A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

Synthesis and Application of Pinene-Pyridine Derivatives in Asymmetric Catalysis

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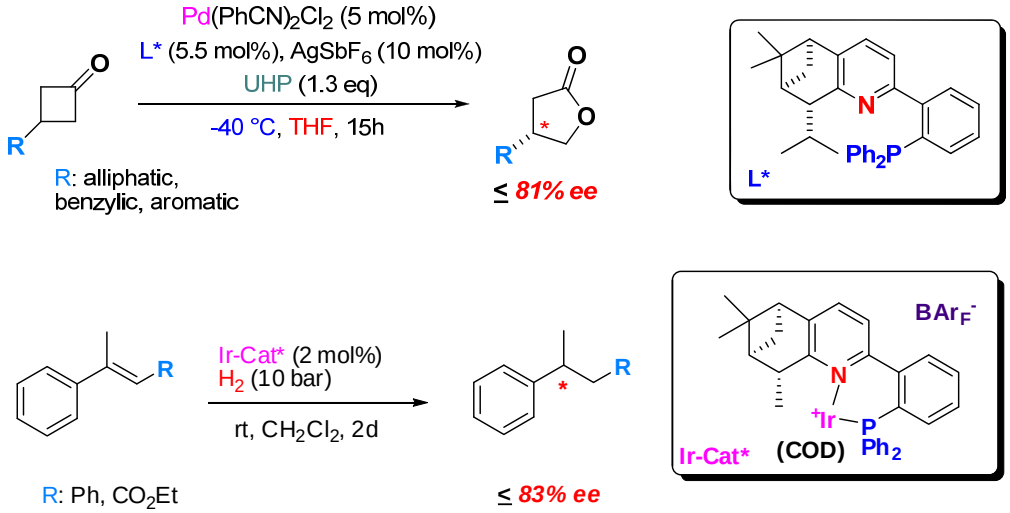
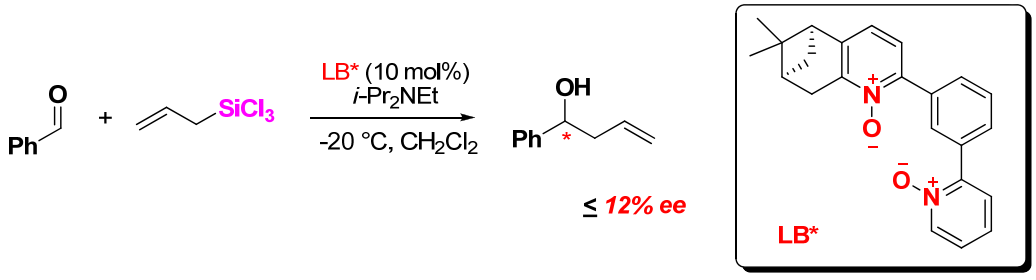
Abstract

The research described herein focuses on the synthesis of chiral pinene-pyridine derivatives, and their application in asymmetric catalysis. Both transition metal catalysed and organocatalytic transformations were investigated.

Chiral pyridine-phosphines based on α-pinene were synthesised and applied as efficient *P*,*N*-ligands for the enantioselective palladium(II)-catalysed Baeyer-Villiger oxidation of prochiral 3-substituted cyclobutanones to furnish chiral γ-butyrolactones in up to **81% ee**. Complexes of these ligands with iridium can also promote asymmetric hydrogenation of olefins in up to **83% ee**.



Novel *N*,*N*'-dioxides were synthesised from α-pinene and a range of 2-pyridine-acetophenones by employing Kröhnke annulation reaction as the key cyclisation step. Although poor enantioselectivity was achieved (up to **12% ee**), high reactivity of the catalysts is, however, promising.



Acknowledgement

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For my parents

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Abbreviations

n-BuLi	*n*-Butyl lithium
BAr_F	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BSA	Bis(trimethylsilyl)acetamide
COD	Cyclooctadiene
m-CPBA	3-Chloroperbenzoic acid
°C	Degrees centigrade
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
ee	Enantiomeric excess
L*	Chiral ligand
LB	Lewis Base
LDA	Lithium diisopropylamide
MW	Microwave
Naph	Naphthyl
p-NBA	*p*-Nitrobenzoic acid
NOE	Nuclear Overhauser Effect
Py	Pyridine
rt	Room temperature
TBDMS	*tert*-Butyldimethylsilyl
Tf	Triflic or Trifluoromethanesulfonic
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPP	5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine
UHP	Urea Hydrogen Peroxide

Preface

The demand for enantiopure chiral compounds is continuously rising over the years, primarily due to the development of pharmaceuticals but also for the flavour and aroma chemicals as well as agricultural chemicals. The global annual sales of single-enantiomer compounds are expected to exceed £7 billion by the end of 2009.[1]

