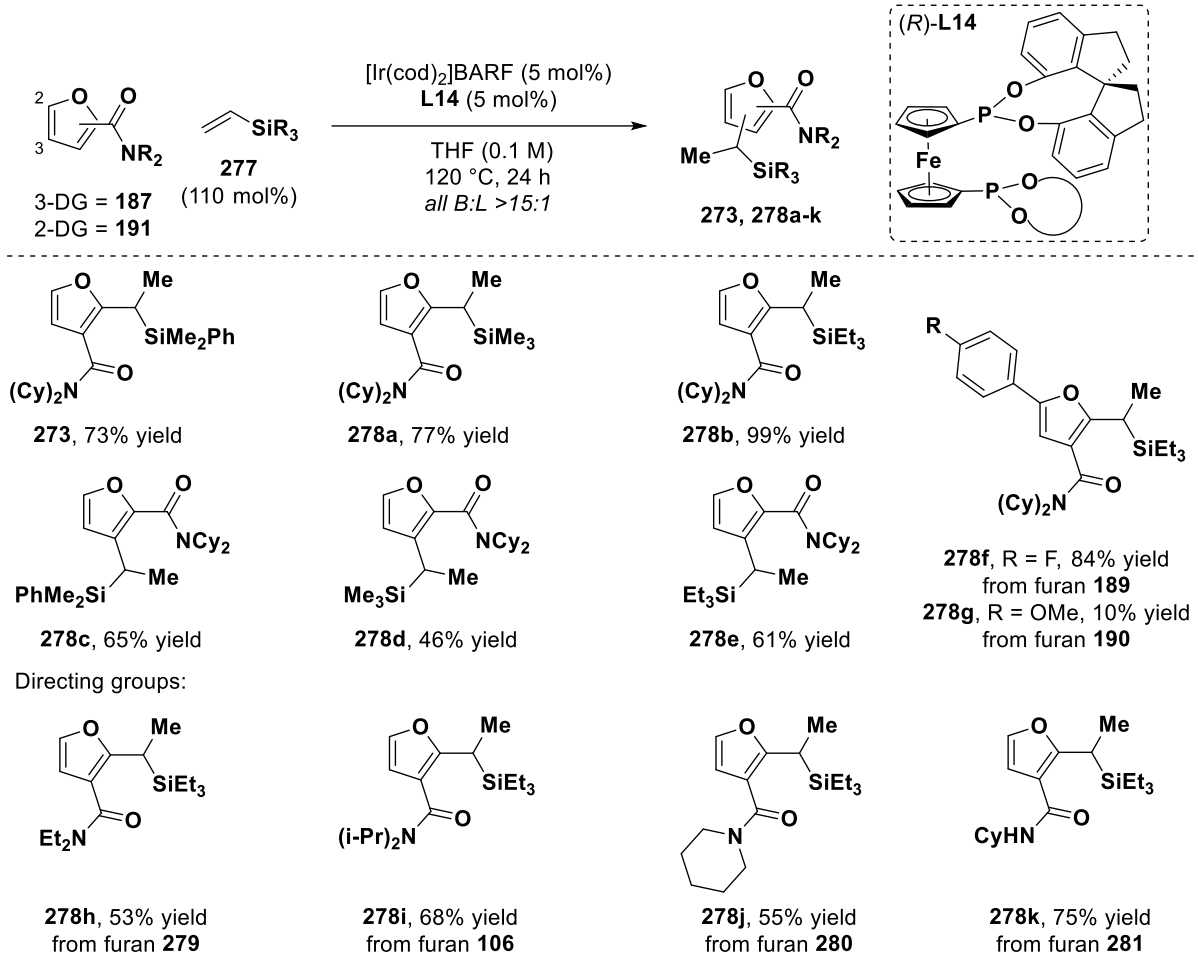


Table 28: *Scope of the vinyl silane, arene and directing group components.*

Having investigated the scope of the vinyl silane coupling partners, subsequent studies found that a range of heteroaromatic substrates were also suitable coupling partners (**Table 29**). In addition to furan substrates, it was found that thiophene substrates, functionalised with a C-2 directing group, were tolerated (**280a–c**). For instance, reaction with dimethylphenylvinylsilane produced **280a** in 68% yield. Additionally, reaction using pyrrole substrates also proceeded smoothly (**280d–g**), albeit at a longer reaction time of 48 hours. For example, using triethylsilane afforded **280e** in 80% yield. We postulated whether the longer required reaction times could be due to use of a less lewis-basic urea-derived directing group on the heteroatom of the pyrrole. However, use of an amide-derived directing group at the C-3 position led to the corresponding regioisomeric product **280g** to be formed in 62% yield, also after 48 hours. The regiochemical outcomes were assigned from nOe experiments. As seen in **Chapter 3**, benzamides were found to be suitable substrates in the enantioselective hydroarylation of styrenes and aliphatic alkenes. Accordingly, benzamide **281** was subjected to Ir(I)-catalysed conditions with triethylvinylsilane. However, no reactivity was observed and starting material was recovered. Similarly, use of acetanilide substrate **236** was unsuccessful. This latter result corroborates with previous results obtained in the group using a dppf-derived ligand.[108]

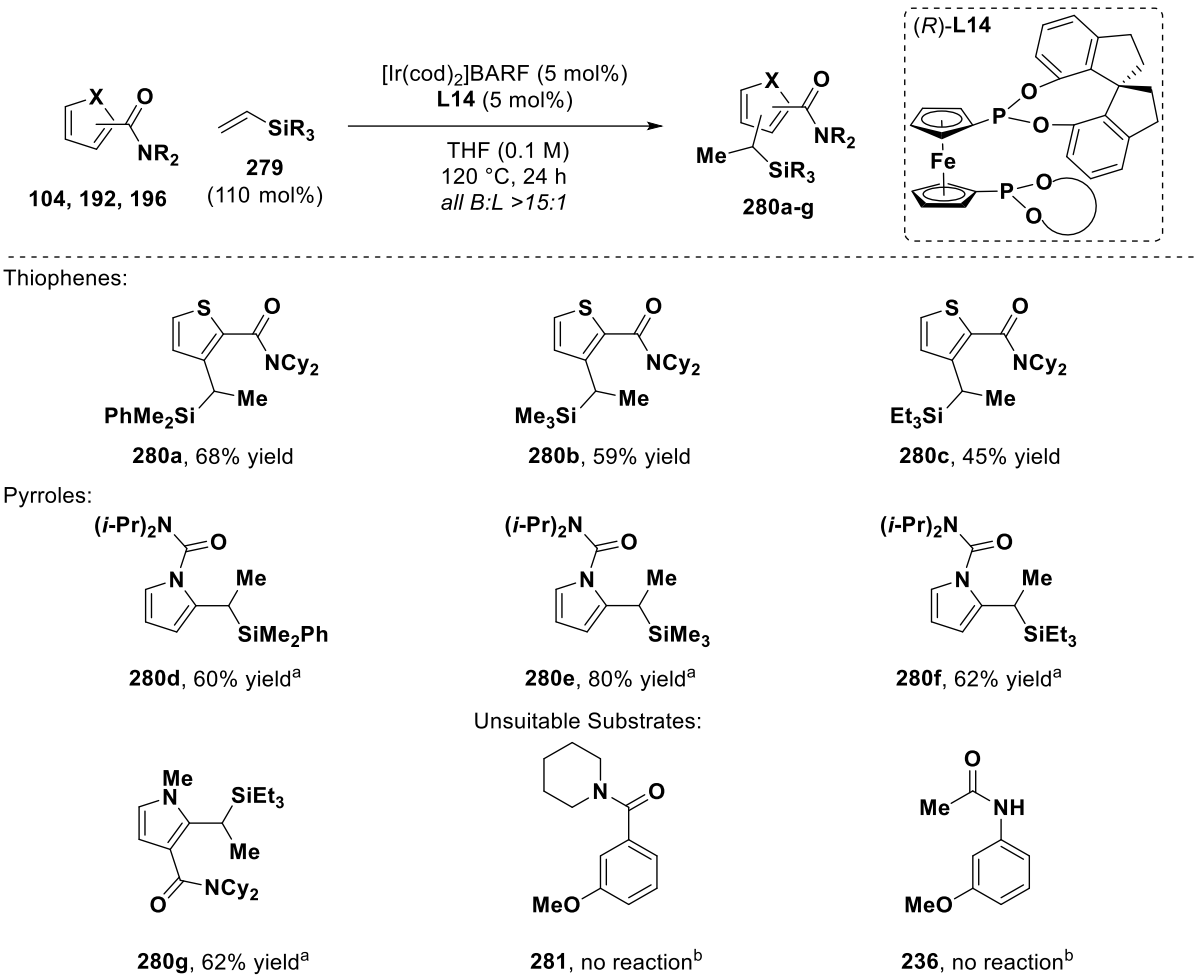


Table 29: *Scope of the hydroarylation reaction of vinyl silanes with heterocyclic substrates; [a]Reaction conducted for 48 h; [b]Reaction conducted for 72 h.*

4.5 Reaction scope using allyl silanes

At this point, we had successfully demonstrated the broad applicability of heteroaromatic substrates in the branched selective hydroarylation of vinyl silanes. Subsequently, we were eager to employ allyl silanes in the methodology (**Table 30**). This reaction manifold would give access to the corresponding one-carbon homologated branched products. Pleasingly, under the same Ir(I)-catalysed conditions, we found that reaction of allyltrimeththylsilane with furan **187**, gave **283a** in 88% yield. Other allyl silanes were tolerated to afford triphenyl-**283b** and dimethylphenyl-**283c** in 88% and 90% yields, respectively. As seen previously, furan substrates with a C-2 directing group are tolerated in hydroarylation methodologies. Likewise, reaction with allyltriphenylsilane afforded **283d** in 85% yield. In terms of heteroaromatic substrate scope, so far only thiophenes are tolerated, as shown by **283e**, which was obtained in 70% yield. Reaction of allyl silanes with pyrrole substrates remains elusive, as demonstrated by **196** which was unreactive under the catalysis conditions after 72 hours. In this case, low reactivity could be attributed to larger steric bulk of an allyl silane compared to a vinyl silane.

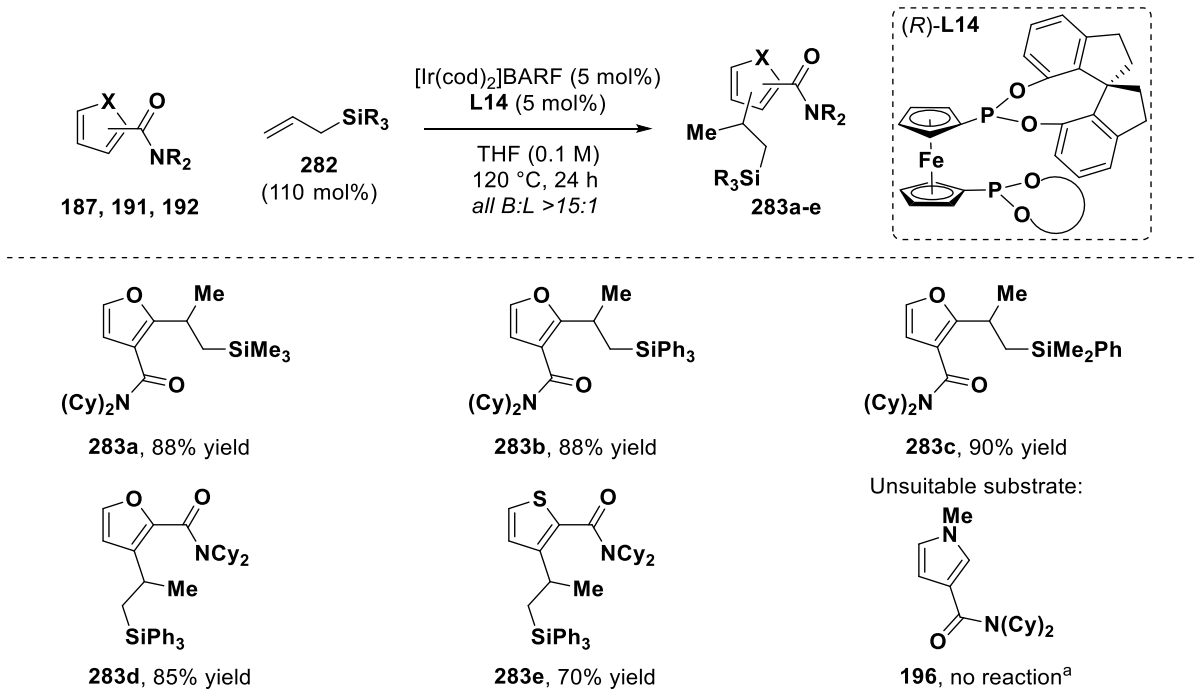


Table 30: *Scope of the hydroarylation reaction of allyl silanes with heterocyclic substrates; [a]Reaction conducted for 72 h.*

4.6 Summary and conclusions

Through extensive screening of a range of phosphine-derived ligands, a methodology for the branch selective hydroarylation of alkenyl silanes with heteroaromatic substrates has been achieved. The methodology was applicable to a range of vinyl and allyl silanes with a broad scope of furan, thiophene and pyrrole substrates. The products are formed in good to excellent yields (upto 99%) in very high alkene regiocontrol (B:L >15:1). It is anticipated that the newly installed silicon-containing functional group can act as a useful motif in a drug discovery programme or as a synthetic handle for further functionalisation. Currently, one limitation is the application of this methodology to carbocylic substrates such as benzamides or acetanilides. This issue could be addressed through further ligand screening and optimisation of the directing group on these substrates. An enantioselective analogue of this methodology could be developed based on the results obtained using (*R*,*R*)-Me-DuPHOS as the chiral ligand.

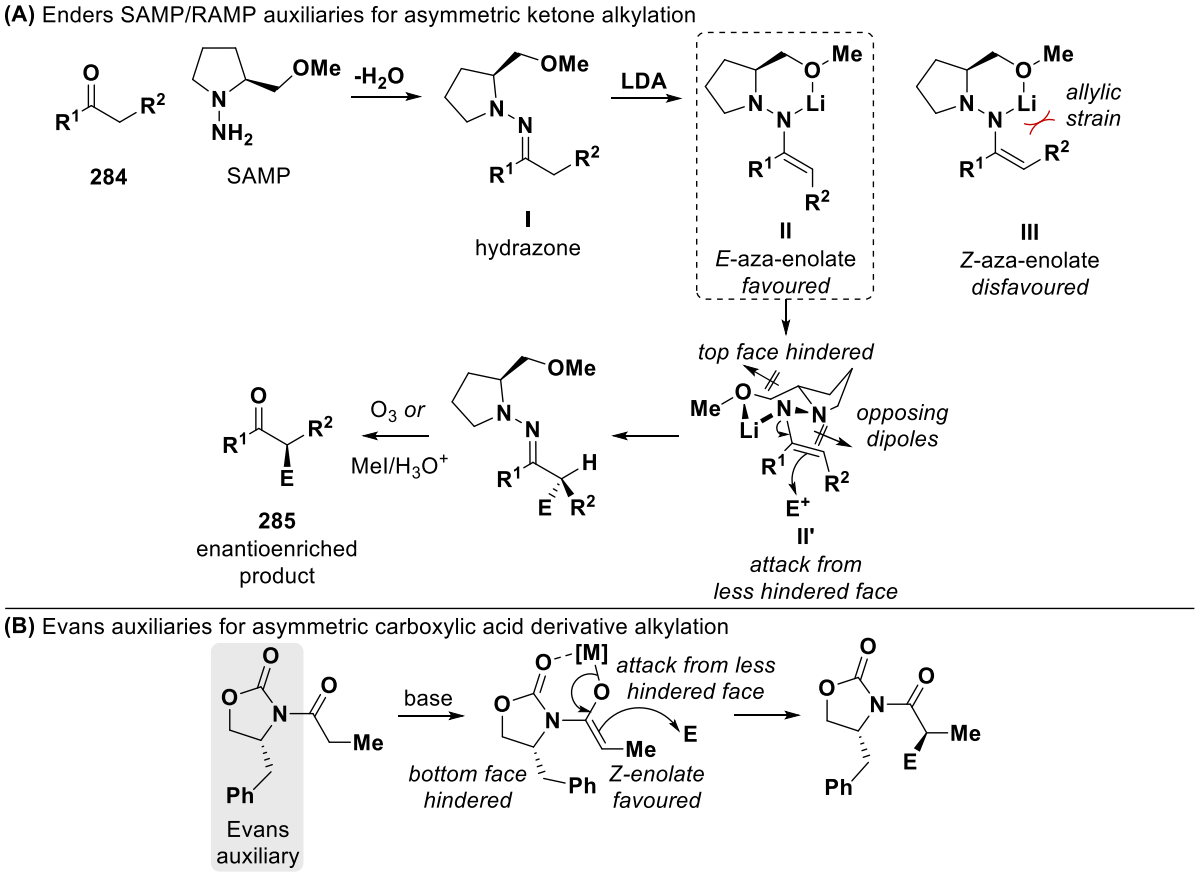
Chapter 5

Enantio- and Branch Selective Hydroalkylation for the Synthesis of Amino Acid Derivatives

Chapter 5 – Enantio- and Branch Selective Hydroalkylation for the Synthesis of Amino Acid Derivatives

5.1 General strategies for the asymmetric α-alkylation of carbonyl compounds

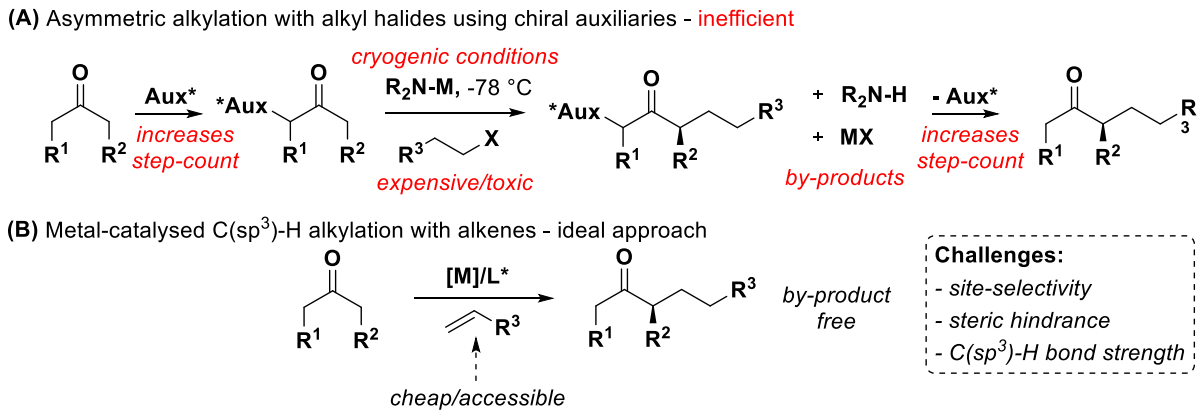
The asymmetric α-alkylation of carbonyl compounds is a fundamental transformation in synthetic chemistry that is widely used in complex molecule synthesis.[201] Conventionally, chiral auxiliaries are employed to generate diastereomeric transition states, wherein addition of the electrophile to either face of the enolate occurs at different rates.[202,203] For asymmetric alkylations of ketones and aldehydes, Enders SAMP/RAMP auxiliaries are often used (SAMP = (*S*)-1-amino-2-methoxymethylpyrrolidine)[204] (**Scheme 60A**). In this process, ketone or aldehyde **284** is condensed with the chiral SAMP hydrazide to afford the corresponding hydrazone **I**. Deprotonation with a strong base generates the *E*-aza-enolate **II** (to minimize allylic strain) in which the metal counter-ion provides configurational stability where dipole-dipole interactions are minimised (**II'**). From here, the electrophile adds at the less hindered face of the enolate before deprotection affords the enantioenriched product of type **285**. Similarly, Evans auxiliaries are employed for the asymmetric alkylation of substrates in the carboxylic acid oxidation state[205] (**Scheme 60B**), while the Schöllkopf method uses valine as a chiral auxiliary for the asymmetric synthesis of chiral amino acids.[206]



Scheme 60: *(A) Enders SAMP/RAMP auxiliaries for asymmetric ketone alkylation; (B) Evans auxiliaries for asymmetric carboxylic acid derivative alkylation.*

5.2 Catalytic methods for the asymmetric α-alkylation of carbonyl compounds

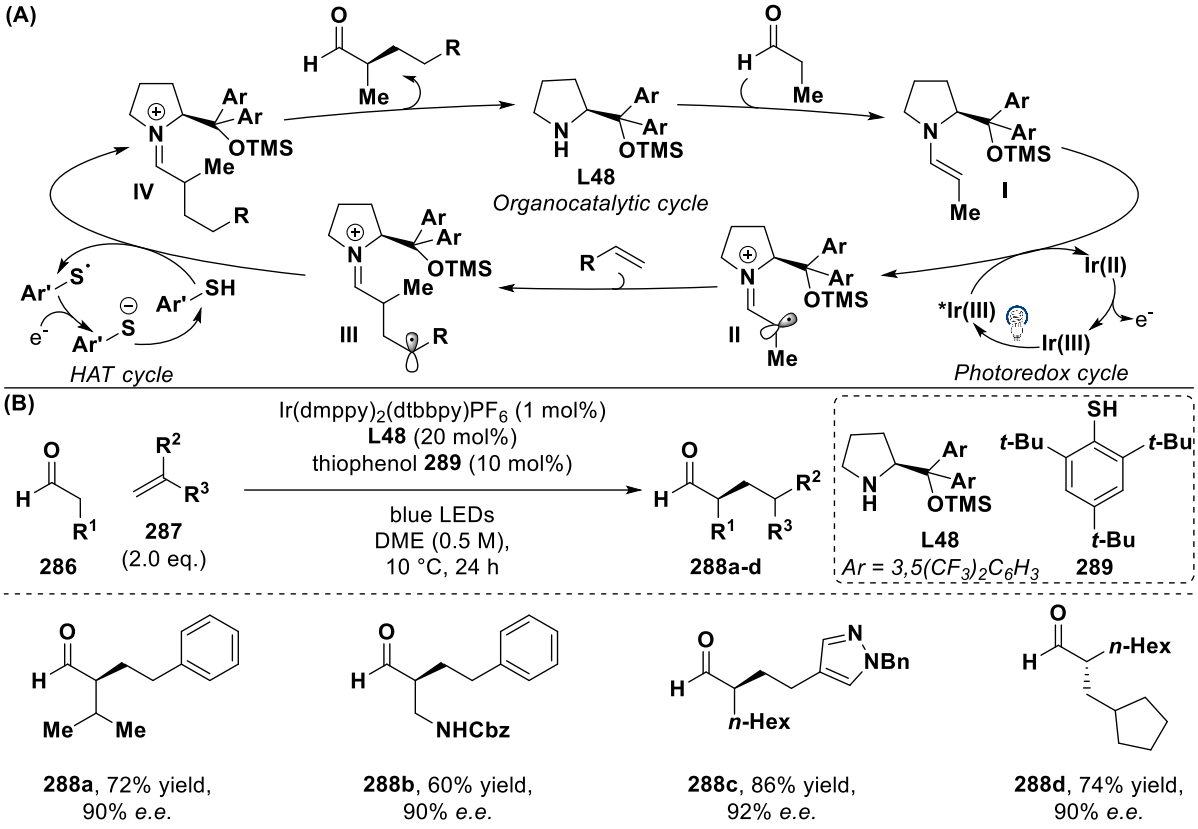
Although effective, classical asymmetric α-alkylation approaches suffer from numerous disadvantages including the use of stoichiometric base and cryogenic conditions. Furthermore, the installation and removal of chiral auxiliaries reduces atom economy (**Scheme 61A**). To improve this, focus has shifted to the development of catalytic asymmetric alkylation methods employing organocatalysis,[207] phase transfer catalysis,[208] chiral amine ligation of ketone-derived lithium enolates,[209] the use of Cr(salen) complexes,[210] and others.[211] While efficient, these methods often require the use of expensive and toxic alkyl halides. A more ideal approach involves the use of simple feedstock alkenes as alkylation reagents in a formal C(sp^3)-H hydroalkylation process (**Scheme 61B**). In this approach, no stoichiometric by-products are generated; however, the direct functionalisation of C(sp^3)-H bonds presents a formidable challenge due to the large kinetic barrier for C-H bond cleavage and ensuing processes. A key issue is the greater steric hindrance of C(sp^3)-H bonds compared to C(sp^2)-H bonds, which are more commonly employed in C-H activation methodologies. Additionally, C(sp^3)-H bonds are ubiquitous in organic compounds, which can make site-selective functionalisation challenging.



Scheme 61: *Use of chiral auxiliaries vs. asymmetric catalytic alkylation to generate enantioenriched products*

The state-of-the-art was disclosed by MacMillan *et al.* who described an enantioselective α-alkylation of aldehydes with unactivated styrenic and aliphatic alkenes.[212] This tri-catalytic process combines organocatalysis (chiral proline derivative **L48**), photoredox catalysis (using $Ir(dmppy)_2(dtbbpy)PF_6$) and HAT catalysis (thiophenol **289**) to enable intra- and intermolecular α-alkylations of aldehydes with alkenes. As shown in **Scheme 62A**, irradiation of $Ir(dmppy)_2(dtbbpy)PF_6$ with visible light generates a powerfully oxidising excited *Ir(III) species that can undergo SET from enamine **II**, formed by condensation of the aldehyde substrate with organocatalyst **L48**. This produces a reduced Ir(II) complex and 3π-electron enaminyl radical species **II** that is subsequently trapped with an olefin coupling partner to form a new C-C bond and a stereogenic centre (**III**). From here, HAT from the thiophenol catalyst to 3π-electron enaminyl radical species **III** provides a thiol radical and iminium ion **IV**. After hydrolysis, the enantioenriched aldehyde product and the organocatalyst **L48** are liberated. Final SET from the highly reducing Ir(II) species to the thiophenol radical regenerates the ground state Ir(III)

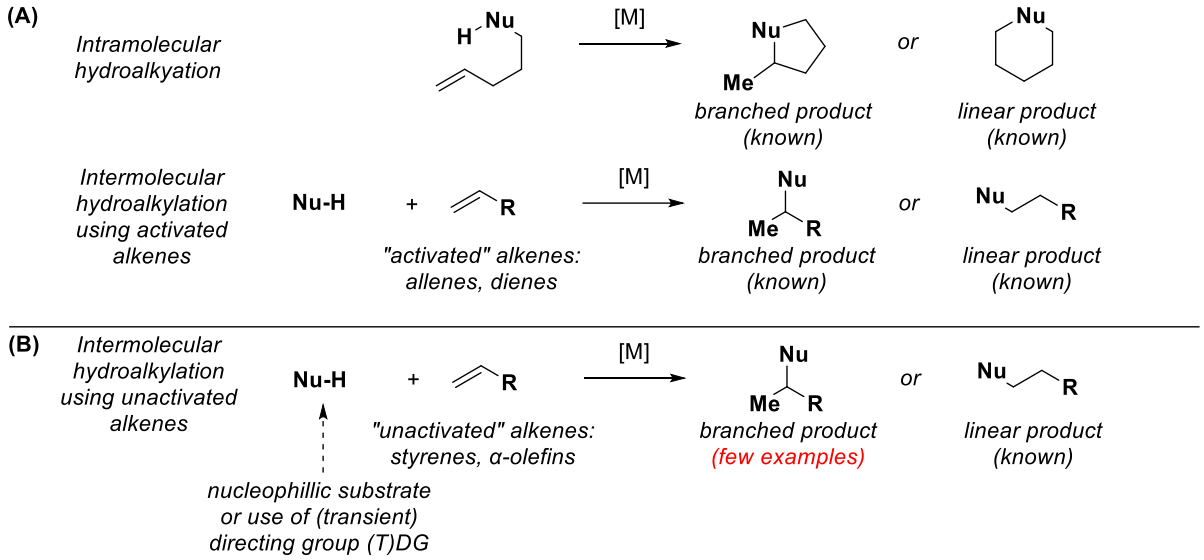
catalyst and HAT thiophenol catalyst after protonation. As illustrated in **Scheme 62B**, a variety of substituted aldehydes are tolerated in the process including β,β-disubstituted (**288a**, 72% yield, 90% *e.e.*) and β-amino aldehydes (**288b**, 60% yield, 90% *e.e.*). Electron-rich and -deficient styrenes could be employed in addition to vinyl heteroarenes (**288c**, 86% yield, 92% *e.e.*). Whereas terminal alkenes were found to be less reactive in this process, 1,1-disubstituted alkenes were well-tolerated as shown by the formation of **288d** in 74% yield, 90% *e.e.*



Scheme 62: *(A) Proposed mechanism for MacMillan's enantioselective α-alkylation of aldehydes; (B) Selected reaction scope.*

5.3 Existing protocols for metal-catalysed branch selective hydroalkylation of alkenes

The methodology disclosed by MacMillan *et al.* gives linear products preferentially. A complimentary approach to form the corresponding enantioenriched branched products using minimally-activated alkenes would be of utmost importance. There have been numerous reports of intramolecular branch selective alkene hydroalkylations, and methodologies are known that functionalise activated π-systems such as allenes, dienes, alkynes and 1,2-disubstituted alkenes (**Scheme 63A**);[43,213–216] however, there are limited reports of intermolecular branch selective hydroalkylations of minimally-polarised alkenes (**Scheme 63B**).

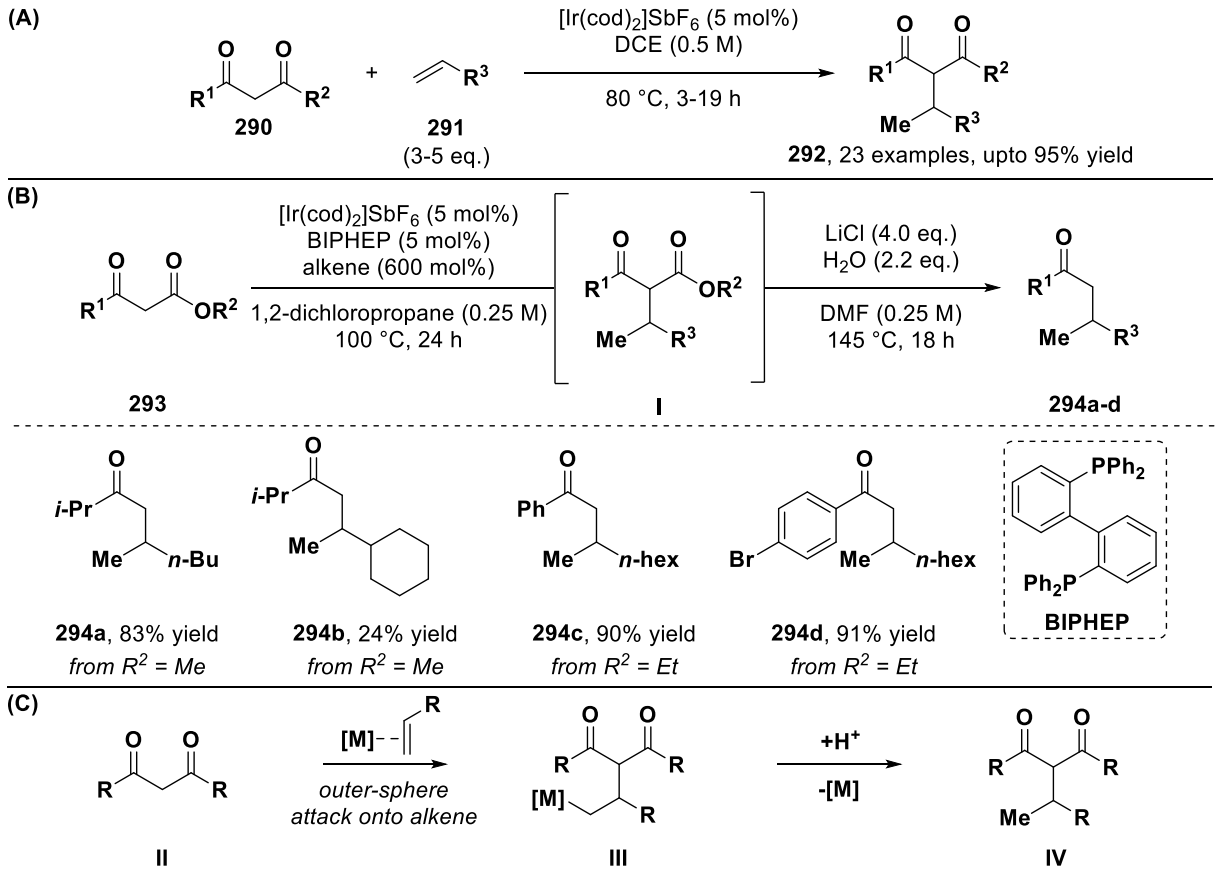


Scheme 63: *Known hydroalkylation frameworks.*

The following section will describe known procedures that use substrates with inherent latent nucleophilicity such as 1,3-diketones or β-ketoesters. In **Sections 5.3.1** and **5.3.2**, examples will be discussed that use of a directing group to generate a nucleophilic substrate and follow a C(sp^2)-H activation mechanism. Miscellaneous nucleophiles are summarised in **Section 5.3.3**.

5.3.1 Hydroalkylation of alkenes using 1,3-dicarbonyl substrates

A range of transition-metal catalysts have been utilised for the branch selective hydroalkylation of styrenes using 1,3-dicarbonyl substrates. Reports by Beller[217], Campagne and Prim[218], and Duan and Wu[219] have demonstrated the use of $FeCl_3$ while Li[220,221] and Yu[222] have disclosed regimes under Au-, Ag-, Sn- or Cu-catalysis. These reports are usually limited to styrenic or strained alkenes, and the use of minimally-polarised aliphatic alkenes in these reactions remains a challenge. In 2019, it was shown by the Takeuchi group that hydroalkylations of aliphatic alkenes **291** with 1,3-diketones **290** can be achieved under Ir(I)-catalysed conditions (**Scheme 64A**).[223] In a later report, the same group expanded the substrate scope to include β-ketoesters (**Scheme 64B**).[224] This work used $[Ir(cod)_2]SbF_6$ in conjunction with the ligand BIPHEP to give branched, α-substituted β-ketoesters **294a–d** in high yields. Krapcho decarboxylation converted these products into the corresponding β-branched ketones, such as **294a** (83% yield) and **294d** (91% yield). Based on similar transition-metal catalysed methodologies, the authors proposed an outer-sphere mechanism as outlined in **Scheme 64C**.[225,226]

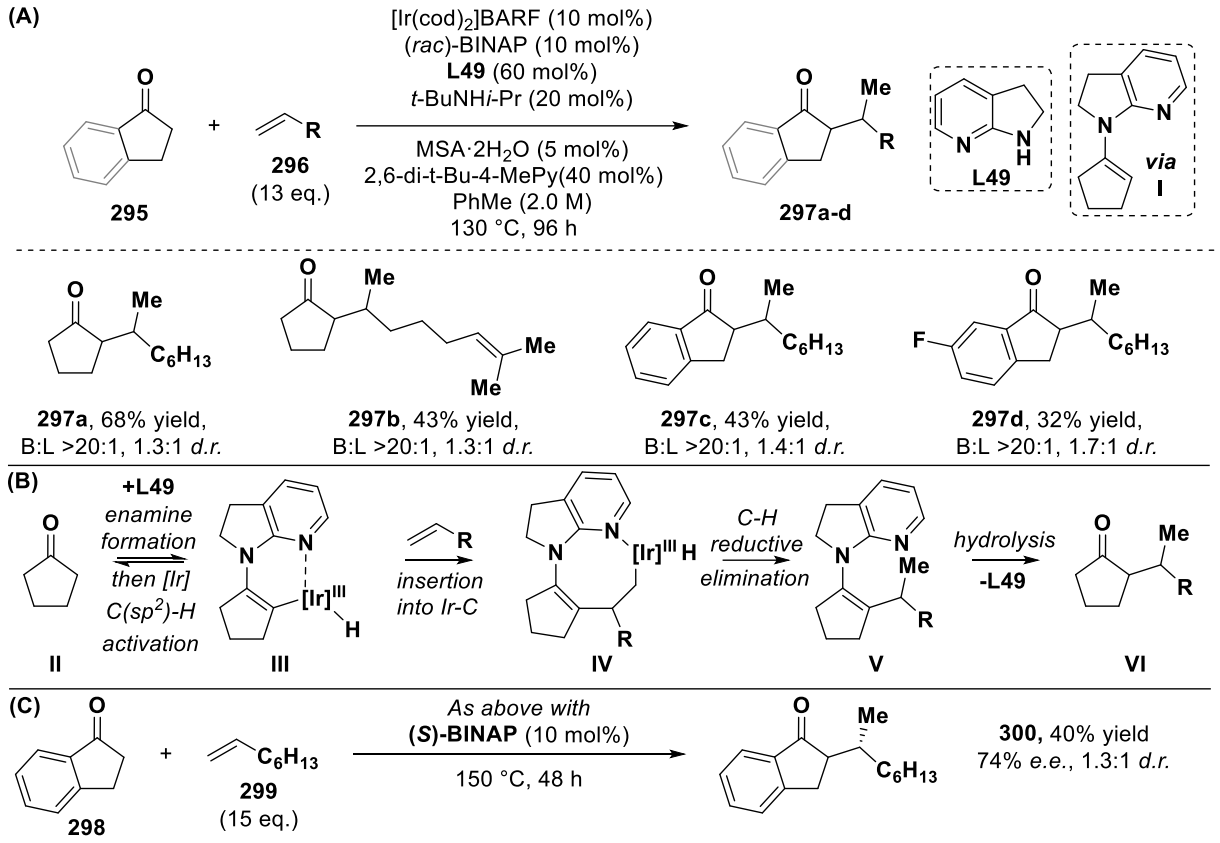


Scheme 64: *(A) Ir(I)-catalysed α-alkylation using (A) 1,3-diketones; (B) β-ketoesters; (C) Proposed reaction mechanism.*

5.3.2 Hydroalkylation of alkenes using ketone substrates

As seen commonly in hydroarylation methodologies, directing groups can be utilised to facilitate C(sp^2)-H activation. Dong and co-workers employed a transient directing group strategy for the branch selective alkylation of cyclic ketones with aliphatic alkenes. (**Scheme 65A**).[227] Under Ir(I)-catalysed conditions, 7-azaindoline, **L49**, was employed in a sub-stoichiometric quantity to form enamine intermediate **I** *in situ*. This then allows *N*-directed C(sp^2)-H activation of the vinyl C-H bond of the enamine, giving intermediate **III** (**Scheme 65B**). Subsequent carbometallation of the alkene affords **IV**. C-H reductive elimination then gives the branched enamine product **V** which is hydrolysed to give the corresponding α-alkylated ketone **VI**.[228,229] DFT calculations suggest that the branch selectivity is determined during Ir-C migratory insertion, with the bulky Ir-centre moving to the less hindered end of the alkene. By employing [Ir(cod)$_2$]BARF with (*rac*)-BINAP, a range of aliphatic alkenes could be coupled with excellent branch selectivity. For instance, coupling of cyclopentanone and 1-octene proceeded smoothly, affording **297a** in 68% yield, B:L >20:1. Indanone substrates were tolerated under the reaction conditions as shown by reaction of 1-octene with indan-1-one (**297c**, 43% yield, B:L >20:1) and 6-fluoroindan-1-one (**197d**, 32% yield, B:L >20:1). A considerable advancement in this process was made by employing chiral ligand (*S*)-BINAP (**Scheme 65C**). By doing so, coupling between 1-octene and indan-1-one delivered enantioenriched **300** in 40% yield and 74% *e.e.* To the best of our

knowledge, this promising result is the only example of a methodology which facilitates intermolecular branch selective and enantioselective hydroalkylation alpha to a carbonyl group. Although significant, the requirement to form an enamine *in situ* limits the protocol to ketones and only aliphatic alkenes are tolerated. Further, the reaction requires a large excess of alkene.

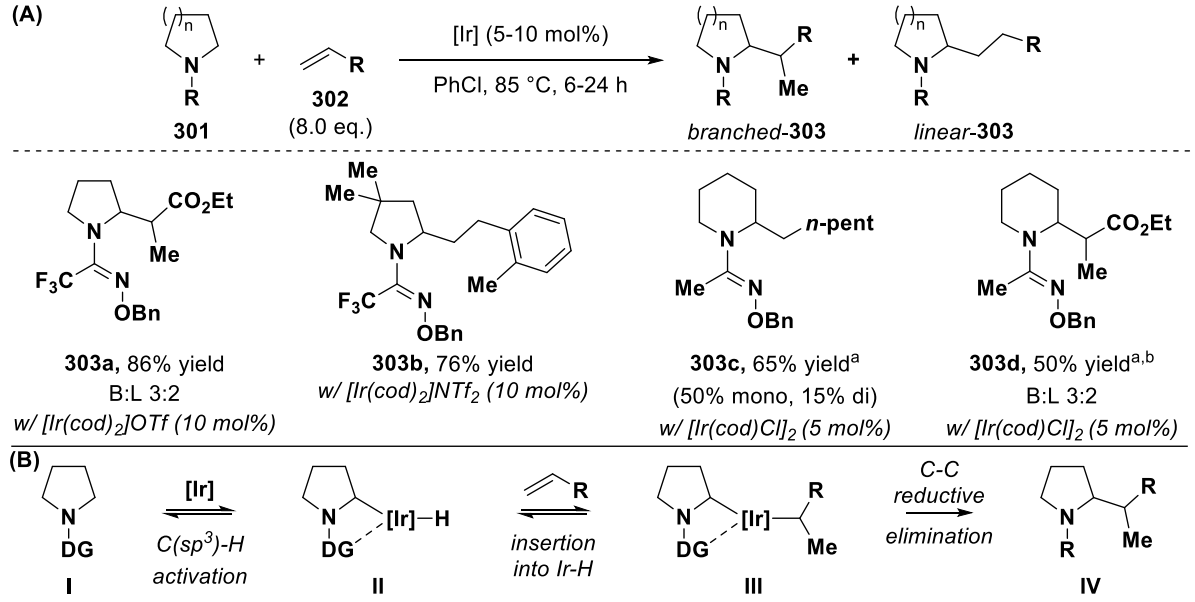


Scheme 65: *(A) Dong's α-alkylation using a transient directing group strategy; (B) Branch and enantioselective α-alkylation (C) Proposed reaction mechanism.*

5.3.3 Hydroalkylation of alkenes using miscellaneous nucleophile substrates

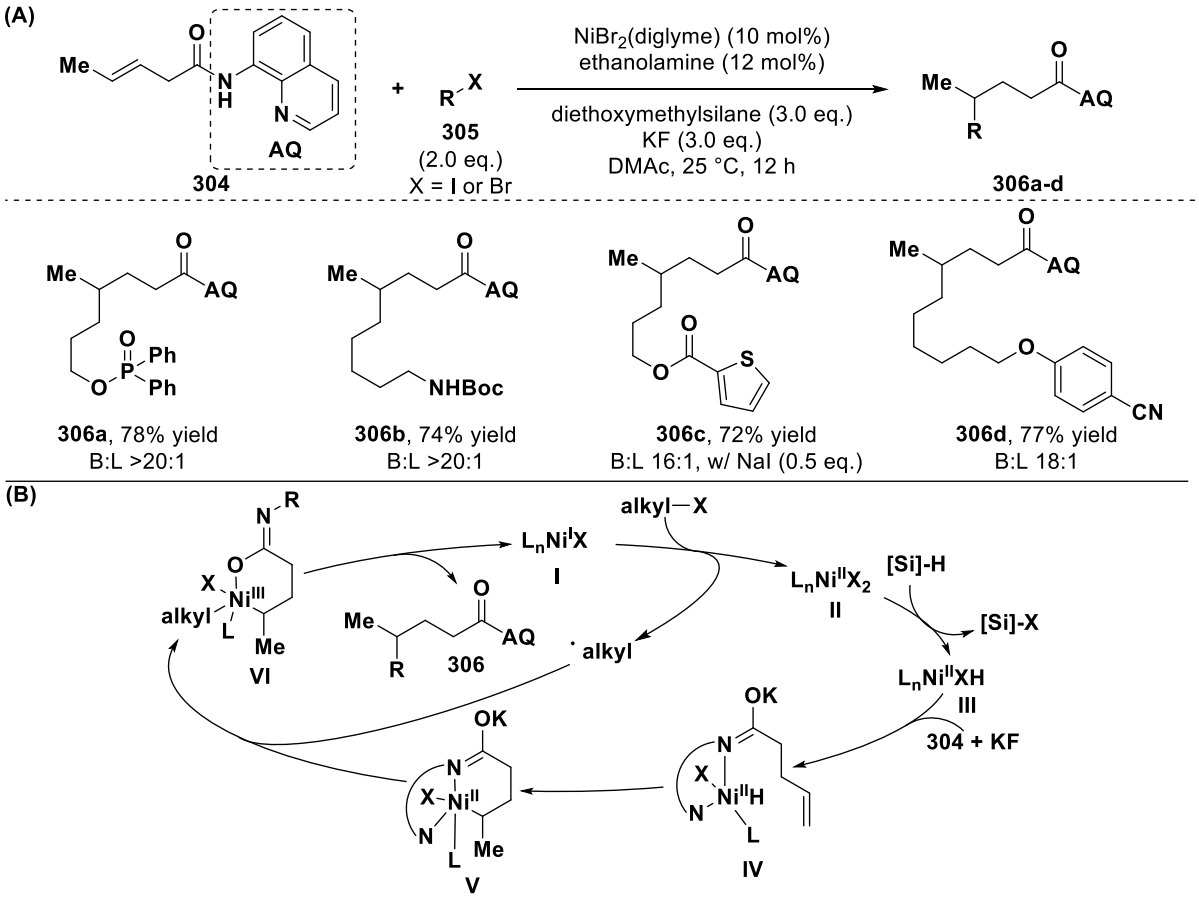
Dong's method involves formation of an enamine to allow subsequent C(sp^2)-H activation. Yu and co-workers disclosed an alternate directing group approach for the C(sp^3)-H alkylation of pyrrolidines and piperidines (**Scheme 66**).[230] Here, a trifluoromethyl *O*-benzyl amidoxime directing group provided α-alkylated pyrrolidines under Ir(I)-catalysed conditions (**Scheme 66A**). Mixtures of branched and linear products were formed using acrylate coupling partners (**303a,** 86% yield, B:L 3:2) while linear products were preferred using styrenic (**303b**, 76% yield) or aliphatic alkenes. Using piperidine substrates, employing alkyl *O*-benzyl amidoximes as directing groups, both aliphatic alkenes (**303c**, 65% yield) and acrylates (**303d**, 50% yield) were tolerated. Again, mixtures of branched and linear products were obtained and poly-alkylation was also observed in some cases. On the basis of deuterium labelling experiments, the authors proposed a mechanism in which the amidoxime group directs oxidative addition of the Ir-catalyst to the proximal C(sp^3)-H bond and C-C bond formation occurs *via* alkene

hydrometallation (**Scheme 66B**). This contrasts to Dong's report in which the Ir-catalyst inserts into a C(sp^2)-H bond and C-C bond formation occurs *via* alkene carbometallation.



Scheme 66: (A*) Ir(I)-catalysed α-alkylation of azacycles by Yu and co-workers [a]with AgOTf (10 mol%) [b]with $HBF_4{\cdot}Et_2O$ (10 mol%); (B) Proposed reaction mechanism.*

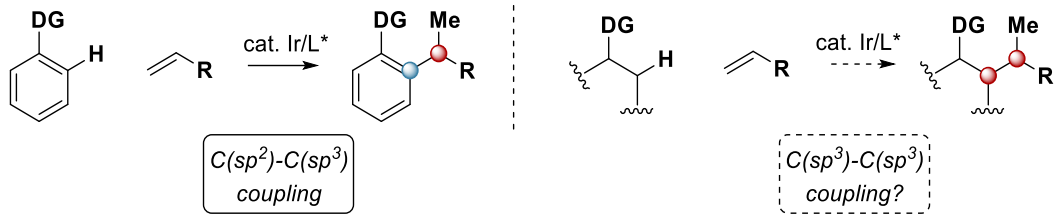
In contrast to strategies that employ directing groups to promote C-H activation, many groups have devised methodologies for the branch selective hydroalkylation of alkenes that utilise *in situ* generated organometallic nucleophiles. While Engle designed a methodology using Pd-catalysis,[231] Ni-catalysis has been utilised by Shenvi,[232] Yang and Koh,[233] and Ouyang and Shu.[234] In a recent report, Lu and Fu showcased an Ni-catalysed hydroalkylation process in which unactivated alkenes were used to provide γ-branched alkyl carboxylic acids and β-, γ- or δ-branched alkyl amines at room temperature (**Scheme 67A**).[235] In this work, Ni(II)X_2 species **II** and an alkyl radical are formed by halide abstraction from an alkyl halide substrate by Ni-species **I** (**Scheme 67B**). This Ni-species undergoes reduction by a silane to afford Ni(II)XH intermediate **III**. Through chelation of an aminoquinoline directing group, alkene hydrometallation occurs (**IV→V**), before alkyl radical capture (**VI**) and reductive elimination affords the desired branched product. The reaction shows good functional group tolerance, as demonstrated by **306b** (74% yield, B:L >20:1) and **306d** (77% yield, B:L 18:1). While powerful, this method is imperfect in terms of step economy due to the use of alkyl halide substrates. Similarly, a silane additive is required for catalytic turnover.



Scheme 67: *(A) Ni-catalysed hydroalkylation by Lu and Fu; (B) Proposed reaction mechanism.*

5.4 Studies towards an enantioselective hydroalkylation methodology

As demonstrated in **Chapter 3**, furan and benzamide substrates can be employed in an enantioselective hydroarylation methodology to give enantioenriched branched products. This process allows for atom-economical C(sp^2)-C(sp^3) bond formation from feedstock chemicals. To advance this technology, we postulated whether we could adapt this hydroarylation strategy to the formation of C(sp^3)-C(sp^3) bonds (**Scheme 68**). Development of an enantioselective hydroalkylation methodology of unactivated alkenes using a metal catalyst would alleviate (a) the need for pre-functionalised alkylating reagents and (b) the generation of toxic stoichiometric waste (*vide infra*).



Scheme 68: *C(sp^2)-C(sp^3) vs C(sp^3)-C(sp^3) coupling strategies.*

Initially, we were drawn to the work of Takeuchi in which β-ketoester substrates were used for the hydroalkylation of aliphatic alkenes (**Scheme 64**, *vide supra*). This reaction manifold was of particular interest as (i) only monoalkylation was observed, and (ii) the process used a bisphosphine ligand. The latter consideration indicated that enantiocontrol could be achieved by use of a chiral ligand. As discussed above, similar transformations have been reported using Fe-, Au-, Ag-, Sn- and Cu-catalysis but are limited to styrenic alkenes. In these cases, enantioselective protocols have remained elusive. To our knowledge, the example by Dong (**Scheme 65**) remains the only intermolecular branch and enantioselective hydroalkylation alpha to a carbonyl group.

Inspired by the work of Takeuchi**,** we were eager to develop a procedure for the enantioselective hydroalkylation of styrenes using ligands developed in the group. Investigations began by identification of a suitable styrene to couple with **307** under Ir(I)-catalysed conditions used by Takeuchi (**Table 31**). Under these conditions, branched product **I** is first formed before Krapcho decarboxylation affords the desired β-branched ketone products. By employing an Ir(I)-catalyst in conjunction with BINAP, it was found that the hydroalkylation of styrene with **307** gave **308a** in 62% yield, albeit with minimal alkene regiocontrol. Using electron-rich 4-methoxystyrene, **308b** was obtained in 7% yield demonstrating the lower reactivity of electron-rich styrenes; however, branch selectivity increased from B:L 1:1 to 6:1 using 4-methoxystyrene compared to styrene. Employing 4-*tert*-butyl-styrene gave **308c** with 2:1 branch selectivity but in 53% yield. As **308a** was produced in the highest yield (62% yield), optimisation efforts turned to screening chiral ligands for the hydroalkylation of styrene with **307** to induce regio- and enantiocontrol.

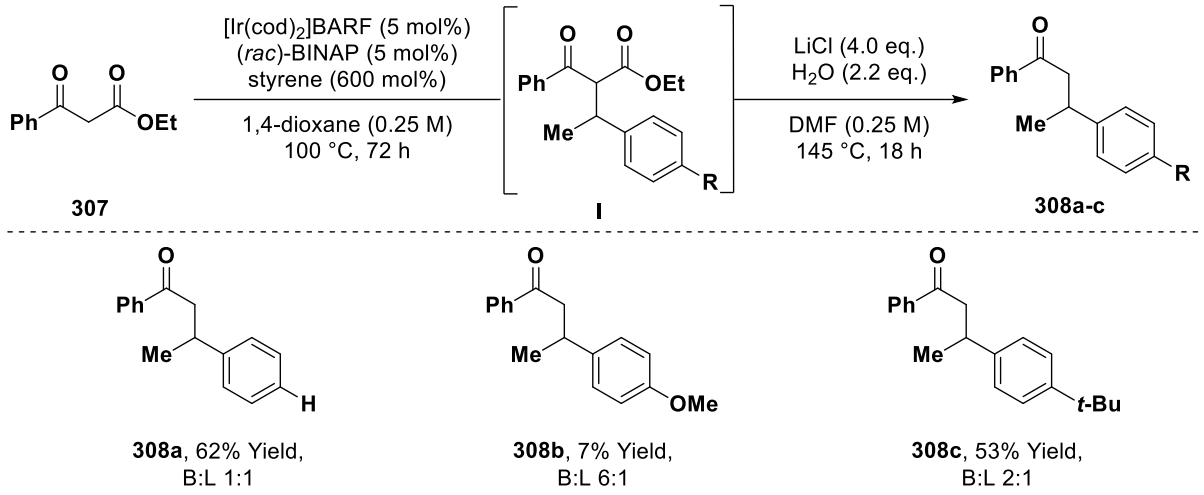


Table 31: *Initial investigations for the hydroalkylation of styrene*

From the outset, we were interested to determine how chiral wide-bite angle, electron-deficient bisphosphonite ligands of type **L50** and bisphosphite ligands **L12**, previously developed in the group, would perform in a hydroalkylation manifold. Accordingly, bisphosphonite ligand **L50**, bearing a pyrenyl substituent at C-4, was tested (**Table 32A**). Ligands of this type have previously been used for the enantioselective hydro(hetero)arylation of heterocyclic and benzamide substrates (**Chapter 3**). Unfortunately, no reactivity was observed and **307** was recovered. Similarly, no yield of **308a** was obtained when chiral bisphosphite ligand **L12** was screened. This ligand has previously been used in enantioselective hydroarylation protocols using acetanilide substrates (**Chapter 1**). From these results it was determined that wide bite angle and electron-deficient ligands were unsuitable for the hydroalkylation procedure.

To gain insight into the electronic and steric requirements, over 20 commercially available chiral bidentate ligands were screened for the hydroalkylation of styrene with **307** (**Table 32B**). Initially, we found that (*R*)-BINAP did not induce any enantiocontrol but did provide **308a** in 77% yield, B:L 1:2 (**Entry 1**). A similar result was obtained using the more electron-rich analogue (*R*)-H_8-BINAP[236], which gave **308a** in 63% yield (B:L 1:2) with minimal enantiocontrol (**Entry 2**). It was found that use of (*R*)-C_3-TunePhos (**Entry 3**) increased reactivity, affording **308a** in 86% yield but in only 2% *e.e.* and with a preference for linear product formation. To investigate the role of steric bulk on the phosphine substituents, **L51** was compared to (*R*)-MeO-BIPHEP (**Entries 4** & **5**). Use of **L51** gave **308a** in 67% yield and 35% *e.e.* whereas (*R*)-MeO-BIPHEP gave **308a** in 14% yield and 2% *e.e.* – suggesting that bulky substituents were beneficial. Screening (*R*)-DM-SEGPHOS (**Entry 6**) saw a drastic increase in reactivity, giving **308a** in 99% yield, but with low enantiocontrol and low branch selectivity. The best outcome for the hydroalkylation process was obtained when screening (*R*)-SDP which afforded **308a** in 83% yield, 46% *e.e.* and B:L 10:1 (**Entry 8**).

With identification of a more suitable ligand remaining elusive, we were interested in how other dicarbonyl substrates would react in this manifold. Specifically, as a possible mechanism follows an enolisation pathway,[224] it was hypothesised that employing substrates with a lower pK_a might increase reactivity. Accordingly, dimethyl malonate **309** (pK_a = 15.9)[237] and 2,2-dimethyl-1,3-dioxane-4,6-dione **310** (Meldrum's acid, pK_a = 7.3)[237] were employed and compared to **307** (pK_a = 14.7).[238] Unfortunately, no reaction was observed when either of these alternative substrates were employed, suggesting that reactivity is not dependent on the substrate pK_a.

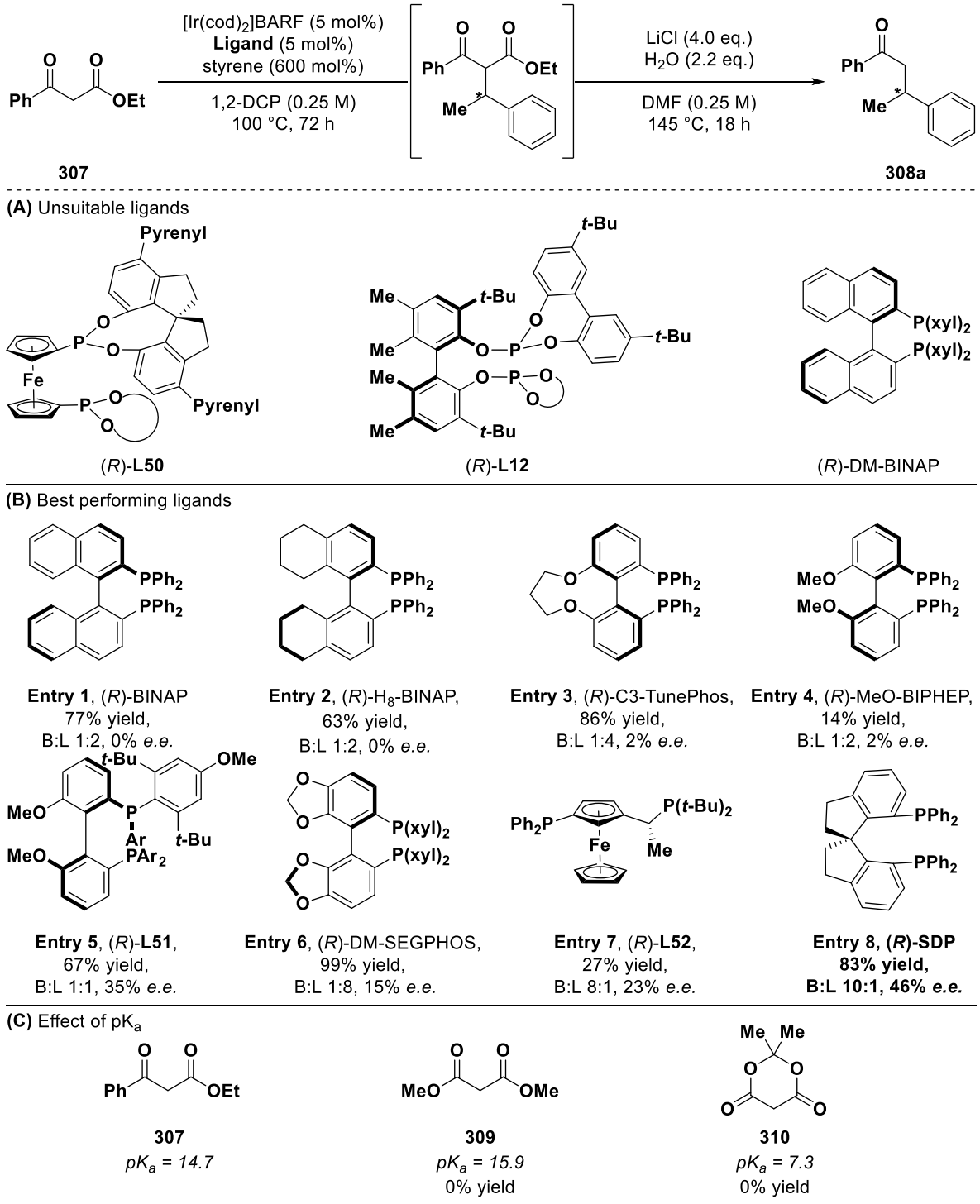


Table 32: *(A/B) Key results for the screening of ligands for the hydroalkylation using β-ketoester **307**; (C) Screening of alternative substrates.*

With a ligand system identified that provided **308a** in high yield and branch selectivity, further optimisation was undertaken by Dr Fenglin Hong to improve enantioselectivity (**Table 33**). It was found that by employing MTBE as the reaction solvent, the branch selectivity of the reaction increased from B:L 10:1 to 15:1, but resulted in a lower yield and *e.e.* of **308a** (**Entry 1**, 80% yield, 38% *e.e.*). Further optimisation efforts were made by exploring different Ir(I) sources and by screening Lewis acidic

additives, however, no improvements in reaction outcome were observed. Accordingly, research was focused towards further ligand optimisation. To address this, a library of ligands based on the structure of (*R*)-SDP was synthesised by Hong with an aim to investigate the use of sterically bulky groups on the phosphorus atoms. As such, (*R*)-SDP-derived ligands **L53** and **L54** were synthesised and trialled in the hydroalkylation process. It was found that higher *e.e.* values were obtained using more sterically bulky ligands. Employing **L54** (**Entry 3**) with sterically-demanding xylyl groups on the phosphorus atoms, provided **308a** in 43% *e.e.* A further increase in *e.e.* was found by lowering the reaction temperature from 100 °C to 70 °C, giving **308a** in 48% *e.e.*

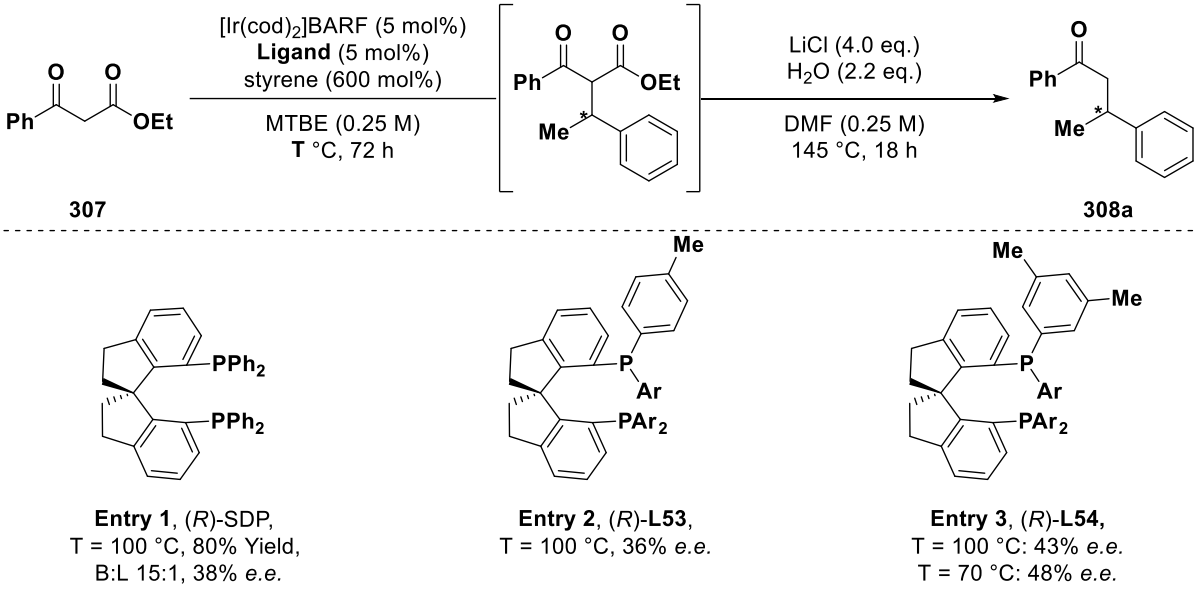


Table 33: *Investigations into (R)-SDP derived ligands conducted by Dr Fenglin Hong.*

As only minimal improvements were made by screening (*R*)-SDP derived ligands, further optimisation focused on alternative alkenes. It has recently been demonstrated that minimally polarised aliphatic alkenes can be successfully coupled with a range of (hetero)aromatic substrates in enantioselective and branch selective processes (**Chapter 3**). The use of these alkenes is notable as they possess no inherent selectivity to form branched products. Hence, Dr Fenglin Hong screened aliphatic alkenes in the hydroalkylation reaction (**Table 34**). Trialling 1-hexene under the reaction conditions gave **311a** in just 10% *e.e.* (**Entry 1**). Unfortunately, no reaction was observed when allyl benzene was employed (**Entry 2**). Ethyl acrylate, a strong conjugate acceptor, was found to be unsuitable, and no reaction occurred (**Entry 3**).

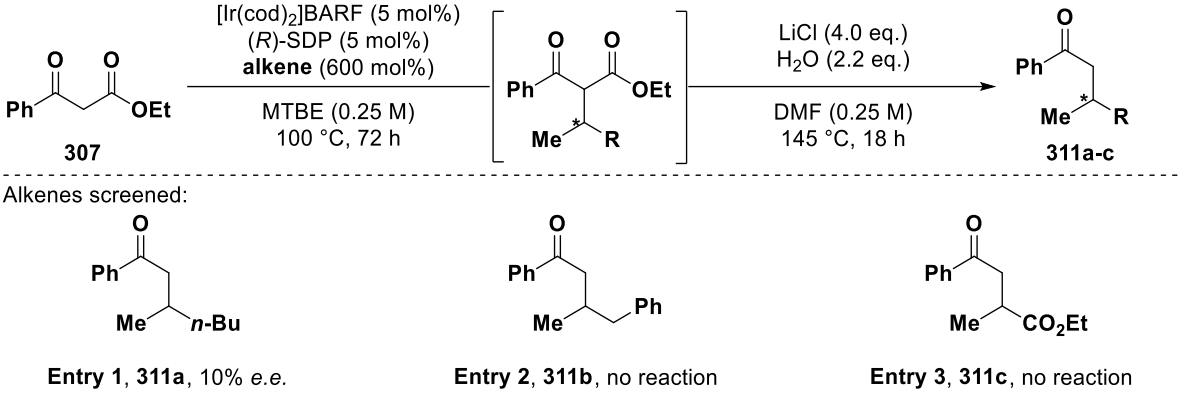


Table 34: *Investigations into alkene scope conducted by Dr Fenglin Hong.*

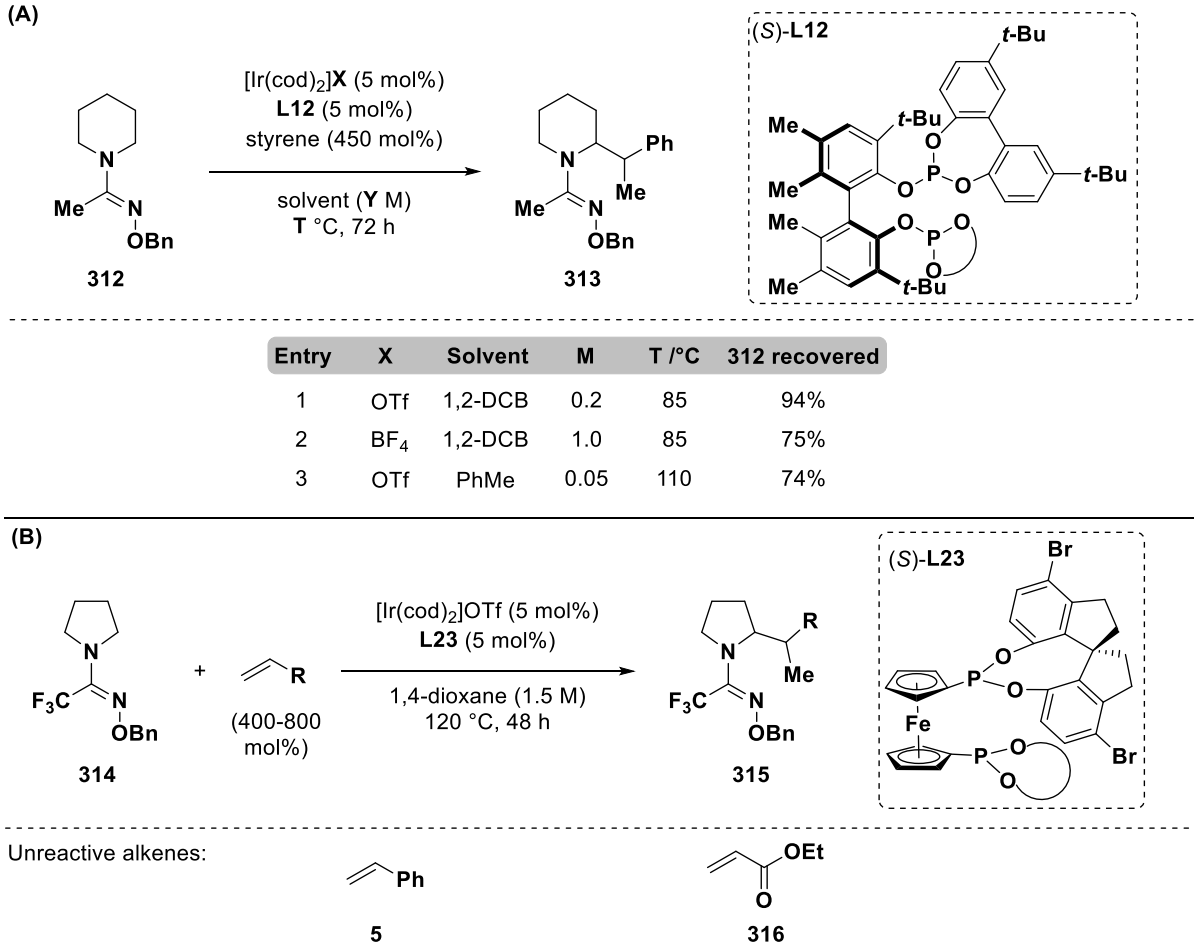
At this point, optimal conditions for the hydroalkylation of styrene with **307** gave **308a** in 83% yield, 46% *e.e.* and B:L 10:1. Multiple efforts had been made to optimise this process further through (i) alteration of the reaction conditions, (ii) synthesis and screening of (*R*)-SDP derived ligands and (iii) employment of other dicarbonyl and alkene substrates. As a result, research into this area ended in favour of more promising projects.

5.5 Investigations into Yu's α-C(sp^3) alkylation of saturated azacycles

As discussed previously (**Scheme 66**), Yu and co-workers disclosed a methodology for the α-C(sp^3) alkylation of saturated azacycles. A variety of styrenic and aliphatic alkenes could be used in addition to acrylates, but mixtures of branched and linear products were often formed. We envisaged we could drive product formation towards the branched product by use of the wide bite angle, electron-deficient chiral bisphosphite ligands of type **L12,** or bisphosphonite ligands of type **L23** used previously for the asymmetric hydro(hetero)arylation of styrenes (**Chapter 3**).

Investigations commenced by screening of bisphosphite ligand **L12** for the hydroalkylation of styrene (**Table 35**). Piperidine **312** was employed as it was shown by Yu to exhibit low propensity towards linear product formation (B:L 3:2). Unfortunately, no reactivity was observed under standard hydroalkylation conditions using [Ir(cod)$_2$]OTf (**Entry 1**) between **312** and styrene. We postulated that the use of HBF$_4$ in Yu's conditions could generate [Ir(cod)$_2$]BF$_4$ *in-situ* which could serve as the active catalyst. Disappointingly, no reactivity was observed when employing [Ir(cod)$_2$]BF$_4$ in the reaction. Likewise, only starting material was observed when **312** was exposed to the Ir(I)-catalysed hydroarylation conditions developed in previously in the group. With no product observed from screening **L12**, we sought to screen bisphosphonite ligand **L23** in this process. This time, pyrrolidine substrate **314** was employed as it was shown to react with styrene under Yu's Ir(I)-catalysed conditions. We envisioned we could force reactivity by employing conditions used for the hydroarylation of styrene using pyrrole substrates (**Chapter 3**, 1,4-dioxane, 1.5 M, 120 °C). Unfortunately, only starting material was recovered when **314** was employed with **L23**. No reaction was observed when a more reactive acrylate coupling partner was employed. From these results it was established that bisphosphite and

bisphosphonite ligands were unsuitable for the α-C(sp^3) alkylation of saturated azacycles. As a result, we focussed efforts towards more promising research areas.



Entry	X	Solvent	M	T /°C	312 recovered
1	OTf	1,2-DCB	0.2	85	94%
2	BF_4	1,2-DCB	1.0	85	75%
3	OTf	PhMe	0.05	110	74%

Table 35: *(A) Evaluation of piperidine **312**; (B) Evaluation of pyrrolidine **314***

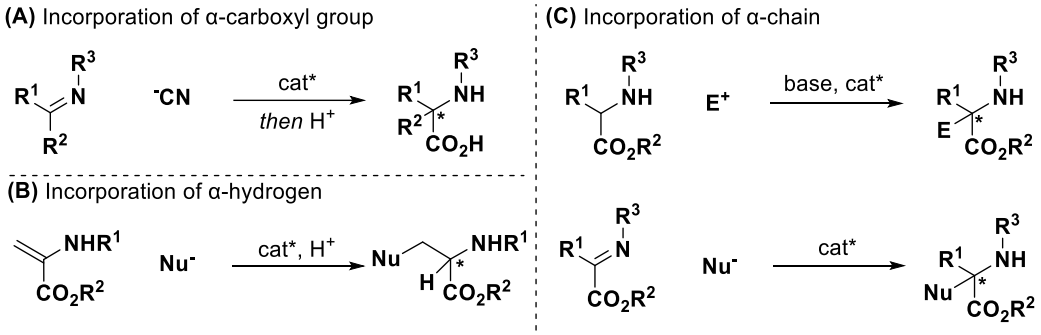
5.6 Development of a hydroalkylation methodology using α-aminoamides

5.6.1 Importance of unnatural amino acids

Non-proteinogenic (unnatural) amino acids have emerged as vital building blocks in synthetic biology and medicinal chemistry. The ability to genetically encode and incorporate unnatural amino acids into proteins beyond the twenty proteinogenic compounds allows expression of those which contain novel side chains including fluorophores, metal ion chelators, photocaged and photocross-linking moieties, uniquely reactive functional groups, and analytical probes.[239–241] Further uses of unnatural amino acid encoded proteins include (but are not limited to) increased enzymatic activity,[242,243] selectivity (therefore minimizing systemic toxicity),[244] and stability.[245] Judicious modifications of the pendant side chain offer solutions to probe protein structure (such as protein folding and conformational transitions) and protein function.[246–248] In medicinal chemistry, amino acids are found in therapeutic natural products such as the antibiotics bacitracin and vancomycin, and in peptides such as insulin. Compared to small molecule drugs, peptide-derived therapeutics possess higher target selectivity and have two-fold higher success rates in drug development programmes.[249] Furthermore, during the current period where intensive research efforts are focused on the "Escape from Flatland",[250] use of protein-derived therapeutics facilitates access to new chemical space and increases compound complexity (as measured by the fraction of C(sp^3) centres in a molecule). As a result of these advantages, peptide-derived therapeutics made up 10% of the pharmaceutical market in 2013 (approx. $40 billion per year);[251] however, current limitations of peptide-derived therapeutics include low bioavailability and metabolic instability. To overcome these, it has been postulated that subtle modifications of amino acid sub-units may optimise membrane permeability without compromising the biologically active peptide conformation.[251,252] As such, methodologies which facilitate the synthesis of enantioenriched unnatural α-amino acids will likely be of paramount importance in the development of novel peptide-based therapeutics.

5.6.2 Catalytic syntheses of enantioenriched unnatural α-amino acid derivatives

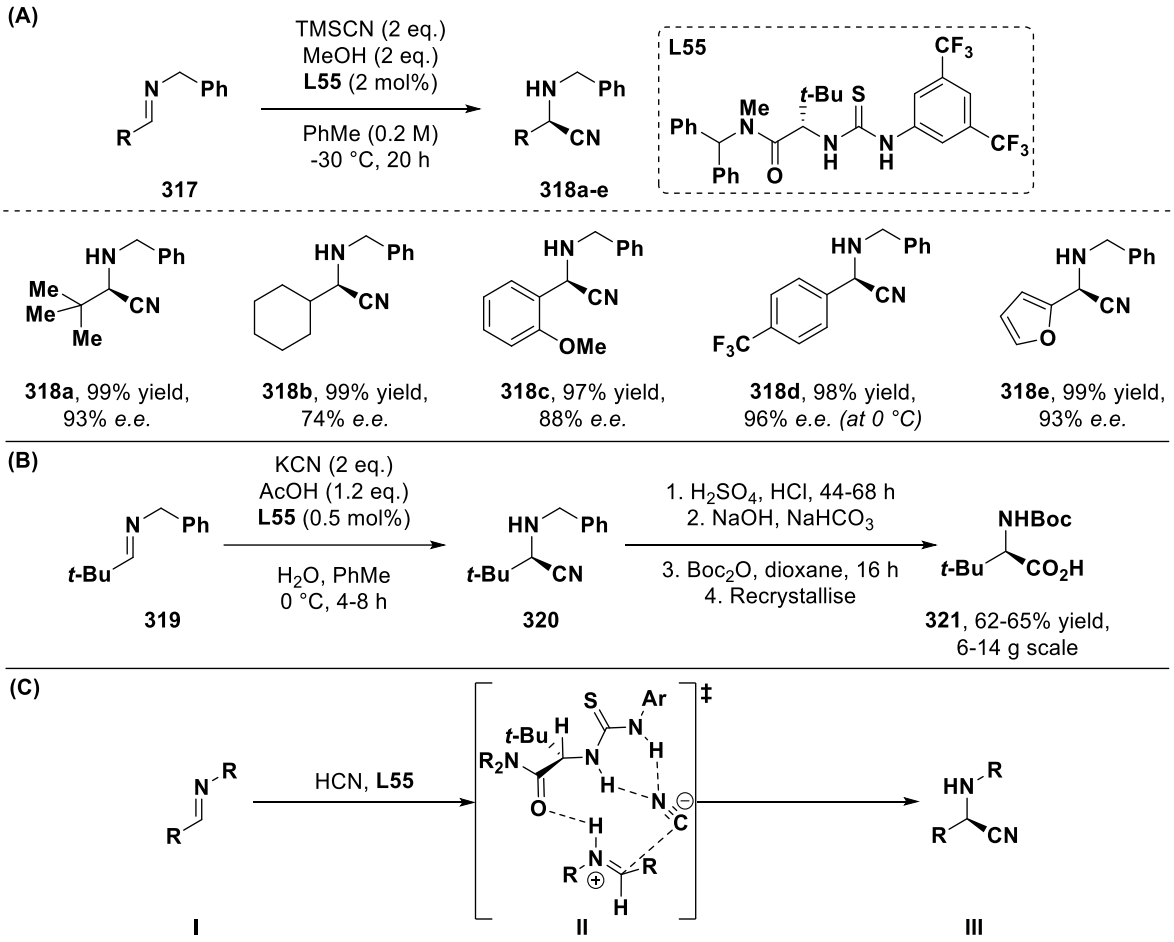
Classically, chiral α-amino acids can be obtained by (a) chemical or enzymatic resolution,[253] (b) isolation from natural sources or (c) employing asymmetric catalysis.[254–256] An example of the latter is demonstrated by asymmetric hydrogenation of a C=C bond in α,β-dehydro-α-amino acids, which allows access to enantioenriched α-amino acids.[254,257–259] To access enantioenriched unnatural α-amino acids, asymmetric methods that employ chiral metal-ligand complexes, or chiral organic molecules (organocatalysis) to unionise a variety of simple achiral fragments offers an appealing atom-economical alternative. To this end, methods are known which allow for the enantioselective incorporation of (i) the carboxyl group (ii) the α-hydrogen and (iii) the α-side chain. Enantioretentive methodologies that couple chiral and achiral fragments have also been reported (**Scheme 69**).[260,261]



Scheme 69: *Selected intermolecular approaches to form enantioenriched α-amino acids.*

5.6.2.1 Enantioselective incorporation of the carboxyl group

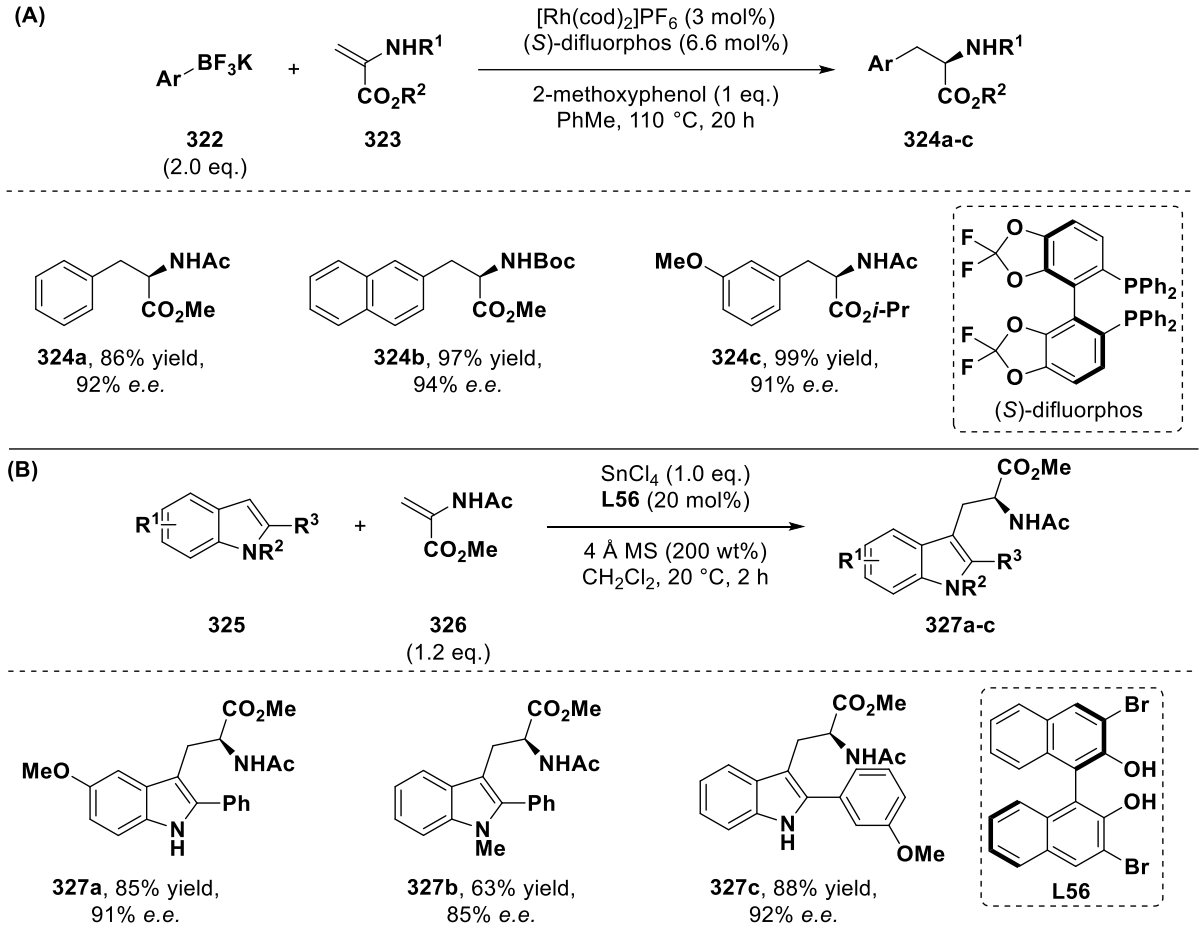
Organocatalytic methods have been used for the synthesis of enantioenriched α-amino acids through incorporation of carboxyl group equivalents. Jacobsen and co-workers disclosed a catalytic enantioselective Strecker synthesis using an amido-thiourea catalyst **L55** (**Scheme 70A**).[262] Under this regime, a variety of imines of type **317** undergo efficient enantioselective hydrocyanation with TMSCN to give enantioenriched α-cyanoamines bearing aliphatic (**318a**, 99% yield, 93% *e.e.*), aromatic (**318c**, 97% yield, 88% *e.e.*) or heteroaromatic (**318e**, 99% yield, 93% *e.e.*) substituents (**Scheme 70B**). To overcome practical and safety issues associated with TMSCN, the authors disclosed an analogous procedure employing KCN as a safer alternative cyanide source and demonstrated its application on multi-gram scale. The resultant α-cyanoamine could be used in a four-step procedure to unveil the α-amino acid moiety as shown by the generation of **321** (62-65% yield 6-14 g scale). From experimental and computational analyses, a mechanism involving initial amide-thiourea induced imine protonation is proposed to occur, through iminium/cyanide ion pair transition state **II** (**Scheme 70C**).[263]



Scheme 70: *(A) Jacobsen's catalytic Strecker synthesis; (B) Multi-gram scale synthesis of α-amino acid **321**; (C) Proposed reaction mechanism.*

5.6.2.2 Enantioselective incorporation of the α-hydrogen

Enantioselective metal-catalysed C(sp^2)-H hydroarylation methodologies can be utilised for the incorporation of the α-hydrogen. The group of Darses disclosed a Rh-catalysed hydroarylation procedure that coupled aryl trifluoroborate salts **322** with aminoacrylates **323** to furnish a range of protected α-amino acids (**Scheme 71A**).[264] $[Rh(cod)_2]PF_6$ and (*S*)-difluorphos were used in conjunction with 2-methoxyphenol as the chosen proton source to deliver protected chiral phenylalanine compounds such as **324a** (86% yield, 92% *e.e.*) and **324b** (97% yield, 94% *e.e.*) in high yield and enantiopurity. Similarly, Reisman and co-workers reported Sn-catalysed hydroheteroarylations of methyl 2-acetamidoacrylate **326** – this approach harnesses the innate nucleophilicity of indole substrates **325** in a Friedel-Crafts-like reaction (**Scheme 71B**).[265] The combination of $SnCl_4$, and (*S*)-BINOL derived ligand **L56** provided access to a range of tryptophan analogues, such as **327a** (85% yield, 91% *e.e.*) and **327b** (63% yield, 85% *e.e.*). In both reports, subsequent cleavage of protecting groups afforded the corresponding unnatural enantioenriched α-amino acids.

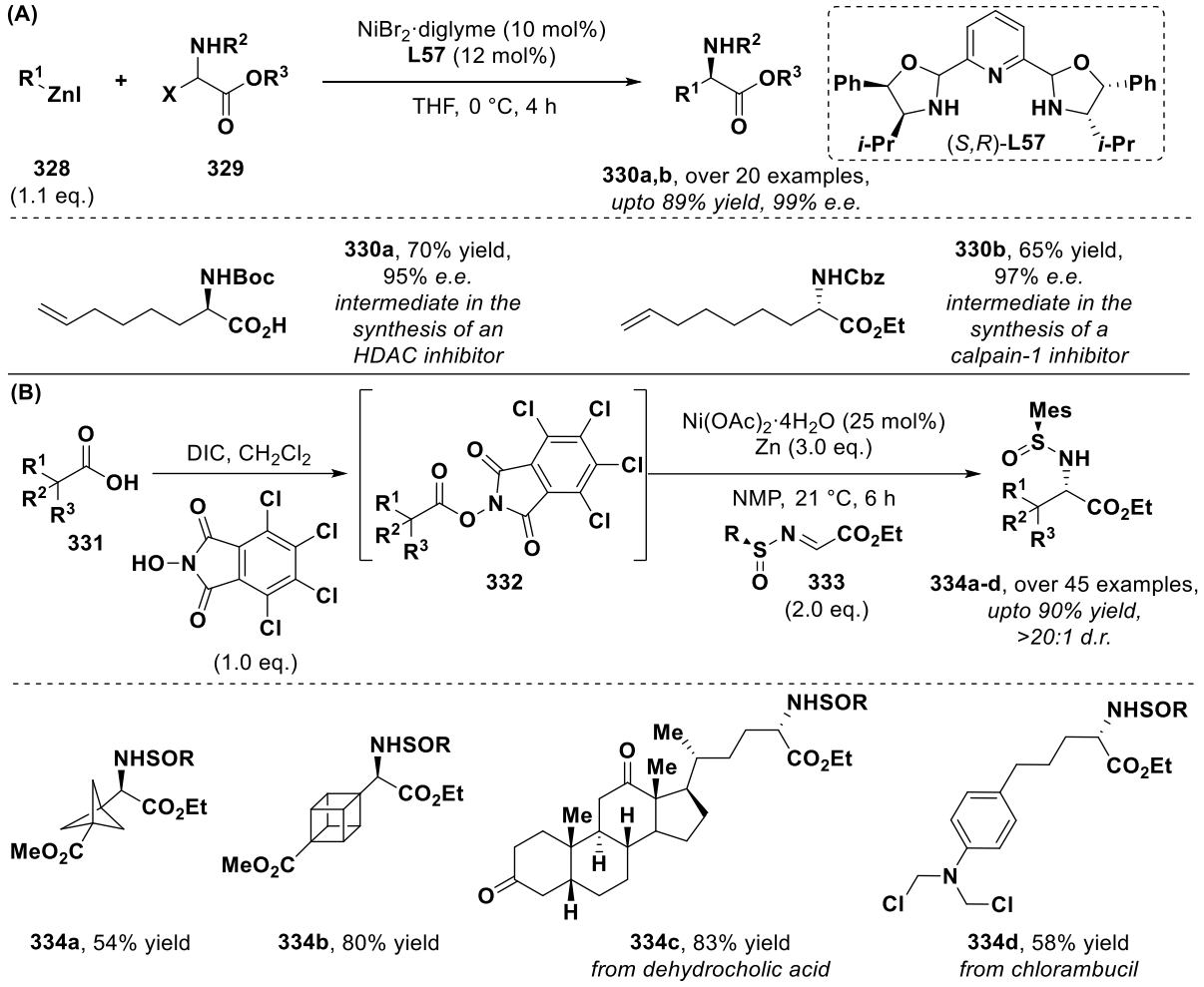


Scheme 71: *(A) Darses' Rh-catalysed hydroarylation using aryl trifluoroborate salts; (B) Reisman's hydroheteroarylation of methyl 2-acetamidoacrylate **326**.*

5.6.2.3 Enantioselective incorporation of the α-side chain

Metal-catalysed methods of incorporating the α-side chain to access α-amino acids that harness the reactivity of radical species are known. In 2021, Fu *et al.* disclosed a Ni-catalysed procedure for the enantioconvergent cross-coupling of organozinc reagents **328** with racemic α-haloglycine derivatives **329** (**Scheme 72A**).[266] This work enabled access to a variety of biologically relevant protected α-amino acids under mild conditions, such as **330a** (70% yield, 95% *e.e.*), which is an intermediate in the synthesis of a histone deacetylase (HDAC) inhibitor. Similarly, Boc-protected α-amino acid **330b,** which serves as an intermediate in the synthesis of a calpain-1-inhibitor, was obtained in 65% yield and 97% *e.e.* Using a similar strategy, the Baran group reported a radical cross-coupling between a glyoxylate-derived sulfinimine **333** and redox active ester **332** derived from alkyl acids **331** and *N*-hydroxytetrachlorophthalimide (**Scheme 72B**).[267] Primary, secondary and tertiary carboxylic acids could be employed and notably, α-amino acid products bearing phenyl bioisoteres such as [1.1.1]propellane (**334a,** 54% yield) and cubane (**334b,** 80% yield) could also be accessed. The broad functional group tolerance was exhibited by employment of complex natural products and drug

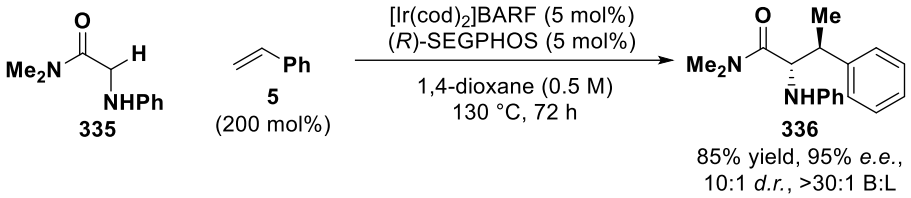
molecules such as **334c** (83% yield from dehydrocholic acid) and **334d** (58% yield from chlorambucil). In both of these Ni-catalysed methodologies, it is proposed that the mechanisms involve radical species.



Scheme 72: *(A) Fu's enantioconvergent coupling using organozinc reagents; (B) Baran's coupling between sulfinimines and redox-active ester **332***

5.7 Development of an enantioselective hydroalkylation methodology using α-aminoamides

As described in **Section 5.4**, a suitable substrate for a branch selective and enantioselective hydroalkylation of unactivated alkenes was not identified. At this point, various 1,3-dicarbonyl compounds, in addition to piperidine and pyrrolidine-derived substrates had been extensively investigated. As such, further research into substrate identification was undertaken with Dr Fenglin Hong. Remarkably, it was found using [Ir(cod)$_2$]BARF in conjunction with commercial (*R*)-SEGPHOS, styrenes react cleanly with α-aminoamides to afford the corresponding products in high yield and branch selectivity. Additionally, high levels of enantio- and diastereocontrol are also achieved. This was first demonstrated using styrene with α-aminoamide **335** to generate **336** (**Scheme 73**, 85% yield, 95% *e.e.*, 10:1 d.r., B:L >30:1).



Scheme 73: *Ir(I)-catalysed enantioselective hydroalkylation of styrene with **335** conducted by Dr Fenglin Hong.*

From here, investigations into the styrene scope ensued in collaboration with Hong (**Table 36**). A plethora of styrenic alkenes were tolerated in the methodology as shown by the use of electron-deficient (**337f**, 74% yield, 97% *e.e.*, d.r = 2:1) or electron-rich styrenes (**337g**, 60% yield, 95% *e.e.*, d.r. = 9:1). Notably, only the branched product was observed in all cases (B:L >25:1). The amide moiety of the substrate could be altered as shown by *N*-methylated **337j** (54% yield, 92% *e.e.*, d.r. = 7:1) morpholine derived **337k** (68% yield, 96% *e.e.*, d.r. = 5:1). Variation of the phenyl group on the amine component was also tolerated, as shown by **337l** (87% yield, 96% *e.e.*, d.r. = 6:1) and **337m** (75% yield, 96% *e.e.*, d.r. = 10:1). Relative stereochemistry of the products was determined by comparsion of ^{1}H NMR spectroscopy spectra with known compounds, while absolute stereochemistry was unambiguously determined by X-ray crystallography (*vide infra*). An appealing facet of this methodology is the formation of two contiguous C(sp^3) stereocentres which are generated from racemic starting materials. To our knowledge, this is the first methodology featuring an intermolecular synthesis of such motifs from simple precursors (**335** is synthesised in one step from commercial materials) and is therefore of significant value to the synthetic community.

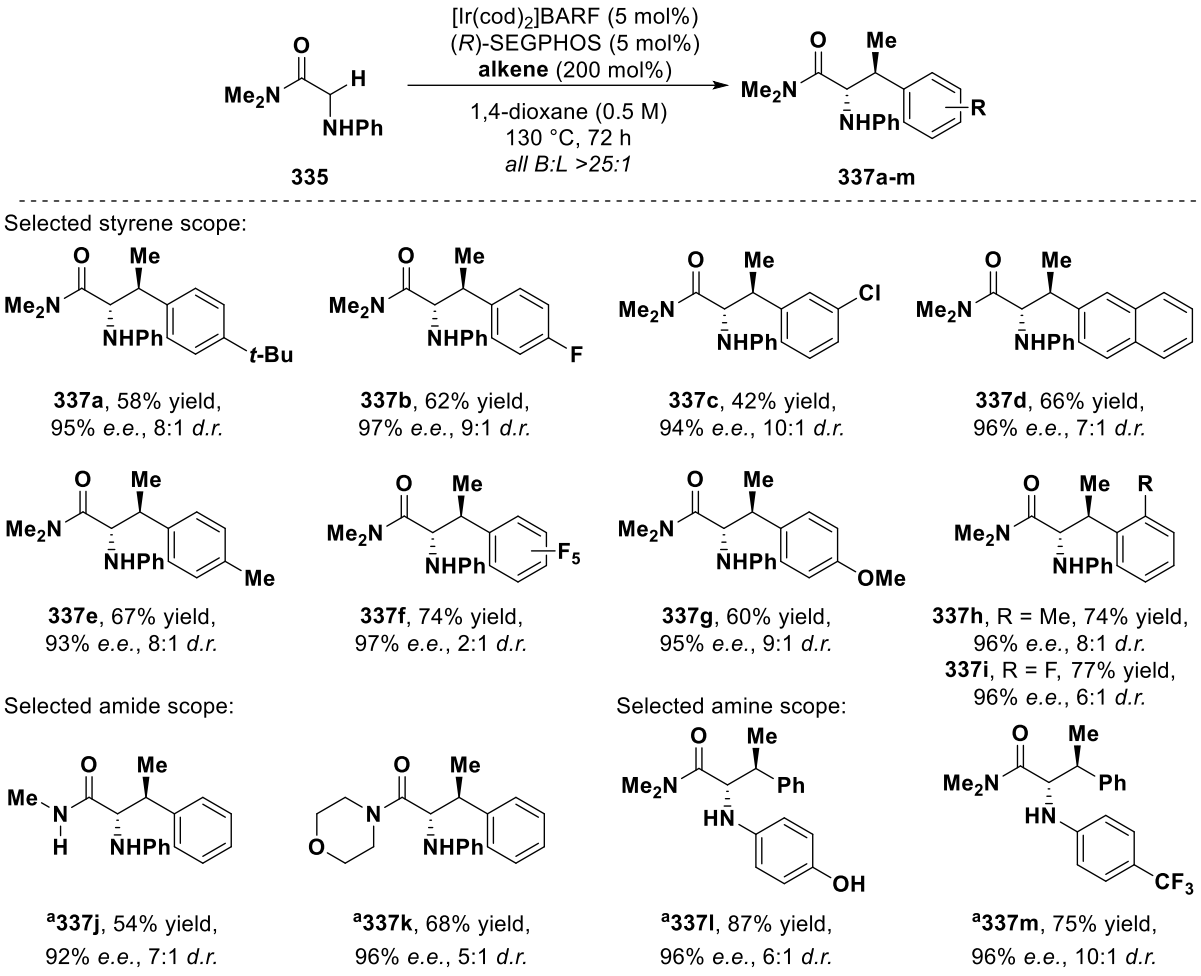
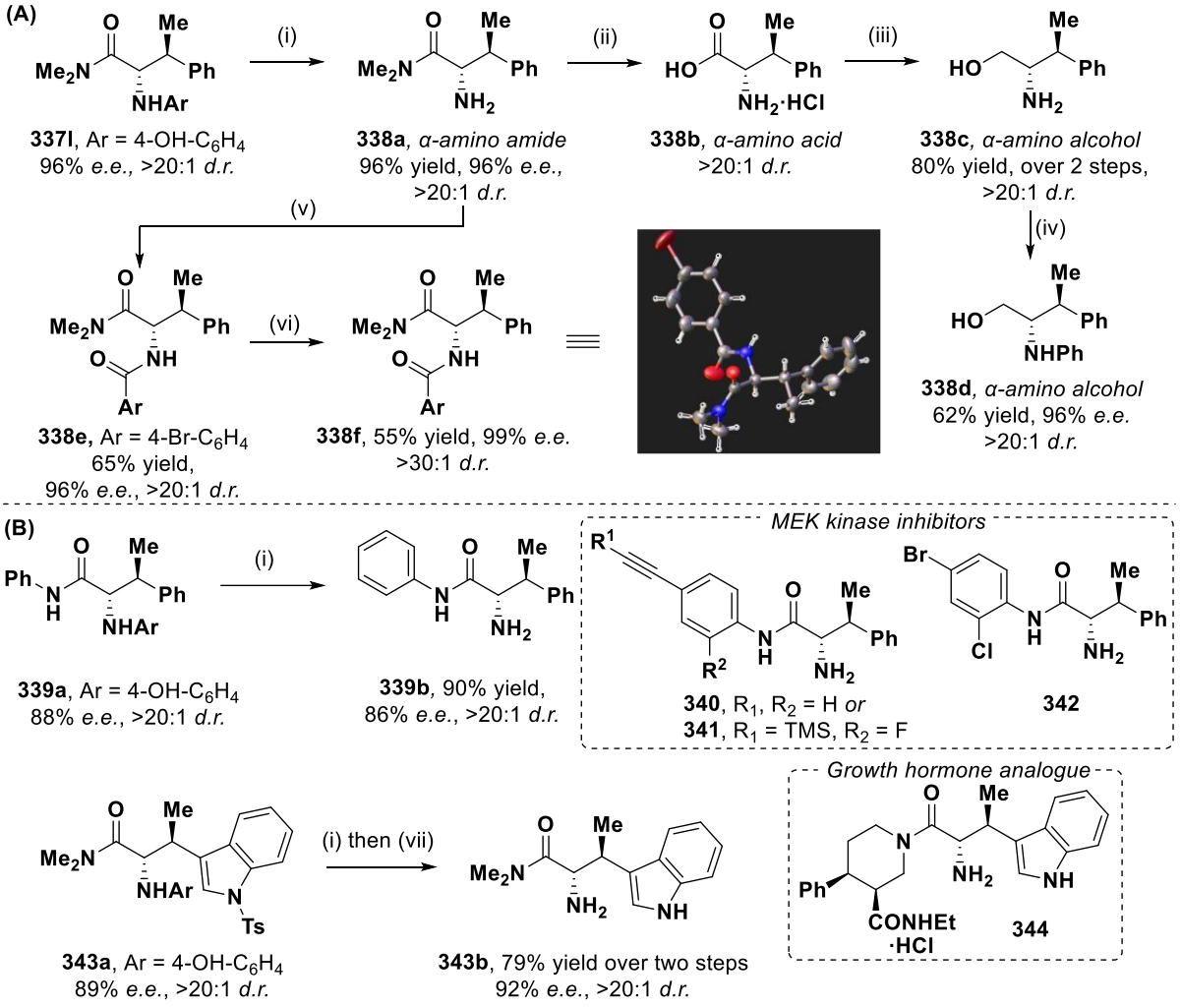


Table 36: *Representative scope of the enantioselective hydroalkylation of α-aminoamides; [a]Reactions conducted by Dr Fenglin Hong*

Importantly, the products formed are amenable to further functionalisation to afford a range of α-amino analogues (**Scheme 74A**). Starting with catalysis product **337l**, reaction with (bis(trifluoroacetoxy)iodo)benzene (PIFA) generated α-amino amide **338a** in 96% yield and 96% *e.e.* Further reaction with HCl/AcOH gave α-amino acid **338b** before reduction with $LiAlH_4$ afforded α-amino alcohol **338c** in 80% yield over two steps. Notably, the high diastereopurity remained intact throughout this sequence. Retention of enantiopurity was determined by protection of the amine in **338c** by reaction with iodobenzene, which gave **338d** in 62% yield and 96% *e.e.*. To investigate the absolute stereochemistry of the products, **338e** was synthesised from **338a** using 4-bromobenzoyl chloride in 65% yield and 96% *e.e.*, which was increased subsequently to 99% *e.e.* by recrystallisation. The absolute stereochemistry was determined unambiguously by X-ray crystallography. The application of the catalysis products was further demonstrated by synthesis of **339b** which was obtained from reaction of **339a** with PIFA in 90% yield and 86% *e.e.* **339b** features a common motif found in MEK kinase inhibitors such as **340**–**342** (**Scheme 74B**). Similarly, a sub-unit of the growth hormone analogue **344**

was accessed by deprotection of indole-derived **343a** to give **343b** in 79% yield and 92% *e.e.* over two steps.

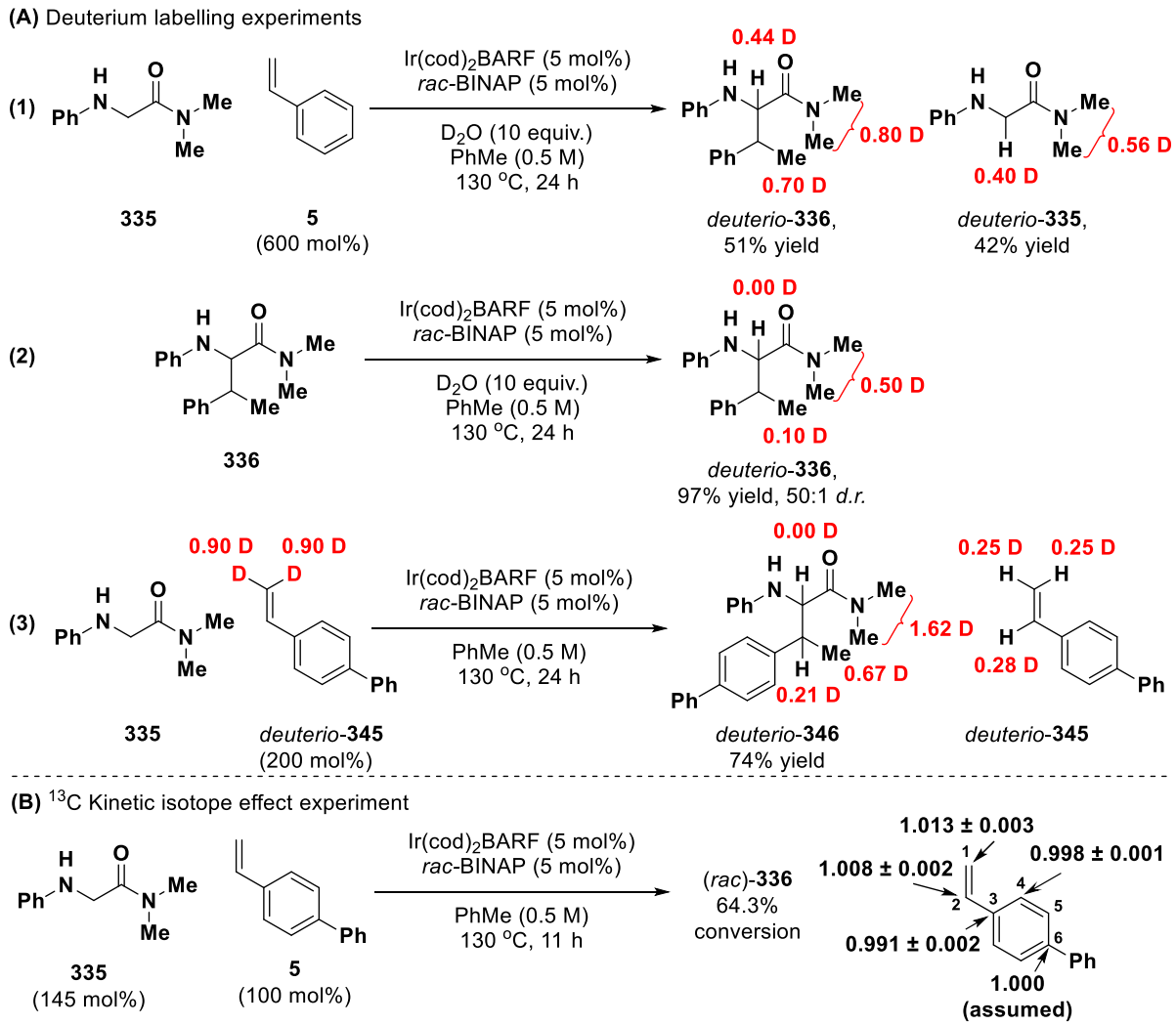


Scheme 74: *(A) Derivatisation of products and crystal structure obtained by X-ray crystallography; (B) Access to MEK kinase inhibitors **340** and **341**, and growth hormone analogue precursor **342**. Reaction conditions: (i) PIFA (120 mol%), MeCN/H₂O, 0 °C, 1 h. (ii) HCl/AcOH, 130 °C, 48 h. (iii) LiAlH₄ (220 mol%), THF, 70 °C, 11 h. (iv) iodobenzene (120 mol%), NaOH (200 mol%), CuI (5 mol%), DMSO/H₂O, 90 °C, 12 h. (v) 4-bromobenzoyl chloride (100 mol%), Et₃N (200 mol%), DCM, 0 °C–r.t., 12 h. (vi) recrystallisation (vii) NaH (200 mol%), DMA, 60 °C, 3 h. PIFA = (Bis(trifluoroacetoxy)iodo)benzene); Reactions conducted by Dr Fenglin Hong.*

5.8 Studies into the mechanism

Following the successful development of an enantioselective hydroalkylation reaction, Dr Fenglin Hong undertook a series of deuterium-labelling experiments to probe a possible reaction mechanism (**Scheme 75A**). As such, **335** was coupled with styrene under standard Ir(I) conditions in the presence of an excess of D_2O (**Reaction 1**). This led to the formation of *deuterio*-**336** in 51% yield with deuterium incorporation at the α-position of the amine (by epimerisation, 0.44 D) as well at the homobenzylic methyl group (0.70 D) and the *N*-methyl groups of the amide (0.80 D). The latter of these suggests the amide carbonyl group can direct insertion of the Ir-species into the proximal *N*-methyl groups to form a 5-membered metallacycle. When catalysis product **336** was subjected to the same conditions,

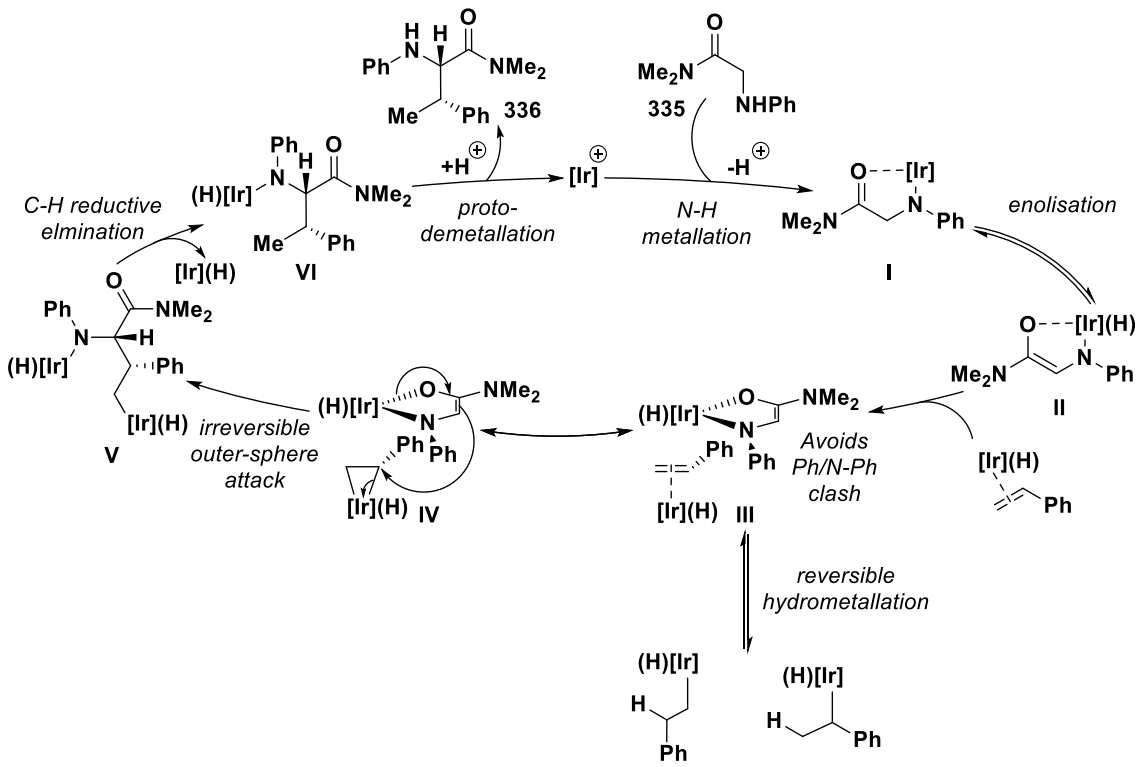
deuterium incorporation was found again at the homobenzylic methyl group (0.10 D), suggesting formation of a 6-membered metallacycle, and amine methyl groups (0.50 D), but no incorporation occurred at the α-position to the amine (0.00 D), presumably limited by increased steric bulk caused by the newly added alkyl group (**Reaction 2**). Further investigations took place using deuterated styrene derivative *deuterio*-**345**. Reaction of *deuterio*-**345** with **335** under Ir(I) conditions formed *deuterio*-**346** in 74% yield (**Reaction 3**). As in the previous experiment, this was determined to have deuterium incorporation at the *N*-methyl groups of the amide (1.62 D) and at the homobenzylic methyl group (0.67 D), but now with additional incorporation at the benzylic position (0.21 D). In this experiment, no deuterium incorporation occurred at the α-position of the amine. Exposure of *deuterio*-**345** to optimised reaction conditions resulted also in scrambling of the deuterium labels in recovered *deuterio*-**345**. Natural abundance ^{13}C kinetic isotope effect (KIE) studies have been used to distinguish which carbon atoms feature in the first irreversible step.[268,269] Accordingly, reaction of **335** with **5** was run to partial conversion (64.3%) and the signals of interest in the ^{13}C spectra of recovered **5** were integrated against internal standard C-6. It was found that significant KIEs were measured at both C-1 (1.013) and C-2 (1.008) with negligible KIEs at all other positions. Kinetic analysis of the reaction revealed second-order kinetics with respect to the Ir-catalyst.[270]



Scheme 75: (A) *Deuterium labelling experiments; (B) ^{13}C KIE studies; Results obtained by Fenglin Hong.*

On the basis of the experiments described above, it is proposed that the mechanism proceeds firstly with N-H metallation of the Ir catalyst forming **I** (**Scheme 76**). This process can be directed and/or stabilised by the amide carbonyl group. Directing group-induced enolisation generates stable 5-membered chelated *cis*-Ir-enolate **II**. It is envisaged that the stability of structure **II** controls the geometry of the formed enolate which, in turn, could control the diastereoselective outcome. From the results in **Reaction 3** (**Scheme 75A**), it is plausible that a non-productive and non-branch selective reversible hydrometallation pathway can occur which results in the scrambling of deuterium labels in *deuterio*-**345**. Natural abundance ^{13}C KIE studies (**Scheme 75B**) indicate that both carbon atoms of the alkene are involved in the first irreversible step of the mechanism. Additionally, kinetic data revealed second order kinetics with respect to the Ir-catalyst. Hence, the reaction may proceed by irreversible outer-sphere attack onto an Ir-alkene-species to form **V**. It is postulated that this step controls the enantioselectivity. Subsequent C-H reductive elimination (**V**→**VI**) and protodemetallation furnishes the branched product. From Reaction 2 (**Scheme 75A**), minimal erosion of diastereoselectivity can be

attributed to the absense of deuterium incorporation at the α-amine position (0.00 D), presumably the newly added alkyl group hinders addition of an Ir-centre, preventing epimerisation.

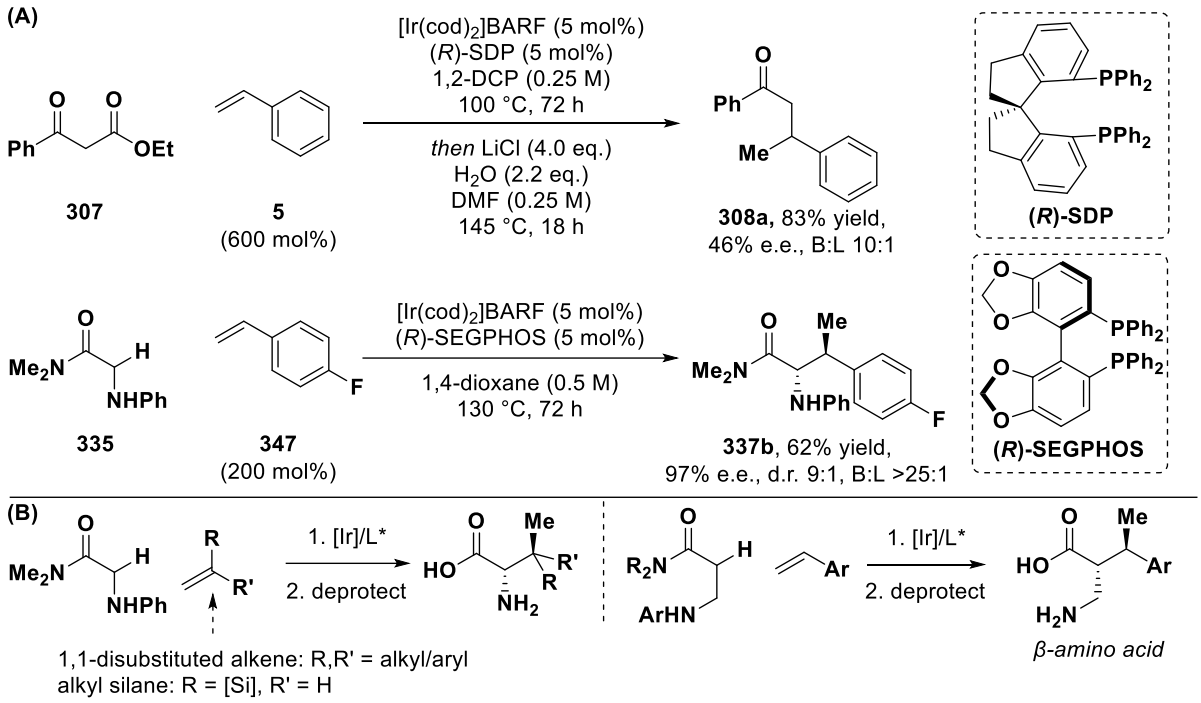


Scheme 76: *Proposed mechanism for the enantioselective hydroalkylation of α-aminoacids*

5.9 Summary and conclusions

Section 5.4 described investigations into an enantioselective hydroalkylation reaction using 1,3-dicarbonyl compounds. After extensive screening of reaction conditions and chiral bisphosphine ligands, our best result gave access to β-branched ketone **308a** in 83% yield and 46% *e.e.*, and with high branch selectivity (**Scheme 77A**). It is anticipated that synthesis and screening of novel chiral ligands would further increase enantiocontrol while maintaining high levels of yield and alkene regiocontrol obtained. A significant, related process is described in **Section 5.7** for the enantioselective hydroalkylation using α-aminoamides of type **337**. This work was conducted in collaboration with Dr Fenglin Hong. Remarkably, this tolerates of a wide variety of styrenes to form branched products with excellent control over absolute and relative stereochemistry. Further investigation demonstrated the catalysis products could be further derivatised into various α-amino analogues (such as α-amino acids) as well as other pharmaceutically-active motifs. Through deuterium-labelling, natural abundance ^{13}C KIE and kinetic experiments, the mechanism was proposed to proceed by an irreversible outer-sphere attack of a *cis*-Ir-enolate onto the Ir-bound alkene. To extend this methodology, unactivated aliphatic alkenes such as silyl alkenes should be trialled, considering the importance and varied uses of unnatural silicon-containing amino acids (**Scheme 77B**).[271] Moreover, greater product complexity could be

achieved by use of 1,1-disubstituted alkenes in this process, which would give access to enantioenriched products bearing contiguous tertiary-quaternary C(sp^3) stereocentres**.** Use of alternative aminoamide structures, such as β-aminoamides should be screened in this process to provide access to enantioenriched β-amino acids (**Scheme 77B**).[272]



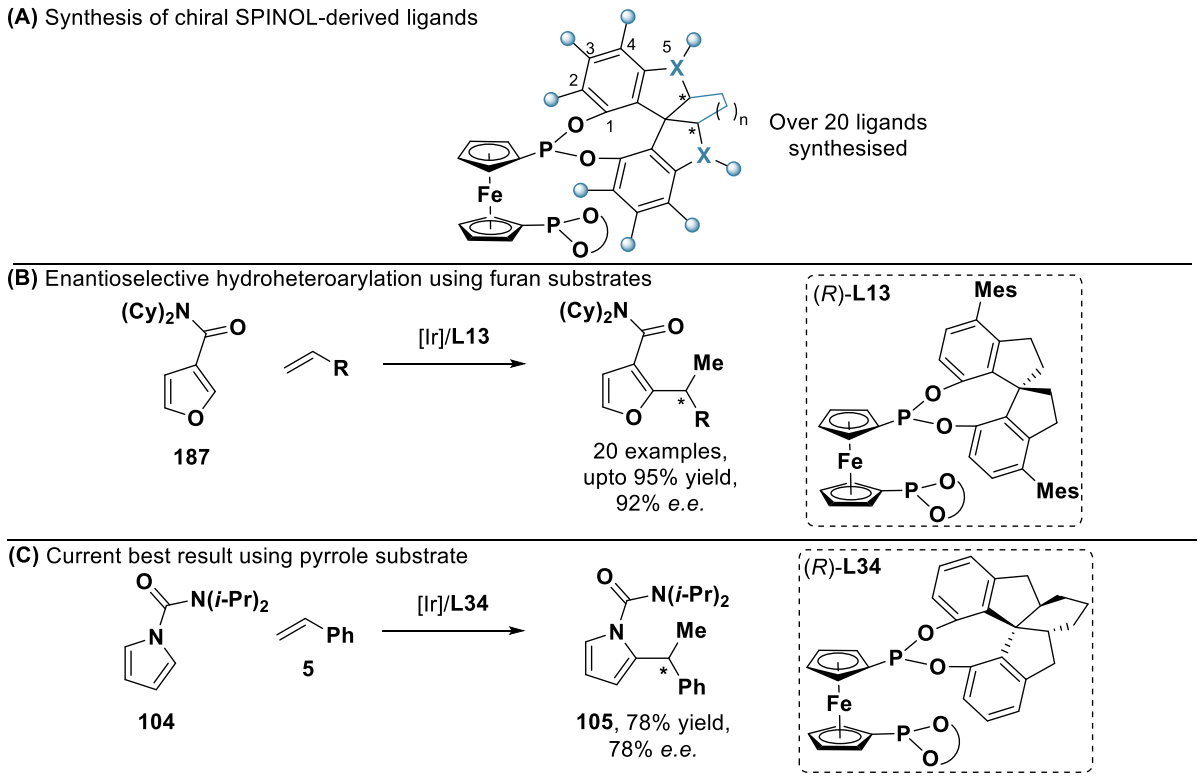
Scheme 77: *(A) Summary of developed Ir(I) hydroalkylation processes; (B) Proposed future research avenues.*

Chapter 6

Overall Summary and Conclusions

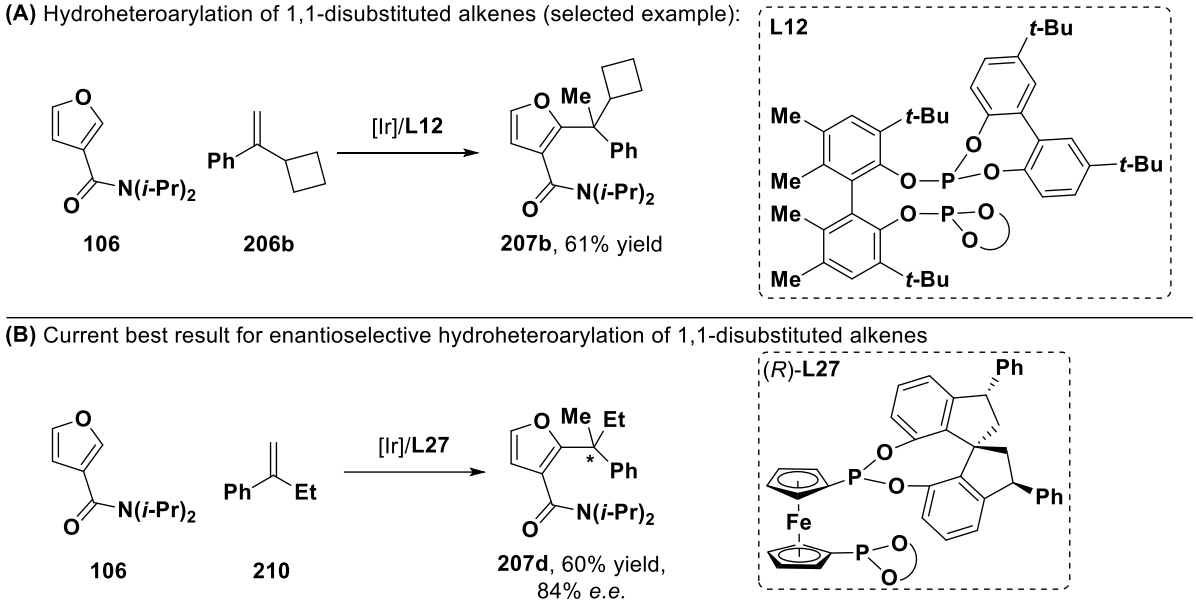
Chapter 6 – Overall Summary and Conclusions

The research in this Thesis has contributed to the development of multiple Ir(I)-catalysed hydrofunctionalisation transformations. **Chapter 2** described the synthesis of a comprehensive library of chiral bisphosphonite and bisphosphite ligands, in collaboration with Dr Andrew Dalling and Dr Raymond Chung, and was based on a previous scaffold developed in the group (**Scheme 78A**). These ligands were employed for the optimisation of enantioselective hydroheteroarylation reactions using furan and pyrrole substrates, as described in **Chapter 3**. Although only minor improvements were made, supporting computational studies gave insight into desired structural features of future ligand targets. Instead of a ligand design approach, an asymmetric methodology using furan substrates was optimised through judicious modification of the directing group (**Scheme 78B**). This process employs [Ir(cod)$_2$]BARF with **L13**, and exhibits broad substrate scope for a wide variety of styrenes and aliphatic alkenes. The products were obtained in high: (i) yield, (ii) site-selectivity, (iii) branch-selectivity and (iv) enantioselectivity. Further utility of this reaction was demonstrated by the use of an α-chiral alkene to deliver a product bearing contiguous 1,2-stereocentres in a catalyst-controlled diastereoselective process. Application of this methodology to pyrrole substrates is ongoing; currently, pyrrole **105** can be obtained in 78% yield and 78% *e.e.* using **L34** (**Scheme 78C**).



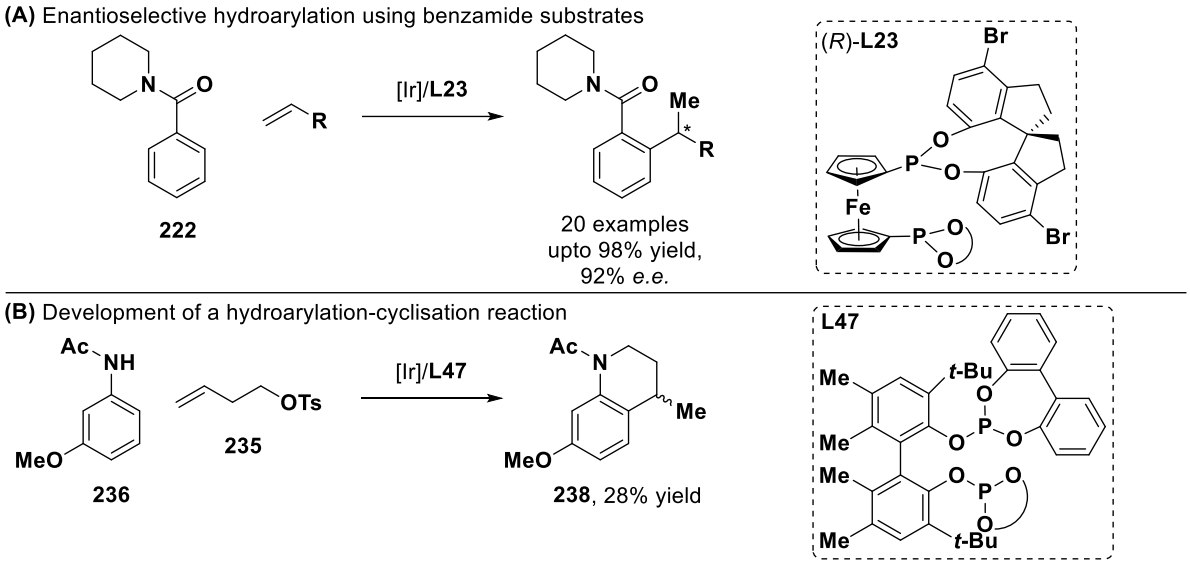
Scheme 78: *Summary of (A) ligand synthesis and (B) asymmetric hydroheteroarylation using furan substrates; (C) Current best result using a pyrrole substrate*

To advance this further, a methodology for the hydro(hetero)arylation of 1,1-disubstituted alkenes was developed in collaboration with Dr Phillippa Cooper and Dr Andrew Dalling to install challenging quaternary stereocentres (**Chapter 3**). Accordingly, **L12** was used in conjunction with $[Ir(cod)_2]BARF$ to afford branched quaternary furan-derived products such as **207b** (**Scheme 79A**). This adds to previous work in the group which employed benzamide, pyrrole and thiophene substrates. Through screening newly synthesised chiral bisphosphonite and bisphosphite ligands, an asymmetric analogue of this reaction was developed; so far, **207d** can be obtained in 60% yield, 84% *e.e.* using **L27** (**Scheme 79B**). Further optimisation of this process is currently ongoing.



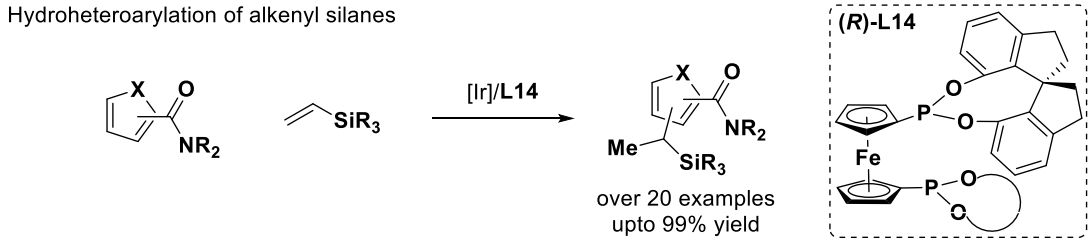
Scheme 79: *(A) Summary of hydroheteroarylation using 1,1-disubstituted alkenes; (B) Current best result for enantioselective analogue*

Subsequently, a variety of directing groups were trialled in the hydroarylation of styrene to augment the substrate scope (**Chapter 3**). From this, an asymmetric hydroarylation using benzamides was developed by Dr Raymond Chung to deliver C-2 alkylated branched products in excellent yield and with high enantiocontrol. Pleasingly, both styrenic and aliphatic alkenes could be employed with C-3 or C-4 functionalised benzamide substrates (**Scheme 80A**). Elaboration of the catalysis products by either reduction or substitution demonstrated the directing group's utility. **Chapter 3** also described efforts to develop a hydroarylation-cyclisation reaction using acetanilides (**Scheme 80B**). Further work on this project should investigate the use of different directing groups and leaving groups, or the effect of different ligands upon the system.



Scheme 80: *(A) Summary of enantioselective hydroarylation using benzamide substrates; (B) Summary of hydroarylation-cyclisation reaction.*

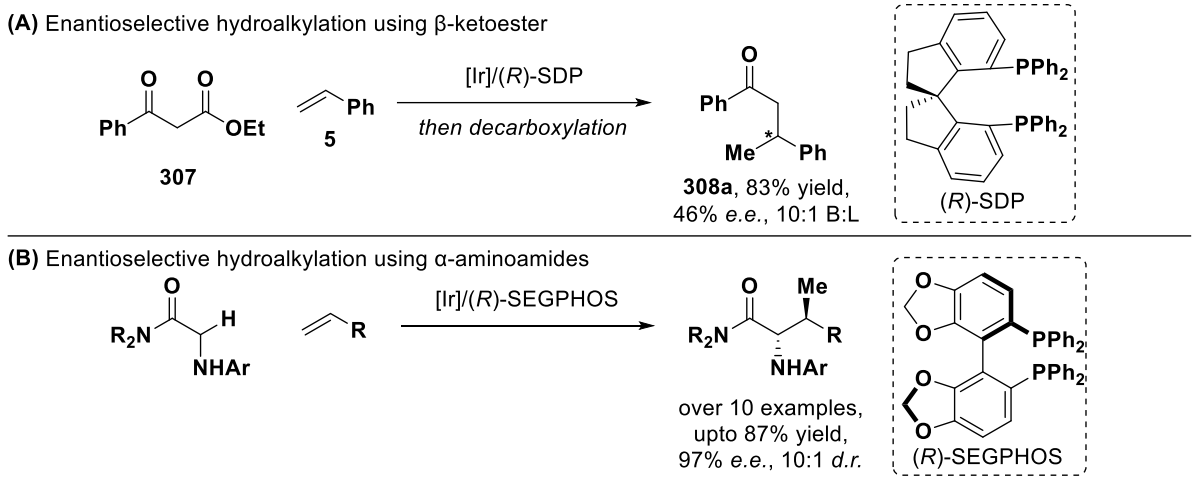
Chapter 4 discussed the development of a hydroheteroarylation reaction using alkenyl silanes, through extensive screening of a range of phosphine-derived ligands (**Scheme 81**). The methodology was applicable to a range of vinyl and allyl silanes with a broad scope of furan, thiophene and pyrrole substrates. The products were formed in good to excellent yields (upto 99%) and in very high alkene regiocontrol (B:L >15:1). It is anticipated that the newly installed silicon-containing functional group can act as a useful motif in a drug discovery programme or as a synthetic handle for further functionalisation.



Scheme 81: *Summary of hydroheteroarylation of alkenyl silanes.*

Finally, **Chapter 5** described investigations into an enantioselective hydroalkylation reaction using 1,3-dicarbonyl compounds. After extensive screening of reaction conditions and chiral bisphosphine ligands, the best result gave access to β-branched ketone **308a** in 83% yield and 46% *e.e.*, and with high branch selectivity using (*R*)-SDP (**Scheme 82A**). A significant, related process was described the enantioselective hydroalkylation using α-aminoamides in collaboration with Dr Fenglin Hong (**Scheme 82B**). Remarkably, this tolerates of a wide variety of styrenes to form branched products with excellent control over absolute and relative stereochemistry. Further investigation demonstrated the catalysis products could be further derivatised into various α-amino analogues (such as α-amino acids) as well as other pharmaceutically-active motifs. Through deuterium-labelling and natural abundance ^{13}C KIE

studies, as well as other kinetic experiments, a mechanism was involving irreversible outer-sphere attack of a *cis*-Ir-enolate onto the Ir-bound alkene.



Scheme 82: *Summary of hydroalkylation of alkenes.*

Overall, through either ligand design, or judicious choice of substrates and alkenes, a plethora of Ir(I)-catalysed hydrofunctionalisation reactions have been developed. The significance of these is highlighted by the formation of complex and pharmaceutically-relevant structures in high (i) site-selectivity, (ii) branch-selectivity, and where relevant, (iii) enantioselectivity and (iv) diastereoselectivity. These results mark an important contribution to the field, particularly as enantioselective hydrofunctionalisation reactions using minimally-polarised acyclic alkenes are still in their infancy; this demonstrates the considerable potential of Murai-type reactions, which use feedstock alkene substrates to addresses key deficiencies associated with cross-coupling reactions. Going forward, more efficient catalyst systems that offer broad scope are desired – particularly using aliphatic or 1,1-disubstituted alkenes. Ideally, these new methods should use substrates bearing directing groups that can be easily removed or diversified. Methods which promote hydroarylation at "remote" arene sites would also be highly valuable. Finally, as described in **Chapter 5**, branch- and enantioselective Murai-type reactivity can be extended to hydroalkylation methods. This presents a significant advance in a previously underexplored area that is currently limited to a few rare examples. It is predicted that these findings will mark the beginning of a new era for Murai-type reactions.

Chapter 7

Experimental

Chapter 7 – Experimental

7.1 General experimental details

All materials for which a synthetic route is not described or referenced were purchased from commercial sources (Sigma-Aldrich, Alfa Aesar, Fluorochem and Strem). All reagents requiring purification were purified using standard laboratory techniques according to methods published by Perrin, Armarego, and Perrin (Pergamon Press, 1966). Liquid styrene derivatives were distilled using a Hickman distilling head before use. All other commercially available alkenes were used as received without any further purification. Anhydrous solvents were obtained by distillation using standard procedures or by passage through drying columns supplied by Anhydrous Engineering Ltd. Reactions requiring anhydrous conditions were performed under a nitrogen or argon atmosphere, using Schlenk techniques and flame/oven-dried equipment. H_2O content in THF was analysed by Karl-Fisher coulometry using a Mettler Toledo C30 Compact before use; for hydroarylation reactions using alkenyl silanes, < 20 ppm H_2O is desired. The removal of the solvents *in vacuo* was achieved employing rotary evaporators connected with diaphragm pumps (15 mmHg) or, for high-boiling solvents, oil pumps (0.1 mmHg). Materials were dried on a high-vacuum line prior to analysis. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40-63 μm, 230-400 mesh). Certain ligands were purified by chromatography on deactivated silica gel (stirred overnight with 10% *w/w* of Et_3N) or on oven-dried silica gel. These instances are noted where appropriate. Thin layer chromatography was performed using aluminium backed 60 F254 silica plates. Visualisation was achieved by UV fluorescence or standard staining solutions (i.e. $KMnO_4$, vanillin, phosphomolybdic acid) and heat. Proton nuclear magnetic resonance spectra (NMR) were recorded on the following spectrometers: JEOL ECS400, JEOL ECZ400, Varian 400-MR, Bruker Nano400, Varian VNMR 500 and Bruker Avance III HD 500 Cryoprobe (Bristol) and Bruker Avance III HD 500 Cryoprobe and Bruker Avance III HD 400 (Liverpool). ^{1}H NMR spectra were recorded at 400 MHz or 500 MHz as stated. ^{13}C NMR spectra were recorded at 101 MHz or 126 MHz as stated. Chemical shifts (δ) are given in parts per million (ppm). Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m) and broad (br). Coupling constants (*J*) are quoted to the nearest 0.5 Hz. All assignments of NMR spectra were based on 2D NMR data (COSY, HSQC, HMBC, and nOe experiments where appropriate). Quantitative ^{1}H NMR yields were determined by employing 1,4-dinitrobenzene or 1,3,5-trimethoxybenzene as an internal standard. Mass spectra were recorded using the following instruments: Bruker Daltonics FT-ICR-MS Apex 4e 7.0T FT-MS or Bruker Daltonics micrOTOF II (ESI), Shimadzu GCMS QP2010+ or Thermo Scientific Orbitrap Elite (EI), Bruker ultrafleXtreme 2 (MALDI) and Thermo Scientific Orbitrap Elite (APCI) (Bristol) and Agilent 6540 UHD Accurate Mass Q-TOF LC/MS (ESI) (Liverpool). Infrared spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer (Bristol/Liverpool) as neat films. Melting points were determined using a Stuart SMP30 melting point apparatus. Optical rotations were measured using a Bellingham and Stanley ADP440+ polarimeter at

the concentration and temperature stated. Enantiomeric excess was determined using an Agilent 1290 Infinity chiral SFC under the conditions noted for each compound. **Ligands and catalysts:** $[Ir(cod)_2]OTf$, $[Ir(cod)_2]BF_4$, **L12** and d^Fppb were synthesised by former group members; $[Ir(cod)_2]BARF$, **L13–L15** and SPINOL precursors were synthesised from previously reported procedures.[105,107] $[RhCl(\mathbf{L24})]_2$ was synthesised from a literature procedure.[273] **Substrates:** Pyrrole **104** and acetanilide **231** were synthesised by Dr Phillippa Cooper[108], benzamides **222** and **281** were synthesised by Dr Raymond Chung.[105] **Alkenes:** α-Chiral alkene **201** was synthesised by Dr Andrew Dalling.[109]

7.2 General procedures

General Procedure A – Suzuki coupling and hydrolysis: To a flame-dried Schlenk tube was added the corresponding spirocycle (1.0 eq.), boronic acid (3.5 eq.), Na_2CO_3 (4.0 eq.) and tetrakis(triphenylphosphine)palladium(0) (6.0 mol%). The vessel was evacuated and refilled with nitrogen three times before addition of H_2O, EtOH and dimethoxyethane (1:1:3, 0.05 M), then sealed and heated at 130 °C for 16 h. After cooling, aq. 2M HCl (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL), concentrated *in vacuo* and re-dissolved in EtOH, H_2O and THF (1:1:1, 0.05 M). KOH (approx. 1.00 g) was added and the reaction mixture was heated at 80 °C for 1 h. After cooling, aq. 2M HCl (5 mL) was added and the mixture was extracted with Et_2O (3 × 5 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC gave the desired product.

General Procedure B – Reaction of spirocycles with 1,1'-bis(dichlorophosphino)ferrocene, 115: To a flame-dried Schlenk tube was added 1,1'-bis(dichlorophosphino)ferrocene **115** (0.50 eq.), SPINOL derivative (1.0 eq.) and DMAP (0.40 eq.). The tube was evacuated and refilled three times with nitrogen before the addition of CH_2Cl_2 and THF (1:2, 0.04 M). The mixture was cooled to 0 °C before triethylamine (4.8 eq.) was added and the resulting mixture was stirred at room temperature for 16 h. After filtration over Celite® (EtOAc), volatile components were removed *in vacuo* and purification by FCC gave the desired product.

General Procedure C – Rh-catalysed asymmetric conjugate addition: To a flame-dried three-necked round-bottom flask was added **118** (1.0 eq.), [RhCl**L24**]$_2$ (2.0 mol%), boronic acid (6.0 eq.) and KOH (5 mol%, if required). The flask was evacuated and refilled three times with nitrogen before the addition of H_2O and toluene (1:2, 0.04 M). The reaction mixture was stirred at the specified temperature and time. After allowing to cool, H_2O (20 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC gave the desired product.

General Procedure D – Spirocyclisation using $BF_3{\cdot}OEt_2$: To a flame-dried three-necked round-bottom flask was added ketone substrate (1.0 eq.). The flask was evacuated and refilled three times with nitrogen before the addition of toluene (0.10 M) and $BF_3{\cdot}OEt_2$ (10.0 eq.). The reaction mixture was stirred at the specified temperature and time. After allowing to cool, H_2O (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC gave the desired product.

General Procedure E: Asymmetric alkylation using $ZnEt_2$ and (–)-DBNE: To a flame-dried Schlenk tube was added the corresponding aldehyde substrate (1.0 eq.). The vessel was evacuated and refilled three times with nitrogen before (–)-DBNE (7.5 mol%) and hexane (0.5 M) were added. The mixture was cooled to 0 °C before the addition of $ZnEt_2$ (1M in hexanes, 2.3 eq.). The resulting mixture was stirred at 0 °C for 4 h before quenching with 2M HCl. After extracting with CH_2Cl_2 the organic layers

were combined, dried, filtered and volatiles removed *in vacuo*. Purification by FCC gave the desired product.

General Procedure F – Spirocyclisation using *n*-BuLi and diethyl carbonate: To a flame-dried Schlenk tube was added the corresponding enantioenriched alcohol substrate (1.0 eq.). The vessel was evacuated and refilled with nitrogen three times before adding toluene (0.35 M) and cooled to 0 °C. *n*-BuLi (1.6 M in hexanes, 2.0 eq.) was added dropwise and the resulting mixture was stirred at room temperature for 3 h. Diethyl carbonate (0.55 eq.) was added at 0 °C and the mixture was stirred at room temperature for 16 h. The reaction was quenched with acetic acid and the mixture was stirred for a further 4 h. After addition of sat. aq. $NaHCO_3$, the mixture was extracted with CH_2Cl_2. The organic extracts were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC gave the desired product.

General Procedure G – Amide synthesis using oxalyl chloride: To a flame-dried two-necked flask was added the carboxylic acid substrate (1.0 eq.). The flask was evacuated and refilled three times with nitrogen before addition of DMF (5 drops) and CH_2Cl_2 (0.5 M). The solution was cooled to 0 °C and oxalyl chloride (1.1 eq.) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h before volatile components were removed *in vacuo* and the residue was re-dissolved in CH_2Cl_2 (0.5 M). The amine (1.1–2.5 eq.) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with 2M HCl and extracted with CH_2Cl_2. The organic extracts were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo* before purification by FCC afforded the desired amide.

General Procedure H – Amide synthesis using thionyl chloride: To a flame-dried Young's tube was added carboxylic acid derivative (1 eq.). The vessel was evacuated/refilled with nitrogen three times before thionyl chloride (0.1 M) was added and the solution was heated at 85 °C for 5 h. After cooling, volatile components were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 before amine (1.5 eq.) was added dropwise at 0 °C and stirred for 18 h at room temperature. H_2O was added and the emulsion was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC afforded the desired amide.

General Procedure I – Suzuki Coupling: To a flame-dried Young's tube was added aryl bromide (1.0 eq.), boronic acid (350 mol%), $Pd(PPh_3)_4$ (6 mol%) and Na_2CO_3 (400 mol%). The tube was evacuated and refilled with nitrogen three times before a mixture of DME, EtOH and H_2O (3:1:1, 0.1 M) was added. The solution was sparged with a balloon of argon for 10 mins before the tube was sealed and heated at 100 °C for 72 h. After cooling, the mixture was filter over Celite®, extracted with CH_2Cl_2 (3 × 20 mL), dried, filtered and solvent removed *in vacuo*. Purification by FCC afforded the desired product.

General Procedure J – α-methyl styrene substrates: To a flame-dried flask was added methyltriphenylphosphonium bromide (120 mol%) in THF (0.5 M) under nitrogen and the solution was cooled to 0 °C. Potassium *tert*-butoxide (120 mol%) was added portion-wise and the resulting solution was stirred at 0 °C for 1–2 h. The specified ketone (1.0 eq.) was added dropwise and after stirring for 20 min at 0 °C the solution was warmed to ambient temperature and stirred for 16 h. The solution was filtered with hexane and solvent removed *in vacuo*. Purification by FCC afforded the pure styrene.

General Procedure K – Sulfonylation of alcohols: To a solution of alcohol substrate (1.0 eq.) and DMAP (5 mol%) in CH_2Cl_2 (0.30 M) was added the specified sulfonyl chloride (1.1 eq.) followed by triethylamine (1.1 eq.) at 0 °C. The reaction mixture stirred at room temperature for the specified time before H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over sodium sulfate and filtered before volatiles were removed *in vacuo*. Purification by FCC (hexane/EtOAc, 10:1) gave the desired product.

General Procedure L – General hydro(hetero)functionalisation procedure: A flame-dried Young's tube with a magnetic stirrer was charged with substrate (if solid), [Ir], ligand and alkene (if solid). The tube was fitted with a rubber septum and purged with nitrogen. Anhydrous solvent, substrate (if liquid) and alkene (if liquid) were sequentially added. The tube was sealed with a Young's tap and heated at the specified temperature and time before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residue by FCC afforded the pure product.

General Procedure M – Deuterium labelling of substrates: A flame-dried Young's tube with a magnetic stirrer was charged with substrate (if solid), $[Ir(cod)_2]BF_4$ (5 mol%) and ligand (5 mol%). The tube was fitted with a rubber septum and purged with nitrogen before substrate (if liquid), D_2O (30.0 eq.) and anhydrous 1,4-dioxane (1.5 M) were added sequentially. The tube was sealed with a Young's tap and heated at 120 °C for 24 h. After allowing to cool, volatile components were removed *in vacuo* and the crude product was purified by FCC. Deuterium incorporation was calculated by integration of ^{1}H NMR signals.