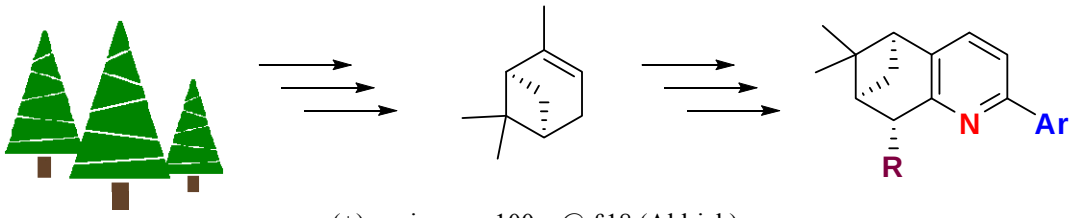
This explosive growth of the enantiopure compounds market is directly linked with the fact that enantiomers of a chiral compound can have dramatically different biological activities. To prevent any tragic accidents such as the Thalidomide case, the U.S. Food & Drug Administration issued, in 1992, a policy on stereoisomeric drugs. Racemates can be sold (FDA still occasionally approves them) but the enantiomers must be characterised pharmacologically and toxicologically. Since one enantiomer could be unsafe or merely inactive baggage, and the cost of characterisation is so high, the drug industry has shifted to making single-enantiomer forms of chiral compounds. Furthermore, the switch from a racemic to a single-enantiomer initially done to improve the therapeutic activities of drugs, is more and more used for economic consideration as it allows pharmaceutical companies to extend the patent protection of their blockbusters.[2]

Chemists possess a variety of chiral technologies to create enantiomerically pure compounds. While the classical resolution of racemates has the obvious drawback of affording molecules with a maximum of 50% yield, asymmetric syntheses involving the chiral pool or chiral auxiliaries[3] are typically more cost effective. Therefore, the most elegant and "atom economic" transformation to introduce chirality into a molecule is by using catalytic asymmetric synthesis. Until recently, the majority of catalytic asymmetric reactions employed two kinds of catalysts: chiral complexes based on transition metals[4] and enzymes.[5] Metals have a large array of reactivity patterns that can easily be tuned by varying ligands. But, due to some drawbacks inherent to metals, such as their cost, their toxicity and the difficulty to remove their traces from the desired product, a complementary type of catalysis has emerged in the last few years, namely organocatalysis.[6,7]

Far too often, catalysts are designed for a particular reaction. Therefore, we aim to develop novel versatile chiral pyridines (based on the inexpensive pinene moiety) which can be used either as ligands for transition metals (**Metal Catalysis**) or on their own (**Organocatalysis**).

Graphical Abstract

Chapter 1. Pinene in Asymmetric Reactions

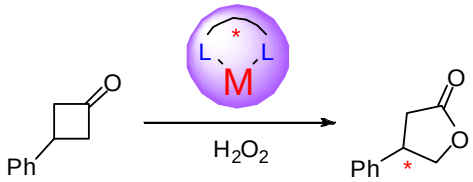


(+)-α-pinene – 100 g @ £18 (Aldrich)

Pinene has been used over the years as an inexpensive source of chirality for various asymmetric reactions.

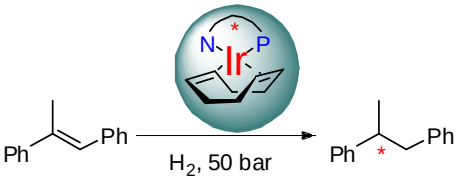
Chapter 2. Metal Catalysed Asymmetric Reactions

A novel class of ligands, the unsymmetrical *P*,*N*-ligands, has recently been developed and showed good level of enantioselectivity in various reactions particularly where the privileged chiral C_2-symmetric ligands fail.



Interestingly, it was only in 1994, more than a century after the reaction discovery, that the first asymmetric Baeyer-Villiger oxidation was reported.
The different metals used will be specially reviewed here.

Asymmetric hydrogenation of unfunctionalised olefins with iridium-based catalysts is a recent breakthrough.
General aspects and recent advances will be particularly highlighted in this chapter.

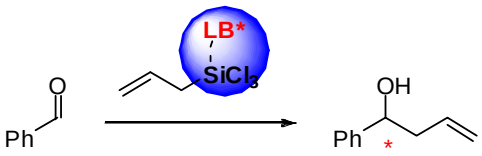


Chapter 3. Synthesis and Application of Pinene-Derivative Pyridines I

In this chapter, the synthesis of six novel *P*,*N*-ligands from (+)-α-pinene is described. Their application for the asymmetric iridium-catalysed hydrogenation of olefins and the palladium-catalysed Baeyer-Villiger oxidation of cyclobutanones will be discussed here.

Chapter 4. Organocatalysis – Activation of Si with Lewis bases

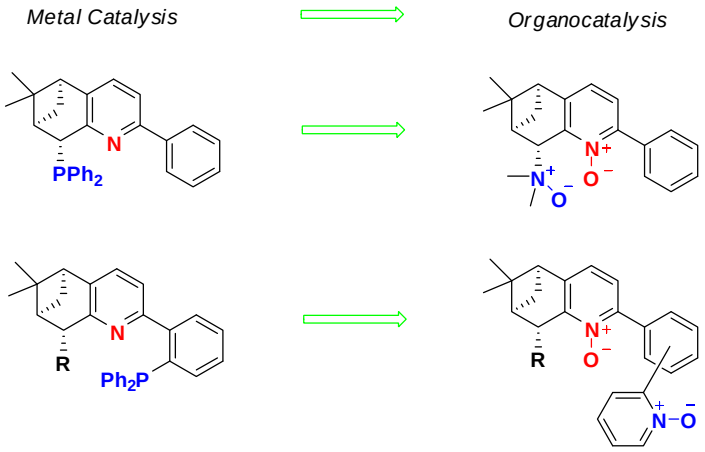
Activation of the cheap and non-toxic silicon atom by a *Lewis* base (LB) has proven to be an efficient method to avoid the use of transition metals.