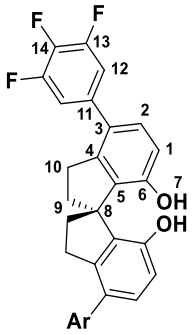
General Procedure N – Hydroalkylation/decarboxylation using β-ketoesters: A flame-dried Young's tube with a magnetic stirrer was charged with substrate (1.0 eq.), $[Ir(cod)_2]$BARF (5 mol%) and (*rac*)-BINAP (5 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Anhydrous 1,4-dioxane (0.25 M) and styrene (600 mol%) were sequentially added. The tube was sealed with a Young's tap and the reaction mixture was heated at 100 °C for 72 h. After cooling, volatile components were removed *in vacuo*. The residue was dissolved in DMF (0.25 M) and transferred to a clean Young's tube before H_2O (220 mol%) and LiCl (400 mol%) were added. The tube was sealed and

heated at 150 °C for 16 h. After cooling, H_2O (1.0 mL) was added and the mixture was extracted with EtOAc (3 × 2 mL). The organic extracts were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC afforded the target product.

7.3 Experimental procedures for compounds in Chapter 2

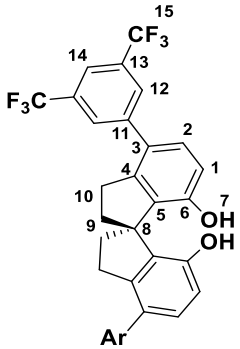
7.3.1 Synthesis of ligands

(*S*)-117a



General Procedure A: using (*S*)-**113** (500 mg, 0.65 mmol) and 3,4,5-trifluorophenylboronic acid (397 mg, 2.26 mmol). Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a white solid (250 mg, 75%); $\mathbf{R_f}$ = 0.65 (hexane/EtOAc, 3:2); **m.p.** = 215.0 – 218.0 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = -30.1 (c = 0.50, CH_2Cl_2); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3541 (m), 3515 (m), 2952 (w), 2932 (w), 2865 (w), 1617 (m), 1600 (m) 1529 (m), 1487 (s), 1041 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2H, H^2), 7.10 – 7.00 (m, 4H, H^{12}), 6.78 (d, *J* = 8.5 Hz, 2H, H^1), 4.78 (s, 2H, H^7), 3.23 – 3.09 (m, 2H, H^{10}), 3.07 – 2.95 (m, 2H, $H^{10'}$), 2.40 (m, 2H, H^9), 2.29 – 2.17 (m, 2H, $H^{9'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2 (C^6), 151.2 (d, *J* = 249.5 Hz, C^{13}), 143.3 (C^4), 138.9 (d, *J* = 252.0 Hz, C^{14}), 136.7 (m, C^{11}), 131.1 (C^5), 130.4 (C^2), 129.0 (C^3), 115.5 (C^1), 113.02 – 112.30 (m, C^{12}), 58.1 (C^8), 37.2 (C^9), 31.3 (C^{10}); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -134.54 (dd, *J* = 20.5, 8.5 Hz, C^{13}-F), -162.95 – -163.15 (m, C^{14}-F); ***m/z*** (negative ion nanospray): calc. for $C_{29}H_{18}F_6O_2$ = 512.12, found: 511.1139 $[M-H]^-$.

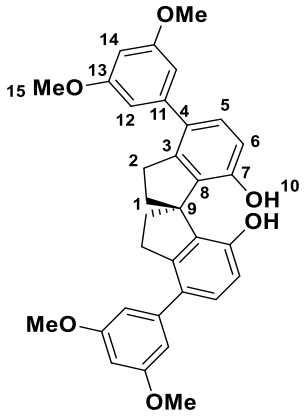
(*R*)-117b



General Procedure A: using (*R*)-**113** (500 mg, 0.650 mmol) and 3,5-bis(trifluoromethyl)phenylboronic acid (398 mg, 2.26 mmol). Purification by FCC (hexane/CH_2Cl_2, 3:2) gave the title compound as a white solid (317 mg, 72%); $\mathbf{R_f}$ = 0.35 (hexane/CH_2Cl_2, 3:2); **m.p.** = 93.3 – 96.6 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = + 27.8 (c = 0.50, CH_2Cl_2); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3528 (w), 2957 (w), 1594 (w), 1275 (s), 1125 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.5 Hz, 4H, H^{12}), 7.85 (*pseudo*-td, *J*

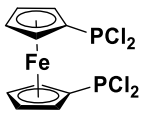
= 1.5, 1.0 Hz, 2H, H^{14}), 7.31 – 7.24 (m, 2H, H^{2}), 6.84 (d, *J* = 8.5 Hz, 2H, H^{1}), 4.82 (s, 2H, H^{7}), 3.31 – 3.14 (m, 2H, H^{10}), 3.08 – 2.93 (m, 2H, $H^{10'}$), 2.51 – 2.40 (m, 2H, H^{9}), 2.27 (m, 2H, $H^{9'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.4 (C^{6}), 143.6 (C^{4}), 142.8 (C^{11}), 131.8 (q, *J* = 33.0 Hz, C^{13}), 131.4 (C^{5}), 130.6 (C^{2}), 129.0 (C^{3}), 128.7 (C^{12}), 123.6 (q, *J* = 273.0 Hz, C^{15}) 120.6 (C^{14}), 115.7 (C^{1}), 58.2 (C^{8}), 37.3 (C^{9}), 31.2 (C^{10}); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.7; ***m/z*** (negative ion nanospray): calc. for $C_{33}H_{20}F_{12}O_2$ = 676.13, found: 675.1196 $[M-H]^-$.

(*R*)-117c



General Procedure A: using (*R*)-**113** (500 mg, 0.65 mmol) and 3,5-dimethoxyboronic acid (412 mg, 2.26 mmol). Purification by FCC (hexane/EtOAc, 3:1) gave the title compound as a white solid (243 mg, 71%); $\mathbf{R_f}$ = 0.40 (hexane/EtOAc, 3:1); **m.p.** = 94.7 – 97.6 °C (hexane); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = + 30.7 (c = 0.33, CH_2Cl_2); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3525 (br), 3399 (br), 2945 (br), 2840 (br), 1593 (s), 1498 (s), 1458 (m), 1153 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H, H^{5}) 6.79 (d, *J* = 8.5 Hz, 2H, H^{6}), 6.59 (d, *J* = 2.0 Hz, 4H, H^{12}), 6.46 (t, *J* = 2.0 Hz, 2H, H^{14}), 4.78 (s, 2H, H^{10}), 3.85 (s, 12H, H^{15}), 3.25 – 3.02 (m, 4H, H^{2}), 2.45 – 2.14 (m, 4H, H^{1}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6 (C^{13}), 152.4 (C^{7}), 143.3 (C^{3}), 142.9 (C^{4}), 131.6 (C^{11}), 131.0 (C^{8}), 130.2 (C^{5}), 114.9 (C^{6}), 106.9 (C^{12}), 98.8 (C^{14}), 58.1 (C^{9}), 55.4 (C^{15}), 37.3 (C^{1}), 31.4 (C^{2}); ***m/z*** (ESI^+): calc. for $C_{33}H_{32}O_6$ = 524.61, found: 525.2252 $[M+H]^+$.

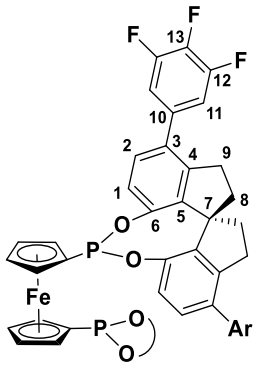
1,1′-Bis(dichlorophosphino)ferrocene, 115



Ferrocene (1.86 g, 10 mmol) was dissolved in dry/degassed hexane (50 mL, 3 × freeze, pump, thaw cycles). Freshly distilled TMEDA (3.15 mL, 21 mmol) was added dropwise before *n*-BuLi (2.5 M in hexane, 8.80 mL, 22 mmol) and the reaction was stirred at room temperature for 24 h. Bis(diethylamino)chlorophosphine (4.42 mL, 21 mmol) was added to dry/degassed THF (15 mL, 3 × freeze, pump, thaw cycles) and was added to the first solution dropwise at -78 °C and stirred at room temperature for 4 days. The reaction was quenched by dropwise addition of HCl (2M in Et_2O, 80 mL)

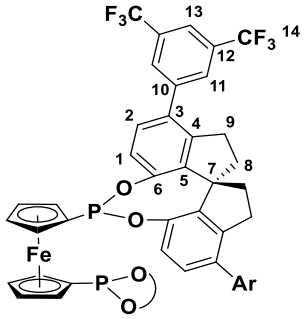
at -78 °C and stirred at room temperature for 16 h. The solids were filtered off and washed with dry hexane under an inert atmosphere (filter stick). The filtrate was concentrated *in vacuo* to afford to title compound as an orange solid (3.00 g, 77%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.72 (s, 1H); **^{31}P NMR** (202 MHz, $CDCl_3$) δ 162.5. *Data in accordance with literature values.*[115]

(*S*)-L17



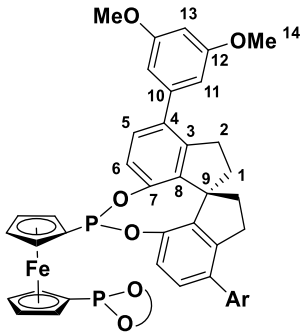
General Procedure B: using (*S*)-**117a** (158 mg, 0.310 mmol). Purification by FCC (hexane/EtOAc, 19:1, deactivated silica with 10% *w/w* of Et_3N) gave the title compound as a yellow solid (48 mg, 25%); **R_f** = 0.70 (hexane/EtOAc, 4:1); **m.p.** = 150.0 – 154.9 °C (hexane/EtOAc); $[\alpha]_D^{22}$ = - 198 (c = 0.50, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H, H^{2}), 7.16 (d, *J* = 8.0 Hz, 2H, H^{1}), 7.09 (dd, *J* = 8.5, 6.5 Hz, 4H, H^{11}), 7.01 – 6.92 (m, 4H, $H^{11'}$), 6.78 (d, *J* = 8.5 Hz, 2H, $H^{2'}$), 6.13 (d, *J* = 8.5 Hz, 2H, $H^{1'}$), 4.68 – 4.58 (m, 4H, ferrocene), 4.37 (td, *J* = 2.5, 1.0 Hz, 2H, ferrocene), 3.79 – 3.72 (m, 2H, ferrocene), 3.27 – 3.08 (m, 4H, H^{9}), 2.88 – 2.73 (m, 4H, $H^{9'}$), 2.41 – 2.29 (m, 4H, H^{8}), 2.10 – 1.96 (m, 4H, $H^{8'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.4 (Ar-C), 150.2 (Ar-C), 146.3 (Ar-C), 143.2 (Ar-C), 142.9 (Ar-C), 142.1 (Ar-C), 141.4 (Ar-C), 136.8 (Ar-C), 132.7 (Ar-C), 131.8 (Ar-C), 129.4 (C^{2}), 127.6 ($C^{2'}$), 123.6 ($C^{1'}$), 122.1 (C^{1}), 113.5 – 112.3 (m, C^{11}), 73.5 (ferrocene), 73.1 (ferrocene), 72.0 (ferrocene), 71.7 (ferrocene), 70.7 (ferrocene), 59.6 (C^{7}), 38.5 (C^{8}), 38.0 ($C^{8'}$), 31.2 (C^{9}), 30.7 ($C^{9'}$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -134.4 (ddd, *J* = 78.0, 20.5, 8.5 Hz, C^{12}-F), -162.6 (d, *J* = 100.5 Hz, C^{13}-F); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 161.0; ***m/z*** (MALDI): calc. for $C_{68}H_{40}F_{12}FeO_4P_2$ = 1266.16, found: 1266.1572 $[M+H]^+$.

(*R*)-L18



General Procedure B: using (*R*)-**117b** (188 mg, 0.28 mmol). Purification by FCC (hexane/EtOAc, 49:1 → 19:1, deactivated silica with 10% *w/w* of Et_3N) gave the title compound as a yellow solid (54 mg, 25%); $\mathbf{R_f}$ = 0.33 (hexane/EtOAc, 19:1); **m.p.** = 178.8 – 180.4 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = + 221 (c = 0.50, CH_2Cl_2); $\mathbf{\nu_{max}/cm^{-1}}$**:** 2956 (w), 2859 (w), 1619 (w), 1599 (w), 1129 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.79 (m, 12H, H^{11}, H^{13}), 7.33 (d, *J* = 8.5 Hz, 2H, H^2), 7.28 – 7.20 (m, 2H, H^1), 6.88 (d, *J* = 8.5 Hz, 2H, $H^{2'}$), 6.21 (d, *J* = 8.5 Hz, 2H, $H^{1'}$), 4.73 – 4.64 (m, 4H, ferrocene), 4.44 (q, *J* = 2.0 Hz, 2H, ferrocene), 3.86 (dt, *J* = 2.5, 1.0 Hz, 2H, ferrocene), 3.33 – 3.13 (m, 4H, H^9), 2.85 – 2.72 (m, 4H, $H^{9'}$), 2.47 – 2.32 (m, 4H, H^8), 2.09 (*pseudo*-q, *J* = 11.5, 8.0 Hz, 4H, $H^{8'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.6 (Ar-C), 146.8 (Ar-C), 143.4 (Ar-C), 143.2 (Ar-C), 142.8 (Ar-C), 142.6 (Ar-C), 142.4 (Ar-C), 141.6 (Ar-C), 132.6 (Ar-C), 132.1 (Ar-C), 132.0 (Ar-C), 131.8 (Ar-C), 131.6 (Ar-C), 129.6 (C^2), 128.9 (C^{11}/C^{13}), 127.9 ($C^{2'}$), 123.8 ($C^{1'}$), 123.5 (q, *J* = 275.0 Hz, C^{14}) 122.4 (C^1), 121.0 (C^{11}/C^{13}), 120.8 (C^{11}/C^{13}), 73.2 (ferrocene), 72.1 (ferrocene), 70.7 (ferrocene), 59.6 (C^7), 38.6 (C^8), 38.0 ($C^{8'}$), 31.0 (C^9), 30.6 ($C^{9'}$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.7 (d, *J* = 12.5 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 161.3; ***m/z*** (MALDI): calc. for $C_{76}H_{44}F_{24}FeO_4P_2$ = 1594.17, found: 1594.1693 $[M+H]^+$.

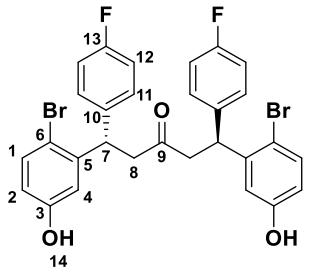
(*R*)-L19



General Procedure B: using (*R*)-**117c** (150 mg, 0.29 mmol). Purification by FCC (hexane/EtOAc, 7:3, deactivated silica with 10% *w/w* of Et_3N) gave the title compound as a yellow solid (96 mg, 53%); $\mathbf{R_f}$ = 0.78 (toluene/acetone, 9:1); **m.p.** = 182.7 – 187.2 °C (hexane); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = + 238 (c = 0.35, CH_2Cl_2); $\mathbf{\nu_{max}/cm^{-1}}$**:** 2958 (w), 2837 (w), 1596 (s), 1154 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 11.0 Hz,

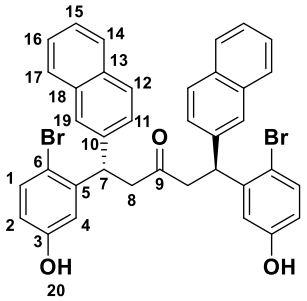
2H, H^5/H^6), 7.16 (d, *J* = 8.5 Hz, 2H, H^5/H^6), 6.86 (d, *J* = 8.5 Hz, 2H, H^5/H^6), 6.58 (d, *J* = 46.0 Hz, 8H, H^{11}), 6.46 (d, *J* = 18.0 Hz, 4H, H^{13}), 6.13 (d, *J* = 8.0 Hz, 2H, H^5/H^6), 4.64 (d, *J* = 21.5 Hz, 4H, ferrocene), 4.37 (br, 2H, ferrocene), 3.84 (d, *J* = 13.5 Hz, 26H, H^{14}, ferrocene), 3.36 – 2.72 (m, 8H, H^1/H^2), 2.40 – 1.94 (m, 8H, H^1/H^2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.7 (C^{12}), 149.6 (Ar-C), 145.8 (Ar-C), 143.1 – 142.3 (m), 142.2 (Ar-C), 141.1 (Ar-C), 135.3 (C^{10}), 134.5 (C^{10}), 129.4 (C^5/C^6), 127.6 (C^5/C^6), 123.1 (C^5/C^6), 121.5 (C^5/C^6), 107.1 (H^{11}), 99.2 (C^{13}), 98.6 ($C^{13'}$), 73.8 – 72.5 (m, Ar-CH), 71.9 (Ar-CH), 71.0 (Ar-C), 59.6 (C^9), 55.5 (C^{14}), 38.6 ($C^1/C^{1'}/C^2/C^{2'}$), 38.0 ($C^1/C^{1'}/C^2/C^{2'}$), 31.4 ($C^1/C^{1'}/C^2/C^{2'}$), 30.9 ($C^1/C^{1'}/C^2/C^{2'}$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 160.3; ***m/z*** (ESI^+) calc. for $C_{76}H_{68}FeO_{12}P_2$ = 1290.35, found: 1291.3608 $[M+H]^+$.

(1*S*,5*S*)-1,5-Bis(2-bromo-5-hydroxyphenyl)-1,5-bis(4-fluorophenyl)pentan-3-one, (*S*)-119a



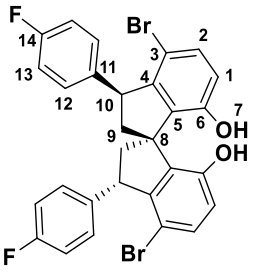
General Procedure C: using **118** (424 mg, 1.00 mmol), 4-fluorophenylboronic acid (424 mg, 1.00 mmol) and KOH (18.8 mg, 50.0 µmol) at 80 °C for 4 h. Purification by FCC (hexane/Et_2O, 1:2) gave the title compound as an off-white solid (475 mg, 77%); **R_f** = 0.30 (hexane/Et_2O, 1:2); **m.p.** = 82.0 – 86.2 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{22}}$ = + 24.0 (c = 0.50, CH_2Cl_2); **ν_{max}/cm^{-1}:** 3362 (br), 1707 (m), 1604 (m), 1576 (m), 1508 (s), 1226 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.5, 0.5 Hz, 2H, H^1), 7.10 – 7.03 (m, 4H, H^{11}), 6.93 – 6.88 (m, 4H, H^{12}), 6.57 – 6.49 (m, 4H, H^2, H^4), 5.65 (br, 2H, H^{14}), 4.91 (t, *J* = 7.5 Hz, 2H, H^7), 3.05 (d, *J* = 7.5 Hz, 4H, H^8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.6 (C^9), 161.7 (d, *J* = 246.0 Hz, C^{13}), 155.3 (C^3), 143.5 (C^5), 137.3 (d, *J* = 3.0 Hz, C^{10}), 134.3 (C^1), 129.6 (d, *J* = 8.0 Hz, C^{11}), 115.8 (C^2/C^4), 115.7 (C^2/C^4) 115.6 (d, *J* = 21.5 Hz, C^{12}), 115.1 (C^6), 48.6 (C^8), 44.1 (C^7); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -115.8 – -116.0 (m); ***m/z*** (MALDI): calc. for $C_{29}H_{22}O_{79}{}^{79}Br_2F_2$ = 613.99, found: 636.9785 $[M+Na]^+$.

(1*S*,5*S*)-1,5-Bis(2-bromo-5-hydroxyphenyl)-1,5-di(naphthalen-2-yl)pentan-3-one, (*S*)-119b



General Procedure C: using **118** (636 mg, 1.50 mmol) and 2-naphthylboronic acid (1.55 g, 9.00 mmol) at 60 °C for 16 h. Purification by FCC (hexane/EtOAc, 2.5:1) gave the title compound as a white solid (1.00 g, 98%); $\mathbf{R_f}$ = 0.41 (hexane/EtOAc, 2.5:1); **m.p.** = 103.7 – 107.2 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = + 7.17 (c = 0.50, CH_2Cl_2); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3372 (br), 3054 (w), 2972 (w), 2901 (w), 1705 (m), 1596 (m), 1575 (s), 1468 (s), 1291 (s), 478 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.0, 1.5 Hz, 2H, H^{14}), 7.63 (d, *J* = 8.5 Hz, 2H, H^{12}), 7.59 (dd, *J* = 8.0, 1.5 Hz, 2H, H^{17}), 7.51 – 7.48 (m, 2H, H^{19}), 7.44 – 7.36 (m, 4H, H^{15}, H^{16}), 7.28 (d, *J* = 8.5 Hz, 2H, H^1), 7.20 (dd, *J* = 8.5, 2.0 Hz, 2H, H^{11}), 6.51 – 6.43 (m, 4H, H^2, H^4), 5.47 (s, 2H, H^{20}), 5.09 (t, *J* = 7.5 Hz, 2H, H^7), 3.24 – 3.06 (m, 4H, H^8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.2 (C^9), 155.2 (C^3), 143.5 (C^5), 139.1 (C^{10}), 134.2 (C^1), 133.4 (C^{18}), 132.4 (C^{13}), 128.5 (C^{12}), 128.0 (C^{17}), 127.7 (C^{14}), 126.8 (C^{11}), 126.3 (C^{19}), 125.9 (C^{15} and C^{16}), 116.2 (C^2/C^4), 115.8 (C^2/C^4), 115.2 (C^6), 48.3 (C^8), 45.0 (C^7); ***m/z*** (MALDI): calc. for $C_{37}H_{28}O_{79}{}^{79}Br_2$ = 678.04, found: 701.0289 $[M+Na]^+$.

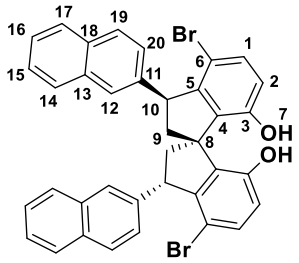
(1*R*,3*R*,3'*S*)-4,4'-Dibromo-3,3'-bis(4-fluorophenyl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol, (*R*)-120a



General Procedure D: using (*S*)-**119a**, (200 mg, 0.32 mmol) at 70 °C for 48 h. Purification by FCC (hexane/Et_2O, 1:1) gave the title compound as a white solid (370 mg, 85%); $\mathbf{R_f}$ = 0.40 (hexane/Et_2O, 1:2); **m.p.** = 200.8 – 204.7 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = + 84.1 (c = 0.50, CH_2Cl_2); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3529 (m), 2932 (w), 2872 (w), 1604 (w), 1576 (w), 1508 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H, H^2), 7.17 (dd, *J* = 8.5, 5.5 Hz, 4H, H^{12}), 6.99 (*pseudo*-t, *J* = 8.5 Hz, 4H, H^{13}), 6.64 (d, *J* = 8.5 Hz, 2H, H^1), 4.85 (s, 2H, H^7), 4.58 – 4.39 (m, 2H, H^{10}), 2.80 (dd, *J* = 13.5, 8.0 Hz, 2H, H^9), 2.23 (dd, *J* = 13.5, 10.0 Hz, 2H, $H^{9'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.7 (d, *J* = 244.5 Hz, C^{14}), 151.9 (C^6), 145.5 (C^4),

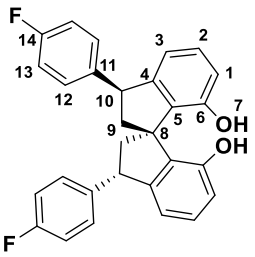
140.0 (d, *J* = 3.5 Hz, C^{11}), 134.8 (C^5), 134.1 (C^2), 129.8 (d, *J* = 8.0 Hz, C^{12}), 117.1 (C^1), 115.5 (d, *J* = 21.0 Hz, C^{13}), 112.0 (C^3), 56.4 (C^8), 50.8 (C^{10}), 50.0 (C^9); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -107.63 – -136.66 (m); ***m/z*** (negative ion nanospray): calc. for $C_{29}H_{20}{}^{79}Br_2F_2O_2$ = 595.98, found: 594.9733 $[M\text{-}H]^-$.

(1*R*,3*R*,3'*S*)-4,4'-Dibromo-3,3'-di(naphthalen-2-yl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol, (*R*)-120b



General Procedure D using: (*S*)-**119b** (500 mg, 0.735 mmol) at 60 °C for 72 h. Purification by FCC (hexane/Et_2O, 1:1) gave the title compound as a white powder (150 mg, 33%); $\mathbf{R_f}$ = 0.26 (hexane/Et_2O, 1:1); **m.p.** = 199.4 – 205.5 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = + 235 (c = 0.50, CH_2Cl_2); $\mathbf{\nu_{max}/cm^{-1}}$**:** 3523 (br), 3056 (w), 2936 (w), 1703 (m), 1580 (m), 1462 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 6H, H^{14}, H^{17}, H^{19}), 7.77 (d, *J* = 1.5 Hz, 2H, H^{12}), 7.54 – 7.44 (m, 4H, H^{15}, H^{16}), 7.36 (dd, *J* = 8.5, 2.0 Hz, 2H, H^{20}), 7.29 (d, *J* = 8.5 Hz, 2H, H^1), 6.64 (dd, *J* = 8.5, 1.0 Hz, 2H, H^2), 5.29 (s, 2H, H^7), 4.69 (dd, *J* = 13.5, 9.0 Hz, 2H, H^{10}), 2.86 (dd, *J* = 13.5, 9.0 Hz, 2H, H^9), 2.40 (dd, *J* = 13.5, 9.0 Hz, 2H, $H^{9'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.1 (C^3), 145.6 (C^5), 141.5 (C^{11}), 134.8 (C^4), 134.2 (C^1), 133.7 (Ar-C), 132.5 (Ar-C), 128.6 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 127.3 (C^{12}), 126.2 (C^{20}), 126.1 (Ar-CH), 125.6 (Ar-CH), 117.2 (C^2), 112.2 (C^6), 56.7 (C^8), 51.8 (C^{10}), 49.7 (C^9); ***m/z*** (MALDI): calc. for $C_{37}H_{26}{}^{79}Br_2O_2$ = 662.42, found: 661.0190 $[M\text{-}H^-]$. *Data in accordance with literature values.*[116]

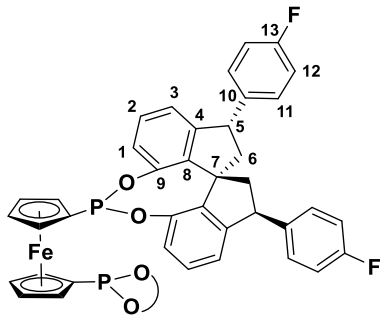
(1*R*,3*R*,3'*S*)-3,3'-Bis(4-fluorophenyl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol, (*R*)-121a



(*R*)-**120a** (400 mg, 0.670 mmol) and Pd/C (60.0 mg, 15 wt%) were added in a round-bottom flask before addition of THF/H_2O (2 mL, 1:1). The flask was evacuated and purged with hydrogen for 10 mins and stirred at room temperature for 16 h. The reaction was quenched with argon for 30 mins before filtering over a plug of Celite® (EtOAc). H_2O was added and the suspension was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over sodium sulfate, filtered and volatiles removed *in*

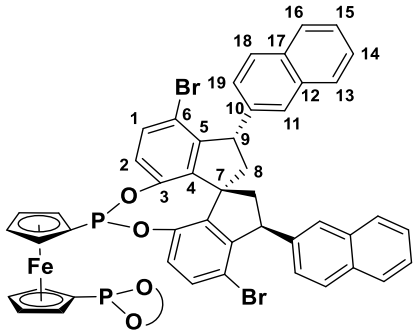
vacuo to afford a white powder (254 mg, 86%); **R_f** = 0.72 (hexane/EtOAc, 1:2); **m.p.** = 233.9 – 236.2 (hexane/EtOAc); $[\alpha]_D^{22}$ = + 47.7 (c= 0.50, CH_2Cl_2); **ν_{max}/cm^{-1}:** 3539 (w), 2929 (w), 1590 (m), 1508 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 4H, H^{12}), 7.17 (t, *J* = 7.5 Hz, 2H, H^2), 7.03 (*pseudo*-t, *J* = 8.5 Hz, 4H, H^{13}), 6.74 (d, *J* = 7.5 Hz, 2H, H^1), 6.54 (d, *J* = 7.5 Hz, 2H, H^3), 4.83 (s, 2H, H^7), 4.46 (dd, *J* = 11.0, 7.5 Hz, 2H, H^{10}), 2.81 (dd, *J* = 13.0, 7.5 Hz, 2H, H^9), 2.34 (dd, *J* = 13.0, 11.0 Hz, 2H, $H^{9'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9 (d, *J* = 244.5 Hz, C^{14}), 152.7 (C^6), 148.8 (C^4), 139.5 (d, *J* = 3.5 Hz, C^{11}), 131.1 (C^5), 130.3 (C^2), 129.9 (d, *J* = 8.0 Hz, C^{12}), 118.2 (C^3), 115.7 (d, *J* = 20.0 Hz, C^{13}), 114.9 (C^1), 55.5 (C^8), 49.5 (C^{10}), 48.1 (C^9); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.1; ***m/z*** (APCI): calc. for $C_{29}H_{22}F_2O_2$ = 440.16, found: 441.1682 $[M+H]^+$.

(*R*)-L25



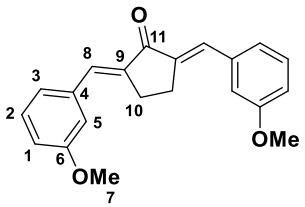
General Procedure B: using (*R*)-**121a** (175 mg, 0.400 mmol). Purification by FCC (hexane/EtOAc, 19:1, deactivated silica with 10% *w/w* of Et_3N) gave the title compound as a yellow solid (121 mg, 54%); **R_f** = 0.26 (hexane/EtOAc, 19:1); **m.p.** = 208.5 °C (degradation, hexane/EtOAc); $[\alpha]_D^{20}$ = + 246 (c = 0.50, CH_2Cl_2); **ν_{max}/cm^{-1}:** 2959 (w), 2926 (w), 1606 (w), 1585 (w), 1509 (s), 1464 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.17 (m, 7H, H^{11}, Ar-C<u>H</u>), 7.12 – 6.99 (m, 10H, H^{12}, Ar-C<u>H</u>), 6.80 (t, *J* = 7.5 Hz, 2H, H^2), 6.76 – 6.70 (m, 5H, $H^{12'}$, Ar-C<u>H</u>), 6.53 (d, *J* = 7.5 Hz, 2H, Ar-C<u>H</u>), 6.12 (d, *J* = 8.0 Hz, 2H, Ar-C<u>H</u>), 4.62 (dt, *J* = 16.5, 2.0 Hz, 4H, ferrocene), 4.54 – 4.37 (m, 6H, H^5, ferrocene), 3.72 (dt, *J* = 2.5, 1.0 Hz, 2H, ferrocene), 2.67 (ddd, *J* = 12.0, 6.0, 1.5 Hz, 4H, H^6), 2.23 – 1.99 (m, 4H, $H^{6'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 243.5 Hz, C^{13}), 161.7 (d, *J* = 243.5 Hz, $C^{13'}$) 150.0 (Ar-<u>C</u>), 148.5 (Ar-<u>C</u>), 147.7 (Ar-<u>C</u>), 146.0 (Ar-<u>C</u>), 142.0 (Ar-<u>C</u>), 140.4 (Ar-<u>C</u>), 139.7 (d, *J* = 3.5 Hz, C^{10}), 139.1 (d, *J* = 3.5 Hz, C^{10}), 130.2 (d, *J* = 8.0 Hz, C^{11}), 129.7 (d, *J* = 8.0 Hz, C^{11}), 127.9 (C^2), 122.9 (Ar-<u>C</u>H), 121.8 (Ar-<u>C</u>H), 121.3 (Ar-<u>C</u>H), 121.1 (Ar-<u>C</u>H), 115.5 (d, *J* = 21.0 Hz, C^{12}), 73.6 (ferrocene), 73.2 (ferrocene), 72.9 (ferrocene), 72.1 (ferrocene), 70.5 (ferrocene), 56.8 (C^7), 49.8 (C^6), 49.2 ($C^{6'}$), 49.1 (C^5), 48.6 ($C^{5'}$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.3; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 159.8; ***m/z*** (nanospray): calc. for $C_{68}H_{48}F_4FeO_4P_2$ = 1122.23, found: 1123.2377 $[M+H]^+$.

(*R*)-L26



General Procedure B: using (*R*)-**120b** (205 mg, 0.310 mmol). Purification by FCC (hexane/EtOAc, 19:1 → 3:2, deactivated silica with 10% *w/w* of Et_3N) gave the title compound as a yellow solid (130 mg, 52%); $\mathbf{R_f}$ = 0.41 (hexane/EtOAc, 4:1); **m.p.** = 241.0 °C (degradation, hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = + 453 (c = 0.29, CH_2Cl_2); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3051 (w), 2960 (w), 2929 (w), 1600 (w), 1507 (w), 1454 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.61 (m, 17H, Ar-C<u>H</u>), 7.47 – 7.40 (m, 12H, Ar-C<u>H</u>), 7.34 – 7.25 (m, 2H, Ar-C<u>H</u>), 7.11 (t, *J* = 8.5 Hz, 4H, Ar-C<u>H</u>), 6.99 (d, *J* = 8.5 Hz, 2H, Ar-C<u>H</u>), 6.13 (d, *J* = 8.5 Hz, 2H, Ar-C<u>H</u>), 4.78 – 4.59 (m, 10H, H^8, ferrocene), 4.09 (s, 2H, ferrocene), 2.78 (dt, *J* = 13.0, 6.0 Hz, 4H, H^8), 2.30 – 2.10 (m, 4H, $H^{8'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.2 (Ar-<u>C</u>), 145.4 (Ar-<u>C</u>), 145.3 (Ar-<u>C</u>), 144.8 (Ar-<u>C</u>), 144.6 (Ar-<u>C</u>), 143.0 (Ar-<u>C</u>), 141.1 (Ar-<u>C</u>), 140.7 (Ar-<u>C</u>), 134.2 (Ar-<u>C</u>H), 133.7 (Ar-<u>C</u>), 133.6 (Ar-<u>C</u>), 132.6 (Ar-<u>C</u>H), 132.5 (Ar-<u>C</u>H), 132.4 (Ar-<u>C</u>H), 128.6 (Ar-<u>C</u>), 128.0 (Ar-<u>C</u>H), 127.9 (Ar-<u>C</u>H), 127.8 (Ar-<u>C</u>H), 127.7 (Ar-<u>C</u>H), 126.2 (Ar-<u>C</u>), 126.1 (Ar-<u>C</u>), 125.7 (Ar-<u>C</u>H), 125.6 (Ar-<u>C</u>H), 124.9 (Ar-<u>C</u>H), 123.8 (Ar-<u>C</u>H), 116.7 (Ar-<u>C</u>), 116.1 (Ar-<u>C</u>), 73.6 (ferrocene), 73.5 (ferrocene), 73.3 (ferrocene), 72.5 (ferrocene), 70.3 (ferrocene), 57.6 (C^7), 51.3 (C^9), 50.6 (C^8); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 161.0; ***m/z*** (MALDI) calc. for $C_{84}H_{56}{}^{79}Br_4FeO_4P_2$ = 1561.97, found: 1562.9784 $[M+H]^+$.

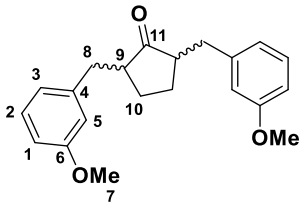
2,5-Bis((*E*)-3-methoxybenzylidene)cyclopentan-1-one, 131



To a solution of NaOH (12 g, 300 mmol) in H_2O/EtOH (1:1, 150 mL) was added a solution of cyclopentanone (6.70 mL, 75 mmol) and *m*-anisaldehyde (18.3 mL, 150 mmol) in EtOH (20 mL). The resulting mixture was stirred at room temperature for 4 h. The yellow suspension was filtered, washed with H_2O (100 mL), recrystallised (THF) and dried *in vacuo* at 50 °C to give the title compound as yellow crystals (23.1 g, 96%); **m.p.** = 144.9 – 145.7 °C (THF, Lit.[274]: 144 – 147 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (s, 2H, H^8), 7.36 (t, *J* = 8.0 Hz, 2H, H^2), 7.20 (dt, *J* = 8.0, 2.0 Hz, 2H, H^3), 7.13 (t, *J* = 2.0 Hz, 2H, H^5), 6.94 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 2H, H^1), 3.85 (s, 6H, H^7), 3.16 – 3.08 (m, 4H, H^{10});

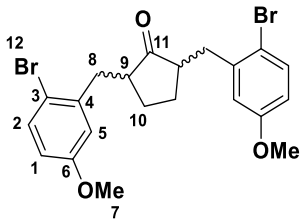
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5 (C^{11}), 159.9 (C^6), 137.7 (C^9), 137.3 (C^4), 134.0 (C^8), 129.9 (C^2), 123.5 (C^3), 116.1 (C^5), 115.2 (C^1), 55.5 (C^7), 26.7 (C^{10}); *Data in accordance with literature values.*[122]

2,5-Bis(3-methoxybenzyl)cyclopentan-1-one, 132



A solution of **131** (5.00 g, 15.6 mmol) in acetone/THF (1:1, 40 mL) was added to a flask charged with Raney-nickel (5.00 g). The mixture was sparged with hydrogen for 10 mins and stirred at room temperature. After two h, the reaction mixture was sparged with argon for 30 mins, filtered over Celite® and concentrated *in vacuo*. H_2O (50 mL) was added and the resulting suspension was extracted with EtOAc (3 × 25 mL), dried over sodium sulfate, filtered and volatiles removed *in vacuo*. Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a colourless liquid (4.62 g, 91%, *cis/trans* = 1.00 : 1.35, *assignments of isomers are based on data for cis-product; see Chem. Eur. J., 2019, **25**, 9491*); **R_f** = 0.56 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 4H, *cis and trans*-H^5), 6.78 – 6.68 (m, 12H, *cis and trans*-H^1,H^2,H^3), 3.79 (s, 6H, *trans*-H^7), 3.78 (s, 6H, *cis*-H^7), 3.16 (dd, *J* = 14.0, 4.0 Hz, 2H, *cis*-H^8), 3.03 (dd, *J* = 14.0, 4.0 Hz, 2H, *trans*-H^8) 2.61 – 2.51 (m, 4H, *cis*-$H^{8'}$ and *trans*-H^9), 2.43 (dd, *J* = 14.0, 10.0 Hz, 2H, *trans*-$H^{8'}$), 2.30 (m, 2H, *cis*-H^9), 2.07 – 1.95 (m, 2H, *cis*-H^{10}), 1.94 – 1.83 (m, 2H, *trans*-H^{10}), 1.64 – 1.52 (m, 2H, *trans*-$H^{10'}$), 1.44 – 1.36 (m, 2H, *cis*-$H^{10'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.8 (*cis or trans*-C^{11}), 220.1 (*cis or trans*-C^{11}), 159.8 (*cis and trans*-C^6), 141.6 (*cis and trans*-C^4), 129.5 (*cis and trans*-C^5), 121.5 (*cis or trans*), 121.4 (*cis or trans*), 114.9 (*cis or trans*), 114.8 (*cis or trans*), 111.7 (*cis or trans*), 111.5 (*cis or trans*), 55.3 (*cis and trans*-C^7), 51.6 (*cis*-C^9), 50.2 (*trans*-C^9), 36.2 (*cis*-C^8), 34.0 (*trans*-C^8), 27.3 (*cis*-C^{10}), 26.0 (*trans*-C^{10}); *Data in accordance with literature values.*[122]

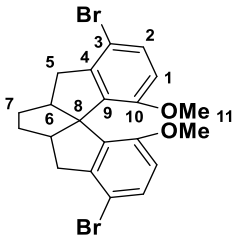
2,5-Bis(2-bromo-5-methoxybenzyl)cyclopentan-1-one, 133



To a solution of **132** (4.57 g, 14.1 mmol) in acetone (30 mL) at 0 °C under nitrogen was added NBS (5.01 g, 28.2 mmol) followed by five drops of 2M HCl. The resulting yellow solution stirred at room temperature until a clear solution was observed (approx. 5-15 mins). The mixture was then concentrated *in vacuo* and the residue was dissolved in Et_2O (20 mL), washed with H_2O (20 mL), brine (20 mL),

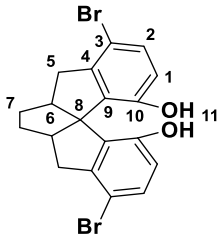
dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a colourless oil (6.53 g, 96%, *cis/trans* = 1.00:1.28, *assignments of isomers based on data for cis-product; see Chem. Eur. J., 2019, **25**, 9491*). $\mathbf{R_f}$ = 0.57 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (m, 4H, *cis and trans*-H^2), 6.76 (m, 4H, *cis and trans*-H^5), 6.65 (m, 4H, *cis and trans-H^1*), 3.78 (s, 6H, *cis or trans*-H^7), 3.76 (s, 6H, *cis or trans*-H^7), 3.34 (dd, *J* = 14.0, 4.5 Hz, 2H, *cis*-H^8), 3.20 (dd, *J* = 14.0, 4.5 Hz, 2H, *trans*-H^8), 2.71 – 2.56 (m, 4H, *cis and trans*-$H^{8'}$ *and trans*-H^9), 2.48 (m, 2H, *cis*-H^9), 2.04 – 1.98 (m, 2H, *cis*-H^{10}), 1.94 – 1.86 (m, 2H, *trans*-H^{10}), 1.71 (m, 2H, *trans*-$H^{10'}$), 1.49 – 1.40 (m, 2H, *cis*-$H^{10'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 219.7 (*cis or trans*-C^{11}), 219.4 (*cis or trans*-C^{11}), 159.0 (*cis and trans*-C^6), 140.4 (*cis and trans*-C^4), 133.5 (*cis and* trans-C^2), 116.8 (*cis or trans*-C^5), 116.7 (*cis or trans*-C^5), 115.3 (*cis or trans*-C^3), 115.1 (*cis or trans*-C^3), 113.7 (*cis and* trans-C^1), 55.6 (*cis and trans-C^7*), 50.1 (*cis*-C^9), 48.8 (*trans*-C^9), 36.4 (*cis*-C^8), 36.0 (*trans*-C^8), 27.3 (*cis*-C^{10}), 25.9 (*trans*-C^{10}). *Data in accordance with literature values.*[122]

(±)-4,9-Dibromo-1,12-dimethoxy-5,5*a*,6,7,7*a*,8-hexahydrocyclopenta[1,2-*a*:1,5-*a*']diindene, 134



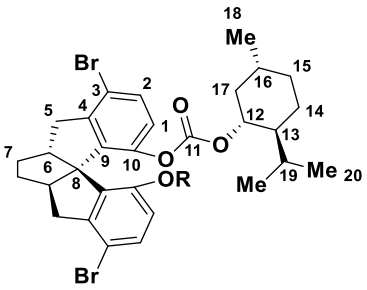
A solution of **133** (6.46 g, 13.4 mmol) in CH_2Cl_2 (10 mL) was added to a round-bottomed flask containing polyphosphoric acid, PPA (64.6 g, 1000 wt%). The gel was heated at 105 °C overnight. After cooling, H_2O (500 mL) was added, and the mixture was extracted with CH_2Cl_2 (5 × 100 mL). The organic layers were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Recrystallization (acetone/hexane) gave the title compound as colourless crystals (2.36 g, 38%). **m.p.** = 206.9 – 207.7 °C (acetone/hexane, Lit.[122]: 193 – 194 °C, no solvent stated); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (d, *J* = 8.5 Hz, 2H, H^2), 6.50 (d, *J* = 8.5 Hz, 2H, H^1), 3.55 (s, 6H, H^{11}), 3.36 (ddd, *J* = 16.5, 8.5, 1.0 Hz, 2H, H^5), 2.81 – 2.62 (m, 4H, $H^{5'}$, H^6), 2.04 (m, 2H, H^7), 1.35 – 1.20 (m, 2H, $H^{7'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.0 (C^{10}), 144.9 (C^4), 137.6 (C^9), 130.7 (C^2), 111.1 (C^1), 111.0 (C^3), 74.5 (C^8), 55.7 (C^{11}), 50.2 (C^6), 40.1 (C^5), 35.1 (C^7). *Data in accordance with literature values.*[122]

(±)-4,9-Dibromo-5,5a,6,7,7a,8-hexahydrocyclopenta[1,2-a:1,5-a']diindene-1,12-diol, 135



To a flame-dried two-necked flask under nitrogen was added a solution of **134** (1.38 g, 2.97 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was cooled to -78 °C before addition of BBr_3 (1M in CH_2Cl_2, 7.43 mL, 7.43 mmol) dropwise. The reaction was stirred at room temperature for 16 h before quenching with sat. aq. $NaHCO_3$ solution at 0 °C. After gas evolution had stopped, the mixture was extracted with CH_2Cl_2 (3 × 15 mL), dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a white powder (1.07 g, 83%). $\mathbf{R_f}$ = 0.50 (hexane/EtOAc, 4:1); **m.p.** = 196.7 – 198.7 °C (hexane/EtOAc); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3525 (w), 3332 (br), 2942 (m), 2854 (w), 1688 (s), 1577 (m), 1281 (s), 1257 (s); **^{1}H NMR** (400 MHz, acetone-d^6) δ 8.03 (s, 2H, H^{11}), 6.98 (d, *J* = 8.5 Hz, 2H, H^2), 6.46 – 6.30 (m, 2H, H^1), 3.30 (ddd, *J* = 16.5, 8.5, 2.0 Hz, 2H, H^5), 2.65 (dddd, *J* = 10.5, 8.5, 6.5, 2.0 Hz, 2H, H^6), 2.59 – 2.51 (m, 2H, H$^{5'}$), 1.99 – 1.86 (m, 2H, H^7), 1.23 – 1.09 (m, 2H, H$^{7'}$); **^{13}C NMR** (101 MHz, acetone-d^6) δ 154.3 (C^{10}), 145.7 (C^4), 136.7 (C^9), 131.2 (C^2), 116.1 (C^1), 109.7 (C^3), 74.9 (C^8), 50.8 (C^6), 40.7 (C^5), 35.6 (C^7); ***m/z*** (ESI$^+$) calc. for $C_{19}H_{16}{}^{79}Br_2O_2$ = 433.95, found: 434.9602 $[M+H]^+$.

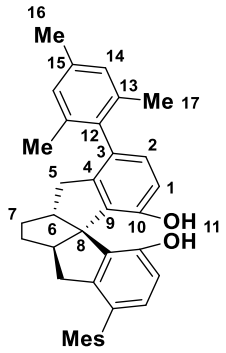
(*R*)-136



To a suspension of TBAB (622 mg, 1.93 mmol) in $CHCl_3$ (10 mL) at 0 °C was added a suspension of **135** (1.68 g, 3.85 mmol) and NaOH (276 mg, 6.89 mmol) in H_2O (10 mL). (1*R*)-(−)-Menthyl chloroformate (2.45 mL, 11.6 mmol) was added dropwise, and the resulting suspension was stirred vigorously at room temperature for 10 mins. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/Et_2O, 19:1) gave the title compound as a white foam (1.07 g, 35%). $\mathbf{R_f}$ = 0.67 (hexane/Et_2O, 19:1); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 2954 (m), 2927 (m), 2869 (m), 1757 (s), 1230 (s); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = -101.3 (c = 0.30, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$)

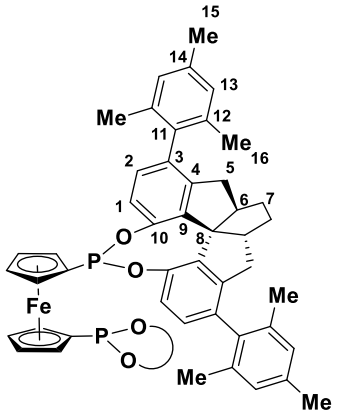
δ 7.34 (d, *J* = 8.5 Hz, 2H, H^{2}), 6.95 (d, *J* = 8.5 Hz, 2H, H^{1}), 4.45 (td, *J* = 11.0, 4.5 Hz, 2H, H^{12}), 3.53 – 3.37 (m, 2H, H^{5}), 2.82 – 2.74 (m, 4H, $H^{5'}$), 2.17 – 1.94 (m, 4H, R-C$\underline{H}_2$), 1.78 – 1.62 (m, 6H, R-C$\underline{H}$, R-C$\underline{H}_2$), 1.53 – 1.22 (m, 14H, R-C$\underline{H}$, R-C$\underline{H}_2$), 1.17 – 0.98 (m, 4H, R-C$\underline{H}_2$), 0.94 (d, *J* = 6.5 Hz, 6H, H^{20}), 0.89 (m, 8H, $H^{20'}$, R-C$\underline{H}$), 0.68 (d, *J* = 7.0 Hz, 6H, H^{18}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.4 (C^{11}), 147.3 (C^{10}), 145.4 (C^{4}), 139.8 (C^{9}), 131.2 (C^{2}), 121.7 (C^{1}), 116.4 (C^{3}), 79.5 (C^{12}), 74.2 (C^{8}), 50.8 (C^{6}), 46.8 (R-$\underline{C}$H), 40.6 (R-$\underline{C}H_2$), 40.1 (C^{5}), 34.7 (C^{7}), 34.1 (R-$\underline{C}H_2$), 31.7 (R-$\underline{C}H_2$), 31.5 (R-$\underline{C}$H), 25.8 (R-$\underline{C}$H), 23.1 (R-$\underline{C}H_2$), 22.8 (R-$\underline{C}H_2$), 22.1 (C^{20}), 21.1 ($C^{20'}$), 16.0 (C^{18}); ***m/z*** (ESI$^+$) calc. for $C_{41}H_{52}{}^{79}Br_2O_6$ = 798.21, found: 821.202561 $[M+Na]^+$.

(5*aR*,7*aR*)-4,9-dimesityl-5,5*a*,6,7,7*a*,8-hexahydrocyclopenta[1,2-*a*:1,5-*a'*]diindene-1,12-diol, (*R*)-137



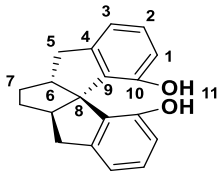
General procedure A: using (*R*)-**136** (500mg, 0.62 mmol) and 2,4,6-trimethylphenylboronic acid (359 mg, 2.19 mmol). Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a white solid (121 mg, 38%). **R_f** = 0.61 (hexane/EtOAc, 4:1); **m.p.** = 253.4 – 259.7 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -178.2 (c = 0.29, CH_2Cl_2); **ν_{max}/cm^{-1}:** 3528 (br), 2941 (s), 2926 (s), 2854 (m), 2732 (w), 1736 (w), 1597 (s), 1504 (m), 1473 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98 (s, 4H, H^{14}), 6.90 (d, *J* = 8.0 Hz, 2H, H^{2}), 6.73 (d, *J* = 8.0 Hz, 2H, H^{1}), 4.50 (s, 2H, H^{11}), 3.15 – 2.91 (m, 4H, H^{5}, H^{6}), 2.37 (s, 8H, $H^{5'}$, H^{16}), 2.02 (d, *J* = 5.0 Hz, 14H, H^{7}, H^{17}), 1.47 (tdd, *J* = 7.5, 5.0, 3.0 Hz, 2H, $H^{7'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.0 (C^{10}), 143.3 (C^{4}), 137.3 (C^{12}), 136.6 (C^{15}), 136.2 (C^{13}), 136.0 (C^{13}), 132.1 (C^{9}), 130.9 (C^{3}), 130.0 (C^{2}), 128.2 (C^{14}), 128.1 ($C^{14'}$), 115.1 (C^{1}), 71.4 (C^{8}), 50.6 (C^{6}), 38.2 (C^{5}), 33.9 (C^{7}), 21.2 (C^{16}), 20.6 (C^{17}), 20.4 ($C^{17'}$); ***m/z*** (ESI$^+$) calc. for $C_{37}H_{38}O_2$: 514.71, found: 515.2953 $[M+H]^+$.

(*R*)-L32



General procedure B: using (*R*)-**137** (114 mg, 0.22 mmol). Purification by FCC (hexane/EtOAc, 19:1, deactivated silica with 10% *w/w* of Et_3N) gave the title compound as an orange solid (21 mg, 15%). $\mathbf{R_f}$ = 0.70 (hexane/EtOAc, 9:1); **m.p.** = 269.3 °C (decomposition, hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = - 218.5 (c = 1.05, $CHCl_3$); $\boldsymbol{\nu_{max}}$**/cm^{-1}:** 3006 (m), 2941 (s), 2926 (s), 2858 (m), 2728 (w), 1744 (w), 1615 (m), 1594 (m), 1467 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.0 Hz, 2H, Ar-C<u>H</u>), 7.00 (d, *J* = 8.0 Hz, 2H, Ar-C<u>H</u>), 6.96 (s, 4H, Ar-C<u>H</u>), 6.91 (d, *J* = 2.5 Hz, 4H, Ar-C<u>H</u>), 6.49 (d, *J* = 8.0 Hz, 2H, H^1), 6.12 (d, *J* = 8.0 Hz, 2H, H^2), 4.59 (d, *J* = 3.5 Hz, 4H, ferrocene), 4.32 (td, *J* = 2.5, 1.0 Hz, 2H, ferrocene), 3.81 (dt, *J* = 2.5, 1.0 Hz, 2H, ferrocene), 2.91 – 2.76 (m, 8H, R-C<u>H</u>$_2$, R-C<u>H</u>), 2.34 (s, 6H, R-C<u>H</u>$_3$), 2.31 (s, 6H, R-C<u>H</u>$_3$), 2.28 – 2.17 (m, 4H, R-C<u>H</u>$_2$), 2.06 (s, 6H, R-C<u>H</u>$_3$), 2.00 (s, 6H, R-C<u>H</u>$_3$), 1.99 (s, 6H, R-C<u>H</u>$_3$), 1.95 (s, 6H, R-C<u>H</u>$_3$), 1.79 (m, 4H, R-C<u>H</u>$_2$), 1.66 – 1.48 (m, 8H, R-C<u>H</u>$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.9 (Ar-<u>C</u>), 145.8 (Ar-<u>C</u>), 143.2 (Ar-<u>C</u>), 143.0 (Ar-<u>C</u>), 142.3 (Ar-<u>C</u>), 140.8 (Ar-<u>C</u>), 137.4 (Ar-<u>C</u>), 137.2 (Ar-<u>C</u>), 136.7 (Ar-<u>C</u>), 136.5 (Ar-<u>C</u>), 136.2 (Ar-<u>C</u>), 135.9 (Ar-<u>C</u>), 135.7 (Ar-<u>C</u>), 133.7 (Ar-<u>C</u>), 132.6 (Ar-<u>C</u>), 129.7 (Ar-<u>C</u>H), 128.3 (Ar-<u>C</u>H), 128.1 (Ar-<u>C</u>H), 128.0 (Ar-<u>C</u>H), 127.8 (Ar-<u>C</u>H), 122.7 (C^2), 121.2 (Ar-<u>C</u>H), 72.2 (ferrocene), 71.9 (ferrocene), 70.9 (ferrocene), 52.9 (CH), 40.6 (R-<u>C</u>H$_2$), 31.9 (R-<u>C</u>H$_2$), 31.5 (R-<u>C</u>H$_2$), 21.2 (R-<u>C</u>H$_3$), 21.0 (R-<u>C</u>H$_3$), 20.5 (R-<u>C</u>H$_3$), 20.4 (R-<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 162.75; ***m/z*** (ESI^+) calc. for $C_{84}H_{80}FeO_4P_2$ = 1270.49, found: 1271.4982 $[M+H]^+$.

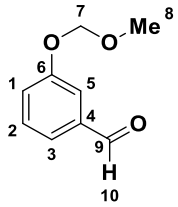
(5*aR*,7*aR*)-5,5*a*,6,7,7*a*,8-hexahydrocyclopenta[1,2-*a*:1,5-*a*']diindene-1,12-diol, (*R*)-138



(*R*)-**136** (350 mg, 0.80 mmol) and Pd/C (20%, 35 mg, 20 wt%) were added to a round bottom flask. MeOH (5 mL) and AcOH (2 mL) were added before the flask was sealed with a rubber septum and evacuated/refilled three times with nitrogen. The solution was sparged with a balloon of hydrogen for 2 mins and stirred at room temperature for 2 h. After completion, the solution was sparged with argon

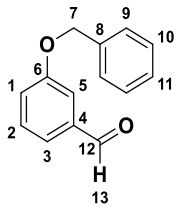
for 15 mins, filtered over Celite® (EtOAc) and concentrated *in vacuo*. The residue was dissolved in EtOAc and basified with sat. aq. solution of $NaHCO_3$. The resulting mixture was extracted with EtOAc (3 × 5 mL), washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo.* Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a colourless wax (194 mg, 87%). $\mathbf{R_f}$ = 0.25 (hexane/EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = - 195.7 (c = 0.49, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.5 Hz, 2H, H^2), 6.84 (dd, *J* = 7.5, 1.0 Hz, 2H, H^3), 6.61 (dd, *J* = 7.5, 1.0 Hz, 2H, H^1), 4.59 (s, 2H, H^{11}) 3.50 – 3.40 (m, 2H, H^5), 2.98 (m, 2H, H^6), 2.84 – 2.75 (m, 2H, $H^{5'}$), 2.12 – 1.94 (m, 2H, H^7), 1.65 – 1.53 (m, 2H, $H^{7'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.1 (C^{10}), 145.2 (C^4), 132.0 (C^9), 129.7 (C^2), 117.6 (C^3), 114.3 (C^1), 70.6 (C^8), 51.0 (C^6), 38.9 (C^5), 33.2 (C^7). *Data in accordance with literature values.*[122]

3-(Methoxymethoxy)benzaldehyde, 145a



To a solution of 3-hydroxybenzaldehyde (2.45 g, 20.0 mmol) and DIPEA (10.5 mL, 60.0 mmol) in CH_2Cl_2 (50 mL) was added chloromethyl methyl ether (1.67 mL, 22.0 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 16 h before quenching with sat. aq. $NaHCO_3$ (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a colourless liquid (2.82 g, 85%). $\mathbf{R_f}$ = 0.61 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.96 (s, 1H, H^{10}), 7.55 – 7.48 (m, 2H, H^3, H^5), 7.43 (t, *J* = 8.0 Hz, 1H, H^2), 7.28 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, H^1), 5.21 (s, 2H, H^7), 3.47 (s, 3H, H^8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.1 (C^9), 157.9 (C^6), 137.9 (C^4), 130.2 (C^2), 123.9 (C^3/C^5), 122.9 (C^1), 116.0 (C^3/C^5), 94.5 (C^7), 56.2 (C^8); ***m/z*** (ESI^+) calc. for $C_9H_{10}O_3$ = 166.18, found: 189.0529 $[M+Na]^+$. *Data in accordance with literature values.*[125]

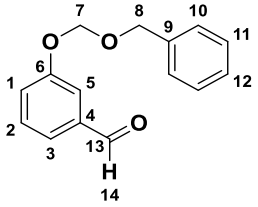
3-(Benzyloxy)benzaldehyde, 145b



To a solution of 3-hydroxybenzaldehyde (3.05 g, 25 mmol) and K_2CO_3 (2.46 g, 17.8 mmol) in EtOH (30 mL) was added benzyl chloride dropwise (4.32 mL, 37.5 mmol). The reaction mixture was heated at 80 °C for 24 h. After cooling, the residue was dissolved in CH_2Cl_2 (10 mL), washed with sat. aq.

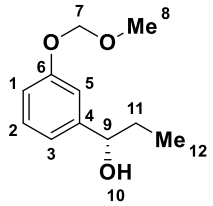
$NaHCO_3$ (3 × 10 mL), dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as colourless crystals (4.58 g, 86%). $\mathbf{R_f}$ = 0.72 (hexane/EtOAc, 9:1); **m.p.** = 55.9 – 57.6 °C (EtOAc/hexane, Lit.[125]: 55 – 56 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.95 (s, 1H, H^{13}), 7.54 – 7.30 (m, 8H, Ar-H), 7.24 (ddd, *J* = 7.5, 2.5, 1.5 Hz, 1H, Ar-H), 5.08 (s, 2H, H^7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.9 (C^{12}), 159.2 (C^6), 137.7 (C^4), 136.3 (C^8), 130.0 (Ar-CH), 128.6 (Ar-CH), 128.1 (Ar-CH), 127.5 (Ar-CH), 123.5 (Ar-CH), 122.0 (Ar-CH), 113.2 (Ar-CH), 70.0 (C^7). *Data in accordance with literature values.*[125]

3-((benzyloxy)methoxy)benzaldehyde, 145c



To a solution of 3-hydroxybenzaldehyde (3.05 g, 25.0 mmol) in DMF (70 mL) was added NaH (60% in mineral oil, 1.50 g, 37.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 mins before BOMCl (5.22 mL, 37.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 3 h then quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (5 × 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 19:1) gave the title compound as a colourless oil (4.56 g, 75%); $\mathbf{R_f}$ = 0.60 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.98 (s, 1H, H^{14}), 7.59 (m, 1H, H^5), 7.54 (*pseudo*-dt, *J* = 7.5, 1.5 Hz, 1H, H^3), 7.46 (t, *J* = 7.5 Hz, 1H, H^2), 7.39 – 7.27 (m, 6H, H^1, H^{10}, H^{11}, H^{12}), 5.35 (s, 2H, H^7), 4.74 (s, 2H, H^8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.1 (C^{13}), 157.9 (C^6), 138.0 (C^4), 137.1 (C^9), 130.3 (C^2), 128.6 (C^{10}/C^{11}/C^{12}), 128.1 (C^{10}/C^{11}/C^{12}), 128.0 (C^{10}/C^{11}/C^{12}), 123.9 (C^3), 122.9 (C^1), 116.3 (C^5), 92.3 (C^7), 70.3 (C^8). *Data in accordance with literature values.*[125]

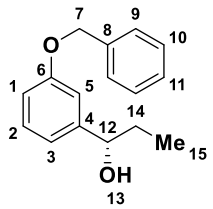
(*S*)-1-(3-(methoxymethoxy)phenyl)propan-1-ol, (*S*)-146a



General procedure E: using **145a** (1.90 g, 11.4 mmol). Purification by FCC (hexane/EtOAc, 9:1 → 4:1) gave the title compound as a colourless oil (1.90 g, 85%). $\mathbf{R_f}$ = 0.28 (hexane/EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = - 11.4 (c = 0.27, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 8.0 Hz, 1H, H^2), 7.01 – 6.98 (m, 1H, H^5), 6.96 – 6.89 (m, 2H, H^3), 5.13 (s, 2H, H^7), 4.50 (t, *J* = 6.5 Hz, 1H, H^9), 3.44 (s, 3H, H^8), 2.66 (br, 1H, H^{10}), 1.73 (m, 2H, H^{11}), 0.89 (t, *J* = 7.5 Hz, 3H, H^{12}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.3

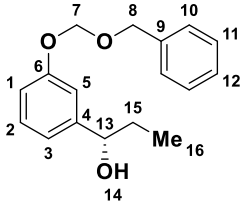
(C^6), 146.6 (C^4), 129.4 (C^2), 119.6 (C^3), 115.1 (C^1), 113.9 (C^5), 94.4 (C^7), 75.7 (C^9), 55.9 (C^8), 31.8 (C^{11}), 10.2 (C^{12}); **SFC Conditions:** DAICEL CHIRALPAK-IB column (25 cm), CO_2/MeOH (99:1), 2 mL/min, 140 bar, 60 °C. Retention times /mins: 19.1 (major), 22.2 (minor), *e.r.* = 96.5:3.5, *e.e.* = 93%. *Data in accordance with literature values.*[125]

(*S*)-1-(3-(Benzyloxy)phenyl)propan-1-ol, (*S*)-146b



General procedure E: using **145b** (2.12 g, 10 mmol). Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a colourless oil (2.08 g, 86%). $\mathbf{R_f}$ = 0.42 (4:1, hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = -17.4 (c = 0.31, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H, H^9), 7.42 – 7.36 (m, 2H, H^{10}), 7.35 – 7.29 (m, 1H, H^{11}), 7.29 – 7.23 (m, 1H, H^2), 7.00 (t, *J* = 1.5 Hz, 1H, H^5), 6.94 (dt, *J* = 7.5, 1.5 Hz, 1H, H^3), 6.89 (ddd, *J* = 7.5, 2.5, 1.5 Hz, 1H, H^1), 5.07 (s, 2H, H^7), 4.58 (td, *J* = 6.5, 3.0 Hz, 1H, H^{12}), 1.88 – 1.66 (m, 3H, H^{13}, H^{14}), 0.92 (t, *J* = 7.5 Hz, 3H, H^{15}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.1 (C^6), 146.5 (C^4), 137.1 (C^8), 129.6 (C^2), 128.7 (C^{10}), 128.1 (C^{11}), 127.7 (C^9), 118.7 (C^3), 114.0 (C^1), 112.6 (C^5), 76.1 (C^{12}), 70.1 (C^7), 32.0 (C^{14}), 10.3 (C^{15}); **SFC Conditions:** DAICEL CHIRALPAK-IA column (25 cm), CO_2/isopropanol (95:5), 1 mL/min, 140 bar, 60 °C. Retention times /mins: 23.4 (minor), 25.7 (major), *e.r.* = 4:96, *e.e.* = 92%. *Data in accordance with literature values.*[125]

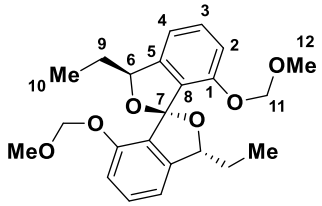
(*S*)-1-(3-((Benzyloxy)methoxy)phenyl)propan-1-ol, (*S*)-146c



General procedure E: using **145c** (606 mg, 2.5 mmol). Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a colourless oil (574 mg, 84%). $\mathbf{R_f}$ = 0.29 (4:1, hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -14.3 (c = 0.23, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 6H, H^2, H^9, H^{10}, H^{11}), 7.08 (*pseudo*-t, *J* = 2.0 Hz, 1H, H^5), 7.04 – 6.97 (m, 2H, H^1, H^3), 5.30 (s, 2H, H^7), 4.74 (s, 2H, H^8), 4.57 (td, *J* = 6.5, 2.5 Hz, 1H, H^{13}), 1.98 (d, *J* = 2.5 Hz, 1H, H^{14}), 1.90 – 1.68 (m, 2H, H^{15}), 0.93 (t, *J* = 7.5 Hz, 3H, H^{16}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6 (C^6), 146.6 (C^4), 137.4 (C^9), 129.6 (C^2), 128.6 (C^{10}/C^{11}/C^{12}), 128.2 (C^{10}/C^{11}/C^{12}), 128.0 (C^{10}/C^{11}/C^{12}), 119.6 (C^1/C^3), 115.3 (C^1/C^3), 114.1 (C^5), 92.4 (C^7), 75.9 (C^{13}), 70.0 (C^8), 32.0 (C^{15}), 10.3 (C^{16}); **SFC Conditions:** DAICEL CHIRALPAK-IA column (25 cm),

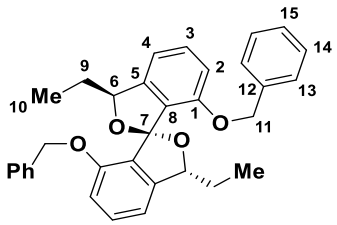
CO_2/isopropanol (96:4), 2 mL/min, 140 bar, 60 °C. Retention times /mins: 19.3 (minor), 20.5 (major), *e.r.* = 5:95, *e.e.* = 90%. *Data in accordance with literature values.*[125]

(3*R*,3'*S*)-3,3'-Diethyl-7,7'-bis(methoxymethoxy)-3*H*,3'*H*-1,1'-spirobi[isobenzofuran], (*R*)-147a



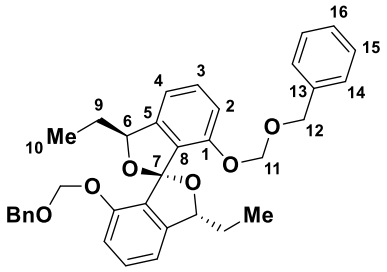
General procedure F: using (*S*)-**146a** (196 mg, 1.00 mmol). Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a colourless oil (108 mg, 27%); $\mathbf{R_f}$ = 0.52 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{19}}$ = 9.27 (c = 0.35, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H, H^3), 6.92 – 6.80 (m, 4H, H^2, H^4), 5.40 – 5.35 (m, 2H, H^6), 4.93 (d, *J* = 6.5 Hz, 2H, H^{11}), 4.80 (d, *J* = 6.5 Hz, 2H, $H^{11'}$), 3.05 (s, 6H, H^{12}), 2.01 – 1.72 (m, 4H, H^9), 1.02 (t, *J* = 7.5 Hz, 6H, H^{10}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.6 (C^1), 145.7 (C^5), 130.7 (C^3), 127.9 (C^8), 116.0 (C^7), 114.1 (C^2/C^4), 112.3 (C^2/C^4), 93.4 (C^{11}), 83.2 (C^6), 55.7 (C^{12}), 28.2 (C^9), 9.8 (C^{10}). *Data in accordance with literature values.*[125]

(3*R*,3'*S*)-7,7'-Bis(benzyloxy)-3,3'-diethyl-3*H*,3'*H*-1,1'-spirobi[isobenzofuran], (*R*)-147b



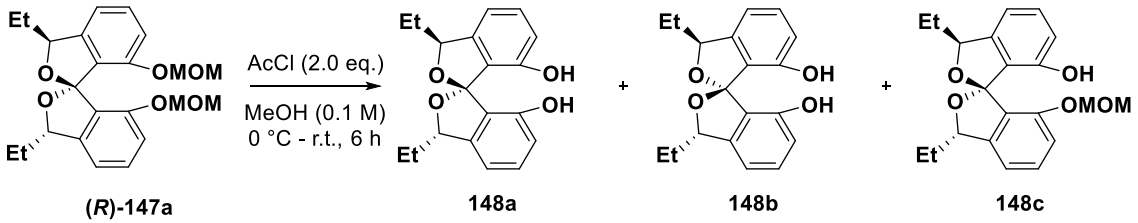
General procedure F: using (*S*)-**146b** (125 mg, 0.52 mmol). Purification by FCC (hexane/EtOAc, 9:1 → 4:1) gave the title compound as a colourless oil (11.0 mg, 4%); $\mathbf{R_f}$ = 0.59 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = -79.5 (c = 0.61, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H, H^3), 7.16 – 7.06 (m, 6H, H^{14}, H^{15}), 6.87 – 6.80 (m, 4H, H^2, H^4), 6.70 – 6.65 (m, 4H, H^{13}), 5.39 (dd, *J* = 7.0, 4.0 Hz, 2H, H^6), 4.89 (m, 4H, H^{11}, $H^{11'}$), 1.84 – 1.60 (m, 4H, H^9), 0.85 (t, *J* = 7.5 Hz, 6H, H^{10}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.4 (C^1), 146.0 (C^5), 136.8 (C^{12}), 130.7 (C^3), 128.1 (C^{14}/C^{15}), 127.6 (C^8), 127.3 (C^{14}/C^{15}), 126.6 (C^{13}), 116.0 (C^7), 113.7 (C^2/C^4), 110.5 (C^2/C^4), 83.3 (C^6), 69.0 (C^{11}), 27.9 (C^9), 9.8 (C^{10}). *Data in accordance with literature values.*[125]

(3*R*,3'*S*)-7,7'-bis((benzyloxy)methoxy)-3,3'-diethyl-3*H*,3'*H*-1,1'-spirobi[isobenzofuran], (*R*)-147c



General procedure F: using (*S*)-**146c** (160 mg, 0.59 mmol). Purification by FCC (hexane/EtOAc, 9:1 → 4:1) gave the title compound as a colourless oil (62 mg, 19%); $\mathbf{R_f}$ = 0.54 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.0, 7.5 Hz, 2H, H^3), 7.31 – 7.24 (m, 6H, H^{15}, H^{16}), 7.10 – 7.03 (m, 4H, H^{14}), 7.02 – 6.98 (m, 2H, H^2), 6.96 (m, 2H, H^4), 5.50 – 5.42 (m, 2H, H^6), 5.07 (d, *J* = 6.5 Hz, 2H, H^{11}), 4.89 (d, *J* = 6.5 Hz, 2H, $H^{11'}$), 4.26 – 4.17 (m, 4H, H^{12}), 2.08 – 1.83 (m, 4H, H^9), 1.07 (t, *J* = 7.5 Hz, 6H, H^{10}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.7 (C^1), 145.9 (C^5), 136.8 (C^{13}), 130.9 (C^3), 128.4 (C^{14}/C^{15}/C^{16}), 128.3 (C^{14}/C^{15}/C^{16}), 127.9 (C^8), 116.1 (C^7), 114.2 (C^2), 112.2 (C^4), 90.4 (C^{11}), 83.4 (C^6), 69.2 (C^{12}), 28.3 (C^9), 10.00 (C^{10}). *Data in accordance with literature values.*[125]

Deprotection of (*R*)-147a

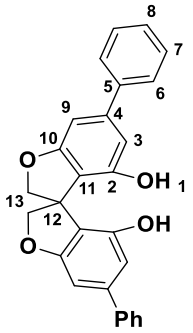


To a flask containing (*R*)-**147a** (95 mg, 0.24 mmol) in MeOH (2.4 mL) was added AcCl (34 µL, 0.47 mmol) dropwise at 0 °C. The reaction was stirred at room temperature for 6 h before adding to a sat. aq. solution of $NaHCO_3$ at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and extracts were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo.* Purification by FCC (hexane/EtOAc, 9:1 → 4:1) afforded an inseparable mixture of **148a** and **148b** (16 mg, 21%, **148a : 148b** = 2.6 : 1.0) and **148c** (20 mg, 24%).

Data for **148a/148b:** $\mathbf{R_f}$ = 0.27 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 2.8H, Ar-C<u>H</u>, 148a, 148b), 6.86 – 6.81 (m, 2.8H, Ar-C<u>H</u>, 148a, 148b), 6.75 (d, *J* = 8.0, 1.9H, Ar-C<u>H</u>, 148a), 6.71 (d, *J* = 8.0 Hz, 0.7H, Ar-C<u>H</u>, 148b), 5.39 (dd, *J* = 7.0, 4.0 Hz, 2H, R-C<u>H</u>, 148a), 5.25 (dd, *J* = 7.0, 4.0 Hz, 0.7H, R-C<u>H</u>, 148b), 2.10 – 1.74 (m, 6.9H, R-C<u>H</u>$_2$, 148a, 148b) 1.05 (t, *J* = 7.5 Hz, 2.9H, R-C<u>H</u>$_3$, 148b), 1.00 (t, *J* = 7.5 Hz, 6H, R-C<u>H</u>$_3$, 148a).

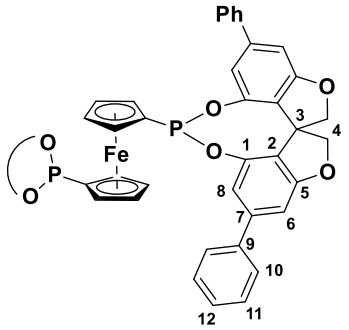
Data for **148c**: **R_f =** 0.25 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (t, *J* = 7.5 Hz, 1H, Ar-C<u>H</u>), 7.30 – 7.25 (t, *J* = 7.5 Hz, 2H, Ar-C<u>H</u>), 6.98 (d, *J* = 7.5 Hz, 1H, Ar-C<u>H</u>), 6.92 (d, *J* = 7.5 Hz, 1H, Ar-C<u>H</u>), 6.81 (d, *J* = 7.5 Hz, 1H, Ar-C<u>H</u>), 6.71 (d, *J* = 7.5 Hz, 1H, Ar-C<u>H</u>), 5.41 (td, *J* = 6.5, 4.0 Hz, 2H, R-C<u>H</u>), 4.99 (d, *J* = 6.5 Hz, 1H, R-C<u>H</u>$_2$), 4.87 (d, *J* = 6.5 Hz, 1H, R-C<u>H</u>$_2$), 4.55 (s, 1H, O<u>H</u>), 3.12 (s, 3H, R-C<u>H</u>$_3$), 2.14 – 1.94 (m, 2H, R-C<u>H</u>$_2$), 1.90 – 1.75 (m, 2H, R-C<u>H</u>$_2$), 1.01 (td, *J* = 7.5, 6.5 Hz, 6H, R-C<u>H</u>$_3$). *Data in accordance with literature values.*[125]

(*R*) or (*S*)-160



To a solution of (*R*) or (*S*)-**159** (210 mg, 0.27 mmol) in EtOH, H_2O and THF (1:1:1, 5.4 mL) was added KOH (152 mg, 2.7 mmol) and the reaction mixture was heated at 80 °C for 1 h. After cooling, aq. 2M HCl (5 mL) was added and the mixture was extracted with Et_2O (3 × 5 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC (acetone/toluene 2:98) gave the title compound as a white solid (76 mg, 69%). **R_f** = 0.23 (hexane/EtOAc, 9:1); **m.p.** = 202.1 – 203.8 °C (hexane/EtOAc); $[\alpha]_D^{24}$ = - 48.9 (c = 0.10, $CHCl_3$); **ν_{max}/cm^{-1}:** 3403 (br), 2928 (w), 1626 (s), 1609 (s), 1576 (m), 1518 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 4H, H^6), 7.45 – 7.39 (m, 4H, H^7), 7.38 – 7.33 (m, 2H, H^8), 6.77 (d, *J* = 1.5 Hz, 2H, H^9), 6.66 (d, *J* = 1.5 Hz, 2H, H^3), 5.12 (s, 2H, H^1) 4.89 (d, *J* = 9.0 Hz, 2H, H^{13}), 4.62 (d, *J* = 9.0 Hz, 2H, H$^{13'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.3 (C^{10}), 153.0 (C^2), 145.1 (C^5), 140.6 (C^4), 128.9 (C^7), 127.9 (C^8), 127.3 (C^6), 113.2 (C^{11}), 109.0 (C^3), 102.3 (C^9), 80.1 (C^{13}), 53.8 (C^{12}); ***m/z*** (ESI$^+$) calc. for $C_{27}H_{20}O_4$ = 408.14, found: 409.1439 $[M+H]^+$.

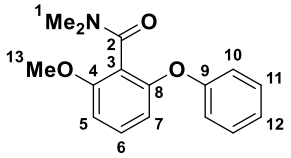
(*R*) or (*S*)-L37



(*R*) or (*S*)

General Procedure B: using (*R*) or (*S*)-**160** (73 mg, 0.18 mmol). Purification by FCC (hexane/EtOAc, 19:1, deactivated silica with 10% *w/w* of Et_3N) afforded the title compound as an orange solid (5.3 mg, 6%). $\mathbf{R_f}$ = 0.50 (hexane/EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +466.7 (c = 0.27, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 16H, Ar-C<u>H</u>), 7.18 – 7.15 (m, 4H, Ar-C<u>H</u>), 6.98 (s, 2H, Ar-C<u>H</u>), 6.93 (s, 2H, Ar-C<u>H</u>), 6.74 (d, *J* = 1.5 Hz, 2H, Ar-C<u>H</u>), 6.07 (d, *J* = 1.5 Hz, 2H, Ar-C<u>H</u>), 4.72 (d, *J* = 8.0 Hz, 4H, H^4, ferrocene), 4.68 (d, *J* = 8.0 Hz, 2H, $H^{4'}$), 4.64 (br. s, 2H, ferrocene), 4.41 – 4.38 (br. m, 2H, ferrocene), 4.30 (dd, *J* = 8.0, 2.0 Hz, 2H, $H^{4''}$), 4.19 (dd, *J* = 8.0, 2.0 Hz, 2H, $H^{4'''}$), 4.05 – 4.02 (br. m, 2H, ferrocene); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.6 (Ar-<u>C</u>), 162.4 (Ar-<u>C</u>), 150.7 (Ar-<u>C</u>), 145.7 (Ar-<u>C</u>), 143.6 (Ar-<u>C</u>), 140.7 (Ar-<u>C</u>), 140.6 (Ar-<u>C</u>), 128.9 (Ar-<u>C</u>H), 128.7 (Ar-<u>C</u>H), 128.0 (C^{12}), 127.7 ($C^{12'}$), 127.4 (Ar-<u>C</u>H), 127.1 (Ar-<u>C</u>H), 121.0 (Ar-<u>C</u>), 119.4 (Ar-<u>C</u>), 116.5 (Ar-<u>C</u>H), 115.1 (Ar-<u>C</u>H), 106.4 (Ar-<u>C</u>H), 105.4 (Ar-<u>C</u>H), 80.8 (C^4), 80.7 ($C^{4'}$), 73.0 (ferrocene), 72.7 (ferrocene), 72.2 (ferrocene), 70.2 (ferrocene), 69.3 (ferrocene), 54.1 (C^3); **^{31}P NMR** (202 MHz, $CDCl_3$) δ 162.9; ***m/z*** (ESI^+) calc. for $C_{64}H_{44}FeO_8P_2$ = 1058.84, found: 1059.1947 $[M+H]^+$.

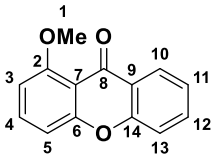
2-Methoxy-*N*,*N*-dimethyl-6-phenoxybenzamide, 162



To a solution of 3-phenoxyanisole (2.50 g, 12.5 mmol) in THF (10 mL) was added *n*-BuLi (6.25 mL, 2.40 M in THF) at -78 °C. The solution was stirred at -78 °C for 2 h then at room temperature for 1 h. This solution was added to a solution of dimethylcarbamoyl chloride (1.15 mL, 12.5 mmol) in THF (12.5 mL) at -78 °C and stirred for 16 h at room temperature. The reaction was quenched with sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL), organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 4:1) afforded the title compound as a yellow oil (2.15 g, 63%). In most cases, the crude material was used without further purification; $\mathbf{R_f}$ = 0.25 (hexane/EtOAc, 4:1); **^{1}H NMR** (500 MHz,

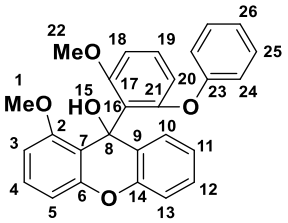
$CDCl_3$) δ 7.35 – 7.28 (m, 2H, Ar-C<u>H</u>), 7.20 (t, *J* = 8.5 Hz, 1H, Ar-C<u>H</u>), 7.10 (tt, *J* = 7.0, 1.0 Hz, 1H, Ar-C<u>H</u>), 7.07 – 7.01 (m, 2H, Ar-C<u>H</u>), 6.66 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-C<u>H</u>), 6.46 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-C<u>H</u>), 3.85 (s, 3H, H^{13}), 3.09 (s, 3H, H^{1}), 2.92 (s, 3H, $H^{1'}$). *Data in accordance with literature values.*[127]

1-Methoxy-9*H*-xanthen-9-one, 163



To a solution of freshly prepared LDA (33.6 mmol, 0.8 M solution in THF) was added a solution of **162** (3.64 g, 13.4 mmol) in THF (46 mL) at -78 °C. The solution was stirred at -78 °C for 15 mins then at 0 °C for 1 h. The reaction was quenched with 2M HCl (100 mL) at 0 °C and extracted with EtOAc (3 × 100 mL), organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc 2:3 → 1:1) gave the title compound as pale-yellow solid (2.43 g, 66%). $\mathbf{R_f}$ = 0.21 (hexane/EtOAc, 4:1); **m.p.** = 134.2 – 136.0 °C (hexane/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.0, 1.5 Hz, 1H, H^{10}), 7.67 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H, H^{12}), 7.60 (t, *J* = 8.5 Hz, 1H, H^{4}), 7.42 (dd, *J* = 8.5, 1.0 Hz, 1H, H^{13}), 7.34 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H, H^{11}), 7.06 (dd, *J* = 8.5, 1.0 Hz, 1H, H^{5}), 6.80 (dd, *J* = 8.5, 1.0 Hz, 1H, H^{3}), 4.03 (s, 3H, H^{10}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.7 (C^{8}), 161.0 (C^{2}), 158.3 (C^{6}), 155.2 (C^{14}), 135.0 (C^{4}), 134.3 (C^{12}), 127.0 (C^{10}), 124.0 (C^{11}), 123.2 (C^{9}), 117.4 (C^{13}), 112.8 (C^{7}), 110.2 (C^{5}), 105.5 (C^{3}), 56.6 (C^{1}). *Data in accordance with literature values.*[127]

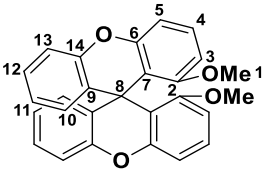
1-Methoxy-9-(2-methoxy-6-phenoxyphenyl)-9*H*-xanthen-9-ol, 164



To a solution of 3-phenoxyanisole (1.00 g, 5.0 mmol) in THF (4.0 mL) was added *n*-BuLi (2.53 mL, 2.37 M in THF) at -78 °C. The solution was stirred at -78 °C for 2 h then at room temperature for 1 h. This solution was added to a solution of **163** (1.13 g, 5.0 mmol) in THF (5.0 mL) at -78 °C and stirred for 16 h at room temperature. The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL), organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Trituration with acetone afforded the title compound as an off-white solid (950 mg, 45%). **m.p.** = 200.7 – 202.8 °C (acetone); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C<u>H</u>), 7.16 – 7.04 (m, 5H, Ar-C<u>H</u>), 7.00 – 6.90 (m, 3H, Ar-C<u>H</u>), 6.86

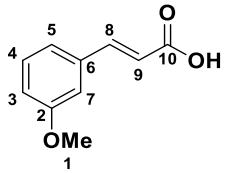
(dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C<u>H</u>), 6.69 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-C<u>H</u>), 6.66 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-C<u>H</u>), 6.54 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-C<u>H</u>), 6.49 (d, *J* = 8.0 Hz, 2H, Ar-C<u>H</u>), 6.37 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-C<u>H</u>), 3.82 (s, 3H, O<u>Me</u>), 3.71 (s, 3H, O<u>Me</u>); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.2 (Ar-<u>C</u>), 158.0 (Ar-<u>C</u>), 157.0 (Ar-<u>C</u>), 154.4 (Ar-<u>C</u>), 150.5 (Ar-<u>C</u>), 149.5 (Ar-<u>C</u>), 129.2 (Ar-<u>C</u>H), 128.7 (Ar-<u>C</u>H), 128.3 (Ar-<u>C</u>H), 128.2 (Ar-<u>C</u>H), 128.1 (Ar-<u>C</u>H), 128.0 (Ar-<u>C</u>H), 127.6 (Ar-<u>C</u>H), 122.7 (Ar-<u>C</u>H), 122.4 (Ar-<u>C</u>H), 117.9 (Ar-<u>C</u>H), 116.4 (Ar-<u>C</u>H), 115.2 (Ar-<u>C</u>H), 113.9 (Ar-<u>C</u>H), 109.2 (Ar-<u>C</u>H), 108.4 (Ar-<u>C</u>H), 105.4 (Ar-<u>C</u>H), 70.7 (C^8), 57.2 (O<u>Me</u>), 55.9 (O<u>Me</u>). *Data in accordance with literature values.*[127]

1,1'-Dimethoxy-9,9'-spirobi[xanthene], 165



To a mixture of conc. HCl (2.50 mL) and AcOH (3.70 mL) was added **164** (426 mg, 1.0 mmol). The reaction was heated at 100 °C for 16 h. After cooling, volatiles were removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and washed sequentially with $NaHCO_3$ and brine then dried over sodium sulfate, filtered and solvent removed *in vacuo*. Trituration with acetone afford the title compound as an off-white powder (417 mg, 99%). **m.p.** = 250.9 °C (degradation, acetone); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.0 Hz, 2H, H^4), 7.09 – 7.02 (m, 4H, H^{10}, H^{12}), 6.84 – 6.74 (m, 6H, H^5, H^{11}, H^{13}), 6.39 (dd, *J* = 8.0, 1.0 Hz, 2H, H^3), 3.24 (s, 6H, H^1); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.2 (C^2), 150.4 (C^6), 149.1 (C^{14}), 131.3 (C^{10}), 130.4 (C^9), 128.2 (C^4), 127.0 (C^{12}), 122.8 (C^{11}), 118.0 (C^7), 114.8 (C^{13}), 108.6 (C^5), 107.4 (C^3), 56.1 (C^1), 38.3 (C^8). *Data in accordance with literature values.*[127]

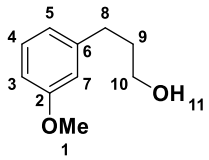
(*E*)-3-(3-Methoxyphenyl)acrylic acid, 167



To a solution of *m*-anisaldehyde (24.3 mL, 200 mmol) and piperidine (1.98 mL, 20 mmol) in pyridine (200 mL) was added malonic acid (22.9 g, 220 mmol). The mixture was heated at 90 °C for 48 h. After cooling, the mixture was acidified to pH 1 with 4M HCl (approx. 200 mL) at 0 °C before the suspension was extracted with EtOAc (5 × 100 mL), washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a white solid (35.4 g, 99%). $\mathbf{R_f}$ = 0.23 (hexane/EtOAc, 4:1); **m.p.** 116.0 – 117.5 °C (hexane/EtOAc, Lit.[275]: 116 – 118 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 16.0 Hz, 1H, H^9), 7.32 (t, *J* = 8.0 Hz, 1H, H^4), 7.15 (dt, *J* = 8.0, 1.5 Hz, 1H, H^5), 7.07 (dd, *J* = 2.5, 1.5 Hz, 1H, H^7), 6.97 (ddd, *J* = 8.0, 2.5, 1.5 Hz, 1H,

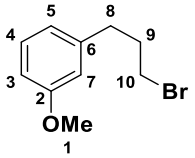
H^3), 6.45 (d, *J* = 16.0 Hz, 1H, H^8), 3.85 (s, 3H, H^1); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.1 (C^{10}), 160.1 (C^2), 147.2 (C^9), 135.5 (C^6), 130.1 (C^4), 121.2 (C^5), 117.6 (C^8), 116.8 (C^3), 113.3 (C^7), 55.5 (C^1). *Data in accordance with literature values.*[276]

3-(3-Methoxyphenyl)propan-1-ol, 168



To a solution of $LiAlH_4$ (7.59 g, 200 mmol) in THF (80 mL) was added a solution of **167** (8.91 g, 50 mmol) in THF (80 mL) dropwise at 0 °C. The mixture was heated at 50 °C for 72 h. The mixture was diluted with Et_2O (100 mL) before sequential addition of H_2O (7.59 mL), NaOH (22.8 mL, 15% w/v in H_2O) and H_2O (22.8 mL) were added dropwise at 0 °C. The mixture was stirred at room temperature for 15 mins before addition of magnesium sulfate (approx. 10 g). After stirring for 15 mins, the solids were filtered and washed with EtOAc before volatile components were removed *in vacuo*. Purification by FCC (hexane/EtOAc, 9:1 → 4:1) gave the title compound as a colourless oil (5.57 g, 67%); $\mathbf{R_f}$ = 0.57 (hexane/EtOAc, 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 1H, H^4), 6.83 – 6.78 (m, 1H, H^5), 6.77 – 6.71 (m, 2H, H^3, H^7), 3.80 (s, 3H, H^1), 3.68 (t, *J* = 6.5 Hz, 2H, H^{10}), 2.69 (t, *J* = 6.5 Hz, 2H, H^8), 1.94 – 1.85 (m, 2H, H^9), 1.36 (br, 1H, H^{11}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.8 (C^2), 143.6 (C^6), 129.5 (C^4), 121.0 (C^5), 114.4 (C^7), 111.3 (C^3), 62.4 (C^{10}), 55.3 (C^1), 34.2 (C^9), 32.3 (C^8). *Data in accordance with literature values.*[277]

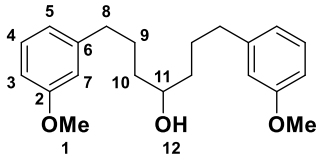
1-(3-Bromopropyl)-3-methoxybenzene, 169



To a solution of triphenylphosphine (15.6 g, 59.6 mmol) in Et_2O (60 mL) was added a solution of **168** (4.95 g, 29.8 mmol) and carbon tetrabromide (19.8 g, 59.6 mmol) in Et_2O (60 mL) at 0 °C. The mixture was stirred at room temperature for 16 h before solids were filtered. To the filtrate was added H_2O (250 mL) and the mixture was extracted with EtOAc (5 × 100 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo.* The crude residue was filtered over a silica plug (EtOAc) and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc 1:99 → 1:9) gave the title compound as a pale yellow liquid (5.15 g, 75%); $\mathbf{R_f}$ = 0.79 (hexane/EtOAc, 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 1H, H^4), 6.80 (m, 1H, H^5), 6.76 (m, 2H, H^3, H^7), 3.81 (s, 3H, H^1), 3.40 (t, *J* = 7.0 Hz, 2H, H^{10}), 2.76 (t, *J* = 7.0 Hz, 2H, H^8), 2.21 – 2.12

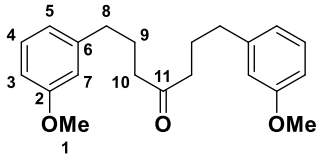
(m, 2H, H^9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9 (C^2), 142.3 (C^6), 129.6 (C^4), 121.1 (C^5), 114.5 (C^7), 111.6 (C^3), 55.3 (C^1), 34.2 (C^9), 34.1 (C^8), 33.2 (C^{10}). *Data in accordance with literature values.*[278]

1,7-Bis(3-methoxyphenyl)heptan-4-ol, 170



Magnesium turnings (601 mg, 24.7 mmol) and one iodine crystal were vigorously stirred for 16 h under nitrogen at 70 °C before a solution of **169** (5.15 g, 22.5 mmol) in THF (22.5 mL) was added dropwise over 15 mins at 60 °C. During this period, the solution changed colour from dark brown to clear to pale yellow. After addition was complete, the solution was heated at 85 °C for a further 3 h before addition of a solution of methyl formate (0.627 mL, 10.1 mmol) in THF (10 mL) dropwise over 10 mins at 0 °C. After addition was complete, the reaction mixture was stirred at room temperature for 16 h. The reaction was acidified to pH 1 using 2M HCl (approx. 50 mL) and extracted with EtOAc (5 × 20 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a colourless liquid (2.89 g, 87%); $\mathbf{R_f}$ = 0.26 (hexane/EtOAc, 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 2H, H^4), 6.79 (d, *J* = 7.5 Hz, 2H, H^5), 6.74 (m, 4H, H^3, H^7), 3.80 (s, 6H, H^1), 3.63 (tt, *J* = 7.5, 4.5 Hz, 1H, H^{11}), 2.68 – 2.55 (m, 4H, H^8), 1.84 – 1.72 (m, 2H, H^{10}), 1.72 – 1.60 (m, 2H, $H^{10'}$), 1.57 (br, 1H, H^{12}), 1.54 – 1.41 (m, 4H, H^9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.7 (C^2), 144.1 (C^6), 129.3 (C^4), 120.9 (C^5), 114.3 (C^7), 111.1 (C^3), 71.7 (C^{11}), 55.2 (C^1), 37.1 (C^9), 36.0 (C^8), 27.4 (C^{10}). *Data in accordance with literature values.*[128]

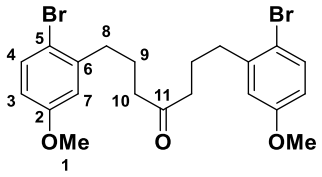
1,7-Bis(3-methoxyphenyl)heptan-4-one, 171



A solution of DMSO (1.44 mL, 20.23 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of $(COCl)_2$ (1.69 mL, 19.69 mmol) in CH_2Cl_2 (60 mL) at -78°C and stirred at this temperature for 15 mins. A solution of **170** (5.88 g, 17.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise at -78 °C and stirred at this temperature for 30 mins before triethylamine (9.36 mL, 67.13 mmol) was added dropwise at -78 °C. The solution was stirred at -78 °C for 15 mins then at room temperature for 3 h before quenching with H_2O (10 mL) and extracting with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by flash FCC (hexane/EtOAc, 4:1) gave title compound as a viscous yellow oil (5.33 g, 91%). $\mathbf{R_f}$ = 0.43

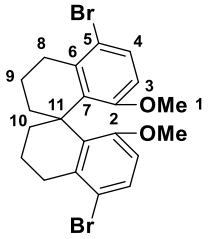
(hexane/EtOAc, 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.5 Hz, 2H, H^4), 6.78 – 6.72 (m, 6H, H^3, H^5, H^7), 3.82 (s, 6H, H^1), 2.61 (t, *J* = 7.5 Hz, 4H, H^8), 2.40 (t, *J* = 7.5 Hz, 4H, H^{10}), 1.96 – 1.87 (m, 4H, H^9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.8 (C^{11}), 159.8 (C^2), 143.4 (C^6), 129.5 (C^4), 121.0 (C^5/C^7), 114.3 (C^5/C^7), 111.4 (C^3), 55.3 (C^1), 42.1 (C^{10}), 35.3 (C^8), 25.2 (C^9). *Data in accordance with literature values.*[128]

1,7-Bis(2-bromo-5-methoxyphenyl)heptan-4-one, 172



N-bromosuccinimide (6.10 g, 34.2 mmol) was added portionwise to a solution of **171** (5.33 g, 16.3 mmol) in acetone (32 mL) at 0 °C before 2M HCl (5 drops) was added dropwise. The solution was stirred at 0 °C for 15 mins then at room temperature for 15 mins. Volatile components were removed *in vacuo* and the residue was dissolved in Et_2O (50 mL), washed with H_2O (50 mL), brine (50 mL), dried over sodium sulfate, filtered and solvent removed *in vacuo.* Purification by flash FCC (hexane/Et_2O, 4:1) gave the title compound as a white solid (7.22 g, 91%); $\mathbf{R_f}$ = 0.37 (hexane/Et_2O, 4:1); **m.p.** = 43.7 – 44.3 °C (hexane/Et_2O, Lit.[128]: 54 – 56 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H, H^4), 6.76 (d, *J* = 3.0 Hz, 2H, H^7), 6.63 (dd, *J* = 8.5, 3.0 Hz, 2H, H^3), 3.77 (s, 6H, H^1), 2.73 – 2.65 (m, 4H, H^8), 2.47 (t, *J* = 7.5 Hz, 4H, H^{10}), 1.90 (p, *J* = 7.5 Hz, 4H, H^9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.4 (C^{11}), 159.1 (C^2), 142.1 (C^6), 133.4 (C^4), 116.2 (C^7), 115.1 (C^5), 113.5 (C^3), 55.6 (C^1), 42.0 (C^{10}), 35.6 (C^8), 24.0 (C^9). *Data in accordance with literature values*[128]

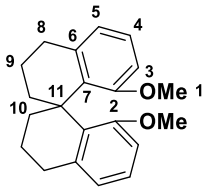
5,5'-Dibromo-8,8'-dimethoxy-3,3',4,4'-tetrahydro-2*H*,2'*H*-1,1'-spirobi[naphthalene], 173



To methanesulfonic acid (14.6 mL) was added **172** (1.77 g, 3.66 mmol) at 0 °C. The reaction mixture was left to stir at room temperature for 16 h before quenching with H_2O (100 mL) at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo*. The crude residue was triturated with EtOAc (5 mL) and the solids were filtered and washed with ice-cold EtOAc to afford the title compound as a white solid (1.09 g, 64%). $\mathbf{R_f}$ = 0.81 (hexane/EtOAc, 9:1); **m.p.** = 212.4 °C (EtOAc, degradation, Lit.[128]: 212 – 214 °C)*;* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 2H, H^4), 6.49

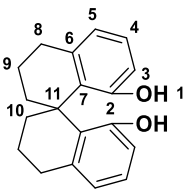
(d, J = 8.5 Hz, 2H, H^3), 3.19 (s, 6H, H^1), 3.10 (m, 2H, H^8), 2.66 – 2.57 (m, 2H, $H^{8'}$), 2.14 – 2.04 (m, 2H, H^{10}), 1.98 (m, 2H, $H^{10'}$), 1.92 – 1.86 (m, 2H, H^9), 1.81 (m, 2H, $H^{9'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.3 (C^2), 138.6 (C^7), 138.3 (C^6), 129.3 (C^4), 116.6 (C^5), 112.2 (C^3), 55.6 (C^1), 40.4 (C^{11}), 33.8 (C^{10}), 31.6 (C^8), 19.9 (C^9). *Data in accordance with literature values.*[128]

8,8'-Dimethoxy-3,3',4,4'-tetrahydro-2*H*,2'*H*-1,1'-spirobi[naphthalene], 174



173 (233 mg, 0.50 mmol) and 10% Pd/C (46 mg, 20 wt%) were added to a round bottom flask. MeOH (10 mL) and AcOH (1.4 mL) were added before the flask was sealed with a rubber septum and evacuated/refilled three times with nitrogen. The solution was sparged with a balloon of hydrogen for 2 mins and stirred at room temperature for 16 h. After completion, the solution was sparged with argon for 15 mins, filtered over Celite® (EtOAc) and concentrated *in vacuo*. The residue was dissolved in EtOAc and basified with sat. aq. solution of $NaHCO_3$. The resulting mixture was extracted with EtOAc (3 × 5 mL), washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo.* Purification by FCC (hexane/EtOAc, 49:1) gave the title compound as a white solid (128 mg, 83%); **R_f** = 0.83 (hexane/EtOAc, 9:1); **m.p.** = 148.9 – 149.9 °C ($CHCl_3$, Lit.[128]: 143 – 145 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.03 (*pseudo*-t, J = 7.5 Hz, 2H, H^4), 6.76 (d, J = 7.5 Hz, 2H, H^5), 6.62 (d, J = 7.5 Hz, 2H, H^3), 3.24 (s, 6H, H^1), 2.96 – 2.78 (m, 4H, H^8), 2.14 (m, 2H, H^{10}), 2.03 (m, 2H, $H^{10'}$), 1.85 (m, 4H, H^9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.4 (C^2), 139.6 (C^6), 136.6 (C^7), 125.2 (C^4), 121.5 (C^5), 111.1 (C^3), 55.6 (C^1), 39.1 (C^{11}), 35.2 (C^{10}), 31.2 (C^8), 20.4 (C^9). *Data in accordance with literature values.*[128]

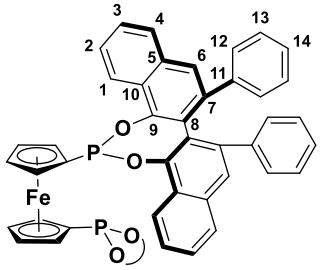
3,3',4,4'-Tetrahydro-2*H*,2'*H*-1,1'-spirobi[naphthalene]-8,8'-diol, 175



To a solution of **174** (520 mg, 1.69 mmol) in CH_2Cl_2 (6.76 mL) was added BBr_3 (4.22 mL, 4.22 mmol, 1M in CH_2Cl_2) at 0 °C. The reaction was stirred at room temperature for 16 h before quenching with sat. aq. $NaHCO_3$ (20 mL) at 0 °C. The mixture was extracted with CH_2Cl_2, organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo.* Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a white foam (364 mg, 77%). **R_f** = 0.13 (hexane/EtOAc, 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.04 (*pseudo*-t, J = 8.0 Hz, 1H, H^4), 6.94 (d, J = 8.0 Hz, 1H, H^5), 6.73 (d, J = 8.0 Hz, 1H, H^3), 6.60 (m, 3H, $H^{3'}$, $H^{4'}$, $H^{5'}$), 4.68 (br, 1H, H^1), 4.54

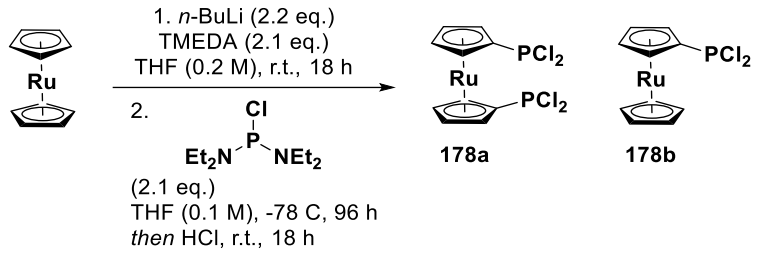
(s, 1H, $H^{1'}$), 2.96 – 2.77 (m, 4H, H^{8}, $H^{8'}$), 2.24 (m, 1H, H^{10}), 2.07 – 1.97 (m, 2H, $H^{10'}$), 1.97 – 1.71 (m, 5H, H^{9}, $H^{9'}$, $H^{10''}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.3 (C^{2}), 154.1 ($C^{2'}$), 139.2 (C^{6}), 138.9 ($C^{6'}$), 135.6 (C^{7}), 131.9 ($C^{7'}$), 130.4 (C^{5}), 127.2 (C^{4}), 121.9 (C^{3}), 115.8 ($C^{3'}$/$C^{4'}$/$C^{5'}$), 115.5 ($C^{3'}$/$C^{4'}$/$C^{5'}$), 115.3 ($C^{3'}$/$C^{4'}$/$C^{5'}$), 40.6 (C^{11}), 40.1 (C^{10}), 33.1 ($C^{10'}$), 31.3 (C^{8}), 30.1 ($C^{8'}$), 19.8 (C^{9}), 19.4 ($C^{9'}$). *Data in accordance with literature values.*[128]

(*R*)-L40

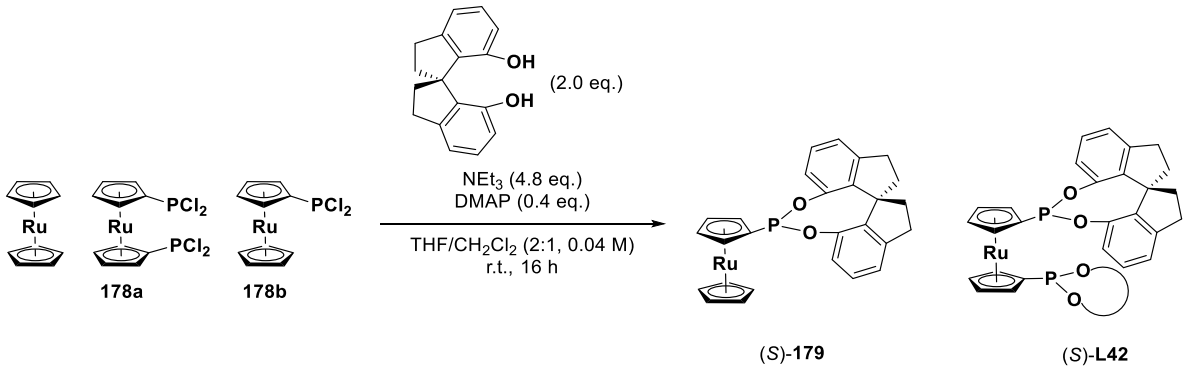


General Procedure B: using (*R*)-VANOL (100 mg, 0.23 mmol). Purification by FCC (hexane/EtOAc, 9:1, deactivated silica with 10% *w/w* of Et_3N) gave the title compound as an orange solid (92 mg, 72%). **R_f** = 0.24 (hexane/EtOAc, 9:1); **m.p.** = 247 °C (degradation, hexane/$CHCl_3$); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = - 391.0 (c = 0.096, CH_2Cl_2); **ν_{max}/cm^{-1}:** 3054 (br), 3029 (br), 2928 (w), 2856 (w), 1631 (w), 1592 (w), 1563 (m), 1488 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 – 8.28 (m, 2H, H^{1}), 7.82 – 7.77 (m, 2H, H^{4}), 7.74 – 7.65 (m, 4H, Ar-H), 7.55 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 2H, H^{2}), 7.48 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 2H, H^{3}), 7.45 (s, 2H, H^{6}), 7.38 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 2H, Ar-CH), 7.34 (s, 2H, $H^{6'}$), 7.30 – 7.23 (m, 2H, Ar-CH), 7.07 – 7.00 (m, 4H, H^{14}), 6.92 – 6.85 (m, 4H, H^{13}), 6.81 (*pseudo*-t, *J* = 8.0 Hz, 4H, $H^{13'}$), 6.51 – 6.46 (m, 4H, H^{12}), 6.45 – 6.41 (m, 4H, $H^{12'}$), 4.98 – 4.94 (m, 2H, ferrocene), 4.71 (d, *J* = 2.5 Hz, 2H, ferrocene), 4.23 (td, *J* = 2.5, 1.0 Hz, 2H, ferrocene), 3.79 (dt, *J* = 2.5, 1.0 Hz, 2H, ferrocene); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.0 (C^{9}), 140.7 (Ar-C), 140.4 (Ar-C), 140.3 (C^{11}), 134.5 (Ar-C), 133.7 (Ar-C), 129.2 (C^{12}), 129.1 ($C^{12'}$), 128.3 (Ar-CH), 127.6 (C^{4}), 127.5 (Ar-CH), 127.4 (C^{13}), 127.0 ($C^{13'}$), 126.8 (Ar-CH), 126.7 (C^{2}), 126.6 (C^{3}), 126.3 (C^{14}), 126.2 ($C^{14'}$), 125.9 (C^{6}), 125.5 (Ar-CH), 125.3 ($C^{6'}$), 124.8 (Ar-CH), 123.0 (Ar-CH), 122.0 (C^{1}), 73.6 (ferrocene), 73.3 (ferrocene), 72.7 (ferrocene), 72.2 (ferrocene), 70.2 (ferrocene); **^{31}P NMR** (202 MHz, $CDCl_3$) δ 193.92; ***m/z*** (ESI^+) calc. for $C_{74}H_{48}FeO_4P_2$ = 1118.24, found: 1119.2432 $[M+H]^+$.

178a/178b:



To a solution of ruthenocene (463 mg, 2.0 mmol) and distilled TMEDA (0.63 mL, 4.2 mmol) in dry, degassed THF (10 mL, 3× freeze, pump, thaw cycles) was added *n*-BuLi (1.87 mL, 2.35 M in hexane). The reaction was stirred for 18 h before addition of a solution of $PCl(NEt_2)_2$ (0.8 mL. 4.2 mmol) in dry, degassed THF (15 mL, 3× freeze, pump, thaw cycles) at -78 °C. The reaction was stirred at room temperature for 96 h before addition of HCl (16 mL, 2M in Et_2O) at -78 °C. After stirring for an additional 18 h at room temperature, the solids were filtered and washed with dry hexane to afford a yellow solid (770 mg) tentatively assigned by ^{1}H NMR analysis as a mixture of **ruthenocene : 178a : 178b** (1.0 : 2.6 : 1.6). The crude mixture was taken through to the next step without further purification; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.07 – 4.87 (m, 1.6H, **178b**), 4.65 (s, 1H, **178a**), 4.55 (s, 2.6H, ruthenocene); **^{31}P NMR** (202 MHz, $CDCl_3$) δ 156.3, 155.4.



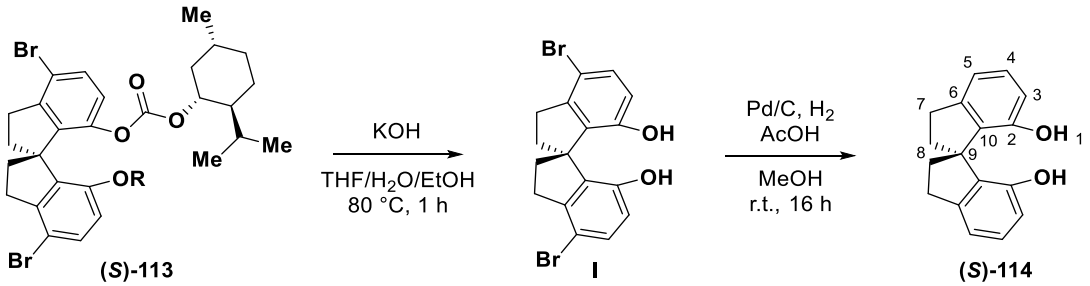
The crude material was added to a flame-dried Schlenk tube (assume 100% purity, 146 mg, 0.34 mmol), (*S*)-SPINOL (170 mg, 0.67 mmol) and DMAP (17 mg, 0.14 mmol). The tube was evacuated and refilled three times with nitrogen before the addition of CH_2Cl_2 (2.8 mL) and THF (5.7 mL). The mixture was cooled to 0 °C before triethylamine (0.23 mL, 1.6 mmol) was added and the resulting mixture was stirred at room temperature for 72 h. After filtration over cotton wool (EtOAc), volatile components were removed *in vacuo*. Purification by FCC (hexane/EtOAc, 19:1, deactivated silica with 10% *w/w* of Et_3N) afforded ruthenocene (29 mg), (*S*)-**179** (36 mg, 21%) and (*S*)-**L42** (12 mg, 5%).

Data for (*S*)-**179**: $\mathbf{R_f}$ = 0.54 (hexane/EtOAc, 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 1H, Ar-C<u>H</u>), 7.07 (t, *J* = 7.5 Hz, 1H, Ar-C<u>H</u>), 6.96 (d, *J* = 7.5 Hz, 1H, Ar-C<u>H</u>), 6.93 – 6.88 (m, 2H, Ar-C<u>H</u>), 6.30 (dt, *J* = 7.5, 1.0 Hz, 1H, Ar-C<u>H</u>), 4.83 – 4.76 (m, 1H, ruthenocene), 4.73 (tt, *J* = 2.5, 1.0 Hz, 1H, ruthenocene), 4.64 (s, 4H, ruthenocene), 4.54 (td, *J* = 2.5, 1.0 Hz, 1H, ruthenocene), 3.96 (dt, *J* = 2.5,

1.0 Hz, 1H, ruthenocene), 3.15 – 3.01 (m, 2H, R-C$\underline{H}_2$), 2.89 – 2.79 (m, 2H, R-C$\underline{H}_2$), 2.28 – 2.18 (m, 2H, R-C$\underline{H}_2$), 2.05 – 1.96 (m, 2H, R-C$\underline{H}_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.1 146.5, 146.4, 145.6, 145.5, 145.0, 142.8, 142.7, 141.0, 140.9, 128.9, 127.4, 122.6, 121.4, 121.4, 120.8, 120.7, 120.6, 80.0, 79.8, 73.7, 73.4, 73.3, 73.2, 72.5, 71.6, 71.4, 70.2, 59.1, 38.7, 38.1, 31.7, 31.2, 30.8, 22.8, 14.3; **^{31}P NMR** (202 MHz, $CDCl_3$) δ 156.0; ***m/z*** (ESI^+) calc. for $C_{27}H_{23}O_2PRu$ = 512.05, found: 513.0561 $[M+H]^+$.

Data for (*S*)-**L42**: **R_f** = 0.33 (hexane/EtOAc, 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.5 Hz, 2H, Ar-C$\underline{H}$), 7.03 (d, *J* = 7.5 Hz, 2H, Ar-C$\underline{H}$), 6.98 – 6.88 (m, 6H, Ar-C$\underline{H}$), 6.28 – 6.25 (m, 2H, Ar-C$\underline{H}$), 4.86 (dd, *J* = 2.0, 1.0 Hz, 2H, ruthenocene), 4.81 (q, *J* = 2.0 Hz, 2H, ruthenocene), 4.58 (td, *J* = 2.0, 1.0 Hz, 2H, ruthenocene), 4.01 (dt, *J* = 2.0, 1.0 Hz, 2H, ruthenocene), 3.12 – 2.98 (m, 4H, R-C$\underline{H}_2$), 2.82 (ddd, *J* = 15.5, 12.5, 8.0 Hz, 4H, R-C$\underline{H}_2$), 2.27 – 2.16 (m, 4H, R-C$\underline{H}_2$), 2.07 – 1.89 (m, 4H, R-C$\underline{H}_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.1, 146.4, 145.4, 145.0, 142.6, 141.0, 128.9, 127.4, 122.5, 121.4, 121.0, 120.6, 81.8, 81.6, 75.0, 74.8, 74.6, 73.7, 73.4, 72.9, 71.6, 59.1, 38.6, 38.1, 31.7, 31.2, 30.8, 22.8, 14.3; **^{31}P NMR** (202 MHz, $CDCl_3$) δ 154.6; ***m/z*** (ESI^+) calc. for $C_{44}H_{36}O_4P_2Ru$ = 792.11, found: 793.1213 $[M+H]^+$.

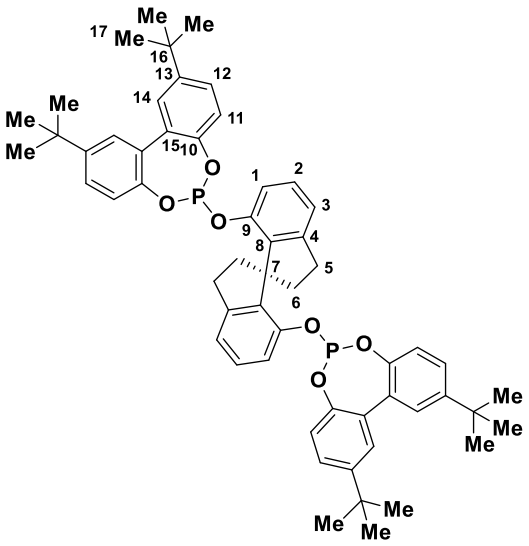
(*S*)-SPINOL, (S)-114



(*S*)-113 (1.50 g, 1.94 mmol) was added to a solution of KOH (1.96 g, 35 mmol) in H_2O/EtOH/THF (1:1:1, 40 mL). The solution was heated at 80 °C for 1 h. After cooling, 2 M HCl was added (20 mL) and the solution was extracted with Et_2O (3 × 10 mL), washed wit brine, dried over sodium sulfate, filtered and solvent removed *in vacuo* to afford a crude white wax, **I**. **I** (645 mg, 1.57 mmol) and 10% Pd/C (65 mg, 20 wt%) were added to a round bottom flask. MeOH (31 mL) and AcOH (4.5 mL) were added before the flask was sealed with a rubber septum and evacuated/refilled three times with nitrogen. The solution was sparged with a balloon of hydrogen for 2 mins and stirred at room temperature for 16 h. After completion, the solution was sparged with argon for 15 mins, filtered over Celite® (EtOAc) and concentrated *in vacuo*. The residue was dissolved in EtOAc and basified with sat. aq. solution of $NaHCO_3$. The resulting mixture was extracted with EtOAc (3 × 5 mL), washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 9:1) afforded the title compound as a white solid (355 mg, 90%); R_f = 0.31 (hexane/EtOAc, 9:1); **m.p.** = 153.1 – 155.9 °C (hexane/EtOAc, Lit.[110]: 155 – 156 °C); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = - 24.3 (c = 0.99, $CHCl_3$); **^{1}H NMR**

(500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.5 Hz, 2H, H^4), 6.90 (d, *J* = 7.5 Hz, 2H, H^5), 6.68 (d, *J* = 7.5 Hz, 2H, H^3), 4.61 (s, 2H, H^1), 3.13 – 2.93 (m, 4H, H^7), 2.37 – 2.15 (m, 4H, H^8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.1 (C^2), 146.0 (C^6), 130.6 (C^{10}), 130.1 (C^4), 117.8 (C^5), 114.5 (C^3), 57.6 (C^9), 37.6 (C^8), 31.4 (C^7). *Data in accordance with literature values.*[111]

(*S*)-L43

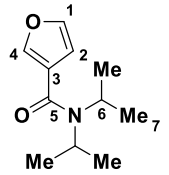


To a flame-dried Young's tube was added **180** (651 mg, 2.2 mmol). The tube was evacuated/refilled with nitrogen three times before PCl_3 (1.92 mL, 22 mmol) was added and the solution was heated at 85 °C for 2 h. After cooling, volatile components were removed *in vacuo* using a high vacuum pump (an additional trap was setup between the reaction tube and Schlenk line) for 2 h. (*S*)-SPINOL (110 mg, 0.44 mmol) and DMAP (10.8 mg, 0.088 mmol) were added before the tube was evacuated/refilled with nitrogen 3 times. THF (22 mL) then Et_3N (0.491 mL, 3.52 mmol) were added at 0 °C and the reaction was stirred at room temperature for 16 h. The mixture was filtered over Celite® (Et_2O) and concentrated *in vacuo*. Purification by FCC (hexane/Et_2O, 50:1, deactivated silica with 10% *w/w* of Et_3N) gave the title compound as a white solid (164 mg, 41%). **R_f** = 0.12 (hexane/Et_2O, 50:1); **m.p.** = 151.0 – 153.9 °C (hexane/EtOAc); $[\alpha]_D^{23}$ = + 27.3 (c = 0.22, CH_2Cl_2); **ν_{max}/cm^{-1}:** 3074 (br), 3062 (br), 2951 (m), 2904 (m), 2904 (m), 1606 (m), 1584 (m), 1496 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 6.5, 2.5 Hz, 4H, Ar-C<u>H</u>), 7.36 – 7.26 (m, 4H, Ar-C<u>H</u>), 7.19 (t, *J* = 7.5 Hz, 2H, H^2), 7.11 – 7.02 (m, 4H, Ar-C<u>H</u>), 6.94 (d, *J* = 8.5 Hz, 2H, H^1/H^3), 6.69 (d, *J* = 8.5 Hz, 2H, H^1/H^3), 3.07 – 2.99 (m, 4H, H^5), 2.43 (dt, *J* = 12.5, 9.0 Hz, 2H, H^6), 2.21 (dt, *J* = 12.5, 9.0 Hz, 2H, $H^{6'}$), 1.40 – 1.36 (m, 36H, H^{17}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.6 (Ar-<u>C</u>), 147.9 (C^{13}), 147.8 ($C^{13'}$), 147.0 (Ar-<u>C</u>), 146.7 (Ar-<u>C</u>), 139.5 (Ar-<u>C</u>), 130.9 (Ar-<u>C</u>), 130.8 (Ar-<u>C</u>), 128.2 (C^2), 126.7 (Ar-<u>C</u>H), 126.5 (Ar-<u>C</u>H), 126.0 (Ar-<u>C</u>H), 125.9 (Ar-<u>C</u>H), 121.8 (C^1/C^3), 121.6 (C^1/C^3), 120.8 (Ar-<u>C</u>H), 118.4 (Cd, 59.6 (C^7), 53.6 (C^{16}), 39.1 (C^6), 31.5 (C^{17}), 31.4 (C^5); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 177.98; ***m/z*** (ESI^+) calc. for $C_{57}H_{62}O_6P_2$ = 904.40, found: 905.4083 $[M+H]^+$.

7.4 Experimental procedures for compounds in Chapter 3

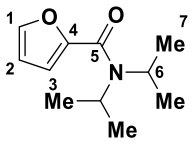
7.4.1 Synthesis of substrates and alkenes

***N,N*-Diisopropylfuran-3-carboxamide, 106**



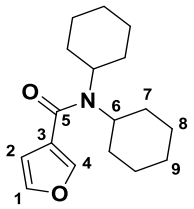
General procedure G: using 3-furoic acid (1.12 g, 10 mmol) and diisopropylamine (2.8 mL, 20 mmol). Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a colourless solid (1.22g, 62%); $\mathbf{R_f}$ = 0.34 (hexane/EtOAc, 4:1); **m.p.** = 42.2 – 43.4 °C (hexane/EtOAc, Lit.[279]: 44 – 45 °C, hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.59 (m, 1H, H^1), 7.37 (*pseudo*-t, *J* = 1.5 Hz, 1H, H^4), 6.54 – 6.43 (m, 1H, H^2), 4.45 – 3.11 (br, 2H, H^6), 1.33 (s, 12H, H^7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.4 (C^5), 142.7 (C^4), 142.1 (C^1), 123.5 (C^3), 109.9 (C^2), 21.0 (C^7). *Data in accordance with literature values*.[279]

***N,N*-Diisopropylfuran-2-carboxamide, 181**



General procedure G: using 2-furoic acid (1.12 g, 10 mmol) and diisopropylamine (2.82 mL, 20 mmol). Purification by FCC (hexane/EtOAc, 4:1) afforded the title compound as a colourless liquid (895 mg, 46%); $\mathbf{R_f}$ = 0.57 (hexane/EtOAc, 3:2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.0 Hz, 1H, H^1), 6.81 (dd, *J* = 3.5, 1.0 Hz, 1H, H^3), 6.42 (dd, *J* = 3.5, 2.0 Hz, 1H, H^2), 4.07 (br. s, 2H, H^6), 1.36 (s, 12H, H^7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.4 (C^5), 149.6 (C^4), 142.9 (C^1), 114.0 (C^3), 111.0 (C^2), 48.2 (C^6), 21.0 (C^7). *Data in accordance with literature values*.[280]

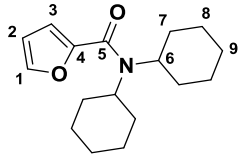
***N,N*-Dicyclohexylfuran-3-carboxamide, 187**



General procedure G: using 3-furoic acid (1.12 g, 10 mmol) and dicyclohexylamine (3.98 mL, 20 mmol). Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a white solid (2.21 g, 80%); $\mathbf{R_f}$ = 0.52 (hexane/EtOAc, 4:1); **m.p.** = 80.0 – 81.1 °C (hexane/EtOAc); **ν_{max}/cm^{-1}:** 3709 (w), 3662 (w), 3110 (w), 2958 (m), 2921 (s), 2852 (m), 1617 (s), 1578 (m); **^{1}H NMR** (500 MHz,

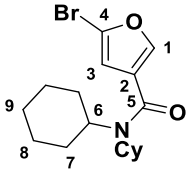
Acetonitrile-d_3, 70 °C) δ 7.64 – 7.57 (m, 1H, H^1), 7.48 – 7.46 (m, 1H, H^4), 6.50 (dd, *J* = 2.0, 1.0 Hz, 1H, H^2), 3.42 (br, 2H, H^6), 2.06 (br, 4H, Cy-H), 1.85 – 1.75 (br, 4H, Cy-H), 1.69 – 1.58 (br, 6H, Cy-H), 1.28 (qt, *J* = 13.0, 3.5 Hz, 4H, Cy-H), 1.23 – 1.13 (m, 2H, Cy-H); **^{13}C NMR** (126 MHz, Acetonitrile-d_3, 70 °C) δ 163.3 (C^5), 142.1 (C^4), 140.7 (C^1), 123.2 (C^3), 109.0 (C^2), 56.9 (C^6), 30.0 (Cy-CH_2), 25.2 (Cy-CH_2), 24.4 (Cy-CH_2); ***m/z*** (ESI$^+$) calc. for $C_{17}H_{25}NO_2$ = 275.19, found: 276.1970 $[M+H]^+$

***N,N*-Dicyclohexylfuran-2-carboxamide, 191**



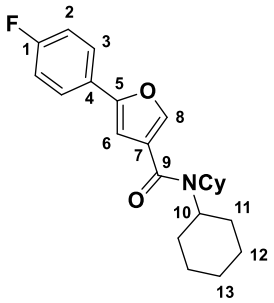
General procedure H: using 2-furoic acid (560 mg, 5 mmol) and dicyclohexylamine (1.09 mL, 5.5 mmol). Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a white solid (895 mg, 65%). **R_f** = 0.80 (hexane/EtOAc, 4:1); **m.p.** = 96.8 – 97.8 °C (hexane/EtOAc, Lit.[281]: 96.5 – 97.4 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 1.0 Hz, 1H, H^1), 6.78 (dd, *J* = 3.5, 1.0 Hz, 1H, H^3), 6.42 (dd, *J* = 3.5, 1.0 Hz, 1H, H^2), 4.00 – 1.46 (m, 16H, Cy-H), 1.31 – 1.10 (m, 6H, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.6 (C^5), 149.7 (C^4), 142.9 (C^1), 114.0 (C^3), 111.0 (C^2), 57.8 (Cy-CH), 31.0 (Cy-CH_2), 26.3 (Cy-CH_2), 25.4 (Cy-CH_2). *Data in accordance with literature values.*[281]

5-Bromo-*N,N*-dicyclohexylfuran-3-carboxamide



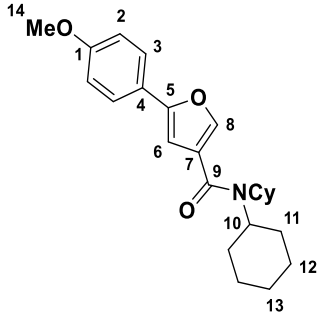
General procedure H: using 5-bromo-3-furoic acid (200 mg, 1.05 mmol) and dicyclohexylamine (0.312 mL, 1.57 mmol). Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a white solid (298 mg, 84%). **R_f** = 0.53 (hexane/EtOAc, 9:1); **m.p.** = 102.0 – 103.9 °C (hexane/EtOAc); **ν_{max}/cm^{-1}**: 3139 (w), 3109 (w), 2929 (s), 2854 (s), 1624 (s), 1574 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.0 Hz, 1H, H^1), 6.40 (d, *J* = 1.0 Hz, 1H, H^3), 1.85 – 1.76 (br, 6H, Cy-H), 1.63 (br, *J* = 11.0 Hz, 8H, Cy-H), 1.32 – 1.11 (br, 8H, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.2 (C^5), 143.6 (C^1), 125.9 (C^2/C^4), 122.9 (C^2/C^4), 111.4 (C^3), 31.7 (Cy-CH_2), 25.3 (Cy-CH_2), 22.8 (Cy-CH_2); ***m/z*** (ESI$^+$) calc. for $C_{17}H_{24}{}^{79}BrNO_2$ = 353.10, found: 354.1065 $[M+H]^+$.

***N,N*-Dicyclohexyl-5-(4-fluorophenyl)furan-3-carboxamide, 189**



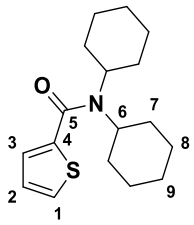
General procedure I: using 4-fluorophenylboronic acid. Purification by FCC (hexane/EtOAc, 9:1 → 4:1) gave the title compound as a pale yellow solid (248 mg, 80%); $\mathbf{R_f}$ = 0.58 (hexane/EtOAc, 4:1); **m.p.** = 150.5 – 152.7 °C (hexane/EtOAc); $\mathbf{\nu_{max}/cm^{-1}}$**:** 3681 (w), 2931 (s), 2856 (s), 1622 (s), 1586 (m), 1542 (w); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 2H, H^3), 7.58 (d, *J* = 1.0 Hz, 1H, H^8), 7.12 – 7.04 (m, 2H, H^2), 6.66 (d, *J* = 1.0 Hz, 1H, H^6), 4.02 – 2.85 (br, 2H, H^{10}), 2.77 – 2.18 (br, 2H, Cy-H), 1.86 – 1.77 (m, 4H, Cy-H), 1.72 – 1.36 (m, 7H, Cy-H), 1.33 – 1.03 (m, 7H, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.3 (C^9), 162.5 (d, *J* = 247.5 Hz, C^1), 153.2 (C^5), 141.1 (C^8), 126.7 (d, *J* = 3.0 Hz, C^4), 125.9 (d, *J* = 9.0 Hz, C^3), 125.5 (C^7), 116.0 (d, *J* = 22.0 Hz, C^2), 104.8 (d, *J* = 1.5 Hz, C^6), 58.1 (br, Cy-CH_2), 31.7 (br, Cy-CH_2), 26.3 (br, Cy-CH_2), 25.4 (br, Cy-CH_2); **^{19}F NMR** (471 MHz, $CDCl_3$) δ -113.4 (t, *J* = 7.0 Hz); ***m/z*** (ESI^+) calc. for $C_{23}H_{28}FNO_2$ = 369.21, found: 370.2174 $[M+H]^+$.

***N,N*-Dicyclohexyl-5-(4-methoxyphenyl)furan-3-carboxamide, 190**



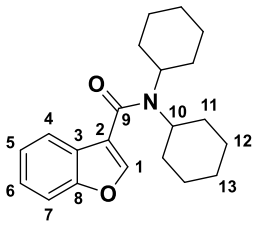
General procedure I: Using 4-methoxyphenylboronic acid. Purification by FCC (hexane/EtOAc, 9:1 → 4:1) gave the title compound as a pale yellow solid (292 mg, 90%); $\mathbf{R_f}$ = 0.42 (hexane/EtOAc, 4:1); **m.p.** = 80.7 – 84.4 °C (hexane/EtOAc); $\mathbf{\nu_{max}/cm^{-1}}$**:** 3011 (w), 2931 (w), 2855 (w), 1768 (w), 1717 (w), 1664 (w), 1615 (s), 1597 (s), 1577 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (m, 1H, H^8), 7.59 (m, 2H, H^2), 6.98 – 6.89 (m, 2H, H^3), 6.61 (d, *J* = 1.0 Hz, 1H, H^6), 3.84 (s, 3H, H^{14}), 3.20 – 2.33 (m, 2H, Cy-H), 1.87 – 1.77 (m, 4H, Cy-H), 1.75 – 1.39 (m, 8H, Cy-H), 1.36 – 1.09 (m, 8H, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.5 (C^9), 159.5 (C^1), 154.1 (C^5), 140.6 (C^2), 125.5 (C^8), 125.3 (C^7), 123.3 (C^4), 114.3 (C^3), 103.4 (C^6), 57.97 (br. d, *J* = 302.0 Hz, Cy-CH_2) 55.4 (C^{14}), 31.7 (Cy-CH_2), 26.3 (Cy-CH_2), 25.4 (Cy-CH_2); ***m/z*** (ESI^+) calc. for $C_{24}H_{31}NO_3$ = 381.23, found: 382.2376 $[M+H]^+$.

***N,N*-Dicyclohexylthiophene-2-carboxamide, 192**



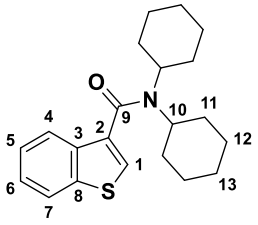
General procedure G: using 2-thiophenecarboxylic acid (641mg, 5.0 mmol) and dicyclohexylamine (2.49 mL, 12.5 mmol). Purification by FCC (hexane/EtOAc, 19:1 → 9:1) afforded the title compound as a white solid (671 mg, 46%). $\mathbf{R_f}$ = 0.58 (hexane/EtOAc, 4:1); **m.p.** = 85.5 – 86.9 °C (hexane/EtOAc); $\mathbf{\nu_{max}/cm^{-1}}$: 2928 (s), 2853 (s), 1612 (s), 1520 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 5.0, 1.0 Hz, 1H, H^3), 7.18 (dd, *J* = 3.5, 1.0 Hz, 1H, H^1), 7.00 (dd, *J* = 5.0, 3.5 Hz, 1H, H^2), 3.47 (br, 2H, Cy-H), 2.68 – 1.44 (br. m, 14H, Cy-H), 1.31 – 0.82 (m, 6H, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.2 (C^5), 140.3 (C^4), 127.5 (Ar-CH), 127.0 (Ar-CH), 126.6 (Ar-CH), 31.0 (Cy-CH_2), 26.3 (Cy-CH_2), 25.4 (Cy-CH_2); ***m/z*** (ESI^+) calc. for $C_{17}H_{25}NOS$ = 291.17, found: 292.1730 $[M+H]^+$.

***N,N*-Dicyclohexylbenzofuran-3-carboxamide, 194**



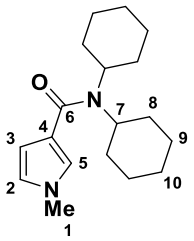
General procedure G: using 1-benzofuran-3-carboxylic acid (405 mg, 2.5 mmol) and dicyclohexylamine (0.99 mL, 5.0 mmol). Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a yellow solid (652 mg, 80%); $\mathbf{R_f}$ = 0.69 (hexane/EtOAc, 4:1); **m.p.** = 125.1 – 126.2 °C (hexane); $\mathbf{\nu_{max}/cm^{-1}}$**:** 3669 (w), 2928 (s), 2854 (s), 1625 (s), 1590 (m), 1561 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 2H, H^1, H^4), 7.50 (d, *J* = 8.0 Hz, 1H, H^7), 7.38 – 7.26 (m, 2H, H^5, H^6), 3.42 (br, 2H, H^{10}), 2.62 – 1.47 (m, 14H, Cy-H), 1.18 (s, 6H, Cy-H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8 (C^9), 154.7 (C^8), 142.3 (C^1), 126.3 (C^3), 125.1 (C^5), 123.4 (C^6), 121.1 (C^4), 119.1 (C^2), 111.6 (C^7), 31.1 (Cy-CH_2), 26.2 (Cy-CH_2), 25.3 (Cy-CH_2); ***m/z*** (ESI^+) calc. for $C_{21}H_{27}NO_2$ = 325.20, found: 326.2113 $[M+H]^+$. *^{13}C signal corresponding to C-10 was not observed due to rotameric behaviour of the molecule.*

***N,N*-Dicyclohexylbenzo[*b*]thiophene-3-carboxamide, 195**



General procedure G: using 1-benzothiophene-3-carboxylic acid (891 mg, 5 mmol) and dicyclohexylamine (1.09 mL, 5.5 mmol). Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a white solid (1.26 g, 74%). $\mathbf{R_f}$ = 0.55 (hexane/EtOAc, 9:1); **m.p.** = 112.0 – 144.0 °C (hexane/EtOAc); $\mathbf{\nu_{max}/cm^{-1}}$**:** 3663 (br), 3065 (w), 2927 (s), 2853 (m), 160 (s), 1559 (w), 1515 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 – 7.84 (m, 1H, Ar-C<u>H</u>), 7.79 – 7.76 (m, 1H, Ar-C<u>H</u>), 7.40 – 7.34 (m, 2H, H^5, H^6), 7.33 (s, 1H, H^1), 3.27 (br, 2H, Cy-<u>H</u>), 2.67 (br, 2H, Cy-<u>H</u>), 1.94 – 0.93 (m, 18H, Cy-<u>H</u>); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.4 (C^9), 139.8 (Ar-<u>C</u>), 137.6 (Ar-<u>C</u>), 134.5 (C^2), 124.9 (Ar-<u>C</u>H), 124.7 (Ar-<u>C</u>H), 123.0 (Ar-<u>C</u>H), 122.7 (Ar-<u>C</u>H), 122.6 (C^1), 31.7 (Cy-<u>C</u>), 31.0 (Cy-<u>C</u>), 26.2 (Cy-<u>C</u>), 25.3 (Cy-<u>C</u>), 22.8 (Cy-<u>C</u>), 14.3 (Cy-<u>C</u>); ***m/z*** (ESI^+) calc. for $C_{21}H_{27}NOS$ = 341.18, found: 342.1881 $[M+H]^+$.

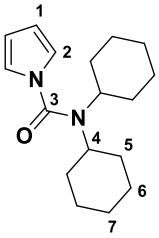
***N,N*-Dicyclohexyl-1-methyl-1*H*-pyrrole-3-carboxamide, 196**



To a solution of 1-methyl-1*H*-pyrrole-3-carboxylic acid (200 mg, 1.60 mmol) in toluene (1 mL) was added thionyl chloride (0.70 mL, 9.59 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 8 h before volatile components were removed *in vacuo* at room temperature. The residue was dissolved in toluene (1 mL) and dicyclohexylamine (0.318 mL, 1.60 mmol) was added dropwise at 0 °C. The resulting suspension was stirred at room temperature for 16 h before H_2O (5 mL) was added, extracted with EtOAc (3 × 5 mL), dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 1:1) gave the title compound as an off-white solid (293 mg, 63%); $\mathbf{R_f}$ = 0.28 (hexane/EtOAc, 1:1); **m.p.** = 81.5 – 83.0 °C (hexane/EtOAc); $\mathbf{\nu_{max}/cm^{-1}}$**:** 3554 (br) 3121 (w) 2969 (m), 2926 (s), 2853 (s), 1701 (m), 1507 (s), 1535 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.93 (m, 1H, H^5), 6.50 (m, 1H, H^2), 6.20 (m, 1H, H^3), 3.63 (s, 3H, H^1), 1.85 – 1.33 (m, 12H, Cy-<u>H</u>), 1.22 (m, 8H, Cy-<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.0 (C^6), 124.5 (C^5), 121.4 (C^2), 111.2 (C^4), 108.5 (C^3), 36.4 (C^1), 31.2 (Cy-<u>C</u>H_2), 26.3 (Cy-<u>C</u>H_2), 25.5 (Cy-CH_2); ***m/z*** (ESI^+) calc. for $C_{18}H_{28}N_2O$ =

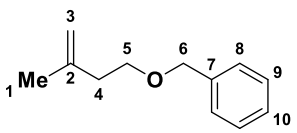
288.22, found: 289.2271 $[M+H]^+$. *^{1}H and ^{13}C signals corresponding to C-7 were not observed due to rotameric behaviour of the molecule.*

_N,N_-Dicyclohexyl-1_H_-pyrrole-1-carboxamide, 184



A flame-dried two-necked flask was charged with triphosgene (594 mg, 2.0 mmol) under a nitrogen atmosphere and dissolved in toluene (6 mL) before dicyclohexylamine (1.31 mL, 6.6 mmol) was added at -5 °C and stirred for 1 h at this temperature. The reaction mixture was stirred at room temperature for 16 h before solids were removed by filtration and washed with toluene (20 mL). Volatile components were removed *in vacuo* to afford dicyclohexylcarbamic chloride which was used in the next step without further purification. A flame-dried round-bottom flask was charged with NaH (60% in mineral oil, 96.2 mg, 2.4 mmol) and suspended in THF (4 mL) under nitrogen. The suspension was cooled to 0 °C before pyrrole (0.139 mL, 2.0 mmol) was added dropwise over 10 mins. The solution was stirred at 0 °C for 1 h, followed by dropwise addition of crude dicyclohexylcarbamic acid in THF (5 mL) over 10 mins. The solution was warmed to room temperature and stirred for 16 h. The reaction was quenched by the addition of sat. aq. NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo.* Purification by FCC (hexane/EtOAc, 9:1) followed by recrystallisation (hexane/EtOAc) gave the title compound as colourless crystals (425 mg, 31%); $\mathbf{R_f}$ = 0.70 (hexane/EtOAc, 4:1); **m.p.** = 99.6 – 100.9 °C (hexane/EtOAc); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 2928 (s), 2854 (m), 1732 (w), 1673 (s), 1567 (w), 1516 (w); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.02 – 6.88 (m, 2H, H^2), 6.24 – 6.18 (m, 2H, H^1), 3.33 (tt, *J* = 12.0, 5.0 Hz, 2H, H^4), 2.07 – 1.93 (m, 4H, H^5), 1.81 (ddd, *J* = 12.0, 5.0, 2.5 Hz, 4H, H^6), 1.72 (*pseudo*-ddt, *J* = 12.0, 5.0, 2.5 Hz, 4H, $H^{5'}$), 1.67 – 1.58 (m, 2H, H^7), 1.32 – 1.09 (m, 6H, $H^{6'}$, $H^{7'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.0 (C^3), 120.2 (C^2), 110.1 (C^1), 58.2 (C^4), 31.3 (C^5), 26.2 (C^6), 25.4 (C^7); ***m/z*** (ESI^+) calc. for $C_{17}H_{26}N_2O$ = 274.20, found: 275.2112 $[M+H]^+$.