Herein, we report the literature overview of several chiral Lewis bases utilised for the asymmetric allylation of benzaldehyde with allyl trichlorosilane.

Chapter 5. Synthesis and Application of Pinene-Derivative Pyridines II

Novel pyridines *N*-oxides were designed after the "privileged" pinene-pyridine fused structure (see chapter 3). Their synthesis and application in the asymmetric allylation reaction of benzaldehyde is reported here.



1 Pinene in Asymmetric Reactions

1.1 Introduction

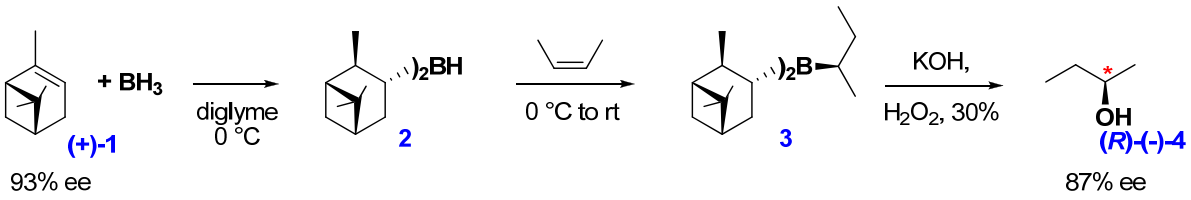
Since Nature has provided a wide variety of chiral materials, they are obvious and usually inexpensive sources to generate new chiral auxiliaries as well as novel chiral ligands for asymmetric catalysis.

Although amino acids and carbohydrates have often been used as chiral pool,[8] terpenes, with their modest functionality that allows convenient structural manipulations, have rather found their utilities as chiral auxiliaries.[3] Among natural monoterpenes, pinene derivatives have become famous in the 80s because of their development as chiral boron reagents.

1.2 Pinene-Based Boron Reagents

The first real potential of pinene in asymmetric synthesis appeared in 1961,[9] when H. C. Brown realised the first asymmetric hydroboration of *cis*-2-butene with diisopinocampheylborane, Ipc_2BH **2**, prepared from (+)-α-pinene **1** and borane in nearly a complete stereoselective way (**Scheme 1**).

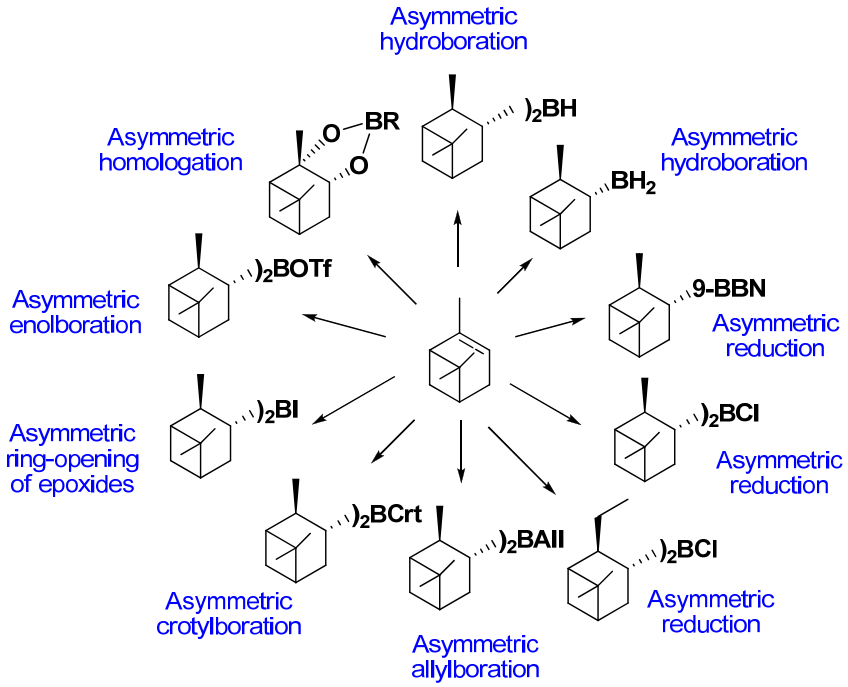
Scheme 1. First asymmetric hydroboration of cis-2-butene with Ipc_2BH



Half a century later, α-pinene and borane have become an inseparable couple, a powerful combination, allowing a wide range of reactions to become enantioselective (**Chart 1**).[2,10] B-Ipc-9-BBN and Ipc_2BCl made asymmetric reduction easy (acetophenone-type ketones were reduced in up to 98% ee). $Ipc_2BAllyl$ and $Ipc_2BCrotyl$ made asymmetric allyl- and crotylboration readily available for asymmetric synthesis (up to 93% ee). The ring-opening reaction of *meso*-epoxides with Ipc_2BI provided a convenient route to enantiomerically pure halohydrins (up to 99% ee). Ipc_2BOTf has been utilised by Paterson[11] for asymmetric

enolboration reactions. Finally, Matteson[12] developed asymmetric homologation reactions using pinanediol boronates.

Chart 1. Use of α-pinene and borane in asymmetric reactions



Although pinene derivatives have a long history of asymmetric induction as chiral auxiliaries (*vide supra*), their application in asymmetric catalysis is rather undeveloped.