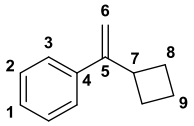
(((3-Methylbut-3-en-1-yl)oxy)methyl)benzene, 206a



To a suspension of NaH (60% in mineral oil, 220 mg, 5.5 mmol) in THF (10 mL) was added methyl-3-buten-1-ol (0.51 mL, 5.0 mmol) then benzyl bromide (0.65 mL, 5.5 mmol) at 0 °C. The reaction was

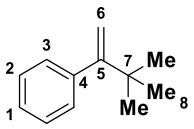
stirred at room temperature for 16 h before the reaction was quenched by the addition of sat. aq. NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC (hexane/Et_2O, 19:1) gave the title compound as a colourless liquid (500 mg, 57%); $\mathbf{R_f}$ = 0.69 (hexane/EtOAc 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 4H, H^8, H^9), 7.30 – 7.27 (m, 1H, H^{10}), 4.79 (br, 1H, H^3), 4.75 (br, 1H, $H^{3'}$), 4.53 (s, 2H, H^6), 3.59 (t, *J* = 7.0 Hz, 2H, H^5), 2.35 (t, *J* = 7.0 Hz, 2H, H^4), 1.75 (s, 3H, H^1); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.0 (C^{11}), 138.6 (C^7), 128.5 (C^8), 127.8 (C^9), 127.7 (C^{10}), 111.6 (C^3), 73.1 (C^6), 68.9 (C^5), 38.0 (C^4), 22.8 (C^1). *Data in accordance with literature values.*[282]

(1-Cyclobutylvinyl)benzene, 206b



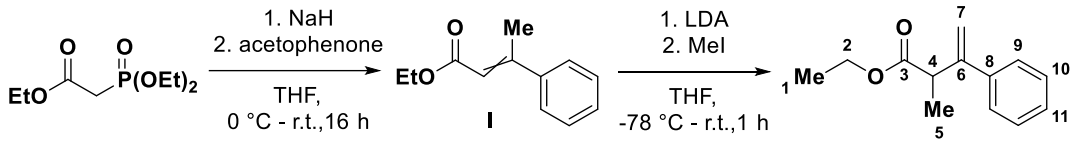
General Procedure J: Purification of the residue by FCC (hexane) afforded the title compound as a colourless oil (473 mg, 60%); $\mathbf{R_f}$ = 0.75 (hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H, H^3), 7.38 – 7.33 (m, 2H, H^2), 7.32 – 7.27 (m, 1H, H^1), 5.39 (d, *J* = 1.5 Hz, 1H, H^6), 5.08 (d, *J* = 1.5 Hz, 1H, $H^{6'}$), 3.57 – 3.46 (m, 1H, H^7), 2.33 – 2.19 (m, 2H, H^8), 2.07 – 1.96 (m, 3H, $H^{8'}$, H^9), 1.89 – 1.77 (m, 1H, $H^{9'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.2 (C^5), 140.9 (C^4), 128.3 (C^2), 127.4 (C^1), 126.2 (C^3), 109.9 (C^6), 39.7 (C^7), 28.6 (C^8), 17.9 (C^9). *Data in accordance with literature values.*[283]

(3,3-Dimethylbut-1-en-2-yl)benzene, 208a



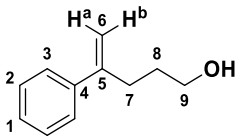
General Procedure J: Purification of the residue by FCC (hexane) afforded the title compound as a colourless oil (221 mg, 69%); $\mathbf{R_f}$ = 0.86 (hexane/EtOAc, 19:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 3H, H^1, H^2), 7.21 – 7.14 (m, 2H, H^3), 5.20 (d, *J* = 1.5 Hz, 1H, H^6), 4.79 (d, *J* = 1.5 Hz, 1H, $H^{6'}$), 1.15 (s, 9H, H^8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.0 (C^5), 143.6 (C^4), 129.2 (C^3), 127.4 (C^2), 126.4 (C^1), 111.6 (C^6), 36.3 (C^7), 29.8 (C^8). *Data in accordance with literature values.*[284]

Ethyl 2-methyl-3-phenylbut-3-enoate, 208b:



To a suspension of NaH (60% in mineral oil, 641 mg, 16 mmol) in THF (10 mL) was added ethyl 2-(diethoxyphosphoryl)acetate (3.2 mL, 16 mmol) dropwise at 0 °C. The reaction was stirred at room temperature for 15 mins before addition of acetophenone (1.17 mL, 10 mmol) dropwise at 0 °C. The reaction was stirred at room temperature for 16 h before quenching with H_2O (20 mL) and extracting with Et_2O (3 × 10 mL). The extracts were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 97:3) afforded **I** as a colourless oil (1.29 g, 68%); $\mathbf{R_f}$ = 0.50 (hexane/EtOAc, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H, Ar-H), 7.41 – 7.32 (m, 3H, Ar-H), 6.14 (q, *J* = 1.5 Hz, 1H, R-CH), 4.22 (*pseudo*-q, *J* = 7.0 Hz, 2H, R-CH_2), 2.58 (d, *J* = 1.5 Hz, 3H, R-CH_3), 1.32 (t, *J* = 7.0 Hz, 3H, R-CH_3). To a solution of diisopropylamine (0.82 mL, 5.8 mmol) in THF (5 mL) was added *n*-BuLi (2.5 M in hexane, 2.5 mL, 5.8 mmol) at -78 °C. A solution of **I** in THF (5 mL) was added dropwise to the first solution at -78 °C and the mixture was stirred at -78 °C for 15 mins before MeI (0.39 mL, 6.3 mmol) was added dropwise at -78 °C. After stirring at 0 °C for 1 h, the reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with Et_2O (3 × 10 mL). The extracts were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 100:0 → 19:1) afforded the title compound as a colourless oil (847 mg, 79%); $\mathbf{R_f}$ = 0.38 (hexane/EtOAc, 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H, H^9), 7.37 – 7.33 (m, 2H, H^{10}), 7.32 – 7.26 (m, 1H, H^{11}), 5.41 (s, 1H, H^7), 5.28 – 5.24 (s, 1H, $H^{7'}$), 4.13 (q, *J* = 7.0 Hz, 2H, H^2), 3.70 (qd, *J* = 7.0, 1.0 Hz, 1H, H^4), 1.42 (d, *J* = 7.0 Hz, 3H, H^5), 1.19 (t, *J* = 7.0 Hz, 3H, H^1); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.6 (C^3), 148.2 (C^6), 141.2 (C^8), 128.4 (C^{10}), 127.7 (C^{11}), 126.6 (C^9), 114.0 (C^7), 60.8 (C^2), 44.7 (C^4), 17.1 (C^5), 14.2 (C^1). *Data in accordance with literature values.*[285]

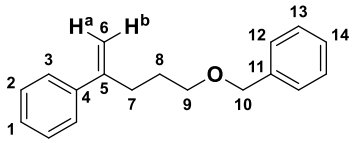
4-Phenylpent-4-en-1-ol



A flame-dried Young's tube was charged with phenylboronic acid (2.92 g, 24 mmol) and tetrakis(triphenylphosphine)palladium(0) (693 mg, 0.60 mmol). The vessel was evacuated/refilled with nitrogen three times before pent-1-yn-5-ol (1.86 mL, 20 mmol), acetic acid (0.23 mL, 4.0 mmol) and

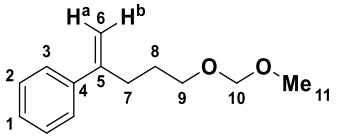
1,4-dioxane (60 mL) were added sequentially. The vessel was sealed and heated at 80 °C for 16 h. After cooling, the mixture was filtered over Celite® (EtOAc) and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a colourless liquid (841 mg, 26%). $\mathbf{R_f}$ = 0.26 (hexane/EtOAc, 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 2H, H^3), 7.36 – 7.31 (m, 2H, H^2), 7.30 – 7.25 (m, 1H, H^1), 5.30 (br, 1H, H^6), 5.10 (br, 1H, $H^{6'}$), 3.67 (td, *J* = 6.5, 1.5 Hz, 2H, H^9), 2.61 (td, *J* = 7.5, 1.5 Hz, 2H, H^7), 1.79 – 1.69 (m, 2H, H^8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.1 (C^5), 141.1 (C^4), 128.5 (C^2), 127.6 (C^1), 126.3 (C^3), 112.7 (C^6), 62.7 (C^9), 31.7 (C^7), 31.3 (C^8). *Data in accordance with literature values.*[286]

(5-(Benzyloxy)pent-1-en-2-yl)benzene, 208c



To a suspension of NaH (88 mg, 2.2 mmol, 60% in mineral oil) in THF (2.0 mL) was added a solution of 4-phenylpent-4-en-1-ol (325 mg, 2.0 mmol) in THF (2.0 mL) at 0 °C. The mixture was stirred for 30 mins before benzyl bromide (0.262 mL, 2.2 mmol) was added dropwise at 0 °C. The reaction was stirred at room temperature for 16 h before quenching with H_2O (10 mL) and extracting with EtOAc (3 × 10 mL). The organic extracts were combined, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/Et_2O, 99:1) gave the title compound as a colourless liquid (233 mg, 46%). $\mathbf{R_f}$ = 0.44 (hexane/Et_2O, 99:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.15 (m, 10H, $H^{1\text{-}3}$, $H^{12\text{-}14}$), 5.21 (br, 1H, H^6), 5.00 (br, 1H, $H^{6'}$), 4.41 (s, 2H, H^{10}), 3.42 (t, *J* = 6.5 Hz, 2H, H^9), 2.54 (t, *J* = 7.5 Hz, 2H, H^7), 1.76 – 1.66 (m, 2H, H^8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.1 (C^5), 141.3 (C^4), 138.8 (C^{11}), 128.5 (Ar-C), 128.4 (Ar-C), 127.8 (Ar-C), 127.6 (Ar-C), 127.5 (Ar-C), 126.3 (Ar-C), 112.6 (C^6), 73.0 (C^{10}), 69.9 (C^9), 32.0 (C^7), 28.5 (C^8). *Data in accordance with literature values.*[287]

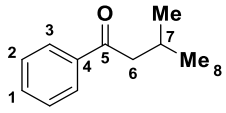
(5-(Methoxymethoxy)pent-1-en-2-yl)benzene, 208d



To a solution of 4-phenylpent-4-en-1-ol (325 mg, 2.0 mmol) and DIPEA (0.742 mL, 4.0 mmol) in CH_2Cl_2 (4.0 mL) was added chloromethyl methyl ether (0.304 mL, 4.0 mmol) dropwise at 0 °C. After stirring for 1 h at room temperature, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over sodium sulfate, filtered and solvent removed i*n vacuo.* Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a colourless liquid (240 mg, 58%). $\mathbf{R_f}$ = 0.78 (hexane/EtOAc, 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (*pseudo*-dt, *J* = 8.0, 1.5 Hz, 2H, H^3), 7.37 – 7.33 (m, 2H, H^2), 7.31 – 7.26 (m, 1H, H^1),

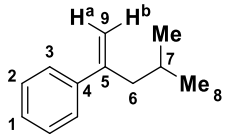
5.32 (br, 1H, H^{6a}), 5.12 (br, 1H, H^{6b}), 4.64 (s, 2H, H^{10}), 3.57 (t, *J* = 6.5 Hz, 2H, H^{9}), 3.39 (s, 3H, H^{11}), 2.67 – 2.60 (m, 2H, H^{7}), 1.84 – 1.74 (m, 2H, H^{8}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.1 (C^{5}), 141.3 (C^{4}), 128.4 (C^{2}), 127.5 (C^{1}), 126.3 (C^{3}), 112.7 (C^{6}), 96.6 (C^{10}) 67.3 (C^{9}), 55.3 (C^{11}), 32.0 (C^{7}), 28.4 (C^{8}). *Data in accordance with literature values.*[287]

3-Methyl-1-phenylbutan-1-one



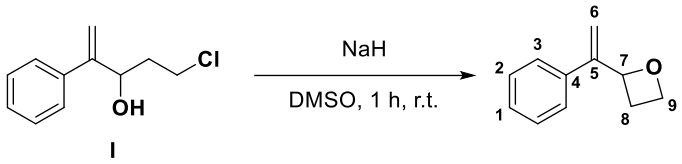
A flame-dried two-necked flask was charged with magnesium turnings (292 mg, 12 mmol) and iodine (one crystal) and stirred at 40 °C for 30 mins under nitrogen before a solution of isobutyl bromide (1.30 mL, 12 mmol) in THF (12 mL) was added dropwise at 40 °C. The mixture was stirred at 40 °C for 1 h before a solution of benzonitrile (1.03 mL, 10 mmol) in THF (5 mL) was added dropwise and stirred at 50 °C for 16 h. The reaction was quenched with H_2SO_4 (6M, 10 mL) at 0 °C and stirred for 6 h at room temperature. The mixture was extracted with Et_2O (3 × 20 mL), organic extracts combined, dried over sodium sulfate, filtered, and solvent removed *in vacuo*. Purification by FCC (hexane/Et_2O, 49:1) gave the title compound as a colourless liquid (840 mg, 52%). $\mathbf{R_f}$ = 0.84 (hexane/EtOAc, 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H, H^{3}), 7.58 – 7.51 (m, 1H, H^{1}), 7.51 – 7.42 (m, 2H, H^{2}), 2.83 (d, *J* = 7.0 Hz, 2H, H^{6}), 2.29 (m, 1H, H^{7}), 1.00 (d, *J* = 6.5 Hz, 6H, H^{8}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.4 (C^{5}), 137.5 (C^{4}), 133.0 (C^{1}), 128.7 (C^{2}), 128.2, (C^{3}), 47.7 (C^{6}), 25.3 (C^{7}), 22.9 (C^{8}). *Data in accordance with literature values.*[288]

(4-Methylpent-1-en-2-yl)benzene, 208e



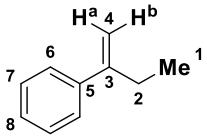
General procedure J: using 3-methyl-1-phenylbutan-1-one (325 mg, 2.0 mmol). Purification by FCC (hexane) gave the title compound as a colourless liquid (170 mg, 80%). $\mathbf{R_f}$ = 0.77 (hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H, H^{3}), 7.33 (m, 2H, H^{2}), 7.26 (m, 2H, H^{1}), 5.27 (d, *J* = 2.0 Hz, 1H, H^{9}), 5.03 (br, 1H, $H^{9'}$), 2.39 (d, *J* = 7.0 Hz, 2H, H^{6}), 1.67 (m, 1H, H^{7}), 0.89 (d, *J* = 7.0 Hz, 6H, H^{8}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.0 (C^{5}), 141.6 (C^{4}), 128.4 (C^{2}), 127.3 (C^{1}), 126.4 (C^{3}), 113.6 (C^{9}), 45.3 (C^{6}), 26.5 (C^{7}), 22.8 (C^{8}). *Data in accordance with literature values.*[289]

2-(1-Phenylvinyl)oxetane, 208f



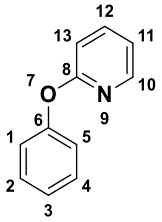
To a solution of **I**[290] in DMSO (15 mL) was added NaH (60% in mineral oil, 147 mg, 3.7 mmol). The reaction was stirred at room temperature for 1 h before quenching with sat. aq. NH_4Cl (20 mL) and extracting with EtOAc (3 × 10 mL). The organic extracts were combined, dried over sodium sulfate, filtered, and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 19:1) gave the title compound as a colourless liquid (129 mg, 23%). $\mathbf{R_f}$ = 0.66 (hexane/EtOAc, 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H, H^1, H^2, H^3), 5.72 (ddt, *J* = 8.0, 7.0, 1.5 Hz, 1H, H^7), 5.61 (t, *J* = 1.5 Hz, 1H, H^6), 5.59 (d, *J* = 1.5 Hz, 1H, $H^{6'}$), 4.85 – 4.77 (m, 1H, H^9), 4.64 – 4.56 (m, 1H, $H^{9'}$), 3.01 – 2.91 (m, 1H, H^8), 2.58 – 2.47 (m, 1H, $H^{8'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.0 (C^5), 137.7 (C^4), 128.6 (Ar-CH), 127.9 (C^1), 126.1 (Ar-CH), 111.1 (C^6), 82.0 (C^7), 68.2 (C^9), 29.2 (C^8). *Data in accordance with literature values.*[290]

But-1-en-2-ylbenzene, 209



General procedure J: using propiophenone (0.67 mL, 5.0 mmol). Purification by FCC (hexane) gave the title compound as a colourless oil (500 mg, 76%). $\mathbf{R_f}$ = 0.83 (hexane/EtOAc, 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H, H^6), 7.35 – 7.31 (m, 2H, H^7), 7.29 – 7.24 (m, 1H, H^8), 5.28 (br, 1H, H^{4a}), 5.06 (*pseudo*-q, *J* = 1.5 Hz, 1H, H^{4b}), 2.52 (m, 2H, H^2), 1.11 (t, *J* = 7.5 Hz, 3H, H^1); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.2 (C^3), 141.7 (C^5), 128.4 (C^7), 127.4 (C^8), 126.2 (C^6), 111.1 (C^4), 28.2 (C^2), 13.1 (C^1). *Data in accordance with literature values.*[291]

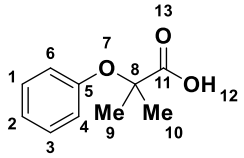
2-Phenoxypyridine, 213



To a flame-dried, two-necked round-bottom flask was added CuI (95.2 mg, 0.500 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and picolinic acid (123 mg, 1.00 mmol). The flask was evacuated and refilled with

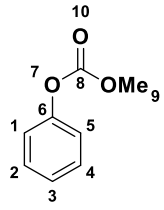
nitrogen three times before the addition of DMSO (10 mL), phenol (0.439 mL, 5.00 mmol) and 2-bromopyridine (0.572 mL, 6.00 mmol). The mixture was heated at 90 °C for 24 h. After allowing to cool, H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried, filtered and solvent removed *in vacuo* before purification by FCC (hexane/EtOAc, 20:1) gave the title compound as a colourless solid (605 mg, 71%); $\mathbf{R_f}$ = 0.38 (hexane/EtOAc, 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar-C<u>H</u>), 7.68 (ddd, *J* = 8.5, 7.0, 2.0 Hz, 1H, Ar-C<u>H</u>), 7.44 – 7.36 (m, 2H, H^2, H^4), 7.24 – 7.18 (m, 1H, H^3), 7.17 – 7.12 (m, 2H, H^1, H^5), 6.99 (ddd, *J* = 7.0, 5.0, 1.0 Hz, 1H, Ar-C<u>H</u>), 6.90 (d, *J* = 8.5 Hz, 1H, Ar-C<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9 (C^8), 154.3 (C^6), 147.9 (Ar-<u>C</u>H), 139.5 (Ar-<u>C</u>H), 129.8 (C^2,C^4), 124.8 (C^3), 121.3 (C^1, C^5), 118.6 (Ar-<u>C</u>H), 111.6 (Ar-<u>C</u>H). *Data in accordance with literature values.*[292]

2-Methyl-2-phenoxypropanoic acid, 215



To a solution of phenol (471 mg, 5.0 mmol) in acetone (5 mL) was added NaOH pellets (1.00 g, 25.0 mmol). The mixture was stirred at 50 °C for 2 h and cooled to room temperature. A solution of α-bromoisobutyric acid (919 mg, 5.50 mmol) in acetone (5 mL) was then added and the resulting reaction mixture was stirred for 16 h at 45 °C. H_2O (20 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, acidified with 2M HCl (10 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried over sodium sulfate, filtered, and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 5:1) gave the title compound as a white solid (430 mg, 48%); $\mathbf{R_f}$ = 0.33 (hexane/EtOAc, 5:1); **m.p.** = 98.3 – 99.1 °C (hexane/EtOAc, Lit.[293]: 95 – 96 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.26 (s, 1H, H^{12}), 7.33 – 7.22 (m, 2H, H^1, H^3), 7.10 – 7.00 (m, 1H, H^2), 6.99 – 6.90 (m, 2H, H^4, H^6), 1.62 (s, 6H, H^9, H^{10}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.2 (C^{11}), 154.8 (C^5), 129.4 (C^1, C^3), 123.1 (C^2), 120.3 (C^4, C^6), 79.3 (C^8), 25.3 (C^9, C^{10}). *Data in accordance with literature values.*[293]

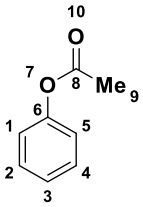
Methyl phenyl carbonate, 217



NaH (60% solution in mineral oil, 441 mg, 11.0 mmol) was added portion-wise to a solution of phenol (941 mg, 10.0 mmol) in THF (10 mL) and the resulting mixture was stirred at room temperature for 30 mins. Methyl chloroformate (0.850 mL, 11.0 mmol) was then added dropwise at 0 °C and the resulting mixture was stirred at room temperature for 16 h. H_2O (20 mL) was added and the mixture was extracted

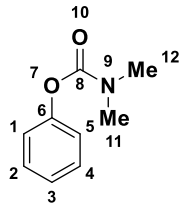
with Et_2O (3 × 20 mL). The organic extracts were washed sequentially with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL) before being dried over sodium sulfate, filtered and solvent removed *in vacuo* to afford the title compound as a colourless liquid (1.35 g, 89%); $\mathbf{R_f}$ = 0.71 (hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H, H^2, H^4), 7.28 – 7.22 (m, 1H, H^3), 7.22 – 7.17 (m, 2H, H^1, H^5), 3.90 (s, 3H, H^9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.4 (C^8), 151.2 (C^6), 129.6 (C^2, C^4), 126.1 (C^3), 121.1 (C^1, C^5), 55.4 (C^9). *Data in accordance with literature values.*[294]

Phenyl acetate, 218



To a solution of phenol (1.89 g, 20.0 mmol) in acetonitrile (20 mL) was added acetic anhydride (2.84 mL, 30.0 mmol) and pyridine (0.971 mL, 12.0 mmol). The resulting mixture was stirred at room temperature for 16 h before H_2O (30 mL) was then added and the mixture was stirred at room temperature for 30 mins. After extraction with EtOAc (3 × 50 mL), the organic extracts were combined and washed sequentially with 2M HCl (25 mL), sat. aq. $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL). The organic extracts were dried over sodium sulfate and filtered before solvent was removed *in vacuo* to afford the title compound as a colourless liquid (2.33 g, 86%); $\mathbf{R_f}$ = 0.70 (hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 2H, H^2, H^4), 7.27 – 7.21 (m, 1H, H^3), 7.14 – 7.06 (m, 2H, H^1, H^5), 2.29 (s, 3H, H^9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.5 (C^8), 150.7 (C^6), 129.4 (C^2, C^4), 125.8 (C^3), 121.6 (C^1, C^5), 21.1 (C^9). *Data in accordance with literature values.*[295]

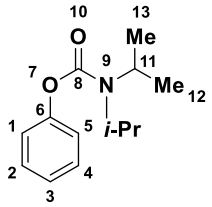
Phenyl dimethylcarbamate, 219



To a solution of phenol (941 mg, 10.0 mmol) in acetonitrile (20 mL) was added K_2CO_3 (2.77 g, 20.0 mmol) followed by dimethylcarbamoyl chloride (1.02 mL, 11.0 mmol). The resulting solution was heated at 85 °C for 16 h. After allowing to cool, H_2O (20 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic extracts were combined and washed sequentially with sat. aq. $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL). The organic extracts were dried over sodium sulfate and filtered before solvent was removed *in vacuo*. Purification by FCC (hexane/EtOAc, 3:1) afforded the title compound as a white solid (1.37 g, 83%); $\mathbf{R_f}$ = 0.34 (hexane/EtOAc, 3:1); **m.p.** = 44.2 – 46.0

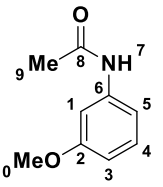
°C (hexane/EtOAc, Lit.[296]: 43 – 45 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H, H^2, H^4), 7.22 – 7.16 (m, 1H, H^3), 7.14 – 7.08 (m, 2H, H^1, H^5), 3.10 (s, 3H, H^{11}/H^{12}) 3.01 (s, 3H, H^{11}/H^{12}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0 (C^8), 151.6 (C^6), 129.3 (C^2, C^4), 125.2 (C^3), 121.8 (C^1, C^5), 36.7 (C^{11}/C^{12}), 36.5 (C^{11}/C^{12}). *Data in accordance with literature values.*[296]

Phenyl diisopropylcarbamate, 220



To a solution of phenol (941 mg, 10.0 mmol) in acetonitrile (20 mL) was added K_2CO_3 (2.77 g, 20.0 mmol) followed by diethylcarbamoyl chloride (1.40 mL, 11.0 mmol). The resulting solution was heated at 85 °C for 48 h. After allowing to cool, H_2O (20 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic extracts were combined and washed sequentially with sat. aq. $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL). The organic extracts were dried over sodium sulfate and filtered before solvent was removed *in vacuo*. Purification by FCC (hexane/EtOAc, 7:1) afforded the title compound as a colourless liquid (1.37 g, 26%); $\mathbf{R_f}$ = 0.39 (hexane/EtOAc, 7:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H, H^2, H^4), 7.22 – 7.09 (m, 3H, H^3, H^1, H^5), 4.04 (br, 2H, H^{11}), 1.32 (s, 12H, H^{12}, H^{13}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.8 (C^8), 151.4 (C^6), 129.2 (C^2, C^4), 124.9 (C^3), 121.8 (C^1, C^5), 46.8 (C^{11}), 46.1 (C^{11}), 21.5 (C^{12}, C^{13}), 20.5 (C^{12}, C^{13}). *Data in accordance with literature values.*[297]

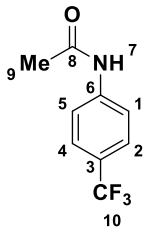
***N*-(3-Methoxyphenyl)acetamide, 236**



To a solution of 3-methoxyaniline (2.25 mL, 20.0 mmol) in acetonitrile (20 mL) was added acetic anhydride (2.08 mL, 22.0 mmol) and pyridine (0.97 mL, 12.0 mmol). The resulting mixture was stirred at room temperature for 16 h. H_2O (20 mL) was then added and the mixture was stirred at room temperature for 30 mins. After extraction with EtOAc (3 × 50 mL), the organic extracts were combined and washed sequentially with 2M HCl (25 mL), sat. aq. $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL). The organic extracts were combined, dried over sodium sulfate and filtered before solvent was removed *in vacuo*. Purification by FCC (hexane/EtOAc, 1:1) and recrystallisation (hexane/EtOAc) gave the title compound as a white solid (2.59 g, 78%); $\mathbf{R_f}$ = 0.41 (hexane/EtOAc, 1:1); **m.p.** = 80.0 – 81.1 °C (hexane/EtOAc, Lit.[106]: 81 – 83 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (br, 1H, H^7), 7.27 (dd, *J* =

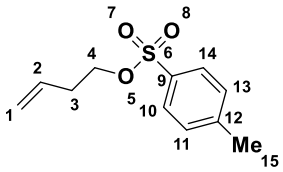
4.5, 2.0 Hz, 1H, H^1), 7.19 (t, *J* = 8.0 Hz, 1H, H^4), 7.01 – 6.93 (d, *J* = 8.0 Hz, 1H, H^5), 6.65 (dd, *J* = 8.0, 2.5 Hz, 1H, H^3), 3.77 (s, 3H, H^{10}), 2.15 (s, 3H, H^9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6 (C^8), 160.3 (C^2), 139.3 (C^6), 129.8 (C^4), 112.1 (C^5), 110.2 (C^3), 105.8 (C^1), 55.4 (C^{10}), 24.8 (C^9). *Data in accordance with literature values.*[106]

_N_-(4-(Trifluoromethyl)phenyl)acetamide, 237



To a solution of 4-(trifluromethyl)aniline (2.51 mL, 20.0 mmol) in acetonitrile (20 mL) was added acetic anhydride (2.08 mL, 22.0 mmol) and pyridine (0.97 mL, 12.0 mmol). The resulting mixture was stirred at room temperature for 16 h. H_2O (20 mL) was then added and the mixture was stirred at room temperature for 30 mins. After extraction with EtOAc (3 × 50 mL), the organic extracts were combined and washed sequentially with 2M HCl (25 mL), sat. aq. $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL). The organic extracts were then dried over sodium sulfate and filtered before solvent was removed *in vacuo*. Recrystallisation (hexane/EtOAc) gave the title compound as a white solid (3.07 g, 75%); **R_f** = 0.71 (hexane/EtOAc, 1:1); **m.p.** = 151.6 – 152.8 °C (hexane/EtOAc, Lit.[298]: 151 – 154 °C); **^{1}H NMR** (400 MHz, DMSO-d^6) δ 10.29 (s, 1H, H^7), 7.81 – 7.76 (m, 2H, H^2, H^4), 7.68 – 7.61 (m, 2H, H^1, H^5), 2.08 (s, 3H, H^9); **^{13}C NMR** (101 MHz, DMSO-d^6) δ 169.0 (C^8), 142.9 (C^6), 126.0 (d, *J* = 4.0 Hz, C^1, C^5), 123.1 (q, *J* = 271.0 Hz, C^{10}), 123.0 (q, *J* = 32.0 Hz, C^3) 118.8 (C^2, C^4), 24.1 (C^9); **^{19}F NMR** (377 MHz, DMSO-d^6) δ -55.6. *Data in accordance with literature values.*[299]

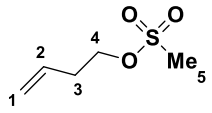
But-3-en-1-yl 4-methylbenzenesulfonate, 235



General procedure K: using 1-buten-4-ol (0.43 mL, 5.00 mmol) and tosyl chloride (1.05 g, 5.50 mmol) followed by triethylamine (0.77 mL, 5.50 mmol) for 72 h. Purification by FCC (hexane/EtOAc, 10:1) gave the title compound as a colourless liquid (1.02 g, 89%); **R_f** = 0.28 (hexane/EtOAc, 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.75 (m, 2H, H^{10}, H^{14}), 7.40 – 7.31 (m, 2H, H^{11}, H^{13}), 5.67 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, H^2), 5.09 (m, 2H, H^1), 5.05 (*pseudo*-t, *J* = 1.5 Hz, $H^{1'}$), 4.06 (t, *J* = 6.5 Hz, 2H, H^4), 2.45 (s, 3H, H^{15}), 2.40 (*pseudo*-qt, *J* = 6.5, 1.5 Hz, 2H, H^3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9 (C^{12}),

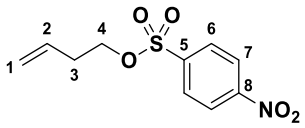
133.3 (C^9), 132.6 (C^2), 130.0 (C^{10}, C^{14}), 128.1 (C^{11}, C^{13}), 118.4 (C^1), 69.6 (C^4), 33.3 (C^{15}), 21.8 (C^3). *Data in accordance with literature values.*[300]

But-3-en-1-yl methanesulfonate, 240



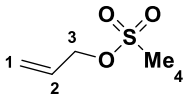
General procedure K: using 1-buten-4-ol (0.86 mL, 10.0 mmol) and mesyl chloride (0.85 mL, 11.0 mmol) for 16 h. Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a colourless liquid (1.50 g, 99%); $\mathbf{R_f}$ = 0.43 (hexane/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.77 (m, 1H, H^2), 5.23 – 5.06 (m, 2H, H^1), 4.25 (t, *J* = 6.5 Hz, 2H, H^4), 3.00 (s, 3H, H^5), 2.52 – 2.44 (m, 2H, H^3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.5 (C^2), 118.6 (C^1), 69.0 (C^4), 37.6 (C^5), 33.5 (C^3). *Data in accordance with literature values.*[301]

But-3-en-1-yl 4-nitrobenzenesulfonate, 241



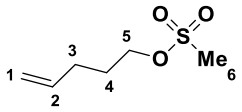
General Procedure K: using 1-buten-4-ol (0.86 mL, 10.0 mmol) and nosyl chloride (2.44 g, 11.0 mmol) for 16 h. Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a white solid (1.94 g, 75%); $\mathbf{R_f}$ = 0.47 (hexane/EtOAc, 4:1); **m.p.** = 50.9 – 52.2 °C (hexane/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 – 8.34 (m, 2H, H^7), 8.10 (d, *J* = 9.0 Hz, 2H, H^6), 5.66 (ddt, *J* = 16.0, 10.5, 6.5 Hz, 1H, H^2), 5.18 – 5.02 (m, 2H, H^1), 4.18 (t, *J* = 6.5 Hz, 2H, H^4), 2.44 (*pseudo*-qt, *J* = 6.5, 1.5 Hz, 2H, H^3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.9 (C^5), 142.0 (C^8), 132.0 (C^2), 129.3 (C^6), 124.6 (C^5), 118.9 (C^1), 70.7 (C^4), 33.2 (C^3). *Data in accordance with literature values.*[302]

Allyl methanesulfonate, 242



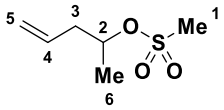
General Procedure K: using 2-propen-1-ol (0.68 mL, 10.0 mmol) and mesyl chloride (0.85 mL, 11.0 mmol) for 16 h. Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a colourless liquid (578 mg, 42%); $\mathbf{R_f}$ = 0.20 (hexane/EtOAc, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.96 (ddt, *J* = 17.0, 10.5, 6.0 Hz, 1H, H^2), 5.46 (*pseudo*-dq, *J* = 17.0, 1.0 Hz, 1H, H^1), 5.38 (*pseudo*-dq, *J* = 10.0, 1.0 Hz, 1H, $H^{1'}$), 4.71 (dt, *J* = 6.0, 1.0 Hz, 2H, H^3), 3.02 (s, 3H, H^4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.5 (C^2), 121.1 (C^1), 70.5 (C^3), 38.2 (C^4). *Data in accordance with literature values.*[303]

Pent-4-en-1-yl methanesulfonate, 243



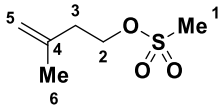
General Procedure K: using pent-4-en-1-ol (1.03 mL, 10.0 mmol) and mesyl chloride (0.85 mL, 11.0 mmol) for 16 h. Volatiles were removed *in vacuo* to give the title compound as a colourless liquid (1.64 g, 99%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, H^2), 5.11 – 4.97 (m, 2H, H^1), 4.23 (t, *J* = 7.0 Hz, 1H, H^5), 2.99 (s, 3H, H^6), 2.24 – 2.12 (*pseudo*-q, *J* = 7.0, 2H, H^3), 1.85 (p, *J* = 7.0 Hz, 2H, H^4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.7 (C^2), 116.2 (C^1), 69.4 (C^5), 37.4 (C^6), 29.5 (C^3), 28.3 (C^4). *Data in accordance with literature values.*[304]

Pent-4-en-2-yl methanesulfonate, 246



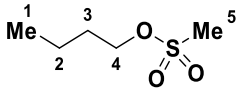
General Procedure K: using pent-4-en-2-ol (1.03 mL, 10.0 mmol) and mesyl chloride (0.851 mL, 11.0 mmol) for 16 h. Volatiles were removed *in vacuo* to give the title compound as a yellow liquid (1.85 g, 99%); $\mathbf{R_f}$ = 0.76 (hexane/EtOAc, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83 – 5.71 (m, 1H, H^4), 5.19 – 5.11 (m, 2H, H^5), 4.81 (m, 1H, H^2), 2.98 (s, 3H, H^1), 2.52 – 2.34 (m, 2H, H^3), 1.41 (d, *J* = 6.5 Hz, 3H, H^6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.5 (C^4), 119.2 (C^5), 79.3 (C^2), 41.0 (C^3), 38.8 (C^1), 20.9 (C^6). *Data in accordance with literature values.*[305]

3-Methylbut-3-en-yl methanesulfonate, 247



General Procedure K: using 3-methylbut-3-en-1-ol (1.01 mL, 10.0 mmol) and mesyl chloride (0.850 mL, 11.0 mmol) for 16 h. Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a colourless liquid (1.32 g, 80%); $\mathbf{R_f}$ = 0.37 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.86 (br, 1H, H^5) 4.78 (br, 1H, $H^{5'}$), 4.32 (t, *J* = 7.0 Hz, 2H, H^2), 3.00 (s, 3H, H^1), 2.45 (t, *J* = 7.0 Hz, 2H, H^3), 1.77 (s, 3H, H^6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3 (C^4), 113.4 (C^5), 68.0 (C^2), 37.6 (C^1), 37.1 (C^3), 22.5 (C^6). *Data in accordance with literature values.*[306]

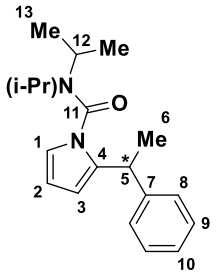
Butyl methanesulfonate, 248



General Procedure K: using butan-1-ol (0.920 mL, 10.0 mmol) and mesyl chloride (0.850 mL, 11.0 mmol) for 16 h. Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a colourless liquid (1.39 g, 91%); $\mathbf{R_f}$ = 0.33 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.26 – 4.16 (t, *J* = 6.5 Hz, 2H, H^4), 3.03 – 2.93 (s, 3H, H^5), 1.78 – 1.65 (m, 2H, H^3), 1.50 – 1.36 (m, 2H, H^2), 0.99 – 0.88 (t, *J* = 6.5 Hz, 3H, H^1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 70.0 (C^4), 37.4 (C^5), 31.2 (C^3), 18.8 (C^2), 13.6 (C^1). *Data in accordance with literature values.*[307]

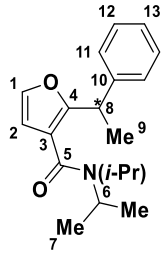
7.4.2 Catalysis products

***N,N*-Diisopropyl-2-(1-phenylethyl)-1*H*-pyrrole-1-carboxamide, 105**



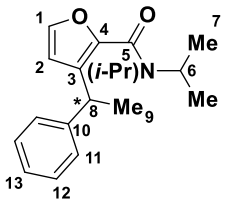
General procedure L: using **104** (19.4 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol) and (*R*)-**L23** (3.73 mg, 5.0 µmol) in 1,4-dioxane (0.067 mL) with styrene (46 µL, 0.40 mmol) at 90 °C for 48 h. Purification by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (29.5 mg, 99% yield, 34% *e.e.*); $\mathbf{R_f}$ = 0.72 (hexane/EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = +2.68 (c = 1.48, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 2H, Ar-C<u>H</u>), 7.17 – 7.10 (m, 3H, Ar-C<u>H</u>), 6.61 (dd, *J* = 3.0, 1.5 Hz, 1H, H^1), 6.23 – 6.19 (m, 1H, Ar-C<u>H</u>), 6.13 (t, *J* = 3.0 Hz, 1H, Ar-C<u>H</u>), 4.53 (q, *J* = 7.0 Hz, 1H, H^5), 3.31 (br. s, 2H, H^{12}), 1.54 (d, *J* = 7.0 Hz, 3H, H^6), 1.39 – 1.02 (m, 12H, H^{13}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.6 (C^{11}), 146.4 (Ar-<u>C</u>), 138.6 (Ar-<u>C</u>), 128.6 (Ar-<u>C</u>H), 127.9 (Ar-<u>C</u>H), 126.3 (Ar-<u>C</u>H), 119.3 (Ar-<u>C</u>), 108.0 (Ar-<u>C</u>H), 107.3 (Ar-<u>C</u>H), 37.0 (C^5), 22.2 (C^6), 20.3 (C^{13}). **Chiral SFC:** (DAICEL CHIRALPAK IE column (25 cm), CO_2:IPA 95:5, 2.5 mL/min, 140 bars, 40 °C). Retention times: 8.0 mins (minor), 9.5 mins (major), *e.r.* = 33:67, *e.e.* = 34%. *Data in accordance with literature values.*[108]

***N*,*N*-Diisopropyl-2-(1-phenylethyl)furan-3-carboxamide, 107**



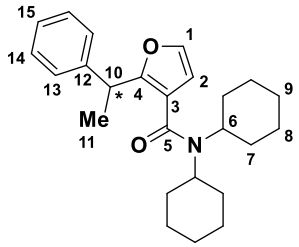
General procedure L: using **106** (19.5 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol) and (*R*)-**L23** (3.73 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with styrene (46 µL, 0.40 mmol) at 90 °C for 48 h. Purification by FCC (hexane/EtOAc, 4:1) afforded the title compound as a colourless oil (26.5 mg, 89% yield, 71% *e.e.*); $\mathbf{R_f}$ = 0.44 (hexane/EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = +2.66 (c = 1.33, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H, Ar-C<u>H</u>), 7.24 – 7.16 (m, 1H, H^1), 6.27 (s, 1H, H^2), 4.43 (q, *J* = 7.5 Hz, 1H, H^8), 3.67 (br, 2H, H^6), 1.67 (d, *J* = 7.5 Hz, 3H, H^9), 1.60 – 0.64 (m, 9H, H^7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.7 (C^5), 157.1 (Ar-<u>C</u>), 144.2 (Ar-<u>C</u>), 140.3 (Ar-<u>C</u>H), 128.6 (Ar-<u>C</u>H), 127.5 (Ar-<u>C</u>H), 126.5 (C^1), 117.8 (Ar-<u>C</u>), 109.3 (C^2), 38.0 (C^8), 20.7 (C^7), 19.5 (C^9); **Chiral SFC:** (DAICEL CHIRALPAK IE column (25 cm), CO_2:MeOH 92.5:7.5, 2 mL/min, 140 bars, 40 °C). Retention times: 9.5 mins (major), 10.2 mins (minor), *e.r.* = 85.5:14.5, *e.e.* = 71%. *Data in accordance with literature values.*[108]

***N*,*N*-Diisopropyl-3-(1-phenylethyl)furan-2-carboxamide, 182**



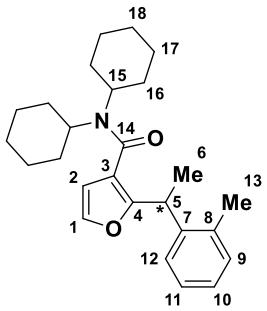
General procedure L: using **181** (19.5 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol) and (*R*)-**L23** (3.73 mg, 5.0 µmol) in toluene (0.1 mL) with styrene (46 µL, 0.40 mmol) at 90 °C for 48 h. Purification by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (22.0 mg, 74% yield, 80% *e.e.*). $\mathbf{R_f}$ = 0.60 (hexane/EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = +23.9 (c = 1.10, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 5H, Ar-C<u>H</u>), 7.20 – 7.15 (m, 1H, H^1), 6.36 (d, *J* = 2.0 Hz, 1H, H^2), 4.48 (q, *J* = 7.0 Hz, 1H, H^8), 3.60 (br. s, 2H, H^6), 1.60 (d, *J* = 7.0 Hz, 3H, H^9), 1.34 (br. s, 12H, H^7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.9 (C^5), 146.2 (Ar-<u>C</u>), 144.6 (Ar-<u>C</u>), 140.9 (Ar-<u>C</u>H), 132.2 (Ar-<u>C</u>), 128.4 (Ar-<u>C</u>H), 127.4 (Ar-<u>C</u>H), 126.1 (C^1), 111.0 (C^2), 34.9 (C^8), 21.3 (C^9), 20.9 (C^7); **Chiral SFC:** (YMC CHIRAL ART Cellulose-SB column (25 cm), CO_2:MeOH 99:1, 2 mL/min, 140 bars, 40 °C). Retention times: 9.4 mins (minor), 10.0 mins (major), *e.r.* = 10:90, *e.e.* = 80%. *Data in accordance with literature values.*[108]

***N,N*-Dicyclohexyl-2-(1-phenylethyl)furan-3-carboxamide, 188**



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol), and (*R*)-**L13** (6.10 mg, 5.0 μmol) in 1,2-DCB (0.2 mL) with styrene (46 μL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (35.4 mg, 93% yield, 92% *e.e.*). $\mathbf{R_f}$ = 0.33 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$ = - 1.91 (c = 0.69, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$: 2929 (m), 2853 (m), 2238 (w), 1618 (m), 1552 (w), 1511 (w); **^{1}H NMR** (500 MHz, DMSO-d^6, 100 °C) δ 7.49 (d, *J* = 2.0 Hz, 1H, H^1), 7.30 – 7.21 (m, 4H, H^{13}, H^{14}), 7.20 – 7.15 (m, 1H, H^{15}), 6.36 – 6.31 (m, 1H, H^2), 4.27 (q, *J* = 7.5 Hz, 1H, H^{11}), 3.27 – 3.13 (br. m, 2H, H^6), 1.97 (br. s, 4H, Cy-H), 1.79 – 1.64 (br. m, 4H, Cy-H), 1.61 – 1.50 (br. m, 7H, H^{11}, Cy-H), 1.45 – 1.36 (br. m, 2H, Cy-H), 1.26 – 1.00 (br. m, 6H, Cy-H); **^{13}C NMR** (126 MHz, DMSO-d^6, 100 °C) δ 164.4 (C^5), 154.6 (C^4), 143.3 (C^{12}), 140.4 (C^1), 127.7 (C^{13}/C^{14}), 126.4 (C^{13}/C^{14}), 125.7 (C^{15}), 117.8 (C^3), 108.6 (C^2), 56.6 (C^6), 36.9 (C^{10}), 29.8 (Cy-CH_2), 25.2 (Cy-CH_2), 24.4 (Cy-CH_2), 18.7 (C^{11}); ***m/z*** (ESI$^+$) calc. for $C_{25}H_{33}NO_2$ = 379.25 found: 380.2586 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 2 mL/min, 140 bars, 40 °C). Retention times: 19.0 mins (major), 22.9 mins (minor), *e.r.* = 96:4, *e.e.* = 92%.

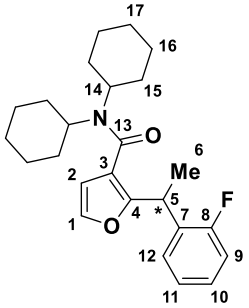
***N,N*-Dicyclohexyl-2-(1-(*o*-tolyl)ethyl)furan-3-carboxamide, 193a**



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol), and (*R*)-**L13** (6.10 mg, 5.0 μmol) in 1,2-DCB (0.2 mL) with 2-methylstyrene (52 μL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (34.5 mg, 88% yield, 80% *e.e.*). $\mathbf{R_f}$ = 0.23 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = -5.43 (c = 1.20, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 2931 (s), 2855 (m), 1625 (s), 1513 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H, H^1, Ar-CH), 7.13 (td, *J* = 6.5, 1.5 Hz, 1H, Ar-CH), 7.10 – 7.04 (m, 2H, Ar-CH), 6.21 (d, *J* =

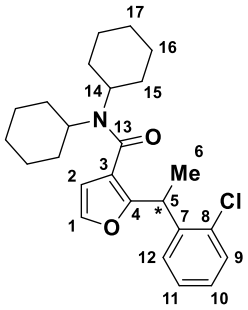
1.5 Hz, 1H, H^2), 4.63 (q, *J* = 7.5 Hz, 1H, H^5), 3.43 – 2.73 (br, 2H, Cy-H), 2.56 (br, 2H, Cy-H), 2.30 (s, 3H, H^6), 1.87 – 0.76 (m, 21H, Cy-H, H^6); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.0 (C^{14}), 157.2 (C^4), 142.7 (C^7), 140.2 (C^1), 135.3 (C^8), 130.3 (Ar-CH), 127.2 (Ar-CH), 126.4 (Ar-CH), 126.3 (Ar-CH), 117.8 (C^3), 109.2 (C^2), 34.1 (C^5), 25.4 (Cy-CH_2), 19.6 (C^{13}), 19.2 (C^6); ***m/z*** (ESI$^+$) calc. for $C_{26}H_{35}NO_2$ = 393.27, found: 394.2742 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 4 mL/min, 140 bars, 40 °C). Retention times: 6.8 mins (major), 8.7 mins (minor), *e.r.* = 90:10, *e.e.* = 80%.

***N,N*-Dicyclohexyl-2-(1-(2-fluorophenyl)ethyl)furan-3-carboxamide, 193b**



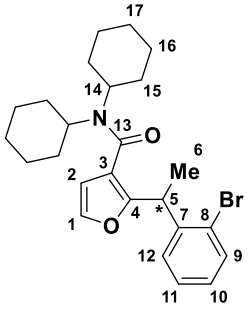
General procedure **L**: using substrate **187** (27.5 mg, 0.1 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol), and (*R*)-**L13** (6.10 mg, 5.0 μmol) in 1,2-DCB (0.2 mL) with 2-fluorostyrene (48 μL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (32.4 mg, 82% yield, 83% *e.e.*); $\mathbf{R_f}$ = 0.23 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = -5.94 (c = 1.05, $CHCl_3$); **ν_{max}/cm^{-1}:** 2929 (s), 2954 (m), 2242 (w), 1778 (w), 1623 (s), 1510 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (*pseudo*-td, *J* = 7.5, 2.0 Hz, 1H, H^{12}), 7.26 (d, *J* = 2.0 Hz, 1H, H^1), 7.15 (*pseudo*-tdd, *J* = 7.5, 5.0, 1.5 Hz, 1H, H^{10}), 7.06 (*pseudo*-td, *J* = 7.5, 1.5 Hz, 1H, H^{11}), 6.96 (ddd, *J* = 9.5, 7.5, 1.5 Hz, 1H, H^9), 6.24 – 6.18 (br, 1H, H^2), 4.69 (q, *J* = 7.5 Hz, 1H, H^6), 3.55 – 2.79 (br, 2H, Cy-H), 2.57 (br, 2H, Cy-H), 1.95 – 0.79 (m, 21H, H^6, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.8 (C^{13}), 160.3 (d, *J* = 245.5 Hz, C^8), 155.5 (C^4), 140.5 (C^1), 131.0 (d, *J* = 14.0 Hz, C^7), 129.1 (d, *J* = 4.0 Hz, C^{12}), 128.1 (d, *J* = 8.0 Hz, C^{10}), 124.3 (d, *J* = 3.5 Hz, C^{11}), 118.3 (C^3), 115.3 (d, *J* = 22.0 Hz, C^9), 109.3 (C^2), 31.2 (d, *J* = 3.5 Hz, C^5), 25.4 (Cy-CH_2), 18.6 (C^6); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -118.7; ***m/z*** (ESI$^+$) calc. for $C_{25}H_{32}FNO_2$ = 397.24, found: 398.2492 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 94:6, 4 mL/min, 140 bars, 40 °C). Retention times: 8.7 mins (major), 10.4 mins (minor), *e.r.* = 91.5:8.5, *e.e.* = 83%.

2-(1-(2-Chlorophenyl)ethyl)-*N*,*N*-dicyclohexylfuran-3-carboxamide, 193c



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), and (*R*)-**L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with 2-chlorostyrene (52 µL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (34.0 mg, 82% yield, 54% *e.e.*); **R$_f$** = 0.26 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = -16.4 (c = 1.35, $CHCl_3$); **ν_{max}/cm^{-1}:** 2930 (s), 2855 (m), 1627 (s), 1511 (w); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.0, 1.5 Hz, 1H, H^{12}), 7.30 (dd, *J* = 8.0, 1.5 Hz, 1H, H^9), 7.27 (d, *J* = 2.0 Hz, 1H, H^1), 7.21 (*pseudo*-td, *J* = 8.0, 1.5 Hz, 1H, H^{11}), 7.12 (*pseudo*-td, *J* = 8.0, 1.5 Hz, 1H, H^{10}), 6.23 (d, *J* = 2.0 Hz, 1H, H^2), 4.84 (q, *J* = 7.0 Hz, 1H, H^5), 3.50 – 2.74 (br, 2H, Cy-H), 2.55 (br, 2H, Cy-H), 1.87 – 0.79 (m, 21H, H^6, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.8 (C^{13}), 155.7 (C^4), 141.4 (C^7), 140.5 (C^1), 133.4 (C^8), 129.6 (C^9), 129.2 (C^{12}), 127.7 (C^{10}), 127.2 (C^{11}), 118.6 (C^3), 109.3 (C^2), 35.0 (C^5), 29.8 (Cy-CH_2), 25.4 (Cy-CH_2), 18.8 (C^6); ***m/z*** (ESI$^+$) calc. for $C_{25}H_{32}ClNO_2$ = 413.21, found: 414.2196 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 2 mL/min, 140 bars, 40 °C). Retention times: 24.3 mins (major), 28.0 mins (minor), *e.r.* = 77:23, *e.e.* = 54%.

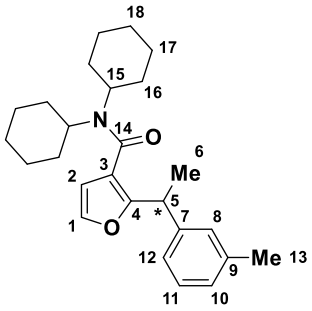
2-(1-(2-Bromophenyl)ethyl)-*N*,*N*-dicyclohexylfuran-3-carboxamide, 193d



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), and (*R*)-**L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with 2-bromostyrene (50 µL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (35.9 mg, 78% yield, 38% *e.e.*). **R$_f$** = 0.23 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = **-** 3.46 (c = 1.30, $CHCl_3$); **ν_{max}/cm^{-1}:** 2929 (s), 2854 (m), 2242 (w), 1623 (s), 1571 (w), 1511 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.0, 1.5 Hz, 1H, H^9), 7.41 (dd, *J* = 8.0, 1.5 Hz, 1H, H^{12}), 7.28 (d, *J* = 2.0 Hz, 1H,

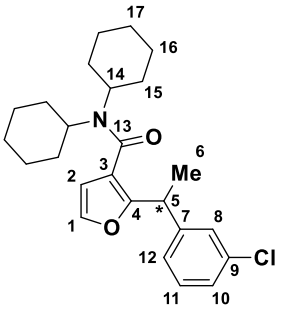
H^1), 7.25 (*pseudo*-td, *J* = 7.5, 1.5 Hz, 1H, H^{11}), 7.04 (*pseudo*-td, *J* = 7.5, 1.5 Hz, 1H, H^{10}), 6.23 (d, *J* = 2.0 Hz, 1H, H^2), 4.80 (q, *J* = 7.0 Hz, 1H, H^5), 3.50 – 2.74 (br, 2H, Cy-H), 2.55 (br, 2H, Cy-H), 1.88 – 0.78 (m, 21H, H^6, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.7 (C^{13}), 155.7 (C^4), 143.1 (C^7), 140.5 (C^1), 132.9 (C^9), 129.4 (C^{12}), 128.0 (C^{10}), 127.8 (C^{11}), 124.0 (C^8), 118.7 (C^3), 109.4 (C^2), 37.8 (C^5), 29.8 (Cy-CH_2), 25.4 (Cy-CH_2), 19.1 (C^6); ***m/z*** (ESI$^+$) calc. for $C_{25}H_{32}{}^{79}BrNO_2$ = 457.16, found: 458.1688 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 87.5:12.5, 2.5 mL/min, 140 bars, 40 °C). Retention times: 11.4 mins (major), 12.6 mins (minor), *e.r.* = 69:31, *e.e.* = 38%.

***N,N*-Dicyclohexyl-2-(1-(*m*-tolyl)ethyl)furan-3-carboxamide, 193e**



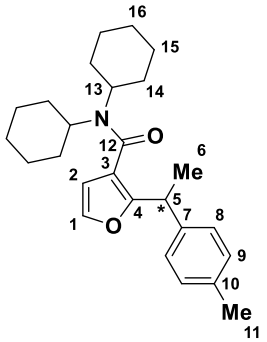
General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), and (*R*)-**L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with 3-methylstyrene (48 µL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (34.9 mg, 89% yield, 91% *e.e.*). $\mathbf{R_f}$ = 0.30 (hexane/EtOAc, (9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = - 4.04 (c = 1.75, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3576 (w), 2969 (m), 2928 (s), 2854 (m), 1625 (s), 1509 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 2.0 Hz, 1H, H^1), 7.15 (*pseudo*-td, *J* = 7.5, 1.5 Hz, 1H, H^{11}), 7.08 – 7.02 (m, 2H, H^8, H^{12}), 6.98 (d, *J* = 7.5 Hz, 1H, H^{10}), 6.21 (d, *J* = 2.0 Hz, 1H, H^2), 4.35 (q, *J* = 7.5 Hz, 1H, H^5), 3.45 – 2.78 (br, 2H, Cy-H), 2.59 (br, 2H, Cy-H), 2.30 (s, 3H, H^{13}), 1.88 – 0.82 (m, 21H, H^6, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.1 (C^{14}), 156.9 (C^4), 144.3 (C^7), 140.3 (C^1), 138.0 (C^9), 128.5 (C^{11}), 128.1 (C^8), 127.2 (C^{10}), 124.5 (C^{12}), 118.0 (C^3), 109.2 (C^2), 37.8 (C^5), 25.4 (Cy-CH_2), 21.6 (C^{13}), 19.5 (C^6); ***m/z*** (ESI$^+$) calc. for $C_{26}H_{35}NO_2$ = 393.27, found: 394.2734 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 4 mL/min, 140 bars, 40 °C). Retention times: 9.8 mins (major), 12.4 mins (minor), *e.r.* = 95.5:5.5, *e.e.* = 91%.

2-(1-(3-Chlorophenyl)ethyl)-*N*,*N*-dicyclohexylfuran-3-carboxamide, 193f



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 μmol), and (*R*)-**L13** (6.10 mg, 5.0 μmol) in 1,2-DCB (0.2 mL) with 3-chlorostyrene (51 μL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (34.5 mg, 83% yield, 90% *e.e.*). $\mathbf{R_f}$ = 0.26 (hexane/EtOAc, 9:1);); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +9.69 (c = 1.73, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3677 (w), 2929 (s), 2854 (m), 2326 (w), 1629 (s), 1573 (m), 1511 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 2.0 Hz, 1H, H^1), 7.23 – 7.12 (m, 4H, H^8, H^{10}, H^{11}, H^{12}), 6.22 (d, *J* = 2.0 Hz, 1H, H^2), 4.38 (q, *J* = 7.5 Hz, 1H, H^5), 3.50 – 2.77 (br, 2H, Cy-H), 2.57 (br, 2H, Cy-H), 1.87 – 0.84 (m, 21H, H^6, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.7 (C^{13}), 156.2 (C^4), 146.4 (C^7), 140.5 (C^1), 134.3 (C^9), 129.8 (Ar-CH), 127.6 (Ar-CH), 126.7 (Ar-CH), 125.8 (Ar-CH), 118.4 (C^3), 109.3 (C^2), 37.6 (C^5), 25.4 (Cy-CH_2), 19.3 (C^6); ***m/z*** (ESI$^+$) calc. for $C_{25}H_{32}ClNO_2$ = 413.21, found: 414.2193 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 97:3, 5 mL/min, 140 bars, 40 °C). Retention times: 21.4 mins (major), 27.8 mins (minor), *e.r.* = 95:5, *e.e.* = 90%.

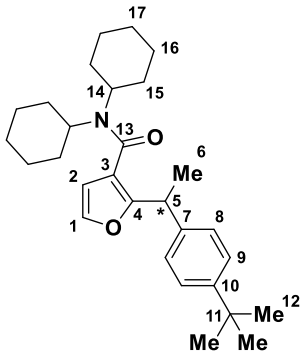
***N*,*N*-Dicyclohexyl-2-(1-(*p*-tolyl)ethyl)furan-3-carboxamide, 193g**



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 μmol), and (*R*)-**L13** (6.10 mg, 5.0 μmol) in 1,2-DCB (0.2 mL) with 4-methylstyrene (48 μL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (35.6 mg, 90% yield, 89% *e.e.*). $\mathbf{R_f}$ = 0.31 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +3.85 (c = 1.15, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 2929 (s), 2854 (s), 1804 (w), 1775 (w), 1624 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 1.5 Hz, 1H, H^1), 7.14 (d, *J* = 8.0 Hz, 2H, H^9), 7.07 (d, *J* = 8.0 Hz, 2H, H^8), 6.21 (d, *J* = 1.5 Hz, 1H, H^2), 4.35 (q, *J* = 7.5 Hz, 1H, H^5), 3.58 – 2.76 (br, 2H, Cy-H), 2.59 (br, 2H, Cy-H), 2.28 (s, 3H,

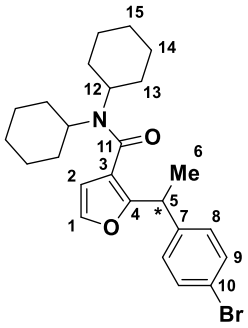
H^{11}), 1.93 – 0.80 (m, 21H, H^6, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.1 (C^{12}), 156.9 (C^4), 141.3 (C^7), 140.3 (C^1), 135.9 (C^{10}), 129.2 (C^8), 127.2 (C^9), 117.8 (C^3), 109.1 (C^2), 37.5 (C^5), 25.4 (Cy-CH_2), 21.1 (C^{11}), 19.6 (C^6); ***m/z*** (ESI^+) calc. for $C_{26}H_{35}NO_2$ = 393.27, found: 394.2744 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 90:10, 3.5 mL/min, 140 bars, 40 °C). Retention times: 18.3 mins (major), 21.9 mins (minor), *e.r.* = 94.5:5.5, *e.e.* = 89%.

2-(1-(4-(*Tert*-butyl)phenyl)ethyl)-*N*,*N*-dicyclohexylfuran-3-carboxamide, 193h



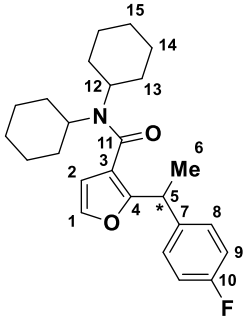
General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol), and (*R*)-**L13** (6.10 mg, 5.0 μmol) in 1,2-DCB (0.2 mL) with 4-*tert*-butylstyrene (73 μL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (41.3 mg, 95% yield, 86% *e.e.*). **R_f** = 0.36 (hexane/EtOAc, 9:1); $[\alpha]_D^{24}$ = +0.14 (c = 1.45, $CHCl_3$); **ν_{max}/cm^{-1}:** 2962 (m), 2931 (s), 2855 (m), 1807 (w), 1771 (w), 1623 (s), 1509 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 3H, H^1, H^8), 7.21 – 7.14 (m, 2H, H^9), 6.20 (d, *J* = 2.0 Hz, 1H, H^2), 4.35 (q, *J* = 7.5 Hz, 1H, H^5), 3.40 – 2.79 (br, 2H, Cy-H), 2.58 (br, 2H, Cy-H), 1.86 – 0.75 (m, 30H, H^6, H^{12}, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.1 (C^{13}), 157.0 (C^4), 149.1 (C^{10}), 141.3 (C^7), 140.2 (C^1), 127.0 (C^9), 125.4 (C^8), 117.8 (C^3), 109.2 (C^2), 37.4 (C^5), 34.5 (C^{11}), 31.5 (C^{12}), 25.4 (Cy-CH_2), 19.5 (C^6); ***m/z*** (ESI^+) calc. for $C_{29}H_{41}NO_2$ = 435.31, found: 436.3211 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 95:5, 4 mL/min, 140 bars, 40 °C). Retention times: 13.2 mins (major), 16.8 mins (minor), *e.r.* = 93:7, *e.e.* = 86%.

2-(1-(4-Bromophenyl)ethyl)-*N*,*N*-dicyclohexylfuran-3-carboxamide, 193i



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), and (*R*)-**L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with 4-bromostyrene (52 µL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (33.8 mg, 74% yield, 87% *e.e.*). $\mathbf{R_f}$ = 0.31 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +14.4 (c = 1.20, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 2929 (s), 2854 (m), 1619 (s), 1512 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H, H^9), 7.25 (d, *J* = 2.0 Hz, 1H, H^1), 7.17 – 7.12 (m, 2H, H^8), 6.21 (d, *J* = 2.0 Hz, 1H, H^2), 4.35 (q, *J* = 7.5 Hz, 1H, H^5), 3.49 – 3.26 (br, 1H, Cy-H), 2.99 – 2.80 (br, 1H, Cy-H), 2.57 (br, 1H, Cy-H), 1.99 – 0.76 (m, 22H, H^6, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.8 (C^{11}), 156.2 (C^4), 143.3 (C^7), 140.5 (C^1), 131.6 (C^9), 129.2 (C^8), 120.3 (C^{10}), 118.2 (C^3), 109.3 (C^2), 37.5 (C^5), 25.3 (Cy-CH_2), 19.4 (C^6); ***m/z*** (ESI$^+$) calc. for $C_{25}H_{32}{}^{79}BrNO_2$ = 457.16, found: 458.1687 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 2 mL/min, 140 bars, 40 °C). Retention times: 24.4 mins (major), 28.9 mins (minor), *e.r.* = 93:6, *e.e.* = 87%.

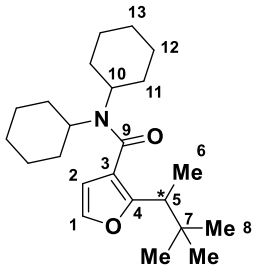
***N*,*N*-Dicyclohexyl-2-(1-(4-fluorophenyl)ethyl)furan-3-carboxamide, 193j**



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), and (*R*)-**L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with 4-fluorostyrene (48 µL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (12.0 mg, 30% yield, 84% *e.e.*). $\mathbf{R_f}$ = 0.31 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = - 3.54 (c = 0.45, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 2930 (s), 2855 (m), 1625 (s), 1509 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 3H, H^1, H^8), 6.99 – 6.91 (m, 2H, H^9), 6.22 (br, 1H, H^2), 4.37 (q, *J* = 7.5 Hz, 1H, H^5), 3.48 – 2.80 (br, 2H, Cy-H), 2.57 (br, 2H, Cy-H), 1.91 – 0.74 (m, 21H, H^6, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ

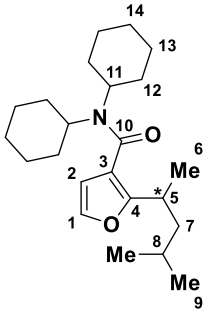
166.0 (C^{11}), 161.3 (d, *J* = 244.5 Hz, C^{10}) 156.7 (C^4), 140.2 (C^7), 139.9 (C^1), 128.9 (d, *J* = 8.0 Hz, C^8), 117.9 (C^3), 115.2 (d, *J* = 21.0 Hz, C^9), 109.4 (C^2), 37.3 (C^5), 25.4 (Cy-$\underline{C}H_2$), 19.7 (C^6); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.1; ***m/z*** (ESI^+) calc. for $C_{25}H_{32}FNO_2$ = 397.24, found: 398.2493 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 95:5, 5 mL/min, 140 bars, 40 °C). Retention times: 5.7 mins (major), 6.8 mins (minor), *e.r.* = 92:8, *e.e.* = 84%.

***N,N*-Dicyclohexyl-2-(3,3-dimethylbutan-2-yl)furan-3-carboxamide, 193k**



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), $[Ir(cod)_2]$BARF (6.36 mg, 5.0 μmol), and (*R*)-**L13** (6.10 mg, 5.0 μmol) in 1,2-DCB (0.2 mL) with *tert*-butylethylene (52 μL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 19:1) afforded the title compound as a colourless oil (30.5 mg, 85% yield, 85% *e.e.*). $\mathbf{R_f}$ = 0.75 (hexane/EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = -25.3 (c = 1.53, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 2962 (m), 2930 (s), 2855 (m), 1625 (s), 1553 (m), 1514 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.0 Hz, 1H, H^1), 6.20 (d, *J* = 2.0 Hz, 1H, H^2), 3.65 (br, 1H, Cy-$\underline{H}$), 2.96 (q, *J* = 7.0 Hz, 1H, H^5), 2.61 (br, 2H, Cy-$\underline{H}$), 1.83 – 1.39 (m, 12H, Cy-$\underline{H}$), 1.30 – 1.00 (m, 10H, H^6, Cy-$\underline{H}$), 0.90 (s, 9H, H^8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.5 (C^9), 158.8 (C^4), 139.9 (C^1), 118.7 (C^3), 108.6 (C^2), 41.7 (C^5), 34.4 (C^7), 28.1 (C^8), 25.4 (Cy-C), 13.8 (C^6); ***m/z*** (ESI^+) calc. for $C_{23}H_{37}NO_2$ = 359.28, found: 360.2892 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 2 mL/min, 140 bars, 40 °C). Retention times: 7.2 mins (major), 8.7 mins (minor), *e.r.* = 92.5:7.5, *e.e.* = 85%.

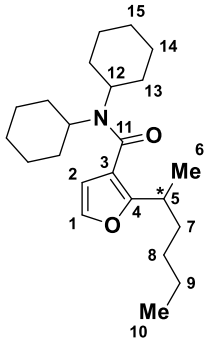
***N,N*-Dicyclohexyl-2-(4-methylpentan-2-yl)furan-3-carboxamide, 193l**



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), $[Ir(cod)_2]$BARF (6.36 mg, 5.0 μmol), and (*R*)-**L13** (6.10 mg, 5.0 μmol) in 1,2-DCB (0.2 mL) with 4-methyl-1-pentene (51 μL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 19:1) afforded the title compound

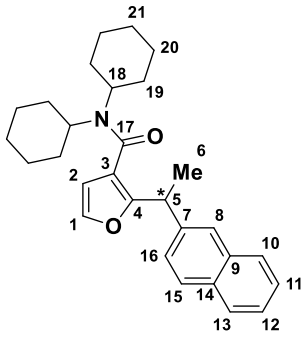
as a colourless oil (20.2 mg, 56% yield, 80% *e.e.*). $\mathbf{R_f}$ = 0.75 (hexane/EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = -17.3 (c = 1.01, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3116 (w), 2959 (m), 2930 (s), 2855 (m), 1626 (s), 1553 (m), 1516 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 2.0 Hz, 1H, H^1), 6.19 (d, *J* = 2.0 Hz, 1H, H^2), 3.61 (br, 1H, Cy-H), 3.17 – 3.06 (m, 1H, H^5), 2.95 (br, 1H, Cy-H), 2.60 (br, 2H, Cy-H), 1.83 – 1.43 (m, 13H, H^7, Cy-H), 1.42 – 1.04 (m, 12H, H^6, $H^{7'}$, H^8, Cy-H), 0.87 – 0.78 (m, 6H, H^9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.3 (C^{10}), 159.2 (C^4), 139.9 (C^1), 117.5 (C^3), 108.9 (C^2), 45.0 (C^7), 30.4 (C^5), 26.1 (C^8), 25.4 (Cy-CH_2), 23.1 (C^9), 22.6 ($C^{9'}$), 19.9 (C^6); ***m/z*** (ESI^+) calc. for $C_{23}H_{37}NO_2$ = 359.28, found: 360.2892 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 2 mL/min, 140 bars, 40 °C). Retention times: 7.4 mins (major), 8.1 mins (minor), *e.r.* = 90:10, *e.e.* = 80%.

***N,N*-Dicyclohexyl-2-(hexan-2-yl)furan-3-carboxamide, 193m**



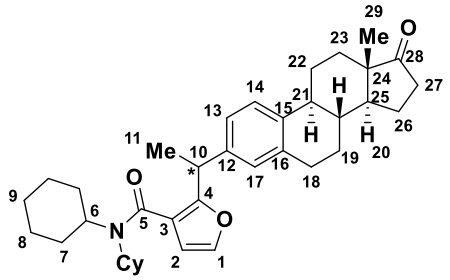
General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), and **(*R*)-L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with 1-hexene (50 µL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 19:1) afforded the title compound as a colourless oil (15.4 mg, 43% yield, 61% *e.e.*). $\mathbf{R_f}$ = 0.75 (hexane/EtOAc, 4:1) ; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = -12.05 (c = 0.77, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 2959 (m), 2929 (s), 2873, (m), 2855 (s), 1628 (s), 1515 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 2.0 Hz, 1H, H^1), 6.19 (d, *J* = 2.0 Hz, 1H, H^2), 3.61 (br, 1H, Cy-H), 2.99 (m, 2H, H^5, Cy-H), 2.60 (br, 2H, Cy-H), 1.85 – 1.39 (m, 14H, R-CH_2), 1.33 – 1.03 (m, 13H, H^6, R-CH_2), 0.84 (t, *J* = 7.5 Hz, 3H, H^{10}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.3 (C^{11}), 159.0 (C^4), 139.9 (C^1), 117.6 (C^3), 108.9 (C^2), 35.6, 32.6 (C^5), 30.0 (R-CH_2), 25.4 (R-CH_2), 22.8 (R-CH_2), 19.6 (C^6), 14.2 (C^{10}); ***m/z*** (ESI^+) calc. for $C_{23}H_{37}NO_2$ = 359.28, found: 360.2892 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 97:3, 5 mL/min, 140 bars, 40 °C). Retention times: 8.8 mins (major), 9.4 mins (minor), *e.r.* = 80.5:19.5, *e.e.* = 61%.

***N*,*N*-Dicyclohexyl-2-(1-(naphthalen-2-yl)ethyl)furan-3-carboxamide, 193n**



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), and **(*R*)-L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with 2-vinylnaphthalene (61 mg, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (35.2 mg, 82% yield, 88% *e.e.*). **R$_f$** = 0.26 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +14.05 (c = 1.76, $CHCl_3$); **ν_{max}/cm^{-1}:** 3677 (br), 2971 (s), 2929 (s), 2855 (s), 2350 (w), 1623 (s), 1508 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 – 7.70 (m, 3H, Ar-C<u>H</u>), 7.68 (d, *J* = 2.0 Hz, 1H, H^8), 7.49 – 7.36 (m, 3H, Ar-C<u>H</u>), 7.27 (d, *J* = 2.0 Hz, 1H, H^1), 6.23 (d, *J* = 2.0 Hz, 1H, H^2), 4.57 (q, *J* = 7.5 Hz, 1H, H^5), 3.45 – 2.73 (br, 2H, Cy-<u>H</u>), 2.59 (br, 2H, Cy-<u>H</u>), 1.87 – 0.64 (m, 21H, H^6, Cy-<u>H</u>); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.0 (C^{17}), 156.8 (C^4), 141.8 (C^7), 140.4 (C^1), 133.7 (Ar-<u>C</u>), 132.4 (Ar-<u>C</u>), 128.2 (Ar-<u>C</u>H), 127.9 (Ar-<u>C</u>H), 127.6 (Ar-<u>C</u>H), 126.2 (Ar-<u>C</u>H), 126.0 (Ar-<u>C</u>H), 125.5 (C^8), 125.4 (Ar-<u>C</u>H), 118.3 (C^3), 109.3 (C^2), 38.1 (C^5), 25.3 (Cy-<u>C</u>H$_2$), 19.3 (C^6); ***m/z*** (ESI$^+$) calc. for $C_{29}H_{35}NO_2$ = 429.27, found: 430.2734 [M+H]$^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 4 mL/min, 140 bars, 40 °C). Retention times: 15.2 mins (major), 18.9 mins (minor), *e.r.* = 94:6, *e.e.* = 88%.

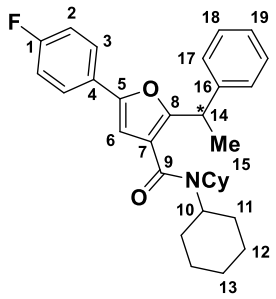
***N*,*N*-Dicyclohexyl-2-(1-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)ethyl)furan-3-carboxamide, 193o**



General procedure L: using substrate **187** (27.5 mg, 0.1 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), and (*R*)-**L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with (8*R*,9*S*,13*S*,14*S*)-13-methyl-3-vinyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (112 mg, 400 mol%)[308] at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 4:1) afforded the title compound as a pale-yellow solid (24.0 mg, 43% yield, 20:1 *d.r.*). **R$_f$** = 0.31 (hexane/EtOAc, (4:1); m.p.: 105.1 – 108.4

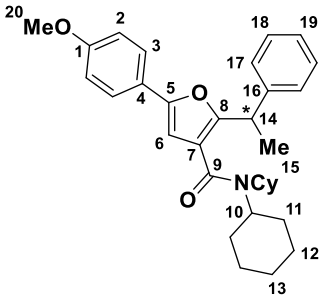
°C (hexane/EtOAc); $[\alpha]_D^{20}$ = +72.9 (c = 1.20, $CHCl_3$); **ν_{max}/cm^{-1}:** 2930 (s), 2855 (m), 1739 (m), 1622 (s), 1500 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 1.5 Hz, 1H, H^{17}), 7.19 (d, *J* = 8.0 Hz, 1H, H^{14}), 7.05 (dd, *J* = 8.0, 2.0 Hz, 1H, H^{13}), 6.98 (d, *J* = 1.5 Hz, 1H, H^1), 6.20 (d, *J* = 1.5 Hz, 1H, H^2), 4.32 (q, *J* = 7.5 Hz, 1H, H^{10}), 3.39 (s, 1H, R-C<u>H</u>), 2.87 (dd, *J* = 9.0, 4.0 Hz, 3H, R-C<u>H</u>$_2$), 2.66 – 2.55 (m, 2H, R-C<u>H</u>$_2$), 2.55 – 2.44 (m, 1H, R-C<u>H</u>$_2$), 2.44 – 2.32 (m, 1H, R-C<u>H</u>$_2$), 2.25 (d, *J* = 10.5 Hz, 1H, R-C<u>H</u>), 2.19 – 2.09 (m, 1H, R-C<u>H</u>$_2$), 2.08 – 1.90 (m, 3H, R-C<u>H</u>$_2$), 1.77 (s, 3H, R-C<u>H</u>$_3$), 1.68 – 1.33 (m, 19H, C^{11}, R-C<u>H</u>$_2$), 1.31 – 0.94 (m, 8H, R-C<u>H</u>$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 220.1 (C^{28}), 166.0 (C^5), 157.0 (C^4), 141.6 (Ar-<u>C</u>), 140.3 (C^{17}), 137.9 (Ar-<u>C</u>), 136.5 (Ar-<u>C</u>), 128.1 (C^1), 125.6 (C^{14}), 124.9 (C^{13}), 117.9 (C^3), 109.2 (C^2), 50.7 (C^{11}), 48.1 (R-<u>C</u>), 44.5 (R-<u>C</u>H), 38.4 (R-<u>C</u>H), 37.5 (C^{10}), 36.0 (R-<u>C</u>H$_2$), 31.8 (R-<u>C</u>H$_2$), 29.7 (R-<u>C</u>H$_2$), 26.7 (R-<u>C</u>H$_2$), 25.9 (R-<u>C</u>H$_2$), 25.4 (R-<u>C</u>H$_2$), 21.7 (R-<u>C</u>H$_2$), 19.4 (C^{11}), 14.0 (C^{29}); ***m/z*** (ESI$^+$) calc. for $C_{37}H_{49}NO_3$ = 555.37, found: 556.3776 $[M+H]^+$.

***N,N*-Dicyclohexyl-5-(4-fluorophenyl)-2-(1-phenylethyl)furan-3-carboxamide, 193p**



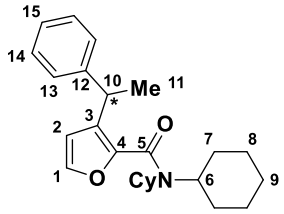
General procedure L: using substrate **189** (36.9 mg, 0.1 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), and **(*S*)-L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with styrene (46 µL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a pale-yellow solid (35.3 mg, 75% yield, 79% *e.e.*). **R_f** = 0.26 (hexane/EtOAc, 9:1); **m.p.** = 73.6 – 76.3 °C (hexane/EtOAc); $[\alpha]_D^{25}$ = +110.06 (c = 0.056, CH_2Cl_2); **ν_{max}/cm^{-1}:** 2931 (m), 2855 (m), 1625 (m), 1556 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (m, 2H, H^3), 7.37 – 7.26 (m, 4H, H^{17}, H^{18}), 7.20 (t, *J* = 7.0, 1H, H^{19}), 7.09 (*pseudo*-td, *J* = 8.5, 2.0 Hz, 2H, H^2), 6.43 (d, *J* = 1.5 Hz, 1H, H^6), 4.43 (q, *J* = 7.5 Hz, 1H, H^{14}), 3.61 – 3.25 (br, 1H, Cy-<u>H</u>), 2.94 (br, 1H, Cy-<u>H</u>), 2.63 (br, 2H, Cy-<u>H</u>), 1.92 – 0.81 (m, 21H, Cy-<u>H</u>, H^{15}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.6 (C^9), 162.3 (d, *J* = 247.5 Hz, C^1), 156.1 (C^8), 150.8 (C^5), 144.2 (C^{16}), 128.6 (Ar-<u>C</u>H), 127.4 (Ar-<u>C</u>H), 127.1 (d, *J* = 3.0 Hz, C^4), 126.5 (C^{19}), 125.6 (d, *J* = 8.0 Hz, C^3), 120.2 (C^7), 115.8 (d, *J* = 22.0 Hz, C^2), 103.9 (C^6), 38.1 (C^{14}), 25.3 (Cy-<u>C</u>H$_2$), 19.8 (C^{15}); **^{19}F NMR** (471 MHz, $CDCl_3$) δ -114.05; ***m/z*** (ESI$^+$) calc. for $C_{31}H_{36}FNO_2$ = 473.27, found: 474.2799 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 85:15, 2 mL/min, 140 bars, 40 °C). Retention times: 13.3 mins (minor), 15.1 mins (major), *e.r.* = 10.5:89.5, *e.e.* = 79%.

***N,N*-Dicyclohexyl-5-(4-methoxyphenyl)-2-(1-phenylethyl)furan-3-carboxamide, 193q**



General procedure L: using substrate **190** (36.9 mg, 0.1 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), and (*S*)-**L13** 6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with styrene (46 µL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a pale-yellow solid (31.4 mg, 70% yield, 86% *e.e.*). **R$_f$** = 0.22 (hexane/EtOAc, 9:1); **m.p.** = 67.6 – 70.3 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +110.32 (c = 0.086, $CHCl_3$); **ν_{max}/cm^{-1}:** 2929 (m), 2854 (w), 1616 (s), 1583 (m), 1559 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.54 (m, 2H, H^2), 7.37 – 7.25 (m, 4H, H^{17},H^{18}), 7.25 – 7.15 (m, 1H, H^{19}), 7.00 – 6.89 (m, 2H, H^3), 6.36 (d, *J* = 1.5 Hz, 1H, H^6), 4.42 (q, *J* = 7.0 Hz, 1H, H^{14}), 3.85 (s, 3H, H^{20}), 3.50 (br, 1H, Cy-H), 2.93 (br, 1H, Cy-H), 2.63 (br, 2H, Cy-H), 1.93 – 0.95 (br, 17H, Cy-H, H^{15}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.9 (C^9), 159.2 (C^1), 155.4 (C^8), 151.7 (C^8), 144.5 (C^{16}), 128.6 (Ar-CH), 127.4 (Ar-CH), 126.4 (C^{19}), 125.3 (C^2), 123.8 (C^4), 120.0 (C^7), 114.3 (C^3), 102.7 (C^6), 55.5 (C^{20}), 38.1 (C^{14}), 31.7 (Cy-CH_2), 25.4 (Cy-CH_2), 22.8 (Cy-CH_2), 19.9 (C^{15}); ***m/z*** (ESI$^+$) calc. for $C_{32}H_{39}NO_3$ = 485.29, found: 486.3001 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 75:25, 2 mL/min, 140 bars, 40 °C). Retention times: 14.1 mins (minor), 17.0 mins (major), *e.r.* = 7:93, *e.e.* = 86%.

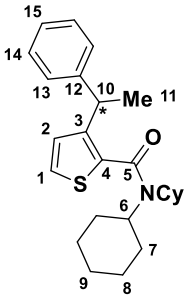
***N,N*-Dicyclohexyl-3-(1-phenylethyl)furan-2-carboxamide, 193r**



General procedure L: using substrate **191** (27.5 mg, 0.1 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), and (*S*)-**L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with styrene (46 µL, 400 mol%) at 120 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (35.1 mg, 92% yield, 65% *e.e.*). **R$_f$** = 0.63 (hexane/EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = -42.2 (c = 1.40, CH_2Cl_2); **ν_{max}/cm^{-1}:** 2926 (m), 2853 (m), 1625 (s), 1552 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 4H, H^{13}, H^{14}), 7.25 (d, *J* = 2.0 Hz, 1H, H^1), 7.17 (m, 1H, H^{15}), 6.35 (d, *J* = 2.0 Hz, 1H, H^2), 4.45 (q, *J* = 7.0 Hz, 1H, H^{10}), 3.05 (br, 2H, Cy-H), 2.76 – 2.26 (br, 2H, Cy-H), 1.94 – 0.72 (m, 21H, H^{11}, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.2 (C^5), 146.2 (C^{12}), 144.8 (C^4), 140.8 (C^1), 131.8 (C^3), 128.4

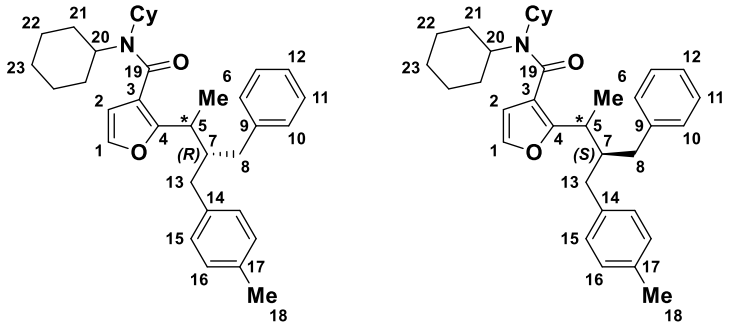
(Ar-CH), 127.4 (Ar-CH), 126.1 (C^{15}), 111.0 (C^{2}), 34.9 (C^{10}), 26.3 (Cy-CH_2), 25.4 (Cy-CH_2), 21.3 (C^{11}); ***m/z*** (ESI^+) calc. for $C_{25}H_{33}NO_2$ = 379.25, found: 380.2579 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 2 mL/min, 140 bars, 40 °C). Retention times: 14.9 mins (minor), 15.9 mins (major), *e.r.* = 17.5:82.5, *e.e.* = 65%.

***N,N*-Dicyclohexyl-3-(1-phenylethyl)thiophene-2-carboxamide, 193s**



General procedure L: using substrate **192** (29.1 mg, 0.1 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), and **(*S*)-L13** (6.10 mg, 5.0 µmol) in 1,2-DCB (0.2 mL) with styrene (46 µL, 400 mol%) at 90 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (33.0 mg, 83% yield, 81% *e.e.*). $\mathbf{R_f}$ = 0.54 (hexane/EtOAc, 4/1); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 2927 (s), 2854 (s), 2242 (w), 1617 (s), 1551 (m); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = -52.6 (c = 0.27, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H, H^{14}), 7.24 – 7.17 (m, 3H, H^1, H^{13}), 7.20 – 7.12 (m, 1H, H^{15}), 6.99 (d, *J* = 5.0 Hz, 1H, H^2), 4.42 (q, *J* = 7.0 Hz, 1H, H^{10}), 3.37 – 2.82 (br, 2H, Cy-H), 2.59 (br, 1H, Cy-H), 1.97 – 0.76 (br. m, 19H, H^{11}, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.0 (C^5), 146.3 (C^4), 144.9 (C^{12}), 132.8 (C^3), 128.5 (C^{14}), 127.4 (C^{13}), 126.9 (C^2), 126.1 (C^{15}), 124.0 (C^1), 38.5 (C^{10}), 30.5 (Cy-CH_2), 26.2 (Cy-CH_2), 25.3 (Cy-CH_2), 22.4 (C^{11}); ***m/z*** (ESI^+) calc. for $C_{25}H_{33}NOS$ = 395.23, found: 396.2394 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 2 mL/min, 140 bars, 40 °C). Retention times: 27.5 mins (minor), 32.0 mins (major), *e.r.* = 9.5:90.5, *e.e.* = 81%.

(*R*)-202, (*S*)-202

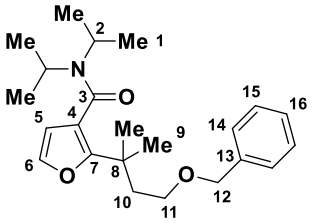


Using (*R*)-alkene: To a flame-dried Young's tube was added **187** (27.5 mg, 0.1 mmol), $[Ir(cod)_2]BARF$ (6.63 mg, 5.00 µmol) and (*S*)-**L13** (6.10 mg, 5.00 µmol). The tube was evacuated and refilled with nitrogen three times before (*R*)-1-(2-benzylbut-3-en-1-yl)-4-methylbenzene (26 mg, 0.11 mmol) and

1,2-DCB (0.2 mL) were added. The tube was sealed and heated at 90 °C for 72 h. After cooling, volatile components were removed *in vacuo*. Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a colourless oil (35.0 mg, 68%, *d.r.* = 3:1). $\mathbf{R_f}$ = 0.61 (hexane/EtOAc, 9:1); $\mathbf{[\alpha]^{25}D}$ = +19.13 (c = 1.77, $CHCl_3$); $\mathbf{\nu_{max}/cm^{-1}}$**:** 3009 (br), 2930 (m), 2855 (m), 1618 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 – 6.92 (m, 15H, Ar-H, major + minor), 6.22 (d, *J* = 2.0 Hz, 1H, H^2, major + minor), 3.57 (br, 1H, H^{20}, major + minor), 3.14 (m, 1H, H^5, major + minor), 2.89 (m, 1H, $H^{20'}$, major + minor), 2.79 (dd, *J* = 14.0, 5.0 Hz, 1H, R-CH_2, **major**), 2.74 (dd, *J* = 14.0, 5.0 Hz, 0.37H, R-CH_2 **minor**), 2.61 – 2.39 (m, 5.6H, R-CH_2, major + minor), 2.36 – 2.22 (m, 6H, H^7, H^{18}, major + minor), 1.90 – 1.67 (m, 18H, Cy-H, major + minor), 1.67 – 0.97 (m, 13.6H, H^6, Cy-H, major + minor); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.2 (C^{19}), 157.3 (Ar-C), 141.5 (Ar-CH), 138.1 (Ar-C), 135.1 (Ar-C), 129.3 (Ar-CH), 129.0 (Ar-CH), 128.9 (Ar-CH), 128.3 (Ar-CH), 125.7 (Ar-CH), 118.5 (Ar-C), 109.1 (C^2), 47.5 (C^7), 37.1 (R-CH_2), 36.9 (R-CH_2), 34.1 (C^5), 21.1 (C^{18}) 14.2 (C^6); ***m/z*** (ESI$^+$) calc. for $C_{35}H_{45}NO_2$ = 511.35, found: 512.3516 $[M+H]^+$.

Using (*S*)-alkene: Purification by FCC (hexane/EtOAc, 9:1) gave the title compound as a colourless oil (37.0 mg, 72%, *d.r.* = 1.3); $\mathbf{R_f}$ = 0.61 (hexane/EtOAc, 9:1); $\mathbf{[\alpha]^{26}D}$ = +21.90 (c = 1.385, $CHCl_3$); $\mathbf{\nu_{max}/cm^{-1}}$**:** 2981 (br), 2930 (m), 2855 (m), 1623 (s); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.29 – 6.90 (m, 13H, Ar-CH, major + minor), 6.22 (d, *J* = 2.0 Hz, 1H, H^2, major + minor), 3.57 (s, 1H, H^{20}, major + minor), 3.18 – 3.09 (m, 1H, H^5, major + minor), 2.96 – 2.84 (m, 1H, $H^{20'}$, major + minor), 2.79 (dd, *J* = 13.5, 5.0 Hz, 0.3H, R-CH_2, **minor**), 2.74 (dd, *J* = 13.5, 5.0 Hz, 1H, R-CH_2, **major**), 2.63 – 2.39 (m, 5.8H, R-CH_2, major + minor), 2.37 – 2.23 (m, 5.3H, H^7, H^{18}, major + minor), 1.89 – 1.37 (m, 15.9H, Cy-H, major + minor), 1.34 – 0.98 (m, 11.9H, H^6, Cy-H, major + minor); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.1 (C^{19}), 157.3 (Ar-C), 141.5 (Ar-C), 140.2 (Ar-CH), 138.2 (Ar-C), 135.2 (Ar-C), 129.2 (Ar-CH), 129.1 (Ar-CH), 129.0 (Ar-CH), 128.3 (Ar-CH), 125.7 (Ar-CH), 118.6 (Ar-C), 109.1 (C^2), 47.4 (C^7), 37.3 (R-CH_2), 36.7 (R-CH_2), 34.2 (C^5), 21.1 (C^{18}), 14.4 (C^6).

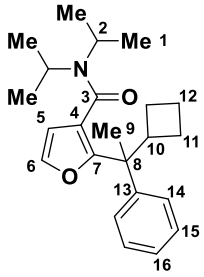
2-(4-(Benzyloxy)-2-methylbutan-2-yl)-*N*,*N*-diisopropylfuran-3-carboxamide, 207a



General Procedure L: using **106** (19.5 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol) and **L12** (4.03 mg, 5.0 μmol) in 1,4-dioxane (0.1 mL) with **206a** (26.4 mg, 0.15 mmol) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 10%) afforded the title compound (28.2 mg, 76%) as a yellow oil. $\mathbf{R_f}$ = 0.38 (hexane/EtOAc 20%); $\mathbf{\nu_{max}/cm^{-1}}$**:** 2967 (s), 2932 (m), 2872 (m), 1630 (s), 1515 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 6H, H^6, H^{14}, H^{15}, H^{16}), 6.15 (d, *J* = 2.0 Hz, 1H, H^5),

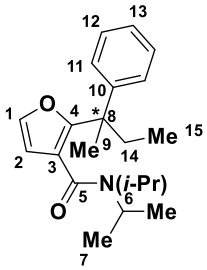
4.43 (s, 2H, H^{12}), 4.00 – 3.90 (m, 1H, H^{2}), 3.48 – 3.37 (m, 3H, $H^{2'}$, H^{11}), 2.03 (t, *J* = 7.0 Hz, 2H, H^{10}), 1.49 (d, *J* = 7.0 Hz, 6H, H^{1}), 1.34 (s, 6H, H^{9}), 1.10 (d, *J* = 7.0 Hz, 6H, $H^{1'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.6 (C^{3}), 157.3 (C^{7}), 139.9 (C^{6}), 138.8 (C^{13}), 128.4 (C^{14}), 127.6 (C^{15}), 127.5 (C^{16}), 117.4 (C^{4}), 109.5 (C^{5}), 72.9 (C^{12}), 67.8 (C^{11}), 50.9 (C^{2}), 45.8 ($C^{2'}$), 41.8 (C^{10}), 36.3 (C^{8}), 27.1 (C^{9}), 20.7 (C^{1}), 20.4 ($C^{1'}$); ***m/z*** (ESI$^+$) calc. for $C_{23}H_{33}NO_3$ = 371.25, found $[M+H]^+$: 372.2531.

2-(1-Cyclobutyl-1-phenylethyl)-*N*,*N*-diisopropylfuran-3-carboxamide, 207b



General Procedure L: using **106** (19.5 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol) and **L12** (4.03 mg, 5.0 μmol) in 1,4-dioxane (0.1 mL) with **206b** (23.7 mg, 0.15 mmol) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 20%) afforded the title compound (21.4 mg, 61%) as a colourless oil. $\mathbf{R_f}$ = 0.56 (hexane/EtOAc 20%); $\mathbf{\nu_{max}/cm^{-1}}$**:** 2969 (m), 2938 (m), 2967 (w), 1703 (w), 1673 (s), 1599 (m), 1511 (m); **^{1}H NMR** (500 MHz, acetone-d_6) δ 7.43 (d, *J* = 2.0 Hz, 1H, H^{6}), 7.29 – 7.20 (m, 4H, H^{14}, H^{15}), 7.18 – 7.14 (m, 1H, H^{16}), 6.37 (d, *J* = 2.0 Hz, 1H, H^{5}), 4.10 – 3.98 (m, 1H, H^{2}), 3.55 – 3.45 (m, 1H, $H^{2'}$), 3.44 – 3.34 (m, 1H, H^{10}), 2.06 – 1.93 (m, 3H, H^{11}), 1.92 – 1.76 (m, 2H, $H^{11'}$, H^{12}), 1.69 – 1.60 (m, 4H, H^{9}, $H^{12'}$), 1.47 – 1.39 (m, 6H, H^{1}), 1.17 (d, *J* = 6.5 Hz, 3H, $H^{1'}$), 1.08 (d, *J* = 6.5 Hz, 3H, $H^{1''}$); **^{13}C NMR** (126 MHz, acetone-d_6) δ 166.5 (C^{3}), 156.9 (C^{7}), 148.1 (C^{13}), 141.5 (C^{6}), 129.0 (C^{15}), 127.7 (C^{14}), 126.8 (C^{16}), 121.0 (C^{4}), 110.6 (C^{5}), 51.5 (C^{2}), 48.0 (C^{8}), 46.2 ($C^{2'}$), 44.6 (C^{10}), 25.3 (C^{11}), 22.7 (C^{9}), 21.0 (C^{1}), 20.8 ($C^{1'}$), 20.7 ($C^{1''}$), 20.6 ($C^{1'''}$), 18.1 (C^{12}); ***m/z*** (ESI$^+$) calc. for $C_{23}H_{31}NO_2$: 353.24. Found $[M+H]^+$: 354.2430.

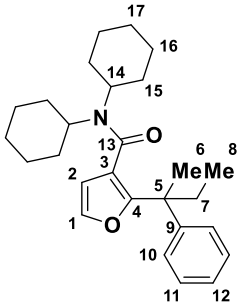
***N*,*N*-Diisopropyl-2-(2-phenylbutan-2-yl)furan-3-carboxamide, 207d**



General procedure L: using **106** (19.5 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol), (*R*)-**L25** (5.61 mg, 5.0 μmol) in 1,4-dioxane (0.1 mL) with **209** (14.6 mg, 0.15 mmol) at 120 °C for 72 h. Purification by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (10.0 mg, 31%

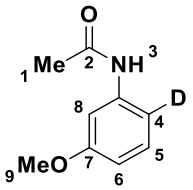
yield, 75% *e.e.*); $\mathbf{R_f}$ = 0.22 (hexane/EtOAc, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 6H, Ar-C<u>H</u>), 7.16 – 7.11 (m, 1H, H^{13}), 6.20 (d, *J* = 2.0 Hz, 1H, H^2), 4.03 – 3.93 (m, 1H, H^6), 3.42 – 3.33 (m, 1H, $H^{6'}$), 2.36 – 2.20 (m, 1H, H^{14}), 2.08 (dq, *J* = 14.5, 7.5 Hz, 1H, $H^{14'}$), 1.63 (s, 3H, H^9), 1.43 (*pseudo*-dd, *J* = 7.0, 3.0 Hz, 6H, H^7), 1.09 (d, *J* = 7.0 Hz, 3H, $H^{7'}$), 1.03 (d, *J* = 7.0 Hz, 3H, $H^{7''}$), 0.76 (t, *J* = 7.5 Hz, 3H, H^{15}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (C^5), 156.8 (C^8), 147.5 (C^4), 140.3 (C^1), 128.3 (Ar-<u>C</u>H), 126.6 (Ar-<u>C</u>H), 126.1 (C^{13}), 125.0 (C^{10}), 119.2 (C^3), 109.6 (C^2), 50.9 (C^6), 45.8 ($C^{6'}$), 32.8 (C^{14}), 24.2 (C^9), 20.8 (C^7), 20.4 ($C^{7'}$), 20.3 ($C^{7''}$), 9.2 (C^{15}); **Chiral SFC:** (DAICEL CHIRALPAK IE column (25 cm), CO_2:MeOH 96:3 → 94:6, 2 mL/min, 140 bars, 40 °C). Retention times: 26.7 mins (major), 27.8 mins (minor), *e.r.* = 87.5:12.5, *e.e.* = 75%. *Data in accordance with literature values.*[108]

***N*,*N*-Dicyclohexyl-2-(2-phenylbutan-2-yl)furan-3-carboxamide, 210**



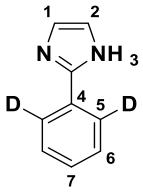
General procedure L: using substrate **187** (36.9 mg, 0.1 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol), (*R*)-**L13** (5.61 mg, 5.0 μmol) in 1,4-dioxane (0.1 mL) with **209** (14.6 mg, 0.15 mmol) at 120 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc, 9:1) afforded the title compound as a colourless oil (24.1 mg, 59% yield, 73% *e.e.*). $\mathbf{R_f}$ = 0.36 (hexane/EtOAc, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +27.7 (c = 0.20, CH_2Cl_2); **ν_{max}/cm^{-1}:** 3003 (br), 2940 (m), 2841 (m), 1807 (m), 1771 (m), 1684 (m), 1609 (s), 1516 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 5H, H^{10}, H^{11}, H^{12}), 7.18 (m, 1H, H^1), 6.22 (d, *J* = 2.0 Hz, 1H, H^2), 3.60 – 3.50 (m, 1H, H^{14}), 2.95 (tt, *J* = 12.0, 4.0 Hz, 1H, $H^{14'}$), 2.61 (s, 2H, Cy-<u>H</u>), 2.41 – 2.30 (m, 1H, H^7), 2.09 (dq, *J* = 14.0, 7.0 Hz, 1H, $H^{7'}$), 1.86 – 1.39 (m, 15H, H^6, Cy-<u>H</u>), 1.25 (m, 3H, Cy-<u>H</u>), 1.17 – 0.99 (m, 3H, Cy-<u>H</u>), 0.80 (t, *J* = 7.5 Hz, 3H, H^8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.8 (C^{13}), 156.3 (C^4), 147.8 (C^9), 140.4 (Ar-<u>C</u>H), 128.3 (Ar-<u>C</u>H), 126.5 (Ar-<u>C</u>H), 126.1 (C^1), 119.6 (C^3), 109.4 (C^2), 59.9 (C^{14}), 56.2 ($C^{14'}$), 45.7 (C^5), 32.7 (C^7), 31.3 (Cy-<u>C</u>H_2), 29.7 (Cy-<u>C</u>H_2), 29.6 (Cy-<u>C</u>H_2), 26.8 (Cy-<u>C</u>H_2), 25.8 (Cy-<u>C</u>H_2), 25.4 (Cy-<u>C</u>H_2), 25.3 (Cy-<u>C</u>H_2), 24.3 (C^6), 9.2 (C^8); ***m/z*** (ESI^+) calc. for $C_{27}H_{37}NO_2$ = 407.29, found: 408.2891 $[M+H]^+$; **Chiral SFC:** (YMC Chiral ART Amylose-SA column (25 cm), CO_2:IPA 95:5, 4 mL/min, 140 bars, 40 °C). Retention times: 4.9 mins (major), 5.7 minutes (minor), *e.r.* = 86.5:13.5, *e.e.* = 73%.

***Deuterio*-211**



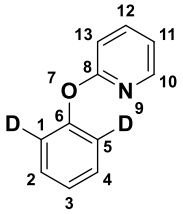
General procedure M: using **211** (33.1 mg, 0.2 mmol) with **L47** (10.1 mg, 0.01 mmol). Purification by FCC (hexane/EtOAc, 1:1) afforded the title compound as a white solid. $\mathbf{R_f}$ = 0.33 (hexane/EtOAc, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (s, 0.87H, H^3), 7.30 – 7.25 (m, 1H, H^8), 7.23 – 7.14 (m, 1H, H^5), 7.00 (*pseudo*-dt, *J* = 8.0, 1.5 Hz, 0.48H, H^4), 6.65 (dd, *J* = 8.0, 2.5 Hz, 1H, H^6), 3.77 (s, 3H, H^9), 2.16 (s, 3H, H^1).

***Deuterio*-212**



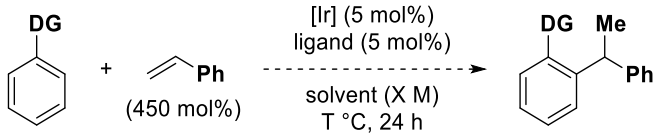
General procedure M: using **212** (14.1 mg, 0.1 mmol) with d^Fppb (3.93 mg, 5.0 μmol). Purification by FCC (hexane/EtOAc, 1:1) afforded the title compound as a white powder. $\mathbf{R_f}$ = 0.22 (hexane/EtOAc, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.96 (br, 1H, H^3), 7.88 (dd, *J* = 6.5, 3.0 Hz, 0.21H, H^5), 7.41 – 7.29 (m, 3H, H^6, H^7), 7.14 (s, 2H, H^1, H^2).

***Deuterio*-213**



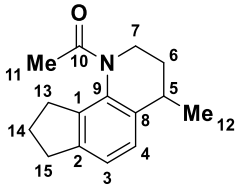
General procedure M: using **213** (17.1 mg, 0.1 mmol) with d^Fppb (3.93 mg, 5.0 μmol). Purification by FCC (hexane/EtOAc, 20:1) afforded the title compound as a colourless solid. $\mathbf{R_f}$ = 0.38 (hexane/EtOAc, 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 – 8.17 (m, 1H, Ar-C<u>H</u>), 7.67 (ddd, *J* = 8.5, 7.0, 2.0 Hz, 1H, Ar-C<u>H</u>), 7.44 – 7.35 (m, 2H, H^2, H^4), 7.22 – 7.16 (m, 1H, H^3), 7.15 – 7.11 (m, 1.65H, H^1, H^5), 6.98 (ddd, *J* = 7.0, 5.0, 1.0 Hz, 1H, Ar-C<u>H</u>), 6.89 (dt, *J* = 8.5, 1.0 Hz, 1H, Ar-C<u>H</u>).

Table S1: *Various directing groups were screened for the hydroarylation of styrene; d^Fppb = 1,4-bis(di(pentafluorophenyl)-phosphino)butane; [a]Yields determined by ^{1}H NMR using 1,4-dinitrobenzene as an internal standard.*



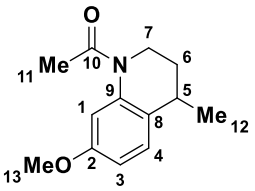
Entry	Substrate	[Ir]	Ligand	Solvent	X /M	Temp /°C	SM Recovered /%	Notes
1	212	$[Ir(cod)_2]BF_4$	d^Fppb	PhMe	1.5	110	54[a]	
2	212	$[Ir(cod)_2(OH)_2]$	d^Fppb	PhMe	1.5	110	78[a]	
3	212	$[Ir(cod)_2Cl_2]$	d^Fppb	PhMe	1.5	110	56[a]	
4	212	$[Ir(coe)_2Cl_2]$	d^Fppb	PhMe	1.5	110	52[a]	
5	213	$[Ir(cod)_2]BF_4$	d^Fppb	PhMe	1.5	110	75[a]	
6	213	$[Ir(cod)_2(OH)_2]$	d^Fppb	PhMe	1.5	110	92[a]	
7	213	$[Ir(cod)_2Cl_2]$	d^Fppb	PhMe	1.5	110	97[a]	
8	213	$[Ir(coe)_2Cl_2]$	d^Fppb	PhMe	1.5	110	73[a]	
9	219	$[Ir(cod)_2]BF_4$	L47	dioxane	1.0	120	85	
10	216	$[Ir(cod)_2]BF_4$	L47	1,2-DCB	1.0	120	99	
11	214	$[Ir(cod)_2]BF_4$	L47	THF	1.0	120	69	
12	220	$[Ir(cod)_2]BF_4$	L47	PhMe	1.0	120	95	
13	217	$[Ir(cod)_2]BF_4$	L47	dioxane	1.0	120	0	Mixture
14	218	$[Ir(cod)_2]BF_4$	L47	1,2-DCB	1.0	120	0	Mixture

1-(4-Methyl-2,3,4,7,8,9-hexahydro-1*H*-cyclopenta[*h*]quinolin-1-yl)ethan-1-one, 234



General procedure L: using **231** (87.6 mg, 0.50 mmol), $[Ir(cod)_2]OTf$ (13.9 mg, 25.0 µmol) and **L47** (19.6 mg, 25.0 µmol) in toluene (2 mL) with **235** (453 mg, 2.00 mmol) at 120 °C for 72 h. Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a pale yellow oil (26 mg, 23%); $\mathbf{R_f}$ = 0.54 (hexane/EtOAc, 1:1); $\mathbf{\nu_{max}/cm^{-1}}$**:** 2953 (br), 2932 (br), 2876 (w), 1655 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 6.95 (m, 2H, Ar-C<u>H</u>), 4.79 – 4.61 (m, 1H, R-C<u>H</u>$_2$), 3.08 – 2.71 (m, 5H, R-C<u>H</u>$_2$), 2.61 – 2.49 (m, 1H, H^5), 2.31 – 2.10 (m, 2H, R-C<u>H</u>$_2$), 2.06 – 1.81 (m, 4H, R-C<u>H</u>$_2$, H^{11}), 1.37 – 1.18 (m, 4H, R-C<u>H</u>$_2$, H^{12}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5 (C^{10}), 144.3 (Ar-<u>C</u>), 139.1 (Ar-<u>C</u>), 138.4 (Ar-<u>C</u>), 136.6 (Ar-<u>C</u>), 122.5 (Ar-<u>C</u>H) 122.1 (Ar-<u>C</u>H), 41.1 (R-<u>C</u>H$_2$), 33.5 (R-<u>C</u>H$_2$), 33.2 (R-<u>C</u>H$_2$), 31.6 (R-<u>C</u>H$_2$), 29.9 (C^5), 26.2 (R-<u>C</u>H$_2$), 21.5 (C^{11}), 17.4 (C^{12}); ***m/z*** (ESI^+): calc. for $C_{15}H_{19}NO$: 229.32, found: 230.1548 $[M+H]^+$.

1-(7-Methoxy-4-methyl-3,4-dihydroquinolin-1(2*H*)-yl)ethan-1-one, 238

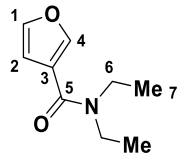


General procedure L: using **236** (16.5 mg, 0.10 mmol), $[Ir(cod)_2]OTf$ (2.79 mg, 5.00 µmol) and **L47** (3.91 mg, 5.0 µmol) in dioxane (0.40 mL) with **235** (60.1 mg, 0.40 mmol) at 120 °C for 72 h. Purification by FCC (hexane/EtOAc, 4:1) gave the title compound as a colourless oil (7.0 mg, 12%); $\mathbf{R_f}$ = 0.44 (hexane/EtOAc, 1:1); $\mathbf{\nu_{max}/cm^{-1}}$**:** 2960 (br), 2929 (br), 2876 (br), 1718 (m), 1655 (s), 1611 (s), 1580 (m), 1500 (s); **^{1}H NMR** (500 MHz, DMSO-d^6, 110 °C) δ 7.14 (d, *J* = 8.5 Hz, 1H, H^4), 7.05 (br, 1H, H^1), 6.72 (d, *J* = 8.5 Hz, 1H, H^3), 3.74 (s, 3H, H^{13}), 3.71 – 3.61 (m, 2H, H^7), 2.83 – 2.69 (m, 1H, H^5), 2.16 (s, 3H, H^{11}), 2.06 – 2.00 (m, 1H, H^6), 1.50 (m, 1H, $H^{6'}$), 1.23 (d, *J* = 7.0 Hz, 3H, H^{12}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.2 (C^{10}), 157.8 (C^2), 139.5 (C^9), 130.3 (C^8), 127.1 (C^4), 110.8 (C^3), 55.8 (C^7), 55.6 (C^{13}), 32.6 (C^6), 30.4 (C^5), 23.4 (C^{11}), 20.2 (C^{12}); ***m/z*** (ESI^+): calc. for $C_{13}H_{17}NO_2$: 219.13, found: 220.1343 $[M+H]^+$.

7.5 Experimental procedures for compounds in Chapter 4

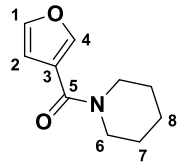
7.5.1 Synthesis of substrates and alkenes

***N,N*-Diethylfuran-3-carboxamide, 279**



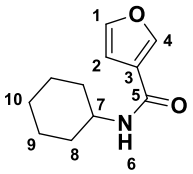
General procedure G: using 3-furoic acid (1.12 g, 10 mmol) and diethylamine (2.07 mL, 20 mmol). Purification by FCC (hexane/EtOAc, 3:2) afforded the title compound as a colourless liquid (1.40 g, 84%); $\mathbf{R_f}$ = 0.39 (hexane/EtOAc, 3:2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (*pseudo*-t, *J* = 1.5 Hz, 1H, H^4), 7.40 (*pseudo*-t, *J* = 1.5 Hz, 1H, H^1), 6.58 (dd, *J* = 1.5, 1.5 Hz, 1H, H^2), 3.47 (q, *J* = 7.0 Hz, 4H, H^6), 1.21 (t, *J* = 7.0 Hz, 6H, H^7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.3 (C^5), 142.9 (C^1/C^4), 142.8 (C^1/C^4), 122.0 (C^3), 110.3 (C^2), 43.0 (C^6), 40.2 ($C^{6'}$), 14.7 (C^7), 13.0 ($C^{7'}$). *Data in accordance with literature values.*[280]

Furan-3-yl(piperidin-1-yl)methanone, 280



General procedure H: using 3-furoic acid (224 mg, 2.00 mmol) and piperidine (0.296 mL, 3.0 mmol). Purification by FCC (hexane/EtOAc, 3:2) gave the title compound as a colourless oil (188 mg, 54%). $\mathbf{R_f}$ = 0.22 (hexane/EtOAc, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 1.5, 1.0 Hz, 1H, H^1), 7.41 (*pseudo*-t, *J* = 1.5 Hz, 1H, H^4), 6.53 (dd, *J* = 1.5, 1.0 Hz, 1H, H^2), 3.60 (br, 4H, H^6), 1.74 – 1.54 (m, 8H, H^7, H^8); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8 (C^5), 143.2 (C^1), 142.9 (C^4), 1 21.5 (C^3), 110.3 (C^2), 26.3 (Cy-$\underline{C}H_2$), 24.8 (Cy-$\underline{C}H_2$). *Data in accordance with literature values.*[309]

***N*-cyclohexylfuran-3-carboxamide, 281**

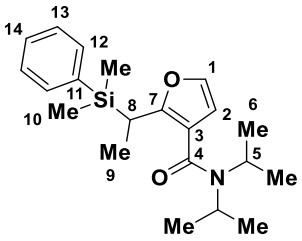


General procedure G: using 3-furoic acid (560 mg, 5.0 mmol) and cyclohexylamine (1.15 mL, 10 mmol). Purification by FCC (hexane/EtOAc, 3:2) gave the title compound as a pale yellow solid (604 mg, 63%); $\mathbf{R_f}$ = 0.47 (hexane/EtOAc, 3:2); **m.p**. = 149.4 – 150.8 °C (hexane/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (*pseudo*-t, *J* = 1.5 Hz, 1H, H^4), 7.42 (*pseudo*-t, *J* = 1.5 Hz, 1H, H^1), 6.60 – 6.56 (m, 1H, H^2), 5.59 (br, 1H, H^6), 3.96 – 3.88 (m, 1H, H^7), 2.03 – 1.96 (m, 2H, H^8), 1.79 – 1.69 (m, 2H,

Cy-H), 1.65 (dt, *J* = 13.0, 4.0 Hz, 1H, Cy-H), 1.47 – 1.34 (m, 2H, Cy-H), 1.26 – 1.13 (m, 3H, Cy-H, $H^{8'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.8 (C^5), 144.6 (C^4), 143.8 (C^1), 123.1 (C^3), 108.4 (C^2), 48.4 (C^7), 33.4 (C^8), 25.7 (Cy-CH_2), 25.1 (Cy-CH_2). *Data in accordance with literature values*.[310]

7.5.2 Catalysis products

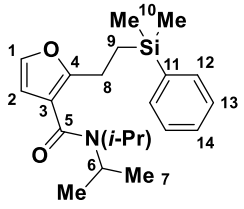
2-(1-(dimethyl(phenyl)silyl)ethyl)-*N*,*N*-diisopropylfuran-3-carboxamide, 270



General procedure L: using **106** (19.5 mg, 0.10 mmol), $[Ir(cod)_2]$BARF (6.36 mg, 5.0 µmol), (*S*)-**L15** (5.25 mg, 5.0 µmol) in THF (0.5 mL) with dimethylphenylvinylsilane (20 µL, 110 mol%) at 90 °C for 48 h. Purification by FCC (hexane/EtOAc, 9:1) to gave the title compound as a colourless oil (24 mg, 67%). **R_f** = 0.83 (hexane/EtOAc, 4:1); **ν_{max}/cm^{-1}:** 3070 (w), 3048 (w), 2965 (m), 2933 (w), 2874 (w), 1621 (s), 1552 (m), 1515 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H, H^{12}), 7.35 – 7.31 (m, 3H, H^{13}, H^{14}), 7.20 (d, *J* = 2.0 Hz, 1H, H^1), 6.24 (d, *J* = 2.0 Hz, 1H, H^2), 3.76 (br, 2H, H^5) 2.86 (q, *J* = 7.5 Hz, 1H, H^8), 1.61 – 0.99 (m, 15H, H^6, H^9), 0.34 (s, 3H, H^{10}), 0.25 (s, 3H, $H^{10'}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.2 (C^4), 160.0 (C^7), 139.3 (C^1), 137.7 (C^{11}), 134.0 (C^{12}), 129.2 (C^{12}/C^{13}), 127.8 (C^{12}/C^{13}), 116.0 (C^3), 109.4 (C^2), 21.8 (C^8), 21.1 (C^6), 13.7 (C^9), -3.5 (C^{10}), -4.7 ($C^{10'}$); ***m/z*** (ESI$^+$) calc. for $C_{21}H_{31}NO_2Si$ = 357.21, found: 358.2206 $[M+H]^+$.

Indicative ^{1}H signals for desilylated product, 275: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 2.0 Hz, 1H, Ar-CH), 6.26 (d, *J* = 2.0 Hz, 1H, Ar-CH), 2.74 (q, *J* = 7.5 Hz, 2H, R-CH_2), 1.24 (t, *J* = 7.5 Hz, 3H, R-CH_3).

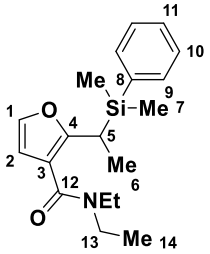
Data for linear compound, 271



R_f = 0.47 (hexane/EtOAc, 4:1); **ν_{max}/cm^{-1}:** 3069 (w), 3049 (w), 3000 (m), 2965 (m), 2932 (m), 2900 (m), 1625 (s), 1512 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H, H^{12}/H^{13}), 7.34 (m, 3H, H^{12}/H^{13}, H^{14}), 7.20 (d, *J* = 2.0 Hz, 1H, H^1), 6.24 (d, *J* = 2.0 Hz, 1H, H^2), 4.25 – 3.26 (br, 2H, H^6), 2.76 – 2.67 (m, 2H, H^8), 1.75 – 0.84 (br, 14H, H^7, H^9), 0.27 (s, 6H, H^{10}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.9 (C^5), 156.7 (C^4), 139.9 (C^1), 138.7 (C^{11}), 133.7 (C^{12}/C^{13}), 129.1 (C^{14}), 127.9 (C^{12}/C^{13}), 117.0 (C^3),

109.4 (C^2), 21.6 (C^8), 20.9 (C^7), 14.3 (C^9), -3.3 (C^{10}); ***m/z*** (ESI^+) calc. for $C_{21}H_{31}NO_2Si$ = 357.21, found: 358.2191 $[M+H]^+$.

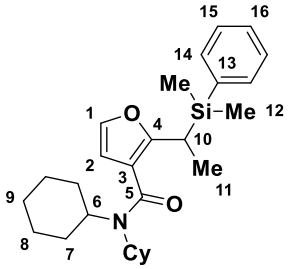
2-(1-(Dimethyl(phenyl)silyl)ethyl)-*N*,*N*-diethylfuran-3-carboxamide, 272



General procedure L: using **279** (16.7 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), (*S*)-**L15** (5.25 mg, 5.0 µmol) in THF (0.5 mL) with dimethylphenylvinylsilane (20 µL, 110 mol%) at 110 °C for 72 h. Purification by FCC (hexane/EtOAc, 4:1) afforded the title compound as a colourless oil (9.0 mg, 27%). $\mathbf{R_f}$ = 0.43 (hexane/EtOAc, 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H, H^9/H^{10}), 7.35 – 7.28 (m, 3H, H^9/H^{10}, H^{11}), 7.21 (d, *J* = 2.0 Hz, 1H, H^1), 6.26 (d, *J* = 2.0 Hz, 1H, H^2), 3.54 – 2.94 (br, 4H, H^{13}), 2.93 (q, *J* = 7.5 Hz, 1H, H^5), 1.30 (d, *J* = 7.5 Hz, 3H, H^6), 1.23 – 0.97 (br, 6H, H^{14}), 0.33 (s, 3H, H^7), 0.26 (s, 3H, $H^{7'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.3 (C^{12}), 160.9, (C^4), 139.4 (C^1), 137.6 (C^8), 134.0 (C^9/C^{10}), 129.2 (C^{11}), 127.8 (C^9/C^{10}), 114.4 (C^3), 109.6 (C^2), 21.9 (C^5), 13.5 (C^6), -4.0 (C^7), -4.5 ($C^{7'}$).

Indicative ^{1}H signal for desilylated product, 274: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (q, *J* = 7.5 Hz, 2H, R-C<u>H</u>$_2$). *Tentatively assigned based on similar signals for desilylated products **275** and **276**.*

***N*,*N*-Dicyclohexyl-2-(1-(dimethyl(phenyl)silyl)ethyl)furan-3-carboxamide, 273**

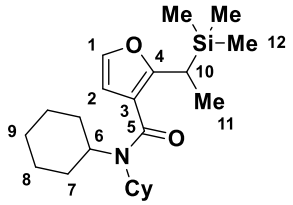


General procedure L: using **187** (27.5 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with dimethylphenylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 4:1) afforded the title compound as a colourless oil (32.0 mg, 73%). $\mathbf{R_f}$ = 0.84 (hexane/EtOAc, 4:1); **ν_{max}/cm^{-1}**: 2929 (s), 2855 (m), 1618 (s), 1552 (m), 1515 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 2H, Ar-C<u>H</u>), 7.36 – 7.29 (m, 3H, Ar-C<u>H</u>, H^{16}), 7.18 (d, *J* = 2.0 Hz, 1H, H^1), 6.20 (d, *J* = 2.0 Hz, 1H, H^2), 4.02 – 3.33 (br, 1H, Cy-<u>H</u>), 2.90 (m, 2H, Cy-<u>H</u>, H^{10}), 2.58 (br, 1H, Cy-<u>H</u>), 2.09 – 0.69 (m, 21H, H^{11}, Cy-<u>H</u>), 0.33 (s, 3H, H^{12}), 0.23 (s, 3H,

$H^{12'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.4 (C^5), 160.4 (C^4), 139.3 (C^1), 137.7 (C^{13}), 134.0 (Ar-CH), 129.2 (C^{16}), 127.8 (Ar-CH), 116.0 (C^3), 109.2 (C^2), 25.4 (Cy-CH_2), 21.8 (C^{10}), 13.7 (C^{11}), -3.6 (C^{12}), -4.6 ($C^{12'}$); ***m/z*** (ESI^+) calc. for $C_{27}H_{29}O_2Si$ = 437.28, found: 438.2830 $[M+H]^+$.

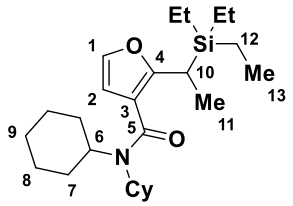
Indicative ^{1}H signals for desilylated product, 276: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 2.0 Hz, 1H, Ar-CH), 6.22 (d, *J* = 2.0 Hz, 1H, Ar-CH), 2.72 (q, *J* = 7.5 Hz, 2H, R-CH_2), 1.22 (t, *J* = 7.5 Hz, 3H, R-CH_3).

***N,N*-Dicyclohexyl-2-(1-(trimethylsilyl)ethyl)furan-3-carboxamide, 278a**



General procedure L: using **187** (27.5 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with trimethylvinylsilane (26 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 9:1) afforded the title compound as a colourless oil (29.0 mg, 77%). **R_f** = 0.67 (hexane/EtOAc, 4:1); **ν_{max}/cm^{-1}**: 2930 (s), 2856 (s), 1624 (s), 1515 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 2.0 Hz, 1H, H^1), 6.20 (d, *J* = 2.0 Hz, 1H, H^2), 3.88 – 2.85 (br, 2H, H^6) 2.62 (q, *J* = 7.5 Hz, 1H, H^{10}), 1.87 – 1.38 (br, 13H, Cy-H), 1.33 – 1.03 (br, 10H, H^{11}, Cy-H), -0.01 (s, 9H, H^{12}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.6 (C^5), 160.7 (C^4), 139.2 (C^1), 115.7 (C^3), 109.1 (C^2), 25.5 (Cy-CH_2), 22.1 (C^{10}), 13.3 (C^{11}), -2.6 (C^{12}); ***m/z*** (ESI^+) calc. for $C_{22}H_{37}NO_2Si$ = 375.26, found: 376.2673 $[M+H]^+$.

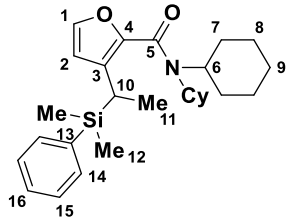
***N,N*-Dicyclohexyl-2-(1-(triethylsilyl)ethyl)furan-3-carboxamide, 278b**



General procedure L: using **187** (27.5 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (16 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 9:1) afforded the title compound as a colourless oil (41.6 mg, 99%). **R_f** = 0.67 (hexane/EtOAc, 4:1); **ν_{max}/cm^{-1}**: 2930 (s), 2874 (s), 2855 (s), 1807 (w), 1622 (s), 1515 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 2.0 Hz, 1H, H^1), 6.19 (d, *J* = 2.0 Hz, 1H, H^2), 3.94 – 2.85 (br, 2H, H^6), 2.75 (q, *J* = 7.5 Hz, 1H, H^{10}), 1.96 – 1.42 (br, 13H, Cy-H), 1.36 – 1.04 (br, 10H, H^{11}, Cy-H), 0.88 (t, *J* = 8.0 Hz, 9H, H^{13}), 0.54 (m, 6H, H^{12}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5

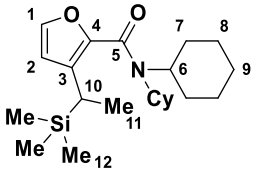
(C^5), 160.9 (C^4), 139.0 (C^1), 115.5 (C^3), 109.3 (C^2), 25.5 (Cy-$\underline{C}H_2$), 19.2 (C^{10}), 13.8 (C^{11}), 7.4 (C^{13}), 2.6 (C^{12}); ***m/z*** (ESI^+) calc. for $C_{25}H_{43}NO_2Si$ = 417.31, found: 418.3140 $[M+H]^+$.

***N,N*-Dicyclohexyl-3-(1-(dimethyl(phenyl)silyl)ethyl)furan-2-carboxamide, 278c**



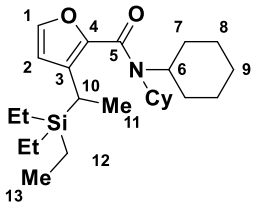
General procedure L: using **191** (27.5 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with dimethylphenylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (28.5 mg, 65%). $\mathbf{R_f}$ = 0.51 (hexane/EtOAc, 9:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2931 (m), 2855 (m), 1611 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H, H^{14}), 7.36 – 7.29 (m, 3H, H^{15}, H^{16}), 7.19 (d, *J* = 2.0 Hz, 1H, H^1), 6.09 (d, *J* = 2.0 Hz, 1H, H^2), 3.60 – 3.14 (br, 2H, Cy-$\underline{H}$), 3.06 (q, *J* = 7.5 Hz, 1H, H^{10}), 2.72 – 2.14 (br, 2H, Cy-$\underline{H}$), 2.01 – 1.46 (b, 12H, Cy-$\underline{H}$), 1.34 – 1.06 (m, 9H, H^{11}, Cy-$\underline{H}$), 0.24 (s, 6H, H^{12}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.4 (C^5), 143.0 (C^4), 140.8 (C^1), 137.6 (C^{13}), 134.3 (C^{14}), 133.0 (C^3), 129.1 (C^{16}), 127.7 (C^{15}), 111.8 (C^2), 31.3 (Cy-$\underline{C}H_2$), 26.5 (Cy-$\underline{C}H_2$), 25.5 (Cy-$\underline{C}H_2$), 18.3 (C^{10}), 15.1 (C^{11}), -4.1 (C^{12}), -5.1 ($C^{12'}$); ***m/z*** (ESI^+) calc. for $C_{27}H_{39}NO_2Si$ = 437.28, found: 438.2143 $[M+H]^+$.

***N,N*-Dicyclohexyl-3-(1-(trimethylsilyl)ethyl)furan-2-carboxamide, 278d**



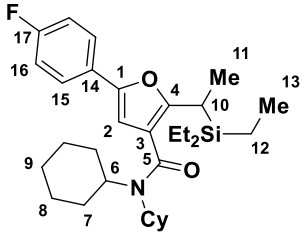
General procedure L: using **191** (27.5 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with trimethylvinylsilane (16 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (17.4 mg, 46%). $\mathbf{R_f}$ = 0.50 (hexane/EtOAc, 9:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2931 (s), 2855 (s), 1622 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.0 Hz, 1H, H^1), 6.27 (d, *J* = 2.0 Hz, 1H, H^2), 3.24 (br, 2H, Cy-$\underline{H}$), 2.78 (q, *J* = 7.5 Hz, 1H, H^{10}), 1.87 – 1.54 (m, 12H, Cy-$\underline{H}$), 1.33 – 1.09 (m, 10H, Cy-$\underline{H}$, H^{11}), -0.05 (s, 9H, H^{12}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.6 (C^5), 142.9 (C^4), 140.9 (C^1), 133.3 (C^3), 111.5 (C^2), 31.4 (Cy-$\underline{C}H_2$), 26.4 (Cy-$\underline{C}H_2$), 25.5 (Cy-$\underline{C}H_2$), 18.5 (C^{10}), 14.6 (C^{11}), -3.2 (C^{12}); ***m/z*** (ESI^+) calc. for $C_{22}H_{37}NO_2Si$ = 375.26, found: 376.2673 $[M+H]^+$.

***N,N*-Dicyclohexyl-3-(1-(trimethylsilyl)ethyl)furan-2-carboxamide, 278e**



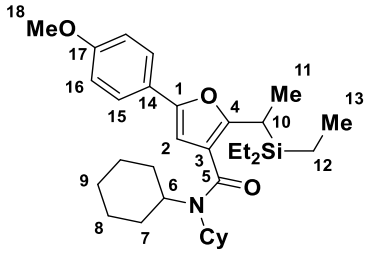
General procedure L: using **191** (27.5 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (25.4 mg, 61%). $\mathbf{R_f}$ = 0.40 (hexane/EtOAc, 9:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2931 (s), 2874 (s), 2855 (s), 1622 (s), 1584 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 2.0 Hz, 1H, H^1), 6.30 (d, *J* = 2.0 Hz, 1H, H^2), 3.56 – 2.95 (br, 2H, Cy-H), 2.88 (q, *J* = 7.5 Hz, 1H, H^{10}), 1.86 – 1.55 (m, 12H, Cy-H), 1.34 – 1.08 (m, 10H, Cy-H, H^{11}), 0.90 (t, *J* = 8.0 Hz, 9H, H^{13}), 0.56 – 0.45 (m, 6H, H^{12}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.5 (C^5), 142.8 (C^4), 140.9 (C^1), 133.3 (C^3), 112.0 (C^{10}), 31.4 (Cy-CH_2), 26.5 (Cy-CH_2), 25.5 (Cy-CH_2), 15.8 (C^{10}), 15.4 (C^{11}), 7.7 (C^{13}), 2.3 (C^{12}); ***m/z*** (ESI$^+$) calc. for $C_{22}H_{43}NO_2Si$ = 417.31, found: 418.3142 $[M+H]^+$.

***N,N*-Dicyclohexyl-5-(4-fluorophenyl)-2-(1-(triethylsilyl)ethyl)furan-3-carboxamide, 278f**



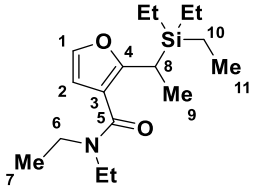
General procedure L: using **189** (36.9 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 9:1) afforded the title compound as a colourless oil (43.0 mg, 84%). $\mathbf{R_f}$ = 0.18 (hexane/EtOAc, 19:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2931 (s), 2874 (s), 2856 (m), 1624 (s), 1553 (m), 1499 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H, H^{15}), 7.06 (*pseudo*-t, *J* = 8.5 Hz, 2H, H^{16}), 6.39 (s, 1H, H^2), 2.74 (q, *J* = 7.5 Hz, 1H, H^{10}), 1.88 – 1.56 (m, 10H, Cy-CH_2), 1.39 (d, *J* = 7.5 Hz, 3H, H^{11}), 1.32 – 1.05 (m, 6H, Cy-CH_2), 0.93 (t, *J* = 8.0 Hz, 9H, H^{13}), 0.61 (qd, *J* = 8.0, 4.0 Hz, 6H, H^{12}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.1 (C^5), 162.0 (q, *J* = 245.0 Hz, C^{17}), 160.3 (C^4), 149.6 (C^1), 127.4 (d, *J* = 3.0 Hz, C^{14}), 125.1 (d, *J* = 8.0 Hz, C^{15}), 117.8 (C^3), 115.9 (d, *J* = 22.0 Hz, C^{16}), 104.1 (C^2), 25.4 (Cy-CH_2), 19.5 (C^{10}), 14.2 (C^{11}), 7.8 (C^{13}), 2.7 (C^{12}); **^{19}F NMR** (471 MHz, $CDCl_3$) δ -114.8; ***m/z*** (ESI$^+$) calc. for $C_{31}H_{46}FNO_2Si$ = 511.33, found: 512.3356 $[M+H]^+$.

***N,N*-Dicyclohexyl-5-(4-methoxyphenyl)-2-(1-(triethylsilyl)ethyl)furan-3-carboxamide, 278g**



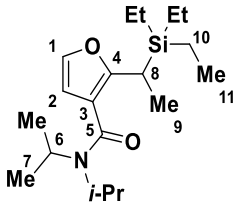
General procedure L: using **190** (38.1 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 9:1) afforded the title compound as a colourless oil (4.7 mg, 10%). **R$_f$** = 0.35 (hexane/EtOAc, 9:1); **ν_{max}/cm^{-1}**: 2931 (s), 2974 (s), 2855 (s), 1624 (s), 1580 (m), 1555 (m), 1502 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H, H^{15}), 6.95 – 6.89 (m, 2H, H^{16}), 6.32 (s, 1H, H^2), 3.83 (s, 3H, H^{18}), 2.74 (q, *J* = 7.5 Hz, 1H, H^{10}), 1.86 – 1.55 (m, 12H, Cy-C$\underline{H}_2$), 1.38 (d, *J* = 7.5 Hz, 3H, H^{11}), 1.29 – 1.09 (m, 8H, Cy-C$\underline{H}_2$), 0.93 (t, *J* = 8.0 Hz, 9H, H^{13}), 0.61 (qd, *J* = 8.0, 4.0 Hz, 6H, H^{12}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.8 (C^5), 159.7 (C^4), 159.0 (C^{17}), 150.5 (C^1), 124.9 (C^{15}), 124.3 (C^{14}), 117.7 (C^3), 114.4 (C^{16}), 102.8 (C^2), 55.5 (C^{18}), 25.5 (Cy-$\underline{C}H_2$), 19.4 (C^{10}), 14.2 (C^{11}), 7.6 (C^{13}), 2.8 (C^{12}); ***m/z*** (ESI$^+$) calc. for $C_{32}H_{49}NO_3Si$ = 523.35, found: 524.3560 [M+H]$^+$.

***N,N*-Diethyl-2-(1-(triethylsilyl)ethyl)furan-3-carboxamide, 278h**



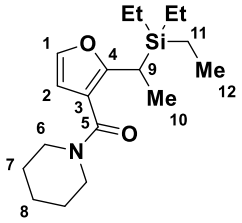
General procedure L: using **279** (19.1 mg, 0.11 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 4:1) afforded the title compound as a colourless oil (18.8 mg, 53%). **R$_f$** = 0.50 (hexane/EtOAc, 4:1); **ν_{max}/cm^{-1}**: 2953 (m), 2940 (m), 2911 (m), 2876 (m), 1623 (s), 1588 (m), 1516 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 2.0 Hz, 1H, H^1), 6.29 (d, *J* = 2.0 Hz, 1H, H^2), 3.54 – 3.29 (br. m, 4H, H^6), 2.76 (q, *J* = 7.5 Hz, 1H, H^8), 1.32 (d, *J* = 7.5 Hz, 3H, H^9), 1.17 (t, *J* = 7.0 Hz, 6H, H^7), 0.88 (t, *J* = 8.0 Hz, 9H, H^{11}), 0.60 – 0.46 (m, 6H, H^{10}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.4 (C^5), 161.4 (C^4), 139.2 (C^1), 113.9 (C^3), 109.7 (C^2), 19.3 (C^8), 13.7 (C^9), 7.4 (C^{11}), 2.6 (C^{10}); ***m/z*** (ESI$^+$) calc. for $C_{17}H_{31}NO_2Si$ = 309.21, found: 310.2199 [M+H]$^+$.

***N,N*-Diisopropyl-2-(1-(triethylsilyl)ethyl)furan-3-carboxamide, 278i**



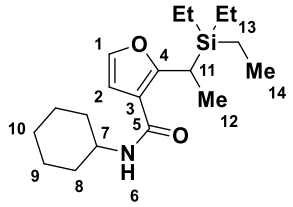
General procedure L: using **106** (19.5 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 9:1) afforded the title compound as a colourless oil (22.9 mg, 68%). $\mathbf{R_f}$ = 0.66 (hexane/EtOAc, 4:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2957 (m), 2811 (m), 2876 (m), 1622 (s), 1515 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 2.0 Hz, 1H, H^1), 6.23 (d, *J* = 2.0 Hz, 1H, H^2), 4.42 – 3.25 (br, 2H, H^6), 2.74 (q, *J* = 7.5 Hz, 1H, H^8), 1.52 – 1.10 (br. m, 15H, H^7, H^9), 0.89 (t, *J* = 8.0 Hz, 9H, H^{11}), 0.55 (m, 6H, H^{10}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.2 (C^5), 160.7 (C^4), 139.0 (C^1), 115.4 (C^3), 109.4 (C^2), 21.1 (C^7), 19.2 (C^8), 13.8 (C^9), 7.4 (C^{11}), 2.6 (C^{10}); ***m/z*** (ESI$^+$) calc. for $C_{19}H_{35}NO_2Si$ = 337.24, found: 338.2511 $[M+H]^+$.

Piperidin-1-yl(2-(1-(triethylsilyl)ethyl)furan-3-yl)methanone, 278j



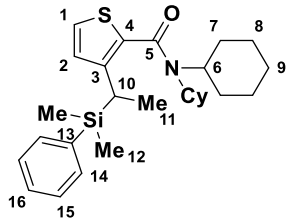
General procedure L: using **280** (20.7 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 4:1) afforded the title compound as a colourless oil (20.5 mg, 55%). $\mathbf{R_f}$ = 0.46 (hexane/EtOAc, 4:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2937 (m), 2875 (m), 2855 (m), 1623 (s), 1585 (m), 1516 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 2.0 Hz, 1H, H^1), 6.27 (d, *J* = 2.0 Hz, 1H, H^2), 3.55 (br, 4H, H^6), 2.76 (q, *J* = 7.5 Hz, 1H, H^9), 1.66 (m, 2H, H^8), 1.57 (m, 4H, H^7), 1.32 (d, *J* = 7.5 Hz, 3H, H^{10}), 0.89 (t, *J* = 8.0 Hz, 9H, H^{12}), 0.55 (m, 6H, H^{11}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.7 (C^5), 161.6 (C^4), 139.2 (C^1), 113.4 (C^3), 110.3 (C^2), 24.8 (C^8), 19.4 (C^9), 13.8 (C^{10}), 7.4 (C^{11}), 2.6 (C^{10}); ***m/z*** (ESI$^+$) calc. for $C_{18}H_{31}NO_2Si$ = 321.21, found: 322.2200 $[M+H]^+$.

***N*-Cyclohexyl-2-(1-(triethylsilyl)ethyl)furan-3-carboxamide, 278k**



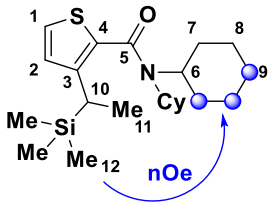
General procedure L: using **281** (19.3 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (25.0 mg, 75%). $\mathbf{R_f}$ = 0.72 (hexane/EtOAc, 4:1); $\mathbf{\nu_{max}/cm^{-1}}$: 3309 (br), 2931 (m), 2876 (m), 2855 (m), 1622 (s), 1583 (s), 1521 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 2.0 Hz, 1H, H^1), 6.33 (d, *J* = 2.0 Hz, 1H, H^2), 5.48 (br. d, *J* = 8.5 Hz, 1H, H^6), 3.99 – 3.82 (m, 1H, H^7), 3.46 (q, *J* = 7.5 Hz, 1H, H^{11}), 2.03 – 1.94 (m, 2H, H^8), 1.77 – 1.68 (m, 2H, Cy-H), 1.63 (dt, *J* = 13.0, 3.5 Hz, 1H, Cy-H), 1.44 – 1.34 (m, 1H, Cy-H), 1.32 (d, *J* = 7.5 Hz, 3H, H^{12}), 1.17 – 1.11 (m, 3H, $H^{8'}$), 0.89 (t, *J* = 8.0 Hz, 9H, H^{14}), 0.55 (qd, *J* = 8.0, 3.5 Hz, 6H, H^{13}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.9 (C^5), 163.5 (C^4), 139.5 (C^1), 113.0 (C^3), 108.2 (C^2), 48.0 (C^7), 33.4 (C^8), 25.7 (Cy-CH_2), 25.1 (Cy-CH_2), 19.7 (C^{11}), 13.6 (C^{12}), 7.4 (C^{14}), 2.7 (C^{13}); ***m/z*** (ESI$^+$) calc. for $C_{19}H_{33}NO_2Si$ = 335.23, found: 336.2360 $[M+H]^+$.

***N,N*-Dicyclohexyl-2-(1-(dimethyl(phenyl)silyl)ethyl)thiophene-3-carboxamide, 280a**



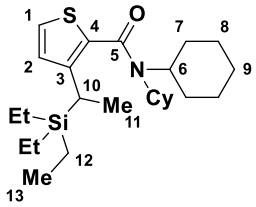
General procedure L: using **192** (29.1 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with dimethylphenylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (30.9 mg, 68%). $\mathbf{R_f}$ = 0.81 (hexane/EtOAc, 4:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2928 (s), 2854 (m), 1623 (s), 1533 (w); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H, H^{14}), 7.41 – 7.30 (m, 3H, H^{15}, H^{16}), 7.13 (d, *J* = 5.0 Hz, 1H, H^1), 6.60 (d, *J* = 5.0 Hz, 1H, H^2), 3.53 – 2.95 (br, 2H, H^6), 2.62 (q, *J* = 7.5 Hz, 1H, H^{10}), 1.89 – 1.50 (br. m, 13H, Cy-H), 1.39 – 1.00 (m, 10H, Cy-H, H^{11}), 0.29 (s, 3H, H^{12}), 0.21 (s, 3H, $H^{12'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.3 (C^5), 144.2 (C^4), 137.9 (C^{13}), 134.3 (C^{14}), 130.1 (C^3), 129.1 (C^{16}), 127.8 (C^{15}), 126.9 (C^2), 124.1 (C^1), 31.1 (Cy-CH_2), 26.3 (Cy-CH_2), 25.4 (Cy-CH_2), 23.6 (C^{10}), 16.3 (C^{11}), -3.3 (C^{12}), -5.4 ($C^{12'}$); ***m/z*** (ESI$^+$) calc. for $C_{27}H_{39}NOSSi$ = 453.25, found: 454.2603 $[M+H]^+$.

***N,N*-Dicyclohexyl-3-(1-(trimethylsilyl)ethyl)thiophene-2-carboxamide, 280b**



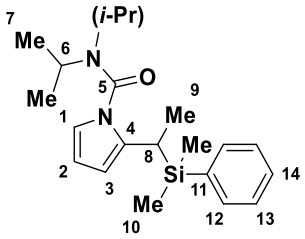
General procedure L: using **192** (29.1 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with trimethylvinylsilane (16 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (23.2 mg, 59%). $\mathbf{R_f}$ = 0.38 (hexane/EtOAc, 9:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2928 (s), 2854 (s), 1625 (s), 1534 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 5.0 Hz, 1H, H^1), 6.79 (d, *J* = 5.0 Hz, 1H, H^2), 3.50 – 2.95 (br, 2H, H^6), 2.40 (q, *J* = 7.5 Hz, 1H, H^{10}), 1.88 – 1.51 (m, 12H, Cy-H), 1.27 (d, *J* = 7.5 Hz, 3H, H^{11}), 1.21 – 1.05 (m, 6H, Cy-H), -0.03 (s, 9H, H^{12}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.4 (C^5), 145.0 (C^3), 129.8 (C^4), 126.8 (C^2), 124.2 (C^1), 31.1 (Cy-CH_2), 26.3 (Cy-CH_2), 25.4 (Cy-CH_2), 23.8 (C^{10}), 16.0 (C^{11}), -2.7 (C^{12}); ***m/z*** (ESI^+) calc. for $C_{22}H_{37}NOSSi$ = 391.24, found: 392.2443 $[M+H]^+$.

***N,N*-Dicyclohexyl-3-(1-(triethylsilyl)ethyl)thiophene-2-carboxamide, 280c**



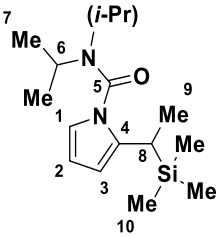
General procedure L: using **192** (29.1 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (20 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (19.5 mg, 45%). $\mathbf{R_f}$ = 0.46 (hexane/EtOAc, 9:1); $\mathbf{\nu_{max}/cm^{-1}}$: 3384 (br), 2929 (s), 2873 (m), 2854 (m), 1625 (s), 1523 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 5.0 Hz, 1H, H^1), 6.83 (d, *J* = 5.0 Hz, 1H, H^2), 3.75 – 2.90 (br, 2H, H^6), 2.53 (q, *J* = 7.5 Hz, 1H, H^{10}), 1.90 – 1.48 (m, 12H, Cy-H), 1.28 (d, *J* = 7.5 Hz, 3H, H^{11}), 1.17 (br, 6H, Cy-H), 0.87 (t, *J* = 8.0 Hz, 9H, H^{13}), 0.55 (qd, *J* = 8.0, 3.0 Hz, 6H, H^{12}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.2 (C^5), 145.1 (C^3), 129.6 (C^4), 127.3 (C^2), 124.2 (C^1), 31.0 (Cy-CH_2), 26.3 (Cy-CH_2), 25.4 (Cy-CH_2), 21.0 (C^{10}), 16.6 (C^{11}), 7.6 (C^{13}), 2.5 (C^{12}); ***m/z*** (ESI^+) calc. for $C_{25}H_{43}NOSSi$ = 433.28, found: 434.2913 $[M+H]^+$.

2-(1-(Dimethyl(phenyl)silyl)ethyl)-*N*,*N*-diisopropyl-1*H*-pyrrole-1-carboxamide, 280d



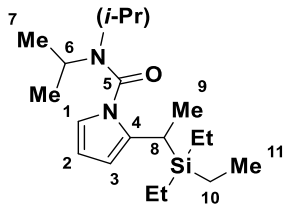
General procedure L: using **104** (19.4 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with dimethylphenylvinylsilane (20 µL, 110 mol%) at 120 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (21.3 mg, 60%). $\mathbf{R_f}$ = 0.54 (hexane/EtOAc, 9:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2966 (m), 2934 (m), 2871 (w), 1683 (s), 1541 (w); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H, H^{12}), 7.37 – 7.31 (m, 3H, H^{13}, H^{14}), 6.57 (dd, *J* = 3.0, 1.5 Hz, 1H, H^1), 6.11 (*pseudo*-t, *J* = 3.0 Hz, 1H, H^2), 5.78 (dd, *J* = 3.0, 1.5 Hz, 1H, H^3), 3.63 – 3.30 (br, 2H, Cy-H), 2.49 (q, *J* = 7.5 Hz, 1H, H^8), 1.37 – 1.25 (m, 12H), 1.23 (d, *J* = 7.5 Hz, 3H. H$^{9'}$), 0.33 (s, 3H, H^7), 0.25 (s, 3H, H$^{7'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.0 (C^5), 138.3 (C^4), 134.3 (C^{12}), 129.1 (C^{14}), 127.8 (C^{13}), 116.9 (C^1), 109.0 (C^2), 105.9 (C^3), 20.6 (Cy-$\underline{C}H_2$), 19.7 (C^8), 16.9 (C^9), -3.2 (C^7), -5.5 (C$^{7'}$); ***m/z*** (ESI$^+$) calc. for $C_{21}H_{32}N_2OSi$ = 356.23, found: 357.2362 [M+H]$^+$.

***N*,*N*-Diisopropyl-2-(1-(trimethylsilyl)ethyl)-1*H*-pyrrole-1-carboxamide, 280e**



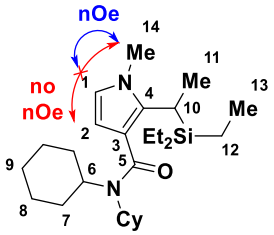
General procedure L: using **104** (19.4 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with trimethylvinylsilane (16 µL, 110 mol%) at 120 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (23.6 mg, 80%). $\mathbf{R_f}$ = 0.58 (hexane/EtOAc, 9:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2965 (m), 2872 (w), 1686 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.56 (dd, *J* = 3.0, 1.5 Hz, 1H, H^1), 6.11 (*pseudo*-t, *J* = 3.0 Hz, 1H, H^2), 5.83 (dd, *J* = 3.0, 1.5 Hz, 1H, H^3), 3.82 – 3.23 (br, 2H, Cy-H), 2.26 (q, *J* = 7.5 Hz, 1H, H^8), 1.39 – 1.28 (br, 11H, Cy-H), 1.26 (d, *J* = 7.5 Hz, 3H, H^9), 0.01 (s, 9H, H^{10}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.1 (C^5), 138.0 (C^4), 116.9 (C^1), 108.9 (C^2), 105.5 (C^3), 21.1 (Cy-$\underline{C}H_2$), 20.7 (Cy-$\underline{C}H_2$), 19.9 (C^8), 16.6 (C^9), -2.7 (C^{10}); ***m/z*** (ESI$^+$) calc. for $C_{16}H_{30}N_2OSi$ = 294.21, found: 295.2206 [M+H]$^+$.

***N,N*-Diisopropyl-2-(1-(triethylsilyl)ethyl)-1*H*-pyrrole-1-carboxamide, 280f**



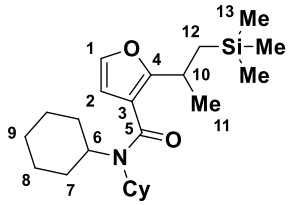
General procedure L: using **104** (19.4 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (20 µL, 110 mol%) at 120 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (21.0 mg, 62%). $\mathbf{R_f}$ = 0.62 (hexane/EtOAc, 9:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2953 (m), 2875 (m), 1686 (s), 1537 (w); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 3.0, 1.5 Hz, 1H, H^1), 6.10 (*pseudo*-t, *J* = 3.0 Hz, 1H, H^2), 5.85 (dd, *J* = 3.0, 1.5 Hz, 1H, H^3), 3.97 – 3.16 (br, 2H, Cy-H), 2.38 (q, *J* = 7.5 Hz, 1H, H^8), 1.50 – 1.14 (m, 15H, Cy-H, C^9), 0.89 (t, *J* = 8.0 Hz, 9H, H^{11}), 0.68 – 0.50 (m, 6H, H^{10}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.9 (C^5), 138.1 (C^4), 116.7 (C^1), 109.0 (C^2), 105.9 (C^3), 20.6 (Cy-CH_2), 17.2 (C^9), 17.0 (C^8), 7.6 (C^{11}), 2.5 (C^{10}); ***m/z*** (ESI$^+$) calc. for $C_{19}H_{36}N_2OSi$ = 336.26, found: 337.2676 $[M+H]^+$.