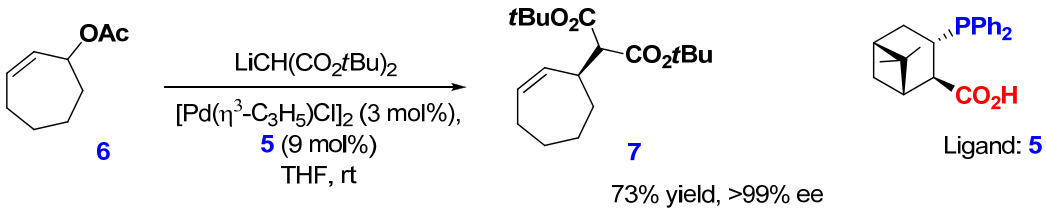
1.3 Pinene in Asymmetric Catalysis

Whereas camphor-derived ligands have been widely used,[13] the corresponding ligands based on pinene have been only rarely explored. There are mainly two types of pinene ligands: those in which the coordination units are pendent to the chiral pinene moiety and those in which the pinene is annulated with a pyridine ring increasing the rigidity of the whole structure.

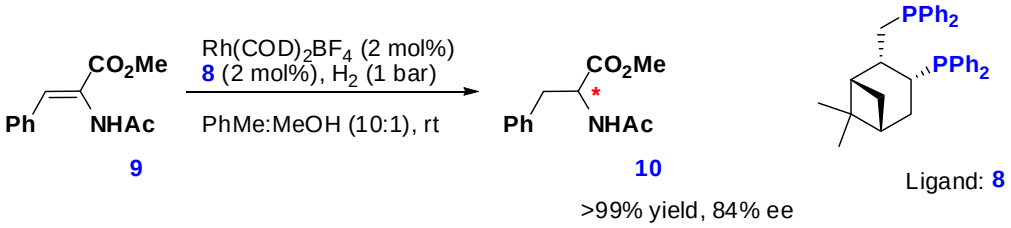
1.3.1 Pendent Pinene Moiety

Phosphine type ligands **5** and **8** developed by Helmchen[14] and Knochel[15] have shown high level of enantioselectivity in both palladium-catalysed allylic alkylations[14] of cyclic substrate **6** (up to 99% ee) (**Scheme 2**) and rhodium-catalysed hydrogenation of methyl acetamidocinnamate **9** (84% ee) (**Scheme 3**).[15] Pinene-derived bipyridines **11a-b**, terpyridines **12a-b** and phenanthrolines **13a-b** developed by Chelucci[16] exhibited low-to-moderate enantioselectivity in the palladium-catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate **14** with dimethyl malonate (up to 50% ee) (**Scheme 4**).

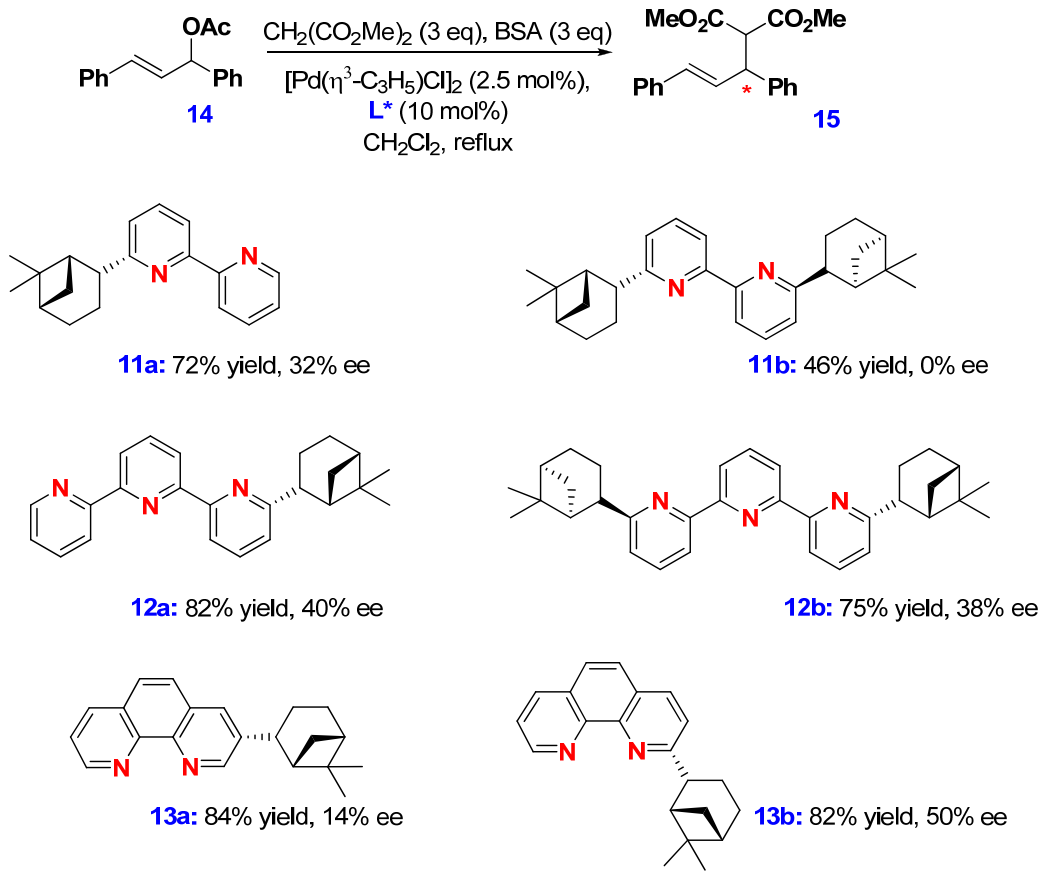
Scheme 2. β-Phosphinocarboxylic acid used in Pd-catalysed asymmetric allylic alkylation



Scheme 3. Diphosphine used in Rh-catalysed hydrogenation



Scheme 4. Bipyridines-, terpyridines- and phenanthrolines-pinene derivatives for the asymmetric Pd-catalysed allylic alkylation



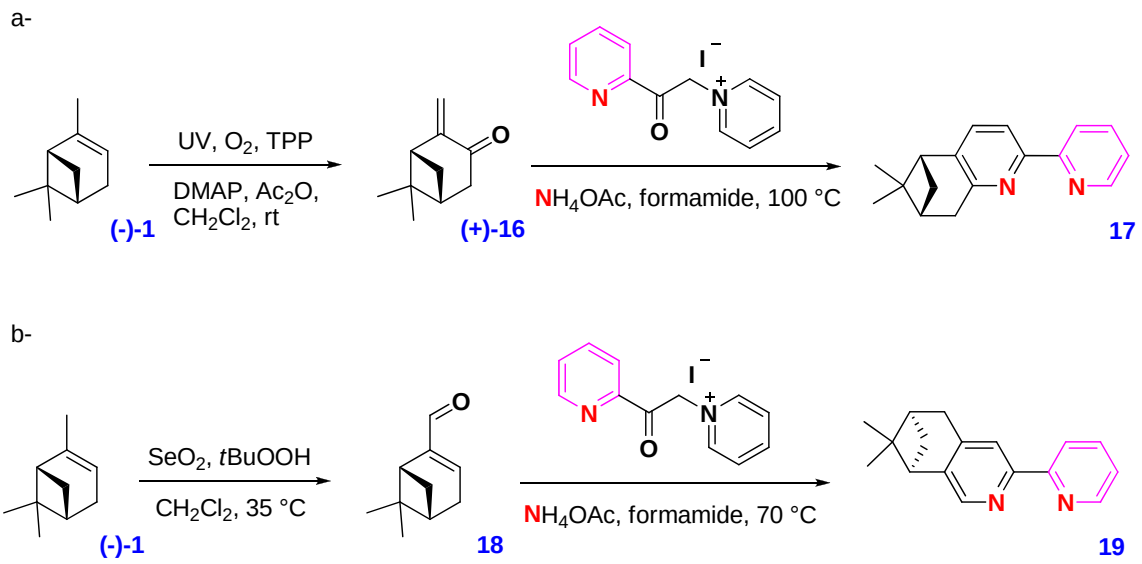
The poor results obtained by Chelucci in his attempt to use pendent pinene ligands (*vide supra*) can be explained by a loose character of the chiral motif which is also relatively far away from the coordinating centres. A more rigid backbone would have the noticeable advantage in reducing the conformational flexibility of the catalysts, which would therefore diminish the number of competing diastereoisomeric pathways.

1.3.2 Pinene Fused to Pyridine Ring

The first ligands containing a rigid pinene-pyridine type framework were reported in 1992 by von Zelewsky *et al.*[17] The chiral bipyridines **17** and **19** (**Scheme 5**) were the first two members of the big CHIRAGEN (CHIRAlity GENerators) ligands family developed by von Zelewsky.[18,19] The pinene-bipyridine core was constructed in only two steps from the commercially available monoterpene (–)-α-pinene **1**. For the formation of the [5,6]-

pinenebipyridine **17** (**Scheme 5-a**), (–)-α-pinene **1** was photochemically oxidised by singlet oxygen into (+)-pinocarvone **16**, followed by a Kröhnke annulation with 2-acetylpyridinepyridinium iodide with an overall yield of 55%.

Scheme 5. Formation of the first rigid pinene-pyridine type framework



In the case of formation of [4,5]-pinenebipyridine **19** (**Scheme 5-b**), (–)-α-pinene **1** was first transformed into myrtenal **18** by allylic oxidation using selenium dioxide in the presence of *tert*-butyl hydroperoxide, followed by the key Kröhnke annulation with 2-acetylpyridinepyridinium iodide (75% overall yield).

The unfused pyridine ring originates from the Kröhnke salt used in the annulation step; it is therefore very easy to introduce other functionalities. Furthermore, deprotonation of **17** and **19** with LDA is fully regiospecific at the benzylic position on the pinene moiety which allows further modification of the structure *via* nucleophilic substitutions of a wide variety of electrophiles. NOE experiments have also shown that the substitution is completely stereoselective,[17] introducing the electrophilic moiety from the sterically less hindered side.

As described before, the fused pinene-pyridine framework is not only easy to build (2 steps synthesis) but it is also the rigid and extremely modular architecture that makes it suitable for incorporating into the chiral backbone of ligands designed for asymmetric catalysis.