***N,N*-Dicyclohexyl-1-methyl-2-(1-(triethylsilyl)ethyl)-1*H*-pyrrole-3-carboxamide, 280g**



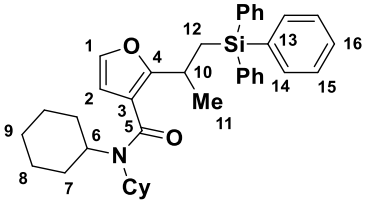
General procedure L: using **196** (28.8 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with triethylvinylsilane (20 µL, 110 mol%) at 120 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc 9:1) afforded the title compound as a colourless oil (26.6 mg, 62%). $\mathbf{R_f}$ = 0.73 (hexane/EtOAc, 4:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2929 (s), 2873 (s), 2854 (m), 1618 (s), 1544 (m), 1498 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.31 (d, *J* = 3.0 Hz, 1H, H^1), 5.92 (d, *J* = 3.0 Hz, 1H, H^2), 3.53 (s, 3H, H^{14}), 1.91 – 1.46 (m, 12H, Cy-CH_2), 1.37 (d, *J* = 8.0 Hz, 3H, H^{11}), 1.27 – 1.06 (m, 6H, Cy-CH_2), 0.87 (t, *J* = 8.0 Hz, 9H, H^{13}), 0.57 (q, *J* = 8.0 Hz, 6H, H^{12}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.3 (C^5), 137.8 (C^4), 119.6 (C^3), 117.4 (C^1), 106.2 (C^2), 35.3 (C^{14}), 25.6 (Cy-CH_2), 17.0 (C^{10}), 15.1 (C^{11}), 7.5 (C^{13}), 3.5 (C^{12}); ***m/z*** (ESI$^+$) calc. for $C_{26}H_{46}N_2OSi$ = 430.34, found: 431.3454 $[M+H]^+$.

***N,N*-Dicyclohexyl-2-(1-(trimethylsilyl)propan-2-yl)furan-3-carboxamide, 283a**



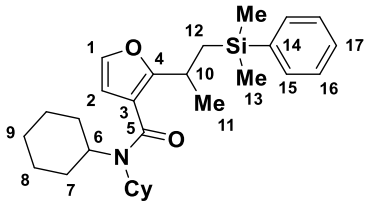
General procedure L: using **187** (27.5 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with allyltrimethylsilane (18 µL, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (34.1 mg, 88%). $\mathbf{R_f}$ = 0.54 (hexane/EtOAc, 9:1); $\boldsymbol{\nu_{max}}$**/cm^{-1}**: 2928 (m), 2855 (m), 1624 (s), 1515 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 2.0 Hz, 1H, H^1), 6.18 (d, *J* = 2.0 Hz, 1H, H^2), 3.65 (br, 1H, Cy-H), 3.27 – 3.17 (m, 1H, H^{10}), 2.94 (br, 1H, Cy-H), 2.61 (br, 2H, Cy-H), 1.88 – 1.38 (br. m, 12H, Cy-H), 1.29 (d, *J* = 7.0 Hz, 3H, H^{11}), 1.27 – 1.04 (br. m, 7H, H^{12}, Cy-H), 0.81 (dd, *J* = 14.5, 6.0 Hz, 1H, H$^{12'}$), -0.14 (s, 9H, H^{13}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.0 (C^5), 160.9 (C^4), 139.4 (C^1), 116.2 (C^3), 109.1 (C^2), 28.7 (C^{10}), 25.9 (Cy-CH_2), 24.0 (C^{12}), 23.9 (C^{11}), -1.4 (C^{13}); ***m/z*** (ESI$^+$) calc. for $C_{23}H_{39}NO_2Si$ = 389.28, found: 390.2825 $[M+H]^+$.

***N,N*-Dicyclohexyl-2-(1-(triphenylsilyl)propan-2-yl)furan-3-carboxamide, 283b**



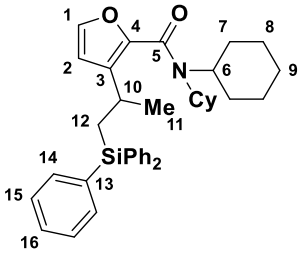
General procedure L: using **187** (27.5 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with allyltriphenylsilane (33 mg, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 9:1) afforded the title compound as a white foam (50.7 mg, 88%). $\mathbf{R_f}$ = 0.36 (hexane/EtOAc, 9:1); $\boldsymbol{\nu_{max}}$**/cm^{-1}**: 3069 (w), 3049 (w), 2929 (m), 2855 (m), 2244 (w), 1615 (m), 1513 (w); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 6H, H^{14}), 7.43 – 7.31 (m, 9H, H^{15}, H^{16}), 7.08 (d, *J* = 2.0 Hz, 1H, H^1), 6.14 (d, *J* = 2.0 Hz, 1H, H^2), 3.52 (br, 1H, Cy-H), 3.41 – 3.31 (m, 1H, H^{10}), 3.11 – 2.78 (br, 1H, Cy-H), 2.56 (br, 2H, Cy-H), 1.96 (dd, *J* = 15.0, 6.0 Hz, 1H, H^{12}), 1.89 – 0.96 (m, 22H, H^{11}, H$^{12'}$, Cy-H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.0 (C^5), 159.7 (C^4), 139.7 (C^1), 135.8 (C^{14}), 135.2 (C^{13}), 129.4 (C^{16}), 127.9 (C^{15}), 116.2 (C^3), 109.0 (C^2), 29.0 (C^{10}), 25.4 (Cy-CH_2), 22.7 (C^{11}), 20.4 (C^{12}); ***m/z*** (ESI$^+$) calc. for $C_{38}H_{45}NO_2Si$ = 575.32, found: 576.3299 $[M+H]^+$.

***N,N*-Dicyclohexyl-2-(1-(dimethyl(phenyl)silyl)propan-2-yl)furan-3-carboxamide, 283c**



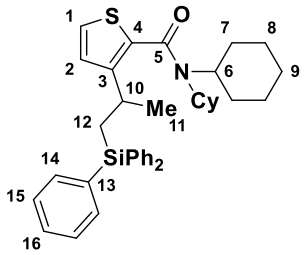
General procedure L: using **187** (27.5 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with allyldimethylphenylsilane (19 mg, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 19:1) afforded the title compound as a colourless oil (40.8 mg, 90%). $\mathbf{R_f}$ = 0.65 (hexane/EtOAc, 4:1); $\mathbf{\nu_{max}/cm^{-1}}$: 2929 (s), 2855 (m), 1625 (s), 1515 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 2H, H^{15}), 7.33 – 7.29 (m, 3H, H^{16}, H^{17}), 7.17 (d, *J* = 2.0 Hz, 1H, H^1), 6.18 (d, *J* = 2.0 Hz, 1H, H^2), 3.76 – 3.48 (br, 1H, Cy-H), 3.30 – 3.21 (m, 1H, H^{10}), 2.94 (br, 1H, Cy-H), 2.60 (br, 2H, Cy-H), 1.86 – 1.42 (br, 11H, Cy-H), 1.39 – 0.98 (br, 12H, Cy-H, H^{11}, H^{12}), 0.20 (s, 3H, H^{13}), 0.07 (s, 3H, H$^{13'}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.9 (C^5), 160.4 (C^4), 139.6 (C^{14}), 139.5 (C^1), 133.6 (C^{15}), 128.9 (C^{17}), 127.8 (C^{16}), 116.3 (C^3), 109.1 (C^2), 28.7 (C^{10}), 25.4 (Cy-$\underline{C}H_2$), 23.8 (C^{11}), 22.9 (C^{12}), -2.9 (C^{13}); ***m/z*** (ESI$^+$) calc. for $C_{28}H_{41}NO_2Si$ = 451.29, found: 452.2979 $[M+H]^+$.

***N,N*-Dicyclohexyl-3-(1-(triphenylsilyl)propan-2-yl)furan-2-carboxamide, 283d**



General procedure L: using **191** (27.5 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with allyltriphenylsilane (33 mg, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 9:1) afforded the title compound as a colourless oil (49.1 mg, 85%). $\mathbf{R_f}$ = 0.32 (hexane/EtOAc, 9:1); $\mathbf{\nu_{max}/cm^{-1}}$: 3069 (w), 3045 (w), 2925 (s), 2856 (m), 1618 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 6H, H^{14}), 7.40 – 7.35 (m, 3H, H^{16}), 7.32 (dd, *J* = 8.0, 6.5 Hz, 6H, H^{15}), 7.08 (d, *J* = 2.0 Hz, 1H, H^1), 6.22 (d, *J* = 2.0 Hz, 1H, H^2), 3.51 – 3.40 (m, 1H, H^{10}), 3.33 – 2.85 (br, 2H, Cy-H), 2.71 – 2.16 (br, 2H, Cy-H), 1.83 – 1.71 (m, 6H, Cy-H, H^{12}), 1.67 – 1.57 (m, 4H, Cy-H), 1.48 (d, *J* = 11.5 Hz, 2H, Cy-H), 1.35 – 0.97 (m, 9H, Cy-H, H^{11}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.0 (C^5), 143.3 (C^4), 140.8 (C^1), 135.8 (C^{14}), 135.5 (C^{13}), 135.2 (C^3), 129.4 (C^{16}), 127.9 (C^{15}), 110.5 (C^2), 31.0 (Cy-$\underline{C}H_2$), 26.4 (Cy-$\underline{C}H_2$), 26.2 (C^{10}), 25.4 (Cy-$\underline{C}H_2$), 25.1 (C^{11}), 22.8 (C^{12}); ***m/z*** (ESI$^+$) calc. for $C_{38}H_{45}NO_2Si$ = 575.32, found: 576.3297 $[M+H]^+$.

***N,N*-Dicyclohexyl-3-(1-(triphenylsilyl)propan-2-yl)thiophene-2-carboxamide, 282e**

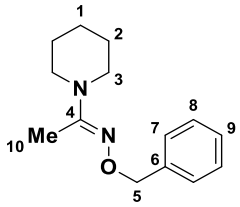


General procedure L: using **192** (29.1 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-**L14** (5.25 mg, 5.0 µmol) in THF (1.0 mL) with allyltriphenylsilane (33 mg, 110 mol%) at 120 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 9:1) afforded the title compound as a colourless oil (41.7 mg, 70%). $\mathbf{R_f}$ = 0.33 (hexane/EtOAc, 9:1); $\boldsymbol{\nu_{max}/cm^{-1}}$: 3069 (w), 3048 (w), 3009 (w), 2928 (m), 2854 (m), 1619 (s), 1542 (w); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.5 Hz, 6H, H^{14}), 7.39 (t, *J* = 7.5 Hz, 3H, H^{16}), 7.34 (t, *J* = 7.5 Hz, 6H, H^{15}), 7.12 (d, *J* = 5.0 Hz, 1H, H^1), 6.94 (d, *J* = 5.0 Hz, 1H, H^2), 3.25 – 3.17 (m, 1H, H^{10}), 1.88 – 1.39 (m, 12H, H^{12}, Cy-H), 1.31 (br. d, *J* = 12.0 Hz, 2H, Cy-H), 1.12 (d, *J* = 7.0 Hz, 9H, Cy-H, H^{11}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.9 (C^5), 148.1 (C^4), 135.9 (C^{14}), 135.3 (C^{13}), 130.6 (C^3), 129.4 (C^{16}), 128.0 (C^{15}), 125.9 (C^2), 124.2 (C^1), 30.3 (C^{10}), 25.3 (Cy-CH_2), 24.4 (Cy-CH_2), 23.1 (C^{12}); ***m/z*** (ESI^+) calc. for $C_{38}H_{45}NOSSi$ = 591.30, found: 592.3073 $[M+H]^+$.

7.6 Experimental procedures for compounds in Chapter 5

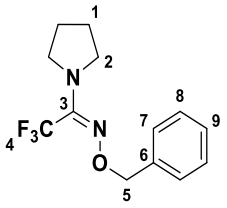
7.6.1 Synthesis of substrates and alkenes

(*E*)-*N*-Benzyl-1-(piperidin-1-yl)ethan-1-imine, 312



To a solution of sodium acetate (197 mg, 2.4 mmol) in H_2O/MeOH (4:1, 27 mL) was added *O*-benzylhydroxylamine hydrochloride (319 mg, 2.0 mmol) then formaldehyde (0.337 mL, 6.0 mmol). The mixture was stirred at room temperature for 2 h before it was extracted with CH_2Cl_2 (3 × 10 mL), dried over sodium sulfate, filtered, and solvent removed *in vacuo*. The resulting colourless liquid (294 mg) was added to a flame-dried flask and dissolved in DMF (1.33 mL). NCS (297 mg, 2.0 mmol) was added portion-wise and the mixture was heated at 70 °C for 2 h. After cooling, piperidine (0.16 mL, 1.7 mmol) was added and the mixture was heated at 70 °C for 16 h. After cooling, H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with sat. aq. $NaHCO_3$ (10 mL) then brine (10 mL), dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC gave the title compound as a yellow oil (131 mg, 28%). $\mathbf{R_f}$ = 0.68 (hexane/EtOAc, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H, H^7), 7.38 – 7.33 (m, 2H, H^8), 7.32 – 7.27 (m, 1H, H^9), 4.98 (s, 2H, H^5), 3.14 (br, 4H, H^3), 1.99 (s, 3H, H^{10}), 1.58 (br, 6H, H^1, H^2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.0 (C^4), 138.7 (C^6), 128.3 (C^7/C^8), 128.2 (C^7/C^8), 127.4 (C^9), 75.3 (C^5), 47.1 (C^3), 25.4 (C^1/C^2), 24.6 (C^1/C^2), 11.9 (C^{10}). *Data in accordance with literature values.*[230]

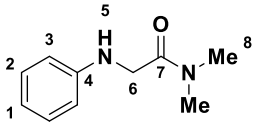
(*E*)-2,2,2-Trifluoro-1-(pyrrolidin-1-yl)ethan-1-one *O*-benzyl oxime, 314



To a flame-dried two-necked flask was added PPh_3 (6.56 g, 25 mmol), CCl_4 (10 mL) then NEt_3 (4.17 mL, 30 mmol). The solution was for 10 mins at 0 °C before trifluoroacetic acid (0.765 mL, 10 mmol) was added. The solution was stirred for a further 10 mins at 0 °C before *O*-benzylhydroxylamine hydrochloride (1.60 g, 10 mmol) was added and heated at 85 °C for 4 h. After cooling, volatile components were removed *in vacuo*. The residue was washed with hexane and the filtrate was concentrated *in vacuo* to give a crude yellow liquid (1.5 g). The crude material was dissolved in CH_2Cl_2 (20 mL) before triethylamine (1.39 mL, 10 mmol) and pyrrolidine (0.693 mL, 8.3 mmol) were added

and the mixture was heated at 50 °C for 16 h. After allowing to cool, H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), washed with $NaHCO_3$, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 49:1) gave the title compound as a colourless oil (305 mg, 11%); $\mathbf{R_f}$ = 0.21 (hexane/EtOAc, 49:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H, H^7, H^8, H^9), 5.05 (s, 2H, H^5), 3.68 – 3.50 (m, 4H, H^2), 1.93 – 1.73 (m, 4H, H^1); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.2 (q, *J* = 30.5 Hz, C^3), 137.4 (C^6), 128.4 (C^7/C^8/C^9), 128.4 (C^7/C^8/C^9), 128.0 (C^7/C^8/C^9), 119.5 (q, *J* = 277.5 Hz, C^4), 77.0 (C^5), 50.0 (d, *J* = 2.0 Hz, C^2), 25.36 (C^1). *Data in accordance with literature values*.[230]

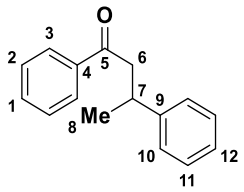
***N,N*-Dimethyl-2-(phenylamino)acetamide, 335**



To a solution of aniline (0.286 mL, 3.13 mmol) and 2-bromo-*N,N*-dimethylethanamide (0.270 mL, 2.50 mmol) in THF (8.0 mL) was added Et_3N (0.437 mL, 3.13 mmol). The reaction mixture was heated at 50 °C for 16 h. After cooling, H_2O (10 mL) was added and the mixture was extracted with Et_2O (5 × 10 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, filtered and solvent removed *in vacuo*. Purification by FCC (hexane/EtOAc, 1:1) afforded the title compound as a white solid (411 mg, 92%). $\mathbf{R_f}$ = 0.39 (hexane/EtOAc, 1:1); **m.p.** = 114.1 – 115.2 °C (hexane/EtOAc, Lit.[311]: 116 – 117 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 2H, H^2), 6.75 (t, *J* = 7.5 Hz, 1H, H^1), 6.68 (d, *J* = 7.5 Hz, 2H, H^3), 3.88 (s, 2H, H^6), 3.04 (s, 6H, H^8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.9 (C^7), 147.2 (C^4), 129.4 (C^2), 118.1 (C^1), 113.5 (C^3), 45.6 (C^6), 36.0 (C^8), 35.9 ($C^{8'}$). *Data in accordance with literature values.*[312]

7.6.2 Catalysis products

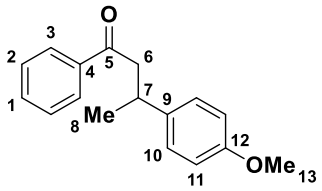
1,3-Diphenylbutan-1-one, 308a



General procedure N: using ethyl 3-oxo-3-phenylpropionate **307** (55 µL, 0.20 mmol) and styrene (0.14 mL, 1.2 mmol). Purification by FCC (hexane/EtOAc, 19:1) gave the title compound as a yellow wax (28.0 mg, 62%, B:L 1:1); $\mathbf{R_f}$ = 0.48 (hexane/EtOAc, 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 4H, Ar-C<u>H</u>), 7.59 – 7.52 (m, 2H, Ar-C<u>H</u>), 7.47 – 7.42 (m, 4H, Ar-C<u>H</u>), 7.34 – 7.27 (m, 6H, Ar-C<u>H</u>), 7.23 – 7.17 (m, 5H, Ar-C<u>H</u>), 3.56 – 3.47 (m, 1H, H^7), 3.31 (dd, *J* = 16.5, 5.5 Hz, 1H, H^6), 3.19 (dd, *J* = 16.5, 8.5 Hz, 1H, $H^{6'}$), 2.99 (t, *J* = 7.5 Hz, 2H, Linear R-CH_2), 2.73 (t, *J* = 7.5 Hz, 2H, Linear

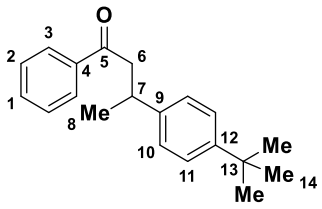
R-CH_2), 2.14 – 2.05 (m, 2H, Linear R-CH_2), 1.35 (d, *J* = 7.0 Hz, 3H, H^8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.3 (R_2C=O), 199.2 (R_2C=O), 146.7 (Ar-C), 141.8 (Ar-C), 137.3 (Ar-C), 137.2 (Ar-C), 133.1 (Ar-CH), 133.0 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 127.0 (Ar-CH), 126.4 (Ar-CH), 126.1 (Ar-CH), 47.2 (C^6), 37.8 (Linear R-CH_2), 35.7 (C^7), 35.3 (Linear R-CH_2), 25.8 (Linear R-CH_2), 22.0 (C^8); **Chiral SFC:** (CHIRAL ART Amylose-SA column (25 cm), CO_2:IPA 95:5, 2.0 mL/min, 140 bars, 40 °C). Retention times: 4.00 mins, 4.41 mins. *Data in accordance with literature values.*[313]

3-(4-Methoxyphenyl)-1-phenylbutan-1-one, 308b



General procedure N: using ethyl 3-oxo-3-phenylpropionate **307** (55 µL, 0.20 mmol) and 4-methoxystyrene (0.16 mL, 1.2 mmol). Purification by FCC (hexane/EtOAc, 19:1) gave the title compound as a yellow wax (3.7 mg, 7%, B:L 6:1); **R_f** = 0.48 (hexane/EtOAc, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 2H, Ar-CH), 7.54 (t, *J* = 7.5 Hz, 1H, H^1), 7.44 (t, *J* = 7.5 Hz, 2H, Ar-CH), 7.19 (d, *J* = 8.5 Hz, 2H, Ar-CH), 6.88 – 6.81 (m, 2H, Ar-CH), 3.78 (s, 3H, H^{13}), 3.51 – 3.41 (m, 1H, H^7), 3.26 (dd, *J* = 16.5, 6.0 Hz, 1H, H^6), 3.15 (dd, *J* = 16.5, 8.0 Hz, 1H, $H^{6'}$), 1.31 (d, *J* = 7.0 Hz, 2H, H^8). *Data in accordance with literature values.*[314]

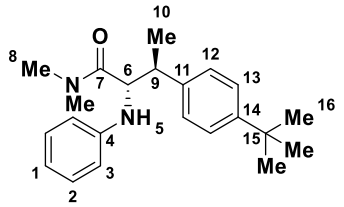
3-(4-(*Tert*-butyl)phenyl)-1-phenylbutan-1-one, 308c



General procedure N: using ethyl 3-oxo-3-phenylpropionate **307** (55 µL, 0.20 mmol) and 4-*tert*-butylstyrene (0.22 mL, 1.2 mmol). Purification by FCC (hexane/EtOAc, 19:1) gave the title compound as a yellow wax (30.0 mg, 53%, B:L 2:1); **R_f** = 0.57 (hexane/EtOAc, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 3H), 7.57 – 7.52 (m, 2H), 7.45 (td, *J* = 8.0, 2.0 Hz, 3H), 7.35 – 7.30 (m, 3H), 7.23 – 7.20 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 1H), 3.54 – 3.42 (m, 1H), 3.30 (dd, *J* = 16.5, 5.5 Hz, 1H), 3.17 (dd, *J* = 16.5, 8.5 Hz, 1H), 2.99 (q, *J* = 7.5 Hz, 1H), 2.70 (t, *J* = 7.5 Hz, 1H), 2.08 (p, *J* = 7.5 Hz, 1H), 1.31 (d, *J* = 2.5 Hz, 18H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.4 (C=O), 199.4 (C=O), 149.2 (Ar-C), 148.9 (Ar-C), 143.6 (Ar-C), 138.7 (Ar-C), 137.4 (Ar-C), 137.2 (Ar-C), 133.1 (Ar-CH), 133.0 (Ar-CH), 128.7 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 126.6 (Ar-CH), 125.5 (Ar-CH), 125.4 (Ar-CH),

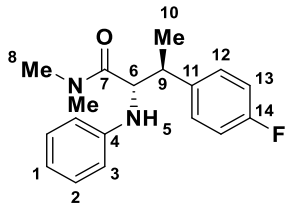
47.3 (C^{6}), 38.0 (Linear R-CH_2), 35.2 (C^{7}), 34.8 (Linear R-CH_2), 34.5 (C^{13}), 31.6 (C^{14}), 25.9 (Linear R-CH_2), 21.8 (C^{8}). *Data in accordance with literature values.*[314]

(2*S*,3*S*)-3-(4-(*Tert*-butyl)phenyl)-*N*,*N*-dimethyl-2-(phenylamino)butanamide, 337a



General procedure L: using **335** (17.8 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-SEGPHOS (3.1 mg, 5.0 µmol) in 1,4-dioxane (0.2 mL) with 4-*tert*-butylstyrene (37 µL, 200 mol%) at 130 °C for 72 h. Purification of the residue by FCC (hexane/EtOAc 7:3) afforded the title compound as a pale-yellow solid (19.8 mg, 58% yield, 95% *e.e.*, *d.r.* = 8:1). $\mathbf{R_f}$ = 0.39 (hexane/EtOAc, 7:3); **m.p.** = 121.0 – 123.3 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ = -2.53 (c = 0.16, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3681 (w), 3350 (br), 2960 (s), 2925 (s), 2868 (m), 1638 (s), 1632 (s), 1502 (s); **^{1}H NMR** (500 MHz, $CDCl_3$, a = major, b = minor) δ 7.34 – 7.29 (m, 2H, H^{12}), 7.19 – 7.12 (m, 3.6H, H^{13}, H^{2a}), 7.11 – 7.06 (m, 0.4H, H^{2b}), 6.70 (t, *J* = 7.5, 1H, H^{1}), 6.64 – 6.60 (m, 1.7H, H^{3a}), 6.51 – 6.47 (m, 0.3H, H^{3b}), 4.73 – 4.43 (br. m, 1.8H, H^{5}, H^{6a}), 4.30 (d, *J* = 7.5 Hz, 0.2H, H^{6b}), 3.31 (*pseudo*-p, *J* = 7.0 Hz, 1H, H^{9}), 2.89 (s, 2.6H, H^{8a}), 2.74 (s, 0.4H, H^{8b}), 2.61 (s, 2.4H, $H^{8a'}$), 2.60 (s, 0.5H, $H^{8b'}$), 1.44 (d, *J* = 7.0 Hz, 0.5H, H^{10b}), 1.35 (d, *J* = 7.0 Hz, 2.7H, H^{10a}), 1.31 (d, *J* = 1.5 Hz, 9H, H^{16}); **^{13}C NMR** (126 MHz, $CDCl_3$, a = major, b = minor) δ 171.7 (C^{7}), 150.0 (C^{14}), 147.0 (C^{4}), 139.5 (C^{11}), 129.4 (C^{13a}), 129.3 (C^{13b}), 127.7 (C^{2a}), 127.6 (C^{2b}), 125.4 (C^{12a}), 125.3 (C^{12b}), 118.1 (C^{1}), 114.2 (C^{3b}), 114.1 (C^{3a}), 60.3 (C^{6b}), 58.5 (C^{6a}), 43.3 (C^{9b}), 41.9 (C^{9a}), 36.9 ($C^{8'}$), 35.8 (C^{8}), 34.6 (C^{15}), 31.5 (C^{16}), 15.9 (C^{10}); ***m/z*** (ESI$^+$) calc. for $C_{22}H_{30}N_2O$ = 338.24, found: 339.2434 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALCEL OD-H column (25 cm), CO_2:IPA 95.5:4.5, 2.5 mL/min, 140 bars, 40 °C). Retention times: 11.5 mins (major), 14.1 mins (minor), *e.r.* = 97.5:2.5, *e.e.* = 95%).

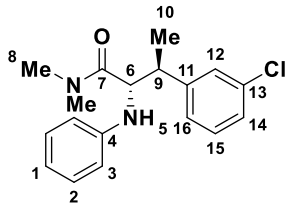
(2*S*,3*S*)-3-(4-Fluorophenyl)-*N*,*N*-dimethyl-2-(phenylamino)butanamide, 337b



General procedure L: using **335** (17.8 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-SEGPHOS (3.1 mg, 5.0 µmol) in 1,4-dioxane (0.2 mL) with 4-fluorostyrene (24 µL, 200 mol%) at 130 °C for 72 h. Purification of the residue by FCC (hexane/EtOAc 7:3) afforded the title compound as a pale-yellow solid (18.7 mg, 62% yield, 97% *e.e.*, *d.r.* = 9:1). $\mathbf{R_f}$ = 0.27 (hexane/EtOAc, 7:3); **m.p.** =

117.0 – 119.6 °C (hexane/EtOAc); $[\alpha]_D^{24}$ = -5.14 (c = 0.19, $CHCl_3$); **ν_{max}/cm^{-1}:** 3709 (w), 3681 (w), 3337 (br), 2968 (m), 2937 (m), 2873 (m), 2845 (m), 1637 (s), 1602 (s), 1508 (s); **^{1}H NMR** (500 MHz, $CDCl_3$, a = major, b = minor) δ 7.30 – 7.26 (m, 0.2H, H^{12b}), 7.23 – 7.18 (m, 1.8H, H^{12a}), 7.14 (t, *J* = 7.5 Hz, 1.8H, H^{2a}), 7.10 (d, *J* = 7.5 Hz, 0.2H, H^{2b}), 6.99 (t, *J* = 8.5 Hz, 2H, H^{13}), 6.71 (t, *J* = 7.5 Hz, 1H, H^1), 6.61 (d, *J* = 7.5 Hz, 1.7H, H^{3a}), 6.52 (d, *J* = 7.5 Hz, 0.2H, H^{3b}), 4.75 – 4.33 (br. m, 1.7H, H^5, H^{6a}), 4.30 (d, *J* = 7.0 Hz, 0.1H, H^{6b}), 3.30 (*pseudo*-p, *J* = 7.0 Hz, 1H, 0.9 H, H^{9a}), 3.11 (*pseudo*-p, *J* = 7.0 Hz, 0.2H, H^{9b}), 2.90 (s, 2.7H, H^{8a}), 2.76 (s, 0.5H, H^{8b}), 2.75 (s, 2.4H, $H^{8a'}$), 2.68 (s, 0.3H, $H^{8b'}$), 1.43 (d, *J* = 7.0 Hz, 0.4H, H^{10b}), 1.36 (d, *J* = 7.0 Hz, 2.7H, H^{10a}); **^{13}C NMR** (126 MHz, $CDCl_3$, a = major, b = minor) δ 172.9 (C^{7b}), 171.7 (C^{7a}), 161.9 (d, *J* = 245.0 Hz, C^{14}), 148.1 (C^{4b}), 147.1 (C^{4a}), 138.9 (d, *J* = 3.0 Hz, C^{11b}), 138.2 (d, *J* = 3.0 Hz, C^{11a}), 129.5 – 129.4 (C^2, C^{12}), 118.4 (C^{1a}), 118.3 (C^{1b}), 115.3 (d, *J* = 21.0 Hz, H^{13a}), 115.2 (d, *J* = 21.0 Hz, H^{13b}), 114.2 (C^{3b}), 114.2 (C^{3a}), 60.1 (C^{6b}), 58.5 (C^{6a}), 43.0 (C^{9b}), 41.9 (C^{9a}), 37.1 ($C^{8a'}$), 37.0 ($C^{8a'}$), 35.8 (C^{8a}), 35.6 (C^{8b}), 16.7 (C^{10b}), 16.5 (C^{10a}); **^{19}F NMR** (471 MHz, $CDCl_3$) δ -115.90; ***m/z*** (ESI^+) calc. for $C_{18}H_{21}FN_2O$ = 300.16, found: 301.1712 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALCEL OD-H column (25 cm), CO_2:IPA 97:3, 2.5 mL/min, 140 bars, 40 °C). Retention times: 15.1 mins (minor), 16.2 mins (major), *e.r.* = 1.5:98.5, *e.e.* = 97%).

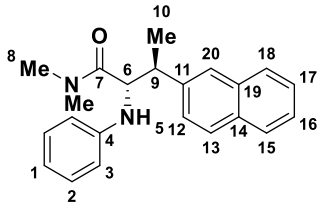
(2*S*,3*S*)-3-(3-Chlorophenyl)-*N*,*N*-dimethyl-2-(phenylamino)butanamide, 337c



General procedure L: using **335** (17.8 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol), (*R*)-SEGPHOS (3.1 mg, 5.0 μmol) in 1,4-dioxane (0.2 mL) with 3-chlorostyrene (25 μL, 200 mol%) at 130 °C for 72 h. Purification of the residue by FCC (hexane/EtOAc 7:3) afforded the title compound as a pale-yellow oil (13.2 mg, 42% yield, 94% *e.e.*, *d.r.* = 10:1). $\mathbf{R_f}$ = 0.29 (hexane/EtOAc, 7:3); $[\alpha]_D^{25}$ = -8.75 (c = 0.29, $CHCl_3$); **ν_{max}/cm^{-1}:** 3668 (w), 3329 (br), 3055 (m), 3025 (m), 2968 (m), 2936 (m), 2877 (m), 1636 (s), 1601 (s), 1572 (s); **^{1}H NMR** (500 MHz, $CDCl_3$, a = major, b = minor) δ 7.25 – 7.18 (m, 3H, Ar-C<u>H</u>), 7.17 – 7.09 (m, 3H, Ar-C<u>H</u>), 6.72 (t, *J* = 7.5 Hz, 1H, H^1), 6.62 (d, *J* = 7.5 Hz, 1.8H, H^{3a}), 6.54 (d, *J* = 7.5 Hz, 0.3H, H^{3b}), 4.77 – 4.27 (br. m, 2H, H^5, H^6), 3.29 (*pseudo*-p, *J* = 7.0 Hz, 0.9H, H^{9a}), 3.10 (*pseudo*-p, *J* = 7.0 Hz, 0.1 Hz, H^{9b}), 2.91 (s, 2.6H, H^{8a}), 2.76 (s, 0.3H, H^{8b}), 2.74 (s, 2.6H, $H^{8a'}$), 2.68 (s, 0.3H, $H^{8b'}$), 1.44 (d, *J* = 7.0 Hz, 0.5H, H^{10b}), 1.35 (d, *J* = 7.0 Hz, 2.7H, H^{10a}); **^{13}C NMR** (126 MHz, $CDCl_3$, a = major, b = minor) δ 171.5 (C^7), 146.9 (C^4), 144.8 (C^{11}), 134.4 (C^{13}), 129.8 (Ar-<u>C</u>H), 129.5 (Ar-<u>C</u>H), 129.4 (Ar-<u>C</u>H), 128.1 (Ar-<u>C</u>H), 128.0 (Ar-<u>C</u>H), 127.2 (Ar-<u>C</u>H), 126.4 (Ar-<u>C</u>H), 118.5 (C^1), 114.3 (C^3), 59.9 (C^{6b}), 58.2 (C^{6a}), 43.6 (C^{9b}), 42.4 (C^{9a}), 37.2 ($C^{8a'}$), 37.0 ($C^{8b'}$), 35.6 (C^8), 16.5 (C^{10b}), 16.2 (C^{10a}); ***m/z*** (ESI^+) calc. for $C_{18}H_{21}ClN_2O$ = 316.13, found: 317.1416 $[M+H]^+$; **Chiral SFC:**

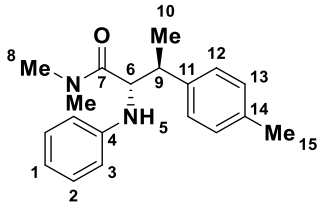
(YMC Chiral ART Cellulose-SC column (25 cm), CO_2:IPA 90:10, 2 mL/min, 140 bars, 40 °C). Retention times: 9.4 mins (minor), 11.8 mins (major), *e.r.* = 3:97, *e.e.* = 94%).

(2*S*,3*S*)-*N*,*N*-Dimethyl-3-(naphthalen-2-yl)-2-(phenylamino)butanamide, 337d



General procedure L: using **335** (17.8 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-SEGPHOS (3.1 mg, 5.0 µmol) in 1,4-dioxane (0.2 mL) with 2-vinylnaphthalene (31 mg, 200 mol%) at 130 °C for 72 h. Purification of the residue by FCC (hexane/EtOAc 7:3) afforded the title compound as a pale-yellow solid (21.8 mg, 66% yield, 96% *e.e.*, *d.r.* = 7:1). **R$_f$** = 0.41 (hexane/EtOAc, 7:3); **m.p.** = 147.8 – 150.9 °C (hexane/EtOAc); $[\alpha]_D^{20}$: = **-** 9.55 (c = 0.17, $CHCl_3$); **ν_{max}/cm^{-1}:** 3334 (br), 3052 (w), 3017 (w), 2968 (w), 2932 (w), 2874 (w), 1636 (s), 1601 (s), 1504 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 3H, Ar-C<u>H</u>), 7.70 (d, *J* = 2.0 Hz, 1H, Ar-C<u>H</u>), 7.51 – 7.42 (m, 2H, Ar-C<u>H</u>), 7.40 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-C<u>H</u>), 7.19 – 7.13 (m, 1.8H, H^{2a}), 7.13 – 7.09 (m, 0.3H, H^{2b}), 6.71 (t, *J* = 7.0 Hz, 1H, H^1), 6.66 (d, *J* = 8.0 Hz, 1.7H, H^{3a}), 6.59 (d, *J* = 8.0 Hz, 0.3H, H^{3b}), 4.84 – 4.37 (br. m, 2H, H^5, H^6), 3.51 (*pseudo*-p, *J* = 7.0 Hz, 1H, H^9), 2.89 (s, 2.6H, H^{8a}), 2.69 (s, 0.4H, H^{8b}), 2.62 (s, 2.6H, H$^{8a'}$), 2.55 (s, 0.4H, H$^{8b'}$), 1.56 (d, *J* = 7.0 Hz, 0.5H, H^{10a}), 1.47 (d, *J* = 7.0 Hz, 2.6H, H^{10b}); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.2 (C^{7b}), 171.7 (C^{7a}), 148.2 (C^{3b}), 147.1 (C^{3a}), 140.6 (C^{11b}), 140.2 (C^{11a}), 133.6 (Ar-<u>C</u>), 132.7 (Ar-<u>C</u>), 129.5 (C^{2a}), 129.4 (C^{2b}), 128.2 (Ar-<u>C</u>H), 128.0 (Ar-<u>C</u>H), 127.9 (Ar-<u>C</u>H), 127.8 (Ar-<u>C</u>H), 127.8 (Ar-<u>C</u>H), 127.7 (Ar-<u>C</u>H), 126.6 (Ar-<u>C</u>H), 126.5 (Ar-<u>C</u>H), 126.4 (Ar-<u>C</u>H), 126.4 (Ar-<u>C</u>H), 126.3 (Ar-<u>C</u>H), 126.2 (Ar-<u>C</u>H), 125.8 (Ar-<u>C</u>H), 118.3 (C^{1b}), 118.2 (C^{1a}), 114.3 (C^{3b}), 114.1 (C^{3a}), 60.0 (C^{6b}), 58.3 (C^{6a}), 44.1 (C^{9b}), 42.6 (C^{9a}), 37.2 (C$^{8a'}$), 37.0 (C$^{8b'}$), 35.8 (C^{8a}), 35.6 (C^{8b}), 16.9 (C^{10b}), 16.2 (C^{10a}); ***m/z*** (ESI$^+$) calc. for $C_{22}H_{24}N_2O$ = 332.19, found: 333.1962 [M+H]$^+$; **Chiral SFC:** (DAICEL CHIRALCEL OD-H column (25 cm), CO_2:IPA 85:15, 2 mL/min, 140 bars, 40 °C). Retention times: 7.9 mins (major), 9.5 mins (minor), *e.r.* = 98:2, *e.e.* = 96%).

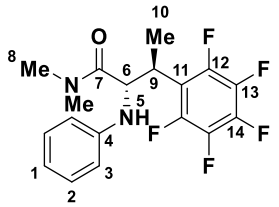
(2*S*,3*S*)-*N*,*N*-Dimethyl-2-(phenylamino)-3-(*p*-tolyl)butanamide, 337e



General procedure L: using **335** (17.8 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-SEGPHOS (3.1 mg, 5.0 µmol) in 1,4-dioxane (0.2 mL) with 4-methylstyrene (26 µL, 200 mol%) at 130 °C for 72 h. Purification of the residue by FCC (hexane/EtOAc 7:3) afforded the title compound as a

pale-yellow solid (19.8 mg, 67% yield, 93% *e.e.*, *d.r.* = 8:1). $\mathbf{R_f}$ = 0.36 (hexane/EtOAc, 7:3); **m.p.** = 121.3 – 123.4 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = +15.1 (c = 0.14, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3379 (br), 3009 (w), 2931 (m), 2855 (m), 1611 (s); **^{1}H NMR** (500 MHz, $CDCl_3$, a = major, b = minor) δ 7.18 – 7.09 (m, 6H, H^2, H^{12}, H^{13}), 6.70 (t, *J* = 7.0 Hz, 1H, H^1), 6.63 (d, *J* = 8.0 Hz, 1.8H, H^{3a}), 6.54 (d, *J* = 8.0 Hz, 0.2H, H^{3b}), 4.79 – 4.38 (br. m, 1.8H, H^5, H^{6a}), 4.32 (d, *J* = 7.6 Hz, 0.2H, H^{6b}), 3.34 – 3.25 (m, 1H, H^9), 2.90 (s, 2.7H, H^{8a}), 2.75 (s, 0.3H, H^{8b}), 2.67 (s, 2.6H, $H^{8a'}$), 2.62 (s, 0.3H, $H^{8b'}$), 2.32 (s, 3H, H^{15}), 1.43 (d, *J* = 7.0 Hz, 0.3H, H^{10b}), 1.35 (d, *J* = 7.0 Hz, 2.7H, H^{10a}); **^{13}C NMR** (126 MHz, $CDCl_3$, a = major, b = minor) δ 173.2 (C^{7b}), 171.7 (C^{7a}), 148.3 (C^{4b}), 147.1 (C^{4a}), 140.1 (C^{11b}), 139.5 (C^{11a}), 136.6 (C^{14}), 129.4 (C^{13a}), 129.3 (C^{13b}), 129.2 (C^{2a}), 129.1 (C^{2b}), 127.9 (C^{12a}), 127.8 (C^{12b}), 118.1 (C^1), 114.2 (C^{3a}), 114.1 (C^{3b}), 60.1 (C^{6b}), 58.5 (C^{6a}), 43.4 (C^{9b}), 42.0 (C^{9a}), 37.1 ($C^{8a'}$), 37.0 ($C^{8b'}$), 35.8 (C^{8a}), 35.6 (C^{8b}), 21.2 (C^{15}), 16.7 (C^{10b}), 16.2 (C^{10a}); ***m/z*** (ESI$^+$) calc. for $C_{19}H_{24}N_2O$ = 296.19, found: 297.1962 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALCEL OD-H column (25 cm), CO_2:IPA 95:5, 2.5 mL/min, 140 bars, 40 °C). Retention times: 11.1 mins (major), 11.6 mins (minor), *e.r.* = 96.5:3.5, *e.e.* = 93%).

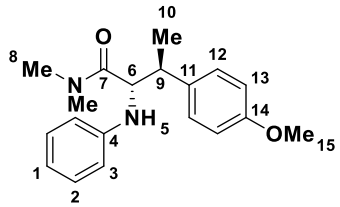
(2*S*,3*S*)-*N*,*N*-Dimethyl-3-(perfluorophenyl)-2-(phenylamino)butanamide, 337f



General procedure L: using **335** (17.8 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol), (*R*)-SEGPHOS (3.1 mg, 5.0 μmol) in 1,4-dioxane (0.2 mL) with 2,3,4,5,6-pentafluorostyrene (27 μL, 200 mol%) at 130 °C for 72 h. Purification of the residue by FCC (hexane/EtOAc 7:3) afforded the title compound as a pale-yellow oil (27.5 mg, 74% yield, 97% *e.e.*, *d.r.* = 2:1). $\mathbf{R_f}$ = 0.50 (hexane/EtOAc, 7:3); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = -95.25 (c = 0.13, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3323 (br), 3058 (w), 3031 (w), 2979 (w), 2940 (w), 2887 (w), 1643 (s), 1602 (s), 1521 (s); **^{1}H NMR** (500 MHz, $CDCl_3$, a = major, b = minor) δ 7.17 (dt, *J* = 8.5, 7.5 Hz, 0.8H, H^{2b}), 7.08 (dt, *J* = 8.5, 7.5 Hz, 1.2H. H^{2a}), 6.74 (tt, *J* = 7.5, 1.0 Hz, 0.4H, H^{1b}), 6.69 (tt, *J* = 7.5, 1.0 Hz, 0.6H, H^{1a}), 6.66 – 6.62 (m, 0.7H, H^{3b}), 6.57 – 6.51 (m, 1.2H, H^{3a}), 4.86 – 4.75 (m, 1H, H^6), 3.73 – 3.62 (m, 1H, H^9), 3.18 (s, 1.8H, H^{8a}), 2.99 (s, 1.8H, $H^{8a'}$), 2.96 (s, 1H, H^{8b}), 2.80 (s, 1H, $H^{8b'}$), 1.46 (d, *J* = 7.0 Hz, 1.2H, H^{10b}), 1.34 (d, *J* = 7.0 Hz, 1.9H, H^{10a}); **^{13}C NMR** (126 MHz, $CDCl_3$, a = major, b = minor) δ 172.6 (C^{7a}), 171.7 (C^{7b}), 147.2 (C^4), 146.9 (C^{11}), 129.6 (C^{2b}), 129.5 (C^{2a}), 119.3 (C^{1a}), 118.7 (C^{1b}), 114.6 (C^{3a}), 113.7 (C^{3b}), 56.4 (C^6), 37.7 (C^{8a}), 37.3 (C^{8b}), 36.0 ($C^{8a'}$), 35.9 ($C^{8b'}$), 35.1 (C^{9a}), 34.9 (C^{9b}), 15.8 (C^{10b}), 15.7 (C^{10a}); **^{19}F NMR** (471 MHz, $CDCl_3$, a = major, b = minor) δ -141.34 (dd, *J* = 22.5, 7.5 Hz, C^{12}-$\underline{F}^b$), -142.52 (dd, *J* = 22.5, 7.5 Hz, C^{12}-$\underline{F}^b$), -156.28 (t, *J* = 21.0 Hz, C^{14}-$\underline{F}^b$), -156.61 (t, *J* = 21.0 Hz, C^{14}-$\underline{F}^a$), -161.85 (td, *J* = 22.5, 7.5 Hz, C^{13}-$\underline{F}^b$), -162.45 (td, *J* = 22.5, 7.5 Hz, C^{13}-$\underline{F}^a$); ***m/z*** (ESI$^+$) calc. for $C_{18}H_{17}F_5N_2O$ = 372.13, found: 373.1333 $[M+H]^+$; **Chiral SFC:** (DAICEL

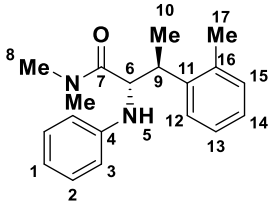
CHIRALPAK IE column (25 cm), CO_2:IPA 98:2, 3.5 mL/min, 140 bars, 40 °C). Retention times: 15.0 mins (minor), 15.8 mins (major), *e.r.* = 1.5:98.5, *e.e.* = 97%).

(2*S*,3*S*)-3-(4-Methoxyphenyl)-*N*,*N*-dimethyl-2-(phenylamino)butanamide, 337g



General procedure L: using **335** (17.8 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-SEGPHOS (3.1 mg, 5.0 µmol) in 1,4-dioxane (0.2 mL) with 4-methoxystyrene (27 µL, 200 mol%) at 130 °C for 72 h. Purification of the residue by FCC (hexane/EtOAc 7:3) afforded the title compound as a pale-yellow oil as a mixture of rotamers (18.4 mg, 60% yield, 95% *e.e.*, *d.r.* = 9:1). $\mathbf{R_f}$ = 0.23 (hexane/EtOAc, 7:3); $\mathbf{\nu_{max}/cm^{-1}}$**:** 3711 (w), 3681 (w), 3344 (br), 2966 (m), 2936 (m), 2873 (m), 2835 (m), 1636 (s), 1602 (s), 1583 (m), 1510 (s); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +2.93 (c = 0.26, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 8.5, 6.5 Hz, 0.3H, Ar-C<u>H</u>), 7.18 – 7.08 (m, 4.1H, Ar-C<u>H</u>), 6.98 (d, *J* = 8.0 Hz, 0.5H Ar-C<u>H</u>), 6.87 – 6.78 (m, 2.8H, Ar-C<u>H</u>), 6.72 – 6.68 (m, 1H, 0.8H, Ar-C<u>H</u>), 6.65 – 6.61 (m, 1H, 1.4H, Ar-C<u>H</u>), 6.57 – 6.52 (m, 0.7H, Ar-C<u>H</u>), 4.52 (d, *J* = 6.0 Hz, 0.7H, RNHC<u>H</u>), 4.46 (d, *J* = 6.0 Hz, 0.3H, RNHC<u>H</u>), 4.30 (d, *J* = 7.5 Hz, 0.14H, RNHC<u>H</u>), 4.23 (d, *J* = 7.5 Hz, 0.07H, RNHC<u>H</u>), 3.81 – 3.76 (m, 4.2H, RO-C<u>H</u>$_3$), 3.32 – 3.23 (m, 1H, H^9), 2.91 – 2.87 (m, 2.6H, RN(C<u>H</u>$_3$)$_2$), 2.75 – 2.73 (m, 0.3H, RN(C<u>H</u>$_3$)$_2$), 2.69 – 2.65 (m, 2.6H, RN(C<u>H</u>$_3$)$_2$) 2.64 – 2.62 (m, 0.4H, RN(C<u>H</u>$_3$)$_2$), 1.55 – 1.51 (m, 1H, R-C<u>H</u>$_3$), 1.44 – 1.39 (m, 0.4H, R-C<u>H</u>$_3$), 1.36 – 1.31 (m, 2.7H, R-C<u>H</u>$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.7 (C^7), 158.7 (Ar-<u>C</u>), 147.1 (Ar-<u>C</u>), 134.6 (Ar-<u>C</u>), 129.5 (Ar-<u>C</u>H), 129.4 (Ar-<u>C</u>H), 129.0 (Ar-<u>C</u>H), 128.9 (Ar-<u>C</u>H), 128.6 (Ar-<u>C</u>H), 128.5 (Ar-<u>C</u>H), 118.2 (Ar-<u>C</u>H), 114.2 (Ar-<u>C</u>H), 114.1 (Ar-<u>C</u>H), 114.0 (Ar-<u>C</u>H), 113.8 (Ar-<u>C</u>H), 113.7 (Ar-<u>C</u>H), 58.6 (RNH<u>C</u>H), 55.5 (RO-<u>C</u>H$_3$), 41.6 (C^9), 37.1 (RN(<u>C</u>H$_3$)$_2$), 35.8 (RN(<u>C</u>H$_3$)$_2$), 22.4 (R-<u>C</u>H$_3$), 16.8 (R-<u>C</u>H$_3$), 16.3 (R-<u>C</u>H$_3$); ***m/z*** (ESI$^+$) calc. for $C_{19}H_{24}N_2O_2$ = 312.18, found: 313.1912 [M+H]$^+$; **Chiral SFC:** (YMC Chiral ART Cellulose-SC column (25 cm), CO_2:IPA 85:15, 3 mL/min, 140 bars, 40 °C). Retention times: 5.6 mins (minor), 6.9 mins (major), *e.r.* = 2.5:97.5, *e.e.* = 95%),

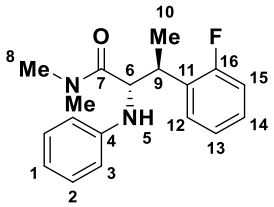
(2*S*,3*S*)-*N*,*N*-Dimethyl-2-(phenylamino)-3-(*o*-tolyl)butanamide, 337h



General procedure L: using **335** (17.8 mg, 0.10 mmol), [Ir(cod)$_2$]BARF (6.36 mg, 5.0 µmol), (*R*)-SEGPHOS (3.1 mg, 5.0 µmol) in 1,4-dioxane (0.2 mL) with 2-methylstyrene (26 µL, 200 mol%) at 130

°C for 72 h. Purification of the residue by FCC (hexane/EtOAc 7:3) afforded the title compound as a pale-yellow solid (22.0 mg, 74% yield, 96% *e.e.*, *d.r.* = 8:1). $\mathbf{R_f}$ = 0.36 (hexane/EtOAc, 7:3); **m.p.** = 134.5 – 137.0 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +19.4 (c = 0.25, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3681 (w), 3329 (br), 3052 (m), 3017 (m), 2967 (m), 2937 (m), 2873 (m), 2845 (m), 1635 (s), 1602 (s); **^{1}H NMR** (500 MHz, $CDCl_3$, a = major, b = minor) δ 7.22 – 7.09 (m, 6H, Ar-C<u>H</u>), 6.71 (t, *J* = 7.5 Hz, 1H, H^1), 6.66 – 6.63 (m, 1.9H, H^{3a}), 6.63 – 6.59 (m, 0.2H, H^{3b}), 4.77 – 4.37 (br. m, 2H, H^5, H^{6a}, H^{6b}), 3.63 (*pseudo*-p, *J* = 7.0 Hz, 1H, H^9), 2.86 (s, 2.8H, H^{8a}), 2.71 (s, 0.3H, H^{8b}), 2.62 (s, 0.3H, $H^{8b'}$), 2.56 (s, 2.8H, $H^{8a'}$), 2.44 (s, 2.8H, H^{17a}), 2.35 (s, 0.3H, H^{17b}), 1.41 (d, *J* = 7.0 Hz, 0.2H, H^{10b}), 1.34 (d, *J* = 7.0 Hz, 2.9H, H^{10a}); **^{13}C NMR** (126 MHz, $CDCl_3$, a = major, b = minor) δ 173.4 (C^{7b}), 171.8 (C^{7a}), 147.0 (C^4), 141.9 (C^{11b}), 140.9 (C^{11a}), 136.2 (C^{16b}), 136.1 (C^{16a}), 130.5 (C^{15}), 129.5 (C^2), 127.1 (Ar-<u>C</u>H), 126.7 (Ar-<u>C</u>H), 126.6 (Ar-<u>C</u>H), 126.5 (Ar-<u>C</u>H), 126.2 (Ar-<u>C</u>H), 126.1 (Ar-<u>C</u>H), 118.3 (C^{1a}), 118.2 (C^{1b}), 114.3 (C^{3a}), 114.0 (C^{3b}), 58.8 (C^{6b}), 56.5 (C^{6a}), 38.9 (C^{9b}), 37.4 (C^{9a}), 37.1 ($C^{8b'}$), 36.8 ($C^{8a'}$), 35.7 (C^8), 19.9 (C^{17a}), 19.8 (C^{17b}), 18.2 (C^{10b}), 15.9 (C^{10a}); ***m/z*** (ESI^+) calc. for $C_{19}H_{24}N_2O$ = 296.19, found: 297.1964 $[M+H]^+$; **Chiral SFC:** (DAICEL CHIRALCEL OD-H column (25 cm), CO_2:IPA 92:8, 2 mL/min, 140 bars, 40 °C). Retention times: 8.6 mins (major), 9.7 mins (minor), *e.r.* = 98:2, *e.e.* = 96%).

(2*S*,3*S*)-3-(2-Fluorophenyl)-*N*,*N*-dimethyl-2-(phenylamino)butanamide, 337i



General procedure L: using **335** (17.8 mg, 0.10 mmol), $[Ir(cod)_2]BARF$ (6.36 mg, 5.0 μmol), (*R*)-SEGPHOS (3.1 mg, 5.0 μmol) in 1,4-dioxane (0.2 mL) with 2-fluorostyrene (24 μL, 200 mol%) at 130 °C for 72 h. Purification of the residue by FCC (hexane/EtOAc 7:3) afforded the title compound as a pale-yellow solid (23.1 mg, 77% yield, 96% *e.e.*, *d.r.* = 6:1). $\mathbf{R_f}$ = 0.32 (hexane/EtOAc, 7:3); **m.p.** = 78.2 – 80.9 °C (hexane/EtOAc); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = -2.18 (c = 0.34, $CHCl_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$**:** 3681 (w), 3333 (br), 2973 (m), 2938 (m), 2874 (m), 2845 (m), 1638 (s), 1602 (s), 1584 (m); **^{1}H NMR** (500 MHz, $CDCl_3$, a = major, b = minor) δ 7.28 – 6.98 (m, 6H, Ar-C<u>H</u>), 6.73 – 6.61 (m, 2.8H, Ar-C<u>H</u>), 6.37 (d, *J* = 8.0 Hz, 0.3H, Ar-C<u>H</u>), 5.06 – 4.25 (br. m, 2H, H^5, H^6), 3.67 (*pseudo*-p, *J* = 7.0 Hz, 0.9H, H^{9a}), 3.46 (*pseudo*-p, *J* = 7.0 Hz, 0.2H, H^{9b}), 3.01 (s, 0.5H, H^{8b}), 2.88 (s, 2.5H, H^{8a}), 2.86 (s, 0.5H, $H^{8b'}$), 2.76 (s, 2.5H, $H^{8a'}$), 1.37 (d, *J* = 7.2 Hz, 3H, H^{10}); **^{13}C NMR** (126 MHz, $CDCl_3$, a = major, b = minor) δ 172.5 (C^{7b}), 171.7 (C^{7a}), 161.25 (d, *J* = 244.0 Hz, C^{16}), 148.5 (C^{4b}), 147.1 (C^{4a}), 130.1 (Ar-<u>C</u>H), 129.53 – 129.18 (m, Ar-<u>C</u>H), 128.5 (d, *J* = 8.5 Hz, Ar-<u>C</u>H), 124.6 (Ar-<u>C</u>H), 124.3 (d, *J* = 3.5 Hz, Ar-<u>C</u>H), 118.2 (Ar-<u>C</u>H), 115.4 (Ar-<u>C</u>H), 115.3 (Ar-<u>C</u>H), 115.1 (Ar-<u>C</u>H), 114.3 (Ar-<u>C</u>H), 114.1 (Ar-<u>C</u>H), 58.5 (C^{6b}), 56.6 (C^{6a}), 37.0 ($C^{8a'}$), 36.5 (C^{9b}), 35.9 (C^{8b}), 35.7 (C^{8a}), 35.6 (C^{9a}), 15.2 (C^{10a}), 14.3 (C^{10b}); **^{19}F NMR** (471 MHz, $CDCl_3$) δ -117.92 (dt, *J* = 12.0, 6.5 Hz), -118.48 (dt, *J* = 12.0, 6.5 Hz); ***m/z*** (ESI^+) calc. for $C_{18}H_{21}FN_2O$ =

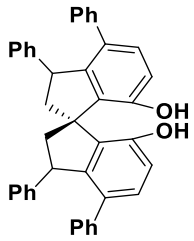
300.16, found: 301.1713 $[M+H]^+$; **Chiral SFC:** (YMC Chiral ART Cellulose-SC column (25 cm), CO_2:IPA 90:10, 2 mL/min, 140 bars, 40 °C). Retention times: 7.6 mins (minor), 9.6 mins (major), *e.r.* = 2:98, *e.e.* = 96%).

7.7 Geometry-Optimised Energies and Coordinates

Table S2: *Calculated d(O¹-O²) and θ(Ph-C-Ph) values for structures **A**–**M**.*

		DFT (B3LYP, 3-21G)					
Label	**Description**	**d(O¹-O²) /Å**	**θ(Ph-C-Ph) /°**	***e.e.* /%**	**Normalised *e.e.***	**Mean *e.e.***	74.84615
A	SPINOL	4.39423	114.680	69	0.525	**S.D.**	10.47096
B	C4-Ph	4.96701	112.060	74	0.650		
C	C4-Mes	4.93861	108.645	88	1.000		
D	C4-naphthyl	4.89783	110.372	79	0.775		
E	C4-3,4,5-F	4.94142	112.026	77	0.725		
F	C4-3,5-CF_3	4.93274	112.048	86	0.950		
G	C4-3,5-OMe	4.94608	112.054	86	0.950		
H	C5-Ph	3.90503	115.727	68	0.500		
I	C-5-4-F	3.93639	115.662	67	0.475		
J	C4-Br & C5-naphthyl	3.75985	116.387	52	0.100		
K	C4 & C5-Ph	3.69887	116.705	64	0.400		
L	Cyclohexyl	5.08645	111.256	81	0.825		
M	C4-Mes, cyclohexyl	5.03225	108.054	82	0.850		

DFT geometry optimisation studies were performed using Gaussian 09 and performed using the B3LYP functional and the 3-21G basis set. Energies are reported in a.u.

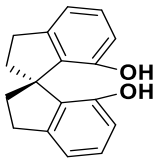


$E_{(RB3LYP)}$ = -1722.59875975

C	1.78838100	2.37845800	2.21786600
C	3.08049400	2.27456200	1.70191400
C	3.36325500	1.44340700	0.60888200
C	2.30650200	0.69076100	0.07045600
C	1.01013100	0.80617300	0.57460900
C	0.73806200	1.65835900	1.64589900
C	2.36459100	-0.32377000	-1.07877800
C	0.91715900	-0.93992800	-1.08455600
C	-0.00001200	0.00007900	-0.22199200
C	-0.91714200	0.94013000	-1.08454100
C	-2.36458900	0.32399000	-1.07882700
C	-2.30654300	-0.69064100	0.07032900
C	-1.01017700	-0.80607700	0.57450800
C	-0.73807700	-1.65838600	1.64568900
C	-1.78835800	-2.37861900	2.21754800
C	-3.36325300	-1.44343400	0.60863500
C	-3.08045100	-2.27473500	1.70155300
H	-3.88077400	-2.86263700	2.13561300
O	0.57821300	-1.75675800	2.09192400

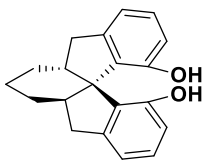
H	0.62686300	-2.37813900	2.86365000
O	-0.57820900	1.75668900	2.09220100
H	-0.62682500	2.37799400	2.86399100
H	-0.52486000	1.05668100	-2.09837200
H	0.52490800	-1.05646300	-2.09840100
H	0.95784300	-1.92126300	-0.61002100
H	-0.95782700	1.92145400	-0.60998300
H	3.88082200	2.86237600	2.13607900
C	3.42922900	-1.39581500	-0.86723600
C	4.42096000	-1.62849000	-1.82503200
C	3.40611200	-2.18626100	0.29329500
C	5.37796400	-2.62860600	-1.63353400
H	4.45525700	-1.01395600	-2.71794600
C	4.36104600	-3.18437800	0.48418800
H	2.62525200	-2.01622300	1.02689800
C	5.35129000	-3.40927800	-0.47778300
H	6.14302000	-2.79311100	-2.38393000
H	4.33504500	-3.79029900	1.38360300
C	-3.42916100	1.39610800	-0.86726100
C	-4.42074600	1.62901600	-1.82515700
C	-3.40609900	2.18641000	0.29336700
C	-5.37767700	2.62919400	-1.63364200
H	-4.45497800	1.01461600	-2.71816900
C	-4.36096400	3.18459100	0.48427600
H	-2.62533700	2.01620600	1.02703700
C	-5.35107100	3.40971000	-0.47778300
H	-6.14261800	2.79388300	-2.38411500
H	-4.33501000	3.79040000	1.38376900
H	2.56675600	0.19491800	-2.02365500
H	-2.56674500	-0.19461300	-2.02375500
H	-6.09256800	4.18603400	-0.32628500
H	6.09283900	-4.18555400	-0.32630000
H	1.59758100	3.03868300	3.05840200
H	-1.59754000	-3.03896400	3.05801600
C	-4.74633800	-1.41184300	0.04654200
C	-5.81284500	-0.89959000	0.79866400
C	-5.00667900	-1.94379400	-1.22550600
C	-7.11079400	-0.90880300	0.28566400
H	-5.61312500	-0.47544300	1.77550100
C	-6.30490300	-1.95349100	-1.73805700
H	-4.18990000	-2.36427200	-1.80134900
C	-7.36049500	-1.43478700	-0.98384900
H	-7.92510900	-0.50001700	0.87304700
H	-6.49433100	-2.37285700	-2.71993200
H	-8.36881100	-1.44212500	-1.38172300
C	4.74628200	1.41157700	0.04670700
C	5.00645200	1.94345300	-1.22542800
C	5.81285600	0.89925900	0.79866800
C	6.30458800	1.95303100	-1.73819000
H	4.18957600	2.36392800	-1.80116600
C	7.11072400	0.90833800	0.28544100
H	5.61327800	0.47514500	1.77554700
C	7.36025800	1.43425800	-0.98412700
H	6.49390000	2.37235200	-2.72010700
H	7.92510200	0.49949800	0.87269700

H	8.36851000	1.44148900	-1.38216600



$E_{(RB3LYP)}$ = -803.46442950

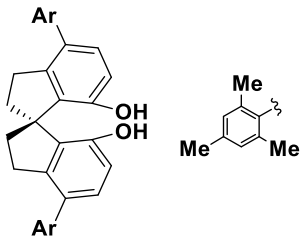
C	2.57938900	-1.75649600	-1.04856200
C	3.68756900	-0.90890600	-1.01909500
C	3.60524500	0.34000200	-0.39900600
C	2.38899200	0.72547000	0.16389800
C	1.26351700	-0.10591300	0.11724200
C	1.36429300	-1.37041100	-0.46886200
H	2.65991100	-2.73094900	-1.52121500
H	4.61620000	-1.23029600	-1.47665100
H	4.46667100	0.99659100	-0.36097000
C	2.07408600	2.00893700	0.92073100
H	2.47776700	1.94490600	1.94017400
H	2.49870300	2.89462100	0.43729600
C	0.51706900	2.03452400	0.93363500
H	0.10320200	2.51135800	1.82563000
H	0.16449400	2.54901500	0.03896800
C	0.06374700	0.53512800	0.82422300
C	-0.20091800	-0.13816300	2.22472500
H	-0.56998900	0.63252400	2.91113800
H	0.70827200	-0.58138600	2.63676000
C	-1.32974200	-1.18247500	1.97815500
H	-0.89245100	-2.13310000	1.65610400
H	-1.96156500	-1.33942900	2.85751100
C	-2.08216600	-0.59436300	0.79440800
C	-1.27642200	0.33008400	0.11936800
C	-1.74388200	0.92829700	-1.05303500
C	-3.02937400	0.61337200	-1.51193600
C	-3.35849300	-0.91804100	0.33796000
C	-3.82969500	-0.29847900	-0.82263900
H	-3.40644900	1.08780600	-2.41317600
H	-3.97328600	-1.63447600	0.87031700
H	-4.82271300	-0.52300400	-1.19512000
O	-0.91675900	1.82890400	-1.71966400
H	-1.37793300	2.17099500	-2.52888200
O	0.25491100	-2.20814500	-0.43956700
H	0.44465800	-3.03664600	-0.95128800



$E_{(RB3LYP)}$ = -919.57178789

C	2.76442800	-1.81971800	1.39118500
C	3.64736200	-1.76060100	0.31332400

C	3.34016800	-0.98088200	-0.80253500
C	2.14068900	-0.26927400	-0.81263400
C	1.24215700	-0.32102500	0.26158000
C	1.56010900	-1.10555000	1.37534500
H	3.01400100	-2.42336000	2.25892200
H	4.57487200	-2.32031500	0.35142800
H	4.02121400	-0.92577200	-1.64383000
C	1.60135500	0.60630100	-1.92612600
H	2.37157000	1.25394300	-2.35923800
H	1.16635900	-0.02848700	-2.70026600
C	0.47547100	1.42721600	-1.23057800
H	-0.36023900	1.61665500	-1.90992100
C	-0.00007900	0.54709200	-0.00005300
C	-0.47577400	1.42766900	1.23006700
H	0.35981300	1.61726000	1.90949900
C	-1.60188300	0.60712700	1.92571200
H	-1.16711600	-0.02735500	2.70023200
H	-2.37214900	1.25498700	2.35840600
C	-2.14098500	-0.26898100	0.81253100
C	-1.24215500	-0.32131000	-0.26142100
C	-1.55966700	-1.10669100	-1.37470100
C	-2.76390600	-1.82100800	-1.39038300
C	-3.34036800	-0.98072800	0.80259500
C	-3.64716400	-1.76124600	-0.31282900
H	-3.01313500	-2.42527200	-2.25779000
H	-4.02163300	-0.92514100	1.64368100
H	-4.57459400	-2.32110000	-0.35080700
O	-0.67777600	-1.15303400	-2.45064400
H	-1.02750600	-1.77235500	-3.14180000
O	0.67858700	-1.15121300	2.45162600
H	1.02899100	-1.76943500	3.14343100
C	1.06295200	2.75433000	-0.70510800
H	1.86878500	2.50468900	-0.00318100
H	1.51709700	3.30688900	-1.53672400
C	-0.00033100	3.63282200	-0.00100400
H	-0.49405100	4.28177700	-0.73457800
H	0.49301300	4.28298400	0.73175000
C	-1.06326500	2.75463900	0.70412900
H	-1.86942100	2.50467400	0.00268700
H	-1.51703200	3.30762100	1.53567300

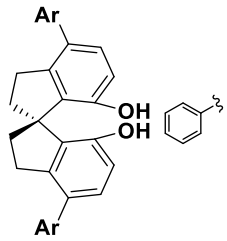


$E_{(RB3LYP)}$ = -1497.66152962

C	1.47197200	-2.53129900	-1.06729800
C	2.79333500	-2.08240600	-1.05724200
C	3.18677900	-1.02837400	-0.22289100

C	2.21710300	-0.45687400	0.61070500
C	0.88315100	-0.87571000	0.58001500
C	0.50254100	-1.92063700	-0.26577000
H	1.18929000	-3.35062700	-1.72168000
H	3.52407600	-2.54375400	-1.71179200
C	2.41633200	0.68989200	1.58876900
H	3.25777800	0.50308500	2.26300500
H	2.59619600	1.61482700	1.03859400
C	1.05605300	0.76795900	2.34343600
H	0.73915500	1.79697200	2.52515300
C	0.00001100	0.00004400	1.47302200
C	-1.05595900	-0.76793300	2.34346900
H	-0.73908600	-1.79698900	2.52498900
C	-2.41635300	-0.68968200	1.58901200
H	-2.59653500	-1.61463600	1.03899100
H	-3.25763700	-0.50263800	2.26339600
C	-2.21713200	0.45698500	0.61083000
C	-0.88317200	0.87580200	0.58006400
C	-0.50259500	1.92069200	-0.26577400
C	-1.47206800	2.53139300	-1.06723000
C	-3.18683200	1.02846100	-0.22276000
C	-2.79345000	2.08258300	-1.05703100
H	-1.18940900	3.35072000	-1.72162300
H	-3.52422800	2.54395700	-1.71152200
O	0.83547000	2.32364900	-0.28797000
H	0.94057900	3.09984800	-0.89644900
O	-0.83550500	-2.32368800	-0.28780300
H	-0.94059000	-3.10005000	-0.89607900
H	-1.13986400	-0.24757500	3.30410000
H	1.14012500	0.24746100	3.30398000
C	4.57093900	-0.46386800	-0.27740700
C	4.82386400	0.63834000	-1.12054500
C	5.60507900	-0.99981000	0.51226400
C	6.11153200	1.18302800	-1.16277600
C	6.88258900	-0.43125300	0.44496900
C	7.15233600	0.65846700	-0.38826500
H	6.30546700	2.03280300	-1.81058300
H	7.67812100	-0.84382200	1.05800200
C	-4.57093800	0.46383300	-0.27736400
C	-5.60519600	0.99967200	0.51226600
C	-4.82370200	-0.63836900	-1.12052700
C	-6.88259700	0.43096400	0.44495500
C	-6.11133100	-1.18323500	-1.16277500
C	-7.15219100	-0.65882000	-0.38831100
H	-7.67819700	0.84341400	1.05798800
H	-6.30514800	-2.03302200	-1.81059600
C	3.71521800	1.21634000	-1.98780100
H	3.42575600	0.49839900	-2.76515800
H	2.81574400	1.43647000	-1.40235200
H	4.05864100	2.13282800	-2.47936400
C	5.33546100	-2.17647600	1.43555400
H	4.53373500	-1.93862500	2.14374700
H	5.01526700	-3.05613800	0.86594900
H	6.23558500	-2.43648700	2.00093500
C	8.55058700	1.24754800	-0.47196100

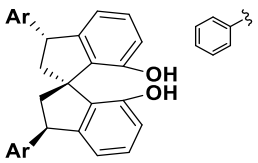
H	9.12451400	1.02481100	0.43326300
H	9.09556800	0.83012200	-1.32874200
H	8.51146500	2.33507600	-0.59640700
C	-5.33575500	2.17652400	1.43537100
H	-4.53314500	1.93939500	2.14278000
H	-5.01692900	3.05650700	0.86546200
H	-6.23559200	2.43573000	2.00158100
C	-3.71500600	-1.21618400	-1.98783800
H	-3.42570500	-0.49819600	-2.76520300
H	-2.81544600	-1.43613700	-1.40245500
H	-4.05829100	-2.13273700	-2.47937500
C	-8.55051900	-1.24769500	-0.47212100
H	-9.12160600	-1.03233300	0.43670000
H	-9.09841600	-0.82360900	-1.32376800
H	-8.51147100	-2.33415500	-0.60536000



$E_{(RB3LYP)}$ = -1263.03571092

C	1.87947100	-2.47526300	-1.19841900
C	3.15569900	-1.92928300	-1.09545100
C	3.39531100	-0.78390400	-0.31959500
C	2.30088900	-0.21578300	0.35436000
C	1.01557800	-0.76519400	0.26145000
C	0.79774200	-1.89940100	-0.52427400
H	1.72189000	-3.35813600	-1.81078100
H	3.97809300	-2.38323000	-1.63608300
C	2.29690200	1.00944200	1.25737100
H	3.15373400	1.02699300	1.93638200
H	2.29610300	1.90840000	0.63821400
C	0.93476700	0.90561600	1.99950500
H	0.48077900	1.88226500	2.17917900
C	0.00003500	0.00043600	1.11831600
C	-0.93451500	-0.90449200	1.99992700
H	-0.48037700	-1.88097500	2.18013300
C	-2.29669100	-1.00880300	1.25791700
H	-2.29579300	-1.90794000	0.63903400
H	-3.15346000	-1.02625400	1.93700500
C	-2.30091300	0.21617500	0.35455000
C	-1.01570100	0.76576400	0.26143000
C	-0.79807700	1.89989200	-0.52446200
C	-1.87993600	2.47551400	-1.19859700
C	-3.39544300	0.78399200	-0.31949300
C	-3.15606300	1.92930000	-1.09550900
H	-1.72256600	3.35835300	-1.81106100
H	-3.97856200	2.38302300	-1.63617400
O	0.48460300	2.43285800	-0.59920700