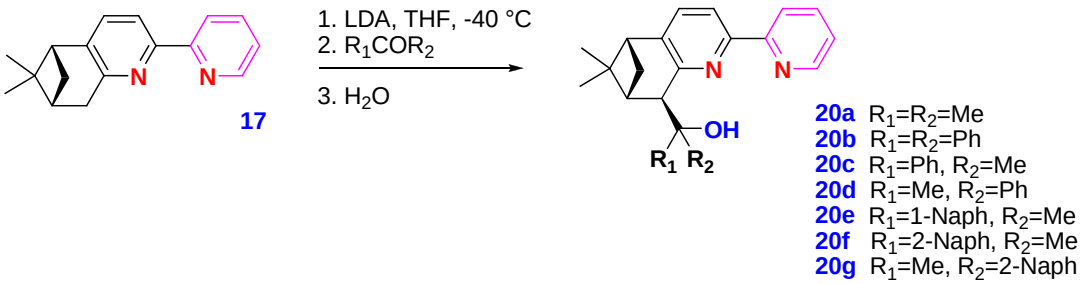
Although [4,5]-pinenebipyridines (such as **19**) have been successfully applied in asymmetric catalysis,[20] we have decided to focus our attention on the use of [5,6]-pinene(bi)pyridine frameworks since any substitutions at the benzylic position will generate a new stereogenic centre closer to the coordinating units, in comparison to their [4,5]-counterparts.

1.3.2.1 [5,6]-Pinenebipyridines in Asymmetric Catalysis

2,2'-Bipyridine and its derivatives have received considerable attention over the last decade due to their remarkable chemistry.[21] Unlike many other common ligands such as cyclopentadienyls and phosphines, they are extremely stable in both aqueous solution and to atmospheric oxygen, which simplifies both their preparation and long-term storage.

[5,6]-pinenebipyridines appeared as asymmetric ligands as early as in 1998, when von Zelewsky reported the use of the bipyridyl alcohols for the enantioselective addition of diethylzinc to benzaldehyde.[22] The ligands **20a-g** were easily prepared from the fused pinene-bipyridine **17** (*vide supra*) by simple deprotonation with LDA and consecutive reaction with a variety of ketones (**Scheme 6**).

Scheme 6. Formation of the bipyridyl alcohols **20a-g**



Ligands **20a-g** were tested in asymmetric addition of diethylzinc to benzaldehyde providing quantitative yield and reasonably high enantioselectivity (**Scheme 7 and Table 1**). Although the configuration of the stereogenic centre at the hydroxyl group does not seem to be a prerequisite for high enantioselectivity (*entries 1&2*), it definitively has a big influence regarding the selectivity of the reaction since the pairs of ligands **20c/20d** (*entries 3&4*) and **20f/20g** (*entries 6&7*) exhibit very different enantioselectivity.

Scheme 7. Enantioselective addition of diethylzinc to benzaldehyde

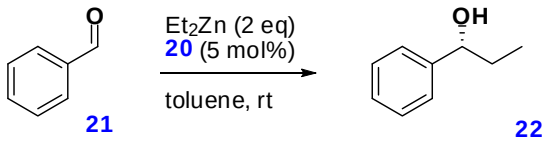
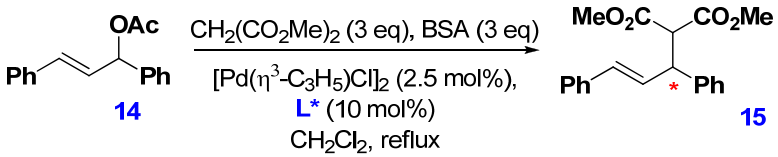


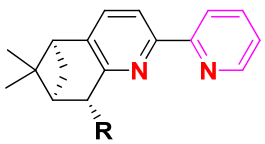
Table 1. Enantioselective addition of diethylzinc to benzaldehyde with **20a-g** (**Scheme 7**)[22]

Entry	Ligand	Yield (%)	ee (%)
1	**20a**	100	73
2	**20b**	100	79
3	**20c**	100	78
4	**20d**	100	52
5	**20e**	99	86
6	**20f**	100	82
7	**20g**	99	47

Inspired by the von Zelewsky's bipyridines, Chelucci reported a set of [5,6]-pinene-bipyridines **23a-f** (**Scheme 8**)[23] for the enantioselective palladium-catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate **14** with dimethyl malonate.

Scheme 8. Bipyridines for the enantioselective Pd-catalysed allylic alkylation





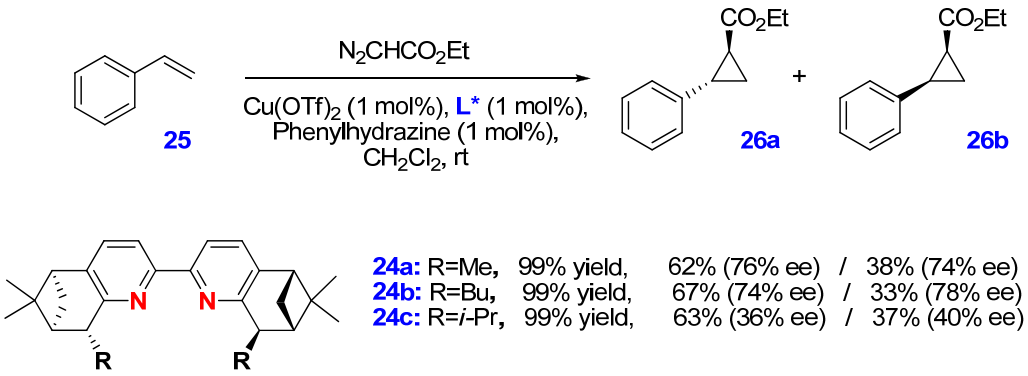
23a: R=H, 93% yield, 11% ee
23b: R=Me, 95% yield, 74% ee
23c: R=Bn, 94% yield, 89% ee
23d: R=*i*-Pr, 91% yield, 79% ee
23e: R=$C(CH_3)_2OMe$, 77% yield, 16% ee
23f: R=$C(CH_3)_2OTMS$, 68% yield, 26% ee

All the catalysts showed good reactivity (yields are above 65%). In terms of enantioselectivity, the group at the benzylic position seems to have a big influence. No

substituent (ligand **23a**) or too sterically demanding substituents (ligands **23e** and **23f**) resulted in poor enantioselectivity. At the same time, methyl, *iso*-propyl and benzyl groups exhibit good to high enantioselectivity (74%, 79% and 89% ee, respectively).