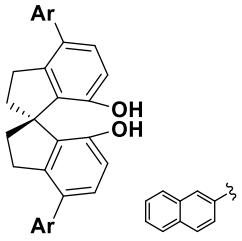
H	0.48579200	3.21526500	-1.20887800
O	-0.48502300	-2.43216600	-0.59898200
H	-0.48639600	-3.21443000	-1.20883400
H	-1.08205300	-0.39653900	2.95963700
H	1.08224300	0.39816100	2.95947500
C	4.77592600	-0.23250400	-0.21962400
C	5.03952300	1.12509100	-0.46703000
C	5.85307300	-1.07776100	0.09781400
C	6.34129700	1.62230700	-0.39654400
C	7.15495000	-0.58036500	0.16527700
C	7.40388800	0.77197900	-0.08075100
C	-4.77589500	0.23220400	-0.21953300
C	-5.85340400	1.07707400	0.09767300
C	-5.03892900	-1.12553300	-0.46678200
C	-7.15509200	0.57916200	0.16505700
C	-6.34050800	-1.62326500	-0.39637000
C	-7.40347100	-0.77331400	-0.08081300
H	-4.22000600	-1.78294200	-0.73171300
H	-8.41421800	-1.16092200	-0.02638800
H	-5.65857200	2.12242500	0.30871700
H	4.22089100	1.78279700	-0.73211600
H	5.65779100	-2.12300100	0.30898300
H	8.41477900	1.15920300	-0.02627500
H	-6.52686300	-2.67258400	-0.59595500
H	-7.97374800	1.24383200	0.41722500
H	7.97331500	-1.24532300	0.41762800
H	6.52809600	2.67152300	-0.59625600



$E_{(RB3LYP)}$ = -1263.03733903

C	0.77319100	-2.87776200	-2.05557500
C	2.05837400	-3.19567500	-1.60625000
C	2.63560600	-2.49053500	-0.54910800
C	1.90575900	-1.45610000	0.03834500
C	0.63081700	-1.12126000	-0.41499100
C	0.04748300	-1.84343600	-1.45816600
H	0.33478400	-3.44074000	-2.87402900
C	2.31861000	-0.58349600	1.22576400
C	1.20996500	0.52896700	1.24892300
C	-0.00003100	-0.00014300	0.39292400
C	-1.21016400	-0.52905300	1.24879600
C	-2.31858000	0.58368100	1.22558700
C	-1.90560700	1.45599700	0.03800400
C	-0.63072600	1.12087400	-0.41528700
C	-0.04735500	1.84270700	-1.45868100
C	-0.77294400	2.87697500	-2.05631900
C	-2.63534800	2.49038300	-0.54968200
C	-2.05806900	3.19518000	-1.60702000
H	-0.33449300	3.43970700	-2.87492000

H	-2.60384400	3.99955500	-2.08649700
O	1.24656800	1.50235700	-1.85186600
H	1.52290000	2.06364100	-2.62166400
O	-1.24646400	-1.50330800	-1.85139600
H	-1.52299700	-2.06519600	-2.62067600
H	-0.90066400	-0.78130000	2.26648600
H	0.90031900	0.78109500	2.26659900
H	-3.63221500	2.72830200	-0.19951200
H	3.63252000	-2.72823700	-0.19892200
H	1.60932100	1.42396700	0.76989800
H	-1.60968400	-1.42390100	0.76964300
H	2.60424500	-4.00009300	-2.08554600
C	3.72397300	-0.01752500	1.07673100
C	4.71239000	-0.27378400	2.03304600
C	4.04547100	0.77298100	-0.03935300
C	6.00077000	0.25003300	1.88664100
H	4.47269200	-0.88354400	2.89842700
C	5.32943100	1.29557800	-0.18440100
H	3.27417500	0.97201600	-0.77607000
C	6.31234200	1.03603000	0.77723700
H	6.75564600	0.04435400	2.63731900
H	5.56877100	1.90532300	-1.04883400
C	-3.72405500	0.01796500	1.07671300
C	-4.71228800	0.27417300	2.03322700
C	-4.04582700	-0.77227600	-0.03948500
C	-6.00075500	-0.24945800	1.88691300
H	-4.47238700	0.88374900	2.89868000
C	-5.32987600	-1.29466700	-0.18445300
H	-3.27463500	-0.97133300	-0.77630900
C	-6.31260000	-1.03518500	0.77739500
H	-6.75548800	-0.04384400	2.63775300
H	-5.56943600	-1.90419400	-1.04897900
H	2.27395500	-1.18475500	2.14359500
H	-2.27371400	1.18500700	2.14333400
H	-7.31035800	-1.44275400	0.66084700
H	7.31002300	1.44376800	0.66062300

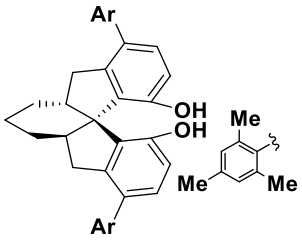


$E_{(RB3LYP)}$ = -1568.62686337

C	-2.09761800	2.91348700	-1.24561400
C	-3.35815500	2.36746200	-1.00984300
C	-3.53817500	1.34855700	-0.06309100
C	-2.41291000	0.91132100	0.65042100
C	-1.14030100	1.43214300	0.39297500
C	-0.97526500	2.44207200	-0.55714500

H	-1.98454000	3.70363300	-1.98184200
H	-4.21358500	2.72302700	-1.57217800
C	-2.36479000	-0.14518000	1.74304000
H	-3.12628500	0.03464200	2.50818600
H	-2.51937200	-1.13286800	1.30660100
C	-0.91744500	-0.02238600	2.30463700
H	-0.47702400	-0.99288200	2.54320400
C	-0.06283800	0.73446200	1.22404100
C	1.01392800	1.67800100	1.87217600
H	0.63890400	2.69967600	1.95551300
C	2.29236800	1.58927500	0.98892400
H	2.29995200	2.41780400	0.27743900
H	3.21568600	1.59946100	1.57462400
C	2.10901700	0.28684500	0.22639200
C	0.79168900	-0.17486900	0.33440100
C	0.40596900	-1.33632100	-0.33810100
C	1.35892800	-2.03903000	-1.08321600
C	3.06891100	-0.40101100	-0.52918000
C	2.67190800	-1.58117700	-1.17528500
H	1.07058900	-2.94745800	-1.60352400
H	3.39562700	-2.13419100	-1.76254100
O	-0.91808200	-1.76357600	-0.24299500
H	-1.02566800	-2.63340900	-0.70708400
O	0.30105500	2.94978200	-0.77841400
H	0.26674300	3.64344900	-1.48657100
H	1.23643600	1.29598900	2.87452300
H	-0.92893000	0.59290900	3.21120500
C	4.46670200	0.11176300	-0.66983200
C	5.56677100	-0.56539800	-0.04461300
C	4.70657600	1.24532300	-1.42442000
C	5.38993400	-1.71858900	0.77148600
C	6.89690200	-0.05576200	-0.23339000
C	6.01777700	1.74820400	-1.60128400
H	3.87091900	1.74738800	-1.89788400
C	6.46836400	-2.34351400	1.35587300
H	4.38497900	-2.09035600	0.92425900
C	7.98797900	-0.72963300	0.38347400
C	7.09042500	1.11017600	-1.02362500
H	6.16967000	2.63668500	-2.20338300
C	7.78144500	-1.84799200	1.15754100
H	6.31680700	-3.21907200	1.97671000
H	8.98935900	-0.33997000	0.23264100
H	8.09885900	1.48636400	-1.15969900
H	8.62018700	-2.35233900	1.62336800
C	-4.89561000	0.76284800	0.14923900
C	-5.18432900	-0.58133100	-0.26685100
C	-5.90090500	1.53523100	0.70159200
C	-4.20472000	-1.42409400	-0.86805200
C	-6.51575400	-1.09143900	-0.09157700
C	-7.20967700	1.02486000	0.87758400
H	-5.67450800	2.54880000	1.01165100
C	-4.53029300	-2.70079200	-1.26984400
H	-3.19196500	-1.05669000	-0.98044000
C	-6.81125100	-2.41667000	-0.51788200
C	-7.51130800	-0.25965400	0.49134900

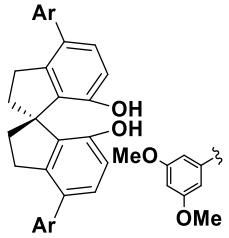
H	-7.97130100	1.65625600	1.32057900
C	-5.84333200	-3.20434500	-1.09599500
H	-3.77902200	-3.33265400	-1.73146400
H	-7.81990500	-2.79219700	-0.38041300
H	-8.51226600	-0.65759200	0.62086700
H	-6.07961900	-4.21109800	-1.42090200



$E_{(RB3LYP)}$ = -1613.76681106

C	1.44573900	1.34185900	-2.56172300
C	2.76397200	1.35787400	-2.10662700
C	3.16050800	0.54204100	-1.03997500
C	2.19891900	-0.29837900	-0.46605100
C	0.86545400	-0.29891100	-0.89191200
C	0.48320600	0.53268300	-1.94930200
H	1.15686800	1.98321100	-3.38926900
H	3.48791400	2.01725400	-2.57172800
C	2.41016700	-1.25374500	0.69185500
H	3.28228400	-1.89650400	0.53112900
H	2.54482900	-0.69078900	1.61609500
C	1.08770000	-2.07475600	0.74450900
H	0.78013900	-2.26710200	1.77614700
C	-0.00000700	-1.20097900	0.00002300
C	-1.08769400	-2.07477100	-0.74446900
H	-0.78014600	-2.26705900	-1.77612100
C	-2.41019800	-1.25380500	-0.69177100
H	-2.54494300	-0.69089400	-1.61602500
H	-3.28227200	-1.89660500	-0.53097500
C	-2.19894100	-0.29840200	0.46609900
C	-0.86547400	-0.29891800	0.89195500
C	-0.48322800	0.53269000	1.94933300
C	-1.44576200	1.34187700	2.56174000
C	-3.16052700	0.54203700	1.04000000
C	-2.76398900	1.35789800	2.10663100
H	-1.15689000	1.98324000	3.38927700
H	-3.48793100	2.01729200	2.57171200
O	0.85020800	0.54533400	2.36813300
H	0.94753800	1.14483500	3.15233700
O	-0.85022900	0.54531100	-2.36811100
H	-0.94754800	1.14474800	-3.15236600
C	1.27532200	-3.40225200	-0.02177900
H	1.54218900	-3.15291200	-1.05715800
H	2.12063900	-3.95410700	0.40681400
C	0.00003800	-4.28011800	0.00000400
H	0.00953000	-4.92967900	0.88372600
H	-0.00943100	-4.92971200	-0.88369500

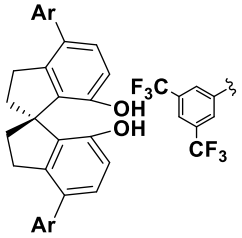
C	-1.27528100	-3.40229800	0.02176600
H	-1.54219000	-3.15300800	1.05714600
H	-2.12056200	-3.95417300	-0.40687200
C	-4.54073900	0.61697200	0.46832100
C	-5.58432700	-0.16949000	0.99052100
C	-4.78035600	1.47354000	-0.62647100
C	-6.85839000	-0.08474400	0.41652000
C	-6.06501500	1.53349700	-1.17647700
C	-7.11533100	0.76290800	-0.66510400
H	-7.66132400	-0.69534600	0.81819600
H	-6.24900900	2.19196600	-2.02026800
C	4.54072800	0.61696800	-0.46831400
C	4.78036700	1.47353100	0.62647100
C	5.58430500	-0.16950400	-0.99052900
C	6.06504300	1.53348800	1.17645200
C	6.85837600	-0.08476100	-0.41655700
C	7.11534500	0.76290400	0.66505800
H	6.24905500	2.19194200	2.02024900
H	7.66129200	-0.69539100	-0.81823300
C	8.50991900	0.86567100	1.25984200
H	9.09463500	-0.03466900	1.04552300
H	9.04744200	1.72565200	0.83934100
H	8.46453600	0.99666700	2.34638100
C	5.32775000	-1.10858800	-2.15763100
H	4.52579400	-1.81583300	-1.91764200
H	5.01387700	-0.55113300	-3.04738400
H	6.23176700	-1.67451700	-2.40252600
C	3.65959900	2.33258100	1.19288000
H	3.33966000	3.07868600	0.45536000
H	2.77869500	1.73215100	1.44628500
H	4.00377200	2.86107100	2.08826400
C	-5.32779200	-1.10857600	2.15762400
H	-4.52607000	-1.81604900	1.91750300
H	-5.01358700	-0.55117200	3.04728600
H	-6.23190300	-1.67426900	2.40271800
C	-3.65957100	2.33258800	-1.19284800
H	-3.33959300	3.07864100	-0.45529300
H	-2.77869200	1.73213700	-1.44629500
H	-4.00373800	2.86113200	-2.08820200
C	-8.50985400	0.86565100	-1.26001400
H	-9.04656700	1.72703900	-0.84137000
H	-8.46442400	0.99422600	-2.34684800
H	-9.09536200	-0.03369000	-1.04369800



$E_{(RB3LYP)}$ = -1718.61459365

C	-1.73111500	2.57232400	-1.20009500
C	-3.03712900	2.10274000	-1.09519900
C	-3.34426000	0.97694200	-0.31467900
C	-2.28579500	0.34720600	0.36188300
C	-0.97075400	0.82105200	0.26792100
C	-0.68572700	1.93729100	-0.52184200
H	-1.52164300	3.44182300	-1.81602600
H	-3.83210700	2.60241300	-1.63616700
C	-2.35139200	-0.87499600	1.26650400
H	-3.20681000	-0.84304700	1.94653200
H	-2.40541700	-1.77202900	0.64713100
C	-0.98421600	-0.85124900	2.00601100
H	-0.58739000	-1.85297900	2.18316500
C	0.00000500	0.00013700	1.12469500
C	0.98422700	0.85165400	2.00588100
H	0.58741200	1.85341500	2.18288700
C	2.35142500	0.87525600	1.26640600
H	2.40549300	1.77218400	0.64688900
H	3.20682200	0.84337200	1.94645900
C	2.28579800	-0.34707500	0.36195600
C	0.97075600	-0.82093400	0.26809100
C	0.68569100	-1.93731400	-0.52144800
C	1.73104200	-2.57241000	-1.19970300
C	3.34424100	-0.97693500	-0.31452900
C	3.03706500	-2.10282600	-1.09489800
H	1.52154100	-3.44196600	-1.81554500
H	3.83202100	-2.60257700	-1.63582700
O	-0.62643800	-2.39236900	-0.59520300
H	-0.67815400	-3.16811400	-1.21104300
O	0.62637300	2.39241700	-0.59565300
H	0.67803900	3.16808500	-1.21159500
H	1.09993300	0.33821800	2.96713500
H	-1.09993600	-0.33765100	2.96717200
C	-4.75654300	0.51200300	-0.21264300
C	-5.08897300	-0.83096100	-0.42487400
C	-5.77048400	1.43521900	0.07236400
C	-6.42073700	-1.24533300	-0.34795700
C	-7.10197100	1.01895900	0.14419000
C	-7.43364800	-0.32363500	-0.06389100
C	4.75653700	-0.51203100	-0.21255900
C	5.77047600	-1.43529300	0.07230700
C	5.08898900	0.83094200	-0.42470200
C	7.10197800	-1.01907200	0.14408300
C	6.42076700	1.24527500	-0.34783600
C	7.43367500	0.32353100	-0.06390800
H	4.33475300	1.56477900	-0.66759300
H	8.46137900	0.64609200	-0.00489200
H	5.54299400	-2.47433700	0.26511100
H	-4.33473700	-1.56476200	-0.66787100
H	-5.54301200	2.47425200	0.26523400
H	-8.46134100	-0.64622400	-0.00484100
O	8.02775400	-2.01163700	0.43672000
O	6.64373300	2.59664100	-0.57904700
O	-6.64368500	-2.59668500	-0.57926300
O	-8.02775000	2.01147800	0.43697900

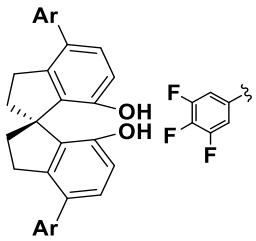
C	-8.01453300	-3.08670200	-0.53146100
H	-8.64673600	-2.60182700	-1.28603600
H	-7.94096200	-4.15299800	-0.74775800
H	-8.46403300	-2.94402500	0.45935700
C	-9.43102100	1.63564000	0.54359000
H	-9.95433200	2.56293100	0.77892700
H	-9.81598200	1.22635200	-0.39900700
H	-9.59746300	0.90645700	1.34653400
C	9.43102900	-1.63581900	0.54333100
H	9.95433700	-2.56313300	0.77858200
H	9.81597300	-1.22645800	-0.39924200
H	9.59749400	-0.90670100	1.34632900
C	8.01460200	3.08660800	-0.53134300
H	8.46418400	2.94387100	0.45943000
H	8.64672300	2.60174500	-1.28599400
H	7.94104900	4.15291600	-0.74758500



$E_{(RB3LYP)}$ = -2603.88825270

C	-1.76095500	-2.55727900	1.19663700
C	-3.06166900	-2.07784900	1.08703300
C	-3.35496600	-0.94733100	0.30647400
C	-2.28941300	-0.32223000	-0.36453700
C	-0.98032500	-0.80917400	-0.26690800
C	-0.70775100	-1.92957000	0.52241400
H	-1.56158100	-3.42773900	1.81368400
H	-3.85953200	-2.57193300	1.62930700
C	-2.33966100	0.90297600	-1.26680300
H	-3.19226600	0.88494700	-1.95127500
H	-2.37959500	1.80021400	-0.64566000
C	-0.97245600	0.86374100	-2.00527800
H	-0.56509500	1.86110200	-2.18152500
C	0.00000300	-0.00002200	-1.12351300
C	0.97247100	-0.86380100	-2.00525400
H	0.56511900	-1.86117500	-2.18144600
C	2.33967700	-0.90300300	-1.26677800
H	2.37964200	-1.80024500	-0.64564100
H	3.19228300	-0.88494600	-1.95125000
C	2.28940600	0.32219900	-0.36451300
C	0.98031400	0.80913500	-0.26689500
C	0.70773000	1.92952100	0.52243800
C	1.76092500	2.55722200	1.19668200
C	3.35495300	0.94729400	0.30651400
C	3.06164300	2.07779900	1.08708800
H	1.56153800	3.42766800	1.81374400
H	3.85949400	2.57187500	1.62938600
O	-0.59812900	2.39272400	0.60014600

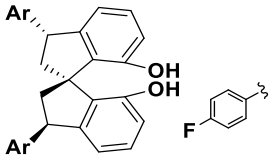
H	-0.64354700	3.18427800	1.19637400
O	0.59811100	-2.39276500	0.60013600
H	0.64352900	-3.18431600	1.19636800
H	1.09426500	-0.35281700	-2.96663200
H	-1.09426400	0.35270600	-2.96662900
C	-4.76003800	-0.47512200	0.19542300
C	-5.09599000	0.87909800	0.34321600
C	-5.79516700	-1.38948100	-0.05386500
C	-6.41935500	1.29546500	0.23464800
C	-7.11462200	-0.95762200	-0.15363900
C	-7.44000000	0.38675800	-0.02081300
C	4.76003000	0.47510100	0.19545700
C	5.79513700	1.38948000	-0.05384900
C	5.09601200	-0.87911300	0.34324000
C	7.11460100	0.95764900	-0.15364200
C	6.41938300	-1.29545100	0.23465500
C	7.44000800	-0.38672300	-0.02081900
H	4.32734900	-1.61468700	0.53313500
H	8.46003600	-0.72266000	-0.14439200
H	5.56897000	2.43568600	-0.21293000
H	-4.32730700	1.61465400	0.53310400
H	-5.56902300	-2.43569200	-0.21294700
H	-8.46002300	0.72271400	-0.14437200
C	8.19838300	1.95638300	-0.37101300
C	6.75814600	-2.72925700	0.45478100
C	-6.75808400	2.72927900	0.45477800
C	-8.19843000	-1.95633200	-0.37099100
F	9.25749200	1.39290800	-1.04346400
F	8.69742100	2.45360700	0.81228200
F	7.73776800	3.03539800	-1.08981700
F	7.84894300	-3.09560900	-0.29874100
F	7.07478000	-3.00055900	1.76711000
F	5.69733800	-3.54298700	0.12721000
F	-5.69726600	3.54298700	0.12718200
F	-7.84888900	3.09565300	-0.29872100
F	-7.07468400	3.00059000	1.76711300
F	-7.73784300	-3.03537000	-1.08978000
F	-9.25752700	-1.39284300	-1.04344800
F	-8.69747600	-2.45352600	0.81231300



$E_{(RB3LYP)}$ = -1855.20094414

C	-1.76282400	2.55388800	-1.19847500
C	-3.06247000	2.07021200	-1.09257100
C	-3.35554200	0.93984400	-0.31207100
C	-2.28958700	0.31909800	0.36206900

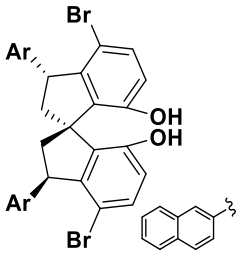
C	-0.98078400	0.80858200	0.26653000
C	-0.70941200	1.92940600	-0.52213900
H	-1.56443100	3.42497100	-1.81520400
H	-3.86067300	2.56048900	-1.63750300
C	-2.33898700	-0.90499500	1.26571900
H	-3.19299700	-0.88637100	1.94820300
H	-2.37804300	-1.80298000	0.64576900
C	-0.97241100	-0.86382300	2.00512700
H	-0.56380800	-1.86052900	2.18266000
C	-0.00000400	-0.00004400	1.12349300
C	0.97238600	0.86369300	2.00517500
H	0.56376900	1.86038400	2.18277000
C	2.33895200	0.90493100	1.26575000
H	2.37796300	1.80293100	0.64581700
H	3.19297300	0.88631900	1.94821700
C	2.28958600	-0.31914000	0.36206500
C	0.98079000	-0.80862800	0.26649700
C	0.70943000	-1.92942400	-0.52222300
C	1.76285200	-2.55387200	-1.19857300
C	3.35555300	-0.93985400	-0.31209200
C	3.06249500	-2.07019300	-1.09263600
H	1.56447200	-3.42492500	-1.81534700
H	3.86070000	-2.56042500	-1.63760700
O	-0.59587300	-2.39779200	-0.59836800
H	-0.63757400	-3.18515700	-1.20034000
O	0.59589800	2.39776200	-0.59826500
H	0.63761400	3.18513100	-1.20022900
H	1.09532500	0.35176200	2.96598900
H	-1.09534000	-0.35194700	2.96597000
C	-4.75942600	0.46201300	-0.20872400
C	-5.08445700	-0.89214800	-0.37051100
C	-5.79691600	1.37637100	0.02725800
C	-6.40242200	-1.30808200	-0.29477700
C	-7.10987800	0.94335600	0.09583300
C	-7.42808600	-0.39985200	-0.06280500
C	4.75943100	-0.46200600	-0.20872900
C	5.79693100	-1.37634300	0.02728300
C	5.08444800	0.89215600	-0.37055100
C	7.10988300	-0.94330500	0.09588200
C	6.40240600	1.30811200	-0.29480000
C	7.42807600	0.39990400	-0.06277400
H	4.31963200	1.62637000	-0.57458400
H	5.58574500	-2.42484800	0.18321000
H	-4.31964600	-1.62637800	-0.57450500
H	-5.58571400	2.42487500	0.18316800
F	6.71970700	2.62772500	-0.45956700
F	8.72483100	0.82017800	0.00968600
F	8.11962900	-1.83311700	0.33384300
F	-6.71973800	-2.62769700	-0.45949700
F	-8.72484400	-0.82011500	0.00967400
F	-8.11961300	1.83318300	0.33377400



$E_{(RB3LYP)}$ = -1460.43699661

C	0.56629000	-2.92518700	-2.07870800
C	1.82936800	-3.32834200	-1.63569100
C	2.45681300	-2.66370700	-0.58101600
C	1.80007900	-1.58322900	0.00935300
C	0.54837900	-1.16293000	-0.43784000
C	-0.08669200	-1.84538100	-1.47801600
H	0.08761000	-3.45772800	-2.89494700
C	2.27892600	-0.74030600	1.19320000
C	1.24442300	0.44191400	1.22832900
C	0.00002400	0.00029200	0.37151300
C	-1.24403800	-0.44179500	1.22860000
C	-2.27905800	0.74000200	1.19368400
C	-1.80039800	1.58361600	0.01026300
C	-0.54858900	1.16387100	-0.43711600
C	0.08643400	1.84713700	-1.47679000
C	-0.56672300	2.92718600	-2.07683900
C	-2.45731900	2.66433800	-0.57947400
C	-1.82993500	3.32977800	-1.63367000
H	-0.08809700	3.46035800	-2.89269900
H	-2.31878300	4.16873300	-2.11512400
O	1.35815900	1.42559800	-1.86528500
H	1.67065400	1.96680300	-2.63565500
O	-1.35826300	-1.42329300	-1.86642200
H	-1.67040400	-1.96329800	-2.63777600
H	-0.95275800	-0.70353700	2.24918800
H	0.95348100	0.70386200	2.24896000
H	-3.43770000	2.96755000	-0.23334600
H	3.43712500	-2.96731300	-0.23503900
H	1.69951700	1.31443000	0.75756200
H	-1.69887900	-1.31455900	0.75805300
H	2.31808300	-4.16708600	-2.11764600
C	3.71553000	-0.26665800	1.02969300
C	4.69821600	-0.57991900	1.97442400
C	4.07684300	0.49799000	-0.09253700
C	6.01428600	-0.14154700	1.81297100
H	4.43578800	-1.16947800	2.84629000
C	5.38685900	0.93700600	-0.25626400
H	3.31331700	0.74618400	-0.82183700
C	6.34637800	0.61323800	0.69791800
H	6.77890000	-0.37865200	2.54060400
H	5.67850000	1.52698800	-1.11526800
C	-3.71547100	0.26582200	1.02981300
C	-4.69840400	0.57871200	1.97443000
C	-4.07637900	-0.49890100	-0.09248000
C	-6.01430800	0.13993400	1.81277900
H	-4.43628000	1.16828400	2.84637900
C	-5.38624100	-0.93833000	-0.25639900
H	-3.31272300	-0.74674600	-0.82175800

C	-6.34600500	-0.61489900	0.69763700
H	-6.77909200	0.37674200	2.54032900
H	-5.67755900	-1.52839900	-1.11545600
H	2.20508200	-1.33783400	2.11150000
H	-2.20564600	1.33720700	2.11218400
F	-7.63663100	-1.04975200	0.53136700
F	7.63718100	1.04762200	0.53180600



$E_{(RB3LYP)}$ = -6691.03730522

C	-0.72534100	-2.91284600	1.95260100
C	-1.96392100	-3.29790800	1.44124300
C	-2.53968600	-2.60124400	0.38520400
C	-1.88368900	-1.49512400	-0.14366300
C	-0.63055600	-1.12422100	0.35156000
C	-0.03870200	-1.83059500	1.39893700
H	-0.29148200	-3.47243400	2.77484200
C	-2.31503100	-0.58746500	-1.29584300
C	-1.20310900	0.52651500	-1.30859900
C	-0.00006400	0.00037300	-0.44812500
C	1.20286000	-0.52598900	-1.30865200
C	2.31505400	0.58763500	-1.29577100
C	1.88386200	1.49551300	-0.14368800
C	0.63055100	1.12497900	0.35142000
C	0.03873300	1.83163000	1.39860900
C	0.72547600	2.91387400	1.95216200
C	2.54002600	2.60153400	0.38514700
C	1.96424500	3.29853100	1.44096100
H	0.29159800	3.47372800	2.77420800
H	2.48135700	4.15234100	1.85729400
O	-1.22131800	1.42990400	1.83309300
H	-1.52248500	2.00856700	2.58032500
O	1.22118400	-1.42853600	1.83362100
H	1.52206600	-2.00671100	2.58134100
H	0.88734900	-0.78090200	-2.32354800
H	-0.88766600	0.78163900	-2.32346500
H	-1.61168200	1.41772500	-0.83123500
H	1.61114700	-1.41743200	-0.83146000
H	-2.48090900	-4.15175700	1.85765200
C	-3.69822000	0.03112400	-1.11332600
C	-4.66221000	-0.04920600	-2.15383400
C	-4.00639700	0.72332600	0.04169100
C	-5.89502700	0.54779900	-2.02698600
H	-4.41434300	-0.59658000	-3.05701300
C	-5.27209700	1.34437500	0.20980900
H	-3.25761200	0.81597500	0.82220100

C	-6.24086400	1.25832800	-0.84584900
H	-6.62298500	0.48108200	-2.82877600
C	3.69811100	-0.03125500	-1.11320600
C	4.66237500	0.04944400	-2.15347800
C	4.00599900	-0.72396500	0.04156000
C	5.89512500	-0.54765800	-2.02659900
H	4.41473500	0.59719200	-3.05649000
C	5.27164900	-1.34517100	0.20969700
H	3.25708900	-0.81683600	0.82191600
C	6.24067200	-1.25870900	-0.84567000
H	6.62327000	-0.48062000	-2.82819500
H	-2.30359500	-1.16306200	-2.22996000
H	2.30384300	1.16326900	-2.22987800
Br	-4.21417900	-3.22744200	-0.33123100
Br	4.21477600	3.22726900	-0.33112400
C	-7.50556800	1.88686100	-0.67458300
C	-5.61479100	2.05669700	1.39411300
C	-7.80282600	2.56831900	0.48346400
H	-8.23371300	1.81807200	-1.47614800
C	-6.84715600	2.65347800	1.52890900
H	-4.88345700	2.11555300	2.19345400
H	-8.76955200	3.04323800	0.60446500
H	-7.09684200	3.19160200	2.43616500
C	5.61398600	-2.05802900	1.39376300
C	6.84627500	-2.65498000	1.52859800
C	7.80219800	-2.56941900	0.48343100
C	7.50528300	-1.88739500	-0.67438000
H	4.88246100	-2.11717800	2.19290700
H	7.09569400	-3.19354100	2.43566800
H	8.76885500	-3.04448000	0.60443800
H	8.23365400	-1.81827200	-1.47571100

References

1 T. P. Aldhous, R. W. C. Chung, A. G. Dalling and J. F. Bower, *Synthesis*, 2021, **53**, 2961.
2 P. J. Harrington and E. Lodewijk, *Org. Process Res. Dev.*, 1997, **1**, 72.
3 Q. Zhang, J. F. Li, G. H. Tian, R. X. Zhang, J. Sun, J. Suo, X. Feng, D. Fang, X. R. Jiang and J. S. Shen, *Tetrahedron: Asymmetry*, 2012, **23**, 577.
4 S. H. Lee, I. S. Kim, Q. R. Li, G. R. Dong, L. S. Jeong and Y. H. Jung, *J. Org. Chem.*, 2011, **76**, 10011.
5 G. P. Taber, D. M. Pfisterer and J. C. Colberg, *Org. Process Res. Dev.*, 2004, **8**, 385.
6 D. Imao, B. W. Glasspoole, V. S. Laberge and C. M. Crudden, *J. Am. Chem. Soc.*, 2009, **131**, 5024.
7 L. Li, S. Zhao, A. Joshi-Pangu, M. Diane and M. R. Biscoe, *J. Am. Chem. Soc.*, 2014, **136**, 14027.
8 E. C. Swift and E. R. Jarvo, *Tetrahedron*, 2013, **69**, 5799.
9 D. Leonori and V. K. Aggarwal, *Angew. Chem. Int. Ed.*, 2015, **54**, 1082.
10 S. Zhao, T. Gensch, B. Murray, Z. L. Niemeyer, M. S. Sigman and M. R. Biscoe, *Science*, 2018, **362**, 670.
11 L. Li, C.-Y. Wang, R. Huang and M. R. Biscoe, *Nat. Chem.*, 2013, **5**, 607.
12 A. Bonet, M. Odachowski, D. Leonori, S. Essafi and V. K. Aggarwal, *Nat. Chem.*, 2014, **6**, 584.
13 J. Llaveria, D. Leonori and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2015, **137**, 10958.
14 M. Odachowski, A. Bonet, S. Essafi, P. Conti-Ramsden, J. N. Harvey, D. Leonori and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2016, **138**, 9521.
15 S. Aichhorn, R. Bigler, E. L. Myers and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2017, **139**, 9519.
16 V. Ganesh, A. Noble and V. K. Aggarwal, *Org. Lett.*, 2018, **20**, 6144.
17 C. M. Wilson, V. Ganesh, A. Noble and V. K. Aggarwal, *Angew. Chem. Int. Ed.*, 2017, **56**, 16318.
18 S. D. Friis, M. T. Pirnot and S. L. Buchwald, *J. Am. Chem. Soc.*, 2016, **138**, 8372.
19 T. Jia, P. Cao, B. Wang, Y. Lou, X. Yin, M. Wang and J. Liao, *J. Am. Chem. Soc.*, 2015, **137**, 13760.
20 X. Cheng, H. Lu and Z. Lu, *Nat. Commun.*, 2019, **10**, 3549.
21 B. L. H. Taylor, M. R. Harris and E. R. Jarvo, *Angew. Chem. Int. Ed.*, 2012, **51**, 7790.
22 Q. Zhou, H. D. Srinivas, S. Dasgupta and M. P. Watson, *J. Am. Chem. Soc.*, 2013, **135**, 3307.
23 Q. Zhou, K. M. Cobb, T. Tan and M. P. Watson, *J. Am. Chem. Soc.*, 2016, **138**, 12057.
24 B. Li, T. Li, M. A. Aliyu, Z. H. Li and W. Tang, *Angew. Chem. Int. Ed.*, 2019, **58**, 11355.
25 P. M. Lundin and G. C. Fu, *J. Am. Chem. Soc.*, 2010, **132**, 11027.
26 E. L. Lucas and E. R. Jarvo, *Nat. Rev. Chem.*, 2017, **1**, 65.
27 J. Kischel, I. Jovel, K. Mertins, A. Zapf and M. Beller, *Org. Lett.*, 2006, **8**, 19.
28 H.-B. Sun, B. Li, R. Hua and Y. Yin, *Eur. J. Org. Chem.*, 2006, **2006**, 4231.
29 S. Y. Lee, A. Villani-Gale and C. C. Eichman, *Org. Lett.*, 2016, **18**, 5034.
30 T. B. Poulsen and K. A. Jørgensen, *Chem. Rev.*, 2008, **108**, 2903.
31 M. Rueping and B. J. Nachtsheim, *Beilstein J. Org. Chem.*, 2010, **6**, 6.
32 H. Matsuzawa, Y. Miyake and Y. Nishibayashi, *Angew. Chem. Int. Ed.*, 2007, **46**, 6488.
33 P. Vicennati and P. G. Cozzi, *Eur. J. Org. Chem.*, 2007, **2007**, 2248.
34 F. Mühlthau, O. Schuster and T. Bach, *J. Am. Chem. Soc.*, 2005, **127**, 9348.
35 F. Mühlthau, D. Stadler, A. Goeppert, G. A. Olah, G. K. S. Prakash and T. Bach, *J. Am. Chem. Soc.*, 2006, **128**, 9668.
36 J. S. Marcum, C. C. Roberts, R. S. Manan, T. N. Cervarich and S. J. Meek, *J. Am. Chem. Soc.*, 2017, **139**, 15580.
37 H. Wang, Z. Bai, T. Jiao, Z. Deng, H. Tong, G. He, Q. Peng and G. Chen, *J. Am. Chem. Soc.*, 2018, **140**, 3542.
38 S. M. Podhajsky, Y. Iwai, A. Cook-Sneathen and M. S. Sigman, *Tetrahedron*, 2011, **67**, 4435.
39 Y.-G. Chen, B. Shuai, X.-T. Xu, Y.-Q. Li, Q.-L. Yang, H. Qiu, K. Zhang, P. Fang and T.-S. Mei, *J. Am. Chem. Soc.*, 2019, **141**, 3395.
40 T.-S. Mei, H. H. Patel and M. S. Sigman, *Nature*, 2014, **508**, 340.

41 C. Zhang, C. B. Santiago, J. M. Crawford and M. S. Sigman, *J. Am. Chem. Soc.*, 2015, **137**, 15668.
42 G. Evano and C. Theunissen, *Angew. Chem. Int. Ed.*, 2019, **58**, 7202.
43 Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, *Chem. Rev.*, 2017, **117**, 9333.
44 C. G. Newton, S.-G. Wang, C. C. Oliveira and N. Cramer, *Chem. Rev.*, 2017, **117**, 8908.
45 A. J. Chalk and J. F. Harrod, *J. Am. Chem. Soc.*, 1965, **87**, 16.
46 T. Matsubara, N. Koga, D. G. Musaev and K. Morokuma, *Organometallics*, 2000, **19**, 2318.
47 S. Sakaki, N. Mizoe and M. Sugimoto, *Organometallics*, 1998, **17**, 2510.
48 S. Sakaki, M. Sumimoto, M. Fukuhara, M. Sugimoto, H. Fujimoto and S. Matsuzaki, *Organometallics*, 2002, **21**, 3788.
49 M. Zhang, L. Hu, Y. Lang, Y. Cao and G. Huang, *J. Org. Chem.*, 2018, **83**, 2937.
50 F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani and S. Murai, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 62.
51 F. Kakiuchi, T. Kochi, E. Mizushima and S. Murai, *J. Am. Chem. Soc.*, 2010, **132**, 17741.
52 L. N. Lewis and J. F. Smith, *J. Am. Chem. Soc.*, 1986, **108**, 2728.
53 S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda and N. Chatani, *Nature*, 1993, **336**, 529.
54 Y. Nakao, N. Kashihara, K. S. Kanyiva and T. Hiyama, *Angew. Chem. Int. Ed.*, 2010, **49**, 4451.
55 Y. Uchimaru, *Chem. Commun.*, 1999, 1133.
56 K. Gao and N. Yoshikai, *J. Am. Chem. Soc.*, 2011, **133**, 400.
57 A. Peneau, C. Guillou and L. Chabaud, *Eur. J. Org. Chem.*, 2018, **2018**, 5777.
58 P. A. Donets and N. Cramer, *Angew. Chem. Int. Ed.*, 2015, **54**, 633.
59 A. S. Tsai, R. M. Wilson, H. Harada, R. G. Bergman and J. A. Ellman, *Chem. Commun.*, 2009, 3910.
60 H. Harada, R. K. Thalji, R. G. Bergman and J. A. Ellman, *J. Org. Chem.*, 2008, **73**, 6772.
61 A. Watzke, R. M. Wilson, S. J. O'Malley, R. G. Bergman and J. A. Ellman, *Synlett*, 2007, **15**, 2383.
62 R. K. Thalji, J. A. Ellman and R. G. Bergman, *J. Am. Chem. Soc.*, 2004, **126**, 7192.
63 J. Diesel, A. M. Finogenova and N. Cramer, *J. Am. Chem. Soc.*, 2018, **140**, 4489.
64 K. Sakamoto and T. Nishimura, *Org. Biomol. Chem.*, 2021, **19**, 684.
65 G. Li, Q. Liu, L. Vasamsetty, W. Guo and J. Wang, *Angew. Chem. Int. Ed.*, 2020, **59**, 3475.
66 Z.-Y. Li, H. H. C. Lakmal, X. Qian, Z. Zhu, B. Donnadieu, S. J. McClain, X. Xu and X. Cui, *J. Am. Chem. Soc.*, 2019, **141**, 15730.
67 Y.-X. Wang, S.-L. Qi, Y.-X. Luan, X.-W. Han, S. Wang, H. Chen and M. Ye, *J. Am. Chem. Soc.*, 2018, **140**, 5360.
68 T. Shibata, N. Ryu and H. Takano, *Adv. Synth. Catal.*, 2015, **357**, 1131.
69 V. S. Shinde, M. V. Mane, L. Cavallo and M. Rueping, *Chem. – A Eur. J.*, 2020, **26**, 8308.
70 H.-H. Lu, H. Liu, W. Wu, X.-F. Wang, L.-Q. Lu and W.-J. Xiao, *Chem. – A Eur. J.*, 2009, **15**, 2742.
71 H. Huang and R. Peters, *Angew. Chem. Int. Ed.*, 2009, **48**, 604.
72 X. Han and R. A. Widenhoefer, *Org. Lett.*, 2006, **8**, 3801.
73 C. Liu, X. Zhu, P. Zhang, H. Yang, C. Zhu and H. Fu, *iScience*, 2018, **10**, 11.
74 Z.-M. Zhang, B. Xu, Y. Qian, L. Wu, Y. Wu, L. Zhou, Y. Liu and J. Zhang, *Angew. Chem. Int. Ed.*, 2018, **57**, 10373.
75 Y. J. Jang, E. M. Larin and M. Lautens, *Angew. Chem. Int. Ed.*, 2017, **56**, 11927.
76 P. Zhang, N. Tsuji, J. Ouyang and B. List, *J. Am. Chem. Soc.*, 2021, **143**, 675.
77 R. Aufdenblatten, S. Diezi and A. Togni, *Monatsh. Chem.*, 2000, **131**, 1345.
78 K. Tsuchikama, M. Kasagawa, Y.-K. Hashimoto, K. Endo and T. Shibata, *J. Organomet. Chem.*, 2008, **693**, 3939.
79 T. Shirai and Y. Yamamoto, *Angew. Chem. Int. Ed.*, 2015, **54**, 9894.
80 M. Nagamoto, J.-I. Fukuda, M. Hatano, H. Yorimitsu and T. Nishimura, *Org. Lett.*, 2017, **19**, 5952.
81 C. S. Sevov and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 2116.
82 M. Chen and J. Montgomery, *ACS Catal.*, 2022, **12**, 11015.

83 Y. Ebe and T. Nishimura, *J. Am. Chem. Soc.*, 2015, **137**, 5899.
84 Y. Ebe, M. Onoda, T. Nishimura and H. Yorimitsu, *Angew. Chem. Int. Ed.*, 2017, **56**, 5607.
85 K. Sakamoto and T. Nishimura, *Adv. Synth. Catal.*, 2019, **361**, 2124.
86 M. Hatano, Y. Ebe, T. Nishimura and H. Yorimitsu, *J. Am. Chem. Soc.*, 2016, **138**, 4010.
87 H. Murakami, K. Sakamoto and T. Nishimura, *Synthesis*, 2022, **54**, 4753.
88 D. Yamauchi, T. Nishimura and H. Yorimitsu, *Chem. Commun.*, 2017, **53**, 2760.
89 A. Romero-Arenas, V. Hornillos, J. Iglesias-Sigüenza, R. Fernández, J. López-Serrano, A. Ros and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2020, **142**, 2628.
90 T. Shibata, M. Michino, H. Kurita, Y.-K. Tahara and K. S. Kanyiva, *Chem. – A Eur. J.*, 2017, **23**, 88.
91 T. Shibata, H. Kurita, S. Onoda and K. S. Kanyiva, *Asian J. Org. Chem.*, 2018, **7**, 1411.
92 S. Satake, T. Kurihara, K. Nishikawa, T. Mochizuki, M. Hatano, K. Ishihara, T. Yoshino and S. Matsunaga, *Nat. Catal.*, 2018, **1**, 585.
93 T. J. Potter, D. N. Kamber, B. Q. Mercado and J. A. Ellman, *ACS Catal.*, 2017, **7**, 150.
94 T. J. Potter and J. A. Ellman, *Org. Lett.*, 2017, **19**, 2985.
95 C. M. Filloux and T. Rovis, *J. Am. Chem. Soc.*, 2015, **137**, 508.
96 T. Shibata and T. Shizuno, *Angew. Chem. Int. Ed.*, 2014, **53**, 5410.
97 S. Pan, N. Ryu and T. Shibata, *J. Am. Chem. Soc.*, 2012, **134**, 17474.
98 P.-S. Lee and N. Yoshikai, *Org. Lett.*, 2015, **17**, 22.
99 J. Loup, D. Zell, J. C. A. Oliveira, H. Keil, D. Stalke and L. Ackermann, *Angew. Chem. Int. Ed.*, 2017, **56**, 14197.
100 F. Pesciaioli, U. Dhawa, J. C. A. Oliveira, R. Yin, M. John and L. Ackermann, *Angew. Chem. Int. Ed.*, 2018, **57**, 15425.
101 Y.-H. Liu, P.-P. Xie, L. Liu, J. Fan, Z.-Z. Zhang, X. Hong and B.-F. Shi, *J. Am. Chem. Soc.*, 2021, **143**, 19112.
102 S. Rodewald and R. F. Jordan, *J. Am. Chem. Soc.*, 1994, **116**, 4491.
103 G. Song, W. N. O. Wylie and Z. Hou, *J. Am. Chem. Soc.*, 2014, **136**, 12209.
104 J.-F. Li, D. Pan, H.-R. Wang, T. Zhang, Y. Li, G. Huang and M. Ye, *J. Am. Chem. Soc.*, 2022, **144**, 18810.
105 G. E. M. Crisenza, N. G. McCreanor and J. F. Bower, *J. Am. Chem. Soc.*, 2014, **136**, 10258.
106 G. E. M. Crisenza, O. O. Sokolova and J. F. Bower, *Angew. Chem. Int. Ed.*, 2015, **54**, 14866.
107 S. Grélaud, P. Cooper, L. J. Feron and J. F. Bower, *J. Am. Chem. Soc.*, 2018, **140**, 9351.
108 P. Cooper, *Ph.D. Thesis*, 2019, University of Bristol.
109 A. G. Dalling, *Ph.D. Thesis*, 2020, University of Bristol.
110 V. B. Birman, A. L. Rheingold and K.-C. Lam, *Tetrahedron: Asymmetry*, 1999, **10**, 125.
111 N. J. Race, A. Faulkner, G. Fumagalli, T. Yamauchi, J. S. Scott, M. Rydé-Landergren, H. A. Sparkes and J. F. Bower, *Chem. Sci.*, 2017, **8**, 1981.
112 B. Andersh, D. L. Murphy and R. J. Olson, *Synth. Commun.*, 2000, **30**, 2091.
113 K. Lan, Z. Shan and S. Fan, *Tetrahedron Lett.*, 2006, **47**, 4343.
114 Z. Li, X. Liang, F. Wu and B. Wan, *Tetrahedron: Asymmetry*, 2004, **15**, 665.
115 L. Qin, X. Ren, Y. Lu, Y. Li and J. Zhou, *Angew. Chem. Int. Ed.*, 2012, **51**, 5915.
116 L. Yin, J. Xing, Y. Wang, Y. Shen, T. Lu, T. Hayashi and X. Dou, *Angew. Chem. Int. Ed.*, 2019, **58**, 2474.
117 A. M. Harned, *Tetrahedron*, 2018, **74**, 3797.
118 K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, **103**, 169.
119 T. Hayashi, M. Takahashi, Y. Takaya and M. Ogasawara, *J. Am. Chem. Soc.*, 2002, **124**, 5052.
120 R. Itooka, Y. Iguchi and N. Miyaura, *J. Org. Chem.*, 2003, **68**, 6000.
121 Z. Zheng, Y. Cao, Q. Chong, Z. Han, J. Ding, C. Luo, Z. Wang, D. Zhu, Q.-L. Zhou and K. Ding, *J. Am. Chem. Soc.*, 2018, **140**, 10374.
122 Z. Zheng, Y. Cao, D. Zhu, Z. Wang and K. Ding, *Chem. – A Eur. J.*, 2019, **25**, 9491.
123 P. E. Eaton, G. R. Carlson and J. T. Lee, *J. Org. Chem.*, 1973, **38**, 4071.
124 P. Haranath, V. S. Kumar, C. S. Reddy, C. N. Raju and C. D. Reddy, *Synth. Commun.*, 2007, **37**, 1697.
125 A. J. Argüelles, S. Sun, B. G. Budaitis and P. Nagorny, *Angew. Chem. Int. Ed.*, 2018, **57**, 5325.
126 G.-Q. Chen, B.-J. Lin, J.-M. Huang, L.-Y. Zhao, Q.-S. Chen, S.-P. Jia, Q. Yin and X. Zhang, *J.*

Am. Chem. Soc., 2018, **140**, 8064.
127 W. Zhang, S. Wu, Z. Zhang, H. Yennawar and X. Zhang, *Org. Biomol. Chem.*, 2006, **4**, 4474.
128 X.-H. Huo, J.-H. Xie, Q.-S. Wang and Q.-L. Zhou, *Adv. Synth. Catal.*, 2007, **349**, 2477.
129 T. Q. Davies, J. J. Murphy, M. Dousset and A. Fürstner, *J. Am. Chem. Soc.*, 2021, **143**, 13489.
130 G. Wilkinson, *J. Am. Chem. Soc.*, 1952, **74**, 6146.
131 M. D. Rausch, E. O. Fischer and H. Grubert, *J. Am. Chem. Soc.*, 1960, **82**, 76.
132 G. L. Hardgrove and D. H. Templeton, *Acta Cryst.*, 1959, **12**, 28.
133 Y. Liu, W. Li and J. Zhang, *Natl. Sci. Rev.*, 2017, **4**, 326.
134 S. Li, B. Wei, P. M. N. Low, H. K. Lee, T. S. A. Hor, F. Xue and T. C. W. Mak, *J. Chem. Soc. Dalt. Trans.*, 1997, 1289.
135 C. A. Tolman, *Chem. Rev.*, 1977, **77**, 313.
136 J. A. Gillespie, D. L. Dodds and P. C. J. Kamer, *Dalt. Trans.*, 2010, **39**, 2751.
137 D. J. Durand and N. Fey, *Acc. Chem. Res.*, 2021, **54**, 837.
138 N. Fey, A. C. Tsipis, S. E. Harris, J. N. Harvey, A. G. Orpen and R. A. Mansson, *Chem. – A Eur. J.*, 2005, **12**, 291.
139 D. J. Durand and N. Fey, *Chem. Rev.*, 2019, **119**, 6561.
140 N. Fey, M. F. Haddow, J. N. Harvey, C. L. McMullin and A. G. Orpen, *Dalt. Trans.*, 2009, 8183.
141 N. Fey, J. N. Harvey, G. C. Lloyd-Jones, P. Murray, A. G. Orpen, R. Osborne and M. Purdie, *Organometallics*, 2008, **27**, 1372.
142 R. P. Dickinson, A. S. Bell, C. A. Hitchcock, S. Narayanaswami, S. J. Ray, K. Richardson and P. F. Troke, *Bioorganic Med. Chem. Lett.*, 1996, **6**, 2031.
143 K. Tamura, M. Furutachi, N. Kumagai and M. Shibasaki, *J. Org. Chem.*, 2013, **78**, 11396.
144 S. Turcaud, W. Gonzalez, J.-B. Michel, B. P. Roques and M.-C. Fournie-Zaluski, *Bioorganic Med. Chem. Lett.*, 1995, **5**, 1893.
145 S. Krautwald, D. Sarlah, M. A. Schafroth and E. M. Carreira, *Science*, 2013, **340**, 1065.
146 C. J. Richards and R. A. Arthurs, *Chem. – A Eur. J.*, 2017, **23**, 11460.
147 J. Feng, M. Holmes and M. J. Krische, *Chem. Rev.*, 2017, **117**, 12564.
148 K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181.
149 J. Christoffers and A. Mann, *Angew. Chem. Int. Ed.*, 2001, **40**, 4591.
150 B. M. Trost and C. Jiang, *Synthesis*, 2006, **3**, 369.
151 I. Denissova and L. Barriault, *Tetrahedron*, 2003, **59**, 10105.
152 T. Ling and F. Rivas, *Tetrahedron*, 2016, **72**, 6729.
153 Y. Liu, S.-J. Han, W.-B. Liu and B. M. Stoltz, *Acc. Chem. Res.*, 2015, **48**, 740.
154 J. P. Das and I. Marek, *Chem. Commun.*, 2011, **47**, 4593.
155 I. Marek, Y. Minko, M. Pasco, T. Mejuch, N. Gilboa, H. Chechik and J. P. Das, *J. Am. Chem. Soc.*, 2014, **136**, 2682.
156 C. Feng and Y. Kobayashi, *J. Org. Chem.*, 2013, **78**, 3755.
157 H. Ohmiya, H. Zhang, S. Shibata, A. Harada and M. Sawamura, *Angew. Chem. Int. Ed.*, 2016, **55**, 4777.
158 L. Chausset-Boissarie, K. Ghozati, E. LaBine, J. L.-Y. Chen, V. K. Aggarwal and C. M. Crudden, *Chem. – A Eur. J.*, 2013, **19**, 17698.
159 K. M. Cobb, J. M. Rabb-Lynch, M. E. Hoerrner, A. Manders, Q. Zhou and M. P. Watson, *Org. Lett.*, 2017, **19**, 4355.
160 L. Wu, F. Wang, P. Chen and G. Liu, *J. Am. Chem. Soc.*, 2019, **141**, 1887.
161 C.-F. Liu, Z.-C. Wang, X. Luo, J. Lu, C. H. M. Ko, S.-L. Shi and M. J. Koh, *Nat. Catal.*, 2022, **5**, 934.
162 P. Cooper, A. G. Dalling, E. H. E. Farrar, T. P. Aldhous, S. Grélaud, E. Lester, L. J. Feron, P. D. Kemmitt, M. N. Grayson and J. F. Bower, *Chem. Sci.*, 2022, **13**, 11183.
163 K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788.
164 A. Tomberg, M. É. Muratore, M. J. Johansson, I. Terstiege, C. Sköld and P.-O. Norrby, *iScience*, 2019, **20**, 373.
165 Z. Huang and J.-P. Lumb, *ACS Catal.*, 2019, **9**, 521.
166 H.-X. Dai, G. Li, X.-G. Zhang, A. F. Stepan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 7567.
167 L. Ackermann, E. Diers and A. Manvar, *Org. Lett.*, 2012, **14**, 1154.

168 A. John and K. M. Nicholas, *J. Org. Chem.*, 2012, **77**, 5600.
169 T.-J. Gong, B. Xiao, Z.-J. Liu, J. Wan, J. Xu, D.-F. Luo, Y. Fu and L. Liu, *Org. Lett.*, 2011, **13**, 3235.
170 X. Zhao, C. S. Yeung and V. M. Dong, *J. Am. Chem. Soc.*, 2010, **132**, 5837.
171 B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi and L. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 468.
172 M. Szostak, M. Spain, A. J. Eberhart and D. J. Procter, *J. Am. Chem. Soc.*, 2014, **136**, 2268.
173 M. Waldron, *Ph.D. Thesis*, 2022, University of Bristol.
174 I. Muthukrishnan, V. Sridharan and J. C. Mendéndez, *Chem. Rev.*, 2019, **119**, 5057.
175 V. V. Kouznetsov, *Tetrahedron*, 2009, **65**, 2721.
176 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
177 S. Bajo, G. Laidlaw, A. R. Kennedy, S. Sproules and D. J. Nelson, *Organometallics*, 2017, **36**, 1662.
178 P. A. Topchiyan, D. B. Vasilchenko, S. V. Tkachev, I. A. Baydina, I. V. Korolkov, D. G. Sheven and S. V. Korenev, *J. Struc. Chem.*, 2019, **60**, 640.
179 C. M. So and F. Y. Kwong, *Chem. Soc. Rev.*, 2011, **40**, 4963.
180 A. K. Franz and S. O. Wilson, *J. Med. Chem.*, 2012, **56**, 388.
181 R. Ramesh and D. S. Reddy, *J. Med. Chem.*, 2018, **61**, 3779.
182 S. Fujii and Y. Hashimoto, *Future Med. Chem.*, 2017, **9**, 485.
183 N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529.
184 S. J. Barraza and S. E. Denmark, *J. Am. Chem. Soc.*, 2018, **140**, 6668.
185 G. A. Showell and J. S. Mills, *Drug Discov.*, 2003, **8**, 551.
186 R. Tacke, F. Popp, B. Müller, B. Theis, C. Burschka, A. Hamacher, M. U. Kassack, D. Schepmann, B. Wünsch, U. Jurva and E. Wellner, *ChemMedChem*, 2008, **3**, 152.
187 R. Tacke, T. Heinrich, R. Bertermann, C. Burschka, A. Hamacher and M. U. Kassack, *Organometallics*, 2004, **23**, 4468.
188 M. Nakamura, D. Kajita, Y. Matsumoto and Y. Hashimoto, *Bioorg. Med. Chem.*, 2013, **21**, 7381.
189 H. Toyama, M. Nakamura, Y. Hasimoto and S. Fujii, *Bioorg. Med. Chem.*, 2015, **23**, 2982.
190 D. Bom, D. P. Curran, S. Kruszewski, S. G. Zimmer, J. T. Strode, G. Kohlhagen, W. Du, A. J. Chavan, K. A. Fraley, A. L. Bingcang, L. J. Latus, Y. Pommier and T. G. Burke, *J. Med. Chem.*, 2000, **43**, 3970.
191 B. Weidmann, *Chimia (Aarau).*, 1992, **46**, 312.
192 S. Pujals, J. Fernández-Carneado, M. J. Kogan, J. Martinez, F. Cavelier and E. Giralt, *J. Am. Chem. Soc.*, 2006, **128**, 8479.
193 B. Vivet, F. Cavelier and J. Martinez, *Eur. J. Org. Chem.*, 2000, **2000**, 807.
194 M. Mortensen, R. Husmann, E. Veri and C. Bolm, *Chem. Soc. Rev.*, 2009, **38**, 1002.
195 R. Tacke, M. Merget, R. Bertermann, M. Bernd, T. Beckers and T. Reissmann, *Organometallics*, 2000, **19**, 3486.
196 Y. Tsuji, H. Yamanaka, T. Fukui, T. Kawamoto and A. Tanaka, *Appl. Microbiol. Biotechnol.*, 1997, **47**, 114.
197 J.-M. Hornsperger, J.-N. Collard, J.-G. Heydt, E. Giacobini, S. Funes, J. Dow and D. Schirlin, *Biochem. Soc. Trans.*, 1994, **22**, 758.
198 S. Rej and N. Chatani, *Chem. Sci.*, 2020, **11**, 389.
199 K. Yamazaki, S. Rej, Y. Ano and N. Chatani, *Organometallics*, 2021, **40**, 3935.
200 I. Fleming and J. A. Langley, *J. Chem. Soc., Perkin Trans., 1*, 1981, 1421.
201 M. B. Smith, *March's Advanced Organic Chemistry*, Wiley, New York, 7th Edn., 2013.
202 G. Wu and M. Huang, *Chem. Rev.*, 2006, **106**, 2596.
203 P. Arya and H. Qin, *Tetrahedron*, 2000, **56**, 917.
204 D. Enders and H. Eichenauer, *Tetrahedron Lett.*, 1977, **18**, 191.
205 M. M. Heravi, V. Zadsirjan and B. Farajpour, *RSC Adv.*, 2016, **6**, 30498.
206 U. Schöllkopf, U. Groth and C. Deng, *Angew. Chem. Int. Ed.*, 1981, **20**, 798.
207 H. Pellissier, *Tetrahedron*, 2007, **63**, 9267.
208 U. H. Dolling, P. Davis and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1984, **106**, 446.
209 M. Imai, A. Hagihara, H. Kawasaki, K. Manabe and K. Koga, *J. Am. Chem. Soc.*, 1994, **116**,

8829.
210 A. G. Doyle and E. H. Jacobsen, *Angew. Chem. Int. Ed.*, 2007, **46**, 3701.
211 T. B. Wright and P. A. Evans, *Chem. Rev.*, 2021, **121**, 9196.
212 A. G. Capacci, J. T. Malinowski, N. J. McAlpine, J. Kuhne and D. W. C. MacMillan, *Nat. Chem.*, 2017, **9**, 1073.
213 Z. Huang, H. M. Lim, F. Mo, M. C. Young and G. Dong, *Chem. Soc. Rev.*, 2015, **44**, 7764.
214 D. F. Fernández, J. L. Mascareñas and F. López, *Chem. Soc. Rev.*, 2020, **49**, 7378.
215 N. T. Patil, R. D. Kavthe and V. S. Shinde, *Tetrahedron*, 2012, **68**, 8079.
216 D. Mandal, S. Roychowdhury, J. P. Biswas, S. Maiti and D. Maiti, *Chem. Soc. Rev.*, 2022, **51**, 7358.
217 J. Kischel, D. Michalik, A. Zapf and M. Beller, *Chem. – An Asian J.*, 2007, **2**, 909.
218 C. D. Zotto, J. Michaux, A. Zarate-Ruiz, E. Gayon, D. Virieux, J.-M. Campagne, V. Terrasson, G. Pieters, A. Gaucher and D. Prim, *J. Organomet. Chem.*, 2011, **696**, 296.
219 Z. Duan, X. Xuan and Y. Wu, *Tetrahedron Lett.*, 2007, **48**, 5157.
220 X. Yao and C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 6884.
221 H. E. Lanman, R.-V. Nguyen, X. Yao, T.-H. Chan and C.-J. Li, *J. Mol. Catal. A Chem.*, 2008, **279**, 218.
222 Y. Li, Z. Yu and S. Wu, *J. Org. Chem.*, 2008, **73**, 5647.
223 R. Takeuchi, J. Sagawa and M. Fujii, *Org. Lett.*, 2019, **21**, 741.
224 T. Sawano, K. Ogihara, J. Sagawa, M. Ono and R. Takeuchi, *Org. Lett.*, 2020, **22**, 6187.
225 X. Yao and C.-J. Li, *J. Org. Chem.*, 2005, **70**, 5752.
226 H. Qian, T. Pei and R. A. Widenhoefer, *Organometallics*, 2005, **24**, 287.
227 D. Xing, X. Qi, D. Marchant, P. Liu and G. Dong, *Angew. Chem. Int. Ed.*, 2019, **58**, 4366.
228 D. Xing and G. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 13664.
229 X. Li, H. Wu, Y. Lang and G. Huang, *Catal. Sci. Technol.*, 2018, **8**, 2417.
230 P. Verma, J. M. Richter, N. Chekshin, J. X. Qiao and J.-Q. Yu, *J. Am. Chem. Soc.*, 2020, **142**, 5117.
231 M. L. O'Duill, R. Matsuura, Y. Wang, J. L. Turnbull, J. A. Gurak Jr, D.-W. Gao, G. Lu, P. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2017, **139**, 15576.
232 S. A. Green, T. R. Huffman, R. O. McCourt, V. van der Puyl and R. A. Shenvi, *J. Am. Chem. Soc.*, 2019, **141**, 7709.
233 X. Chen, W. Rao, T. Yang and M. J. Koh, *Nat. Commun.*, 2020, **11**, 5857.
234 P.-F. Yang, L. Zhu, J.-X. Liang, H.-T. Zhao, J.-X. Zhang, X.-W. Zeng, Q. Ouyang and W. Shu, *ACS Catal.*, 2022, **12**, 5795.
235 X.-X. Wang, Y.-T. Xu, Z.-L. Zhang, X. Lu and Y. Fu, *Nat. Commun.*, 2022, **13**, 1890.
236 T. Uemura, X. Zhang, K. Matsumura, N. Sayo, H. Kumobayashi, T. Ohta, K. Nozaki and H. Takaya, *J. Org. Chem.*, 1996, **61**, 5510.
237 E. M. Arnett, S. G. Maroldo, S. L. Schilling and J. A. Harrelson, *J. Am. Chem. Soc.*, 1984, **106**, 6759.
238 L. G. Van Uitert and W. C. Fernelius, *J. Am. Chem. Soc.*, 1954, **76**, 375.
239 A. Dumas, L. Lercher, C. D. Spicer and B. G. Davis, *Chem. Sci.*, 2015, **6**, 50.
240 K. Wals and H. Ovaa, *Front. Chem.*, 2014, **2**, 1.
241 T. S. Young and P. G. Schultz, *J. Biol. Chem.*, 2010, **285**, 11039.
242 H. Xiao, F. Nasertorabi, S.-H. Choi, G. W. Han, S. A. Reed, R. C. Stevens and P. G. Schultz, *Proc. Natl. Acad. Sci. U.S.A.*, 2015, **112**, 6961.
243 Y. Yu, C. Hu, L. Xia and J. Wang, *ACS Catal.*, 2018, **8**, 1851.
244 J. Y. Axup, K. M. Bajjuri, M. Ritland, B. M. Hutchins, C. H. Kim, S. A. Kazane, R. Halder, J. S. Forsyth, A. F. Santidrian, K. Stafin, Y. Lu, H. Tran, A. J. Seller, S. L. Biroc, A. Szydlik, J. K. Pinkstaff, F. Tian, S. C. Sinha, B. Felding-Habermann, V. V. Smider and P. G. Schultz, *Proc. Natl. Acad. Sci. U.S.A.*, 2012, **109**, 16101.
245 A.-C. C. Carlsson, M. R. Scholfield, R. K. Rowe, M. Coates Ford, A. T. Alexander, R. A. Mehl and P. Shing Ho, *Biochemistry*, 2018, **57**, 4135.
246 D. A. Dougherty, *Curr. Opin. Chem. Biol.*, 2000, **4**, 645.
247 C. A. Royer, *Chem. Rev.*, 2006, **106**, 1769.
248 P. Neumann-Staubitz and H. Neumann, *Curr. Opin. Struct. Biol.*, 2016, **38**, 119.

249 M. A. T. Blaskovich, *J. Med. Chem.*, 2016, **59**, 10807.
250 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.
251 D. J. Craik, D. P. Fairlie, S. Liras and D. Price, *Chem. Biol. Drug Des.*, 2013, **81**, 136.
252 K. Fosgerau and T. Hoffmann, *Drug Discov.*, 2015, **20**, 122.
253 Y.-P. Xue, C.-H. Cao and Y.-G. Zheng, *Chem. Soc. Rev.*, 2018, **47**, 1516.
254 C. Nájera and J. M. Sansano, *Chem. Rev.*, 2007, **107**, 4584.
255 A. Perdih and M. Sollner Dolenc, *Curr. Org. Chem.*, 2007, **11**, 801.
256 K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013.
257 W. S. Knowles, *Acc. Chem. Res.*, 1983, **16**, 106.
258 R. A. A. Abdine, G. Hedouin, F. Colobert and J. Wencel-Delord, *ACS Catal.*, 2021, **11**, 215.
259 S. Ponra, B. Boudet, P. Phansavath and V. Ratovelomanana-Vidal, *Synthesis*, 2021, **53**, 193.
260 T. M. Faraggi, C. Rouget-Virbel, J. A. Rincón, M. Barberis, C. Mateos, S. García-Cerrada, J. Agejas, O. de Frutos and D. W. C. MacMillan, *Org. Process Res. Dev.*, 2021, **25**, 1966.
261 J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs and J.-Q. Yu, *Science*, 2014, **343**, 1216.
262 S. J. Zuend, M. P. Coughlin, M. P. Lalonde and E. N. Jacobsen, *Nature*, 2009, **461**, 968.
263 S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2009, **131**, 15358.
264 L. Navarre, R. Martinez, J.-P. Genet and S. Darses, *J. Am. Chem. Soc.*, 2008, **130**, 6159.
265 M. E. Kieffer, L. M. Repka and S. E. Reisman, *J. Am. Chem. Soc.*, 2012, **134**, 5131.
266 Z.-P. Yang, D. J. Freas and G. C. Fu, *J. Am. Chem. Soc.*, 2021, **143**, 8614.
267 S. Ni, A. F. Garrido-Castro, R. R. Merchant, J. N. de Gruyter, D. C. Schmitt, J. J. Mousseau, G. M. Gallego, S. Yang, M. R. Collins, J. X. Qiao, K.-S. Yeung, D. R. Langley, M. A. Poss, P. M. Scola, T. Qin and P. S. Baran, *Angew. Chem. Int. Ed.*, 2018, **57**, 14560.
268 D. A. Singleton and A. A. Thomas, *J. Am. Chem. Soc.*, 1995, **117**, 9357.
269 L. K. Vo and D. A. Singleton, *Org. Lett.*, 2004, **6**, 2469.
270 J. Burés, *Angew. Chem. Int. Ed.*, 2016, **55**, 2028.
271 E. Rémond, C. Martin, J. Martinez and F. Cavelier, *Chem. Rev.*, 2016, **116**, 11654.
272 B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 1656.
273 K. Okamoto, T. Hayashi and V. H. Rawal, *Chem. Commun.*, 2009, 4815.
274 P.-C. Leow, P. Bahety, C. P. Boon, C. Y. Lee, K. L. Tan, T. Yang and P.-L. R. Ee, *Eur. J. Med. Chem.*, 2014, **71**, 67.
275 Y. Li, X.-F. Lin, M.-Y. Liu, L.-L. Zhang, A.-P. Jin and J.-M. Lu, *J. Chem. Res.*, 2013, **37**, 294.
276 L. Nagarapu, H. R. Vulupala, R. Bantu, Y. Sajja and J. B. Nanubolu, *Tetrahedron: Asymmetry*, 2014, **25**, 578.
277 M. C. Henry, H. M. Senn and A. Sutherland, *J. Org. Chem.*, 2019, **84**, 346.
278 T. Horaguchi, E. Hasegawa, T. Shimizu, K. Tanemura and T. Suzuki, *J. Heterocycl. Chem.*, 1989, **26**, 365.
279 T. Kinoshita, D. Icbinari and J. Sinya, *J. Heterocycl. Chem.*, 1996, **33**, 1313.
280 N. Schröder, F. Lied and F. Glorius, *J. Am. Chem. Soc.*, 2015, **137**, 1448.
281 Y. Xie, B. Yu, J. Luo, B. Yin and H. Jiang, *Chin. J. Chem.*, 2021, **39**, 62.
282 P. A. Cleary and K. A. Woerpel, *Org. Lett.*, 2005, **7**, 5531.
283 J. C. L. Walker and M. Oestreich, *Org. Lett.*, 2018, **20**, 6411.
284 C. Hu, F. Chen, G.-P. Lu and W.-B. Yi, *Chinese Chem. Lett.*, 2022, **33**, 4293.
285 J. H. Kim, Y. S. Chun and S.-G. Lee, *J. Org. Chem.*, 2013, **78**, 11483.
286 S. Harada, R. Masuda, T. Morikawa and A. Nishida, *Eur. J. Org. Chem.*, 2021, **2021**, 4531.
287 H. Shigehisa, M. Hayashi, H. Ohkawa, T. Suzuki, H. Okayasu, M. Mukai, A. Yamazaki, R. Kawai, H. Kikuchi, Y. Satoh, A. Fukuyama and K. Hiroya, *J. Am. Chem. Soc.*, 2016, **138**, 10597.
288 W. Kong, C. Yu, H. An and Q. Song, *Org. Lett.*, 2018, **20**, 349.
289 S. Z. Tasker, A. C. Gutierrez and T. F. Jamison, *Angew. Chem. Int. Ed.*, 2014, **126**, 1889.
290 D. J. Mack, L. A. Batory and J. T. Njardarson, *Org. Lett.*, 2012, **14**, 378.
291 S. Zhang, D. Bedi, L. Cheng, D. K. Unruh, G. Li and M. Findlater, *J. Am. Chem. Soc.*, 2020, **142**, 8910.
292 J. Yao, R. Feng, Z. Wu, Z. Liu and Y. Zhang, *Adv. Synth. Catal.*, 2013, **355**, 1517.

293 J. A. Murphy, J. Garnier, S. R. Park, F. Schoenebeck, S.-Z. Zhou and A. T. Turner, *Org. Lett.*, 2008, **10**, 1227.
294 H. K. Moon, G. H. Sung, Y.-J. Yoon and H. J. Yoon, *Synlett*, 2016, **27**, 1577.
295 G. B. Bajracharya and S. S. Shrestha, *Synth. Commun.*, 2018, **48**, 1688.
296 D. K. Tanwar, A. Ratan and M. S. Gill, *Org. Biomol. Chem.*, 2017, **15**, 4992.
297 W. Xiong, C. Qi, T. Guo, M. Zhang, K. Chen and H. Jiang, *Green Chem.*, 2017, **19**, 1642.
298 N. Vodnola, R. Gujjarappa, C. K. Hazra, D. Kaldhi, A. K. Kabi, U. Beifuss and C. C. Malakar, *Adv. Synth. Catal.*, 2018, **361**, 135.
299 C. Tian, X. Yao, W. Ji, G. An and G. Li, *Eur. J. Org. Chem.*, 2018, **2018**, 5972.
300 J. Fang, Z.-K. Wang, S.-W. Wu, S.-G. Shen, G.-Z. Ao and F. Liu, *Chem. Commun.*, 2017, **53**, 7638.
301 T. H. Jepsen, E. Glibstrup, F. Crestey, A. A. Jensen and J. L. Kristensen, *Beilstein J. Org. Chem.*, 2017, **13**, 988.
302 S. Raghavan and A. Rajender, *Tetrahedron*, 2004, **60**, 5059.
303 F. Olivito, N. Amodio, M. L. Di Gioia, M. Nardi, M. Oliverio, G. Juli, P. Tassone and A. Procopio, *Med. Chem. Commun.*, 2019, **10**, 116.
304 A. Yazici and S. G. Pyne, *Org. Lett.*, 2013, **15**, 5878.
305 X. Creary, B. D. O'Donnel and M. Vervaeke, *J. Org. Chem.*, 2007, **72**, 3360.
306 A. Fernández-Mateos, S. Encinas Madrazo, P. Herrero Teijón and R. Rubio González, *J. Org. Chem.*, 2015, **80**, 4378.
307 J. Wang, Y. Zhao, W. Zhao, P. Wang and J. Li, *J. Carb. Chem.*, 2016, **35**, 445.
308 L. Crespin, L. Biancalana, T. Morack, D. C. Blakemore and S. V. Ley, *Org. Lett.*, 2017, **19**, 1084.
309 N. Zanatta, D. Faoro, S. C. Silva, H. G. Bonacorso and M. A. P. Martins, *Tetrahedron Lett.*, 2004, **45**, 5689.
310 C. Karmel, C. Z. Rubel, E. V. Kharitonova and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2020, **132**, 6130.
311 B. Larizza, *Gazz. Chim. Ital.*, 1959, **89**, 2402.
312 Y. Song, H. Zhang, J. Guo, Y. Shao, Y. Ding, L. Zhu and X. Yao, *Eur. J. Org. Chem.*, 2021, **2021**, 5914.
313 H. Hu, X. Wu, Y. Qiu, C. Wang, W. Wang, G. Yue, H. Wang, J. Feng, G. Wang, H. Ni and P. Zou, *Org. Lett.*, 2022, **24**, 832.
314 Q. Zhu, E. C. Gentry and R. S. Knowles, *Angew. Chem. Int. Ed.*, 2016, **55**, 9939.