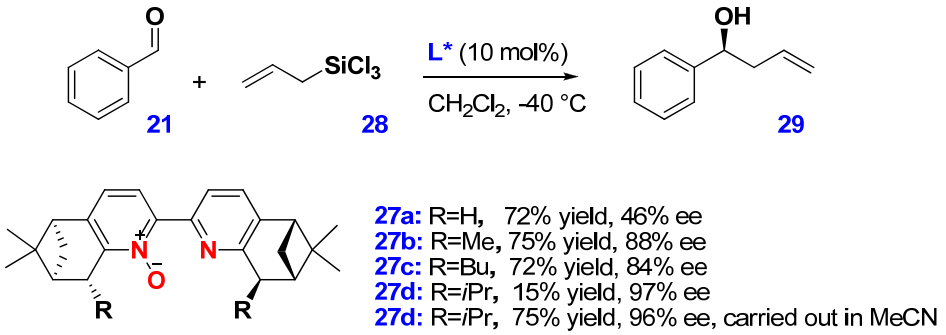
Later, our group reported on the use of C_2-symmetrical [5,6]-pinene-bipyridines **24a-c** in the asymmetric cyclopropanation of styrene (**Scheme 9**).[24] The copper catalysts were generated *in situ*. All the catalysts gave similar ratio of diastereoisomers **26a** and **26b**. However, as previously described, the enantioselectivity was clearly dependent on the substituent at the benzylic position. *iso*-Propyl group proved too bulky, resulting in a drop of enantioselectivity in both products.

Scheme 9. Asymmetric cyclopropanation of styrene using **24a-c**



Since our group is also interested in organocatalysis, terpene-derived bipyridines were oxidised into novel chiral *N*-oxides **27a-d** which proved to be efficient organocatalysts for the asymmetric allylation of benzaldehyde **21** with allyl trichlorosilane **28** (up to 97% ee) (**Scheme 10**).[25] Once again, the unsubstituted catalyst (**27a**) led to lower enantioselectivity in comparison with its alkylated counterparts.

Scheme 10. Enantioselective allylation of benzaldehyde using **27a-d**



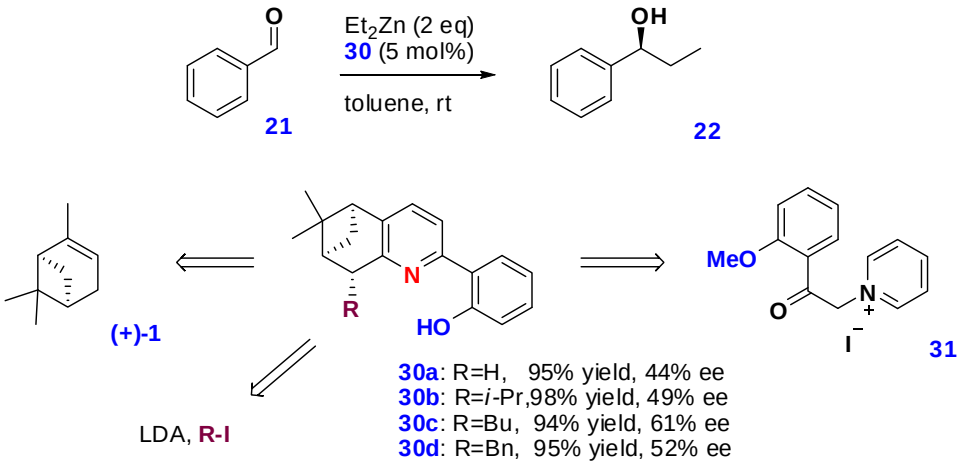
1.3.2.2 [5,6]-Pinenemonopyridines in Asymmetric Catalysis

For a long time, ligands with C_2-symmetric structural architecture dominated the field of asymmetric catalysis. More recently, nonsymmetrical ligands have received considerable attention. By modifying the Kröhnke salt structure, Chelucci advanced the field of unsymmetrical [5,6]-pinenemonopyridines by developing a wide range of *N*,*O*-, *N*,*S*- and *N*,*P*-ligands. [26-28]

N,*O*-Ligands

Monopyridine *N*,*O*-ligands **30a-d** were the first set of pinene-pyridine nonsymmetrical ligands investigated by Chelucci.[26] Their synthesis was relatively short (4 steps), although the phenolic hydroxyl group had to be introduced in methoxy form to prevent possible complications during the alkylation step employing LDA. Catalytic activity of ligands **30a-d** was then examined in the enantioselective addition of diethylzinc to benzaldehyde (**Scheme 11**). However, the results were inferior to those obtained with von Zelewsky's bipyridyl alcohols.[22]

Scheme 11. *N*,*O*-ligands **30a-d** for the enantioselective addition of Et_2Zn to benzaldehyde



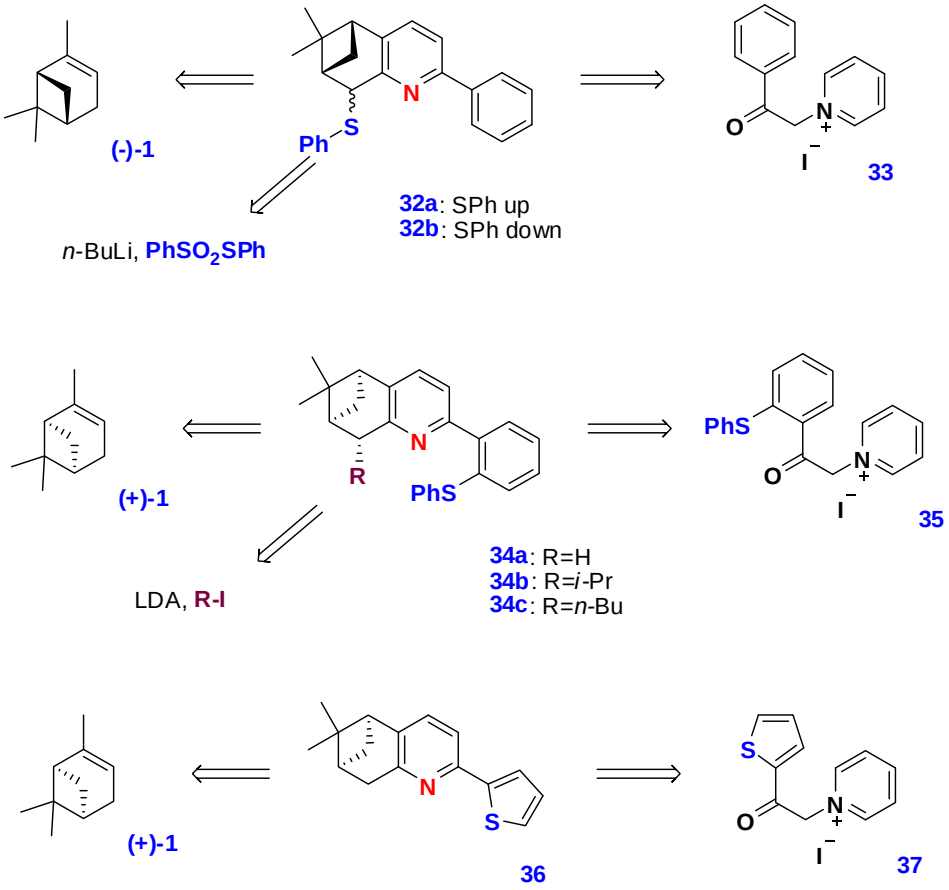
N,*S*-Ligands

As a further extension of the series, Chelucci investigated in detail pinene-derived *N*,*S*-ligands. A wide range of *N*,*S*-ligands were generated by systematically modifying the alkyl chain at the benzylic position and also varying the type of the sulfur donor and its position in the molecule (**Chart 2**).[27] The synthesis of the ligands followed the traditional pattern (between two and three steps) involving the classical Kröhnke annulation and alkylation

sequence. Surprisingly, the introduction of the SPh group in the benzylic position was not as selective as usual, leading to the formation of two diastereoisomers **32a:32b** in a 3:1 ratio in favour of the expected isomer (SPh up).[27a]

All the *N*,*S*-ligands were tested in the enantioselective palladium-catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate **14** with dimethyl malonate (**Scheme 12**), which produced rather contrasting results (**Table 2**). When the coordinating thioether group is directly bonded to the stereogenic benzylic centre (*entries 1&2*), high level of enantioselectivity are obtained (up to 83% ee).[27a] As stated previously, it is the configuration at the benzylic position which controls the configuration of the product (*entries 1&2*). Interestingly, when the thioether group is placed on the phenyl ring,[27b] both the reactivity and the enantioselectivity drop significantly (*entries 1&3*). The size of the alkyl group in the ligand **34a** has a dramatic effect on the outcome of the reaction (*entries 4&5*). The presence of a bulky *iso*-propyl group (**34b**) results in complete deactivation of the catalyst, however the presence of the long chain *n*-butyl (**34c**) leads to a slight improvement of the enantioselectivity (from 20% to 32% ee). It is also interesting to note that when the sulfur atom is incorporated into an aromatic ring (ligand **36**),[27c] the palladium complex with **36** becomes completely inactive (*entry 6*).

Chart 2. *N*,*S*-ligands family



Scheme 12. Enantioselective Pd-catalysed allylic alkylation using the *N*,*S*-ligands family

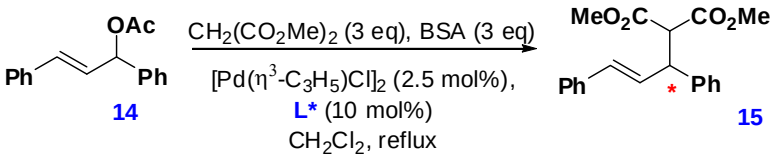


Table 2. Enantioselective Pd-catalysed allylic alkylation using the *N*,*S*-ligands family (**Scheme 12**)[27]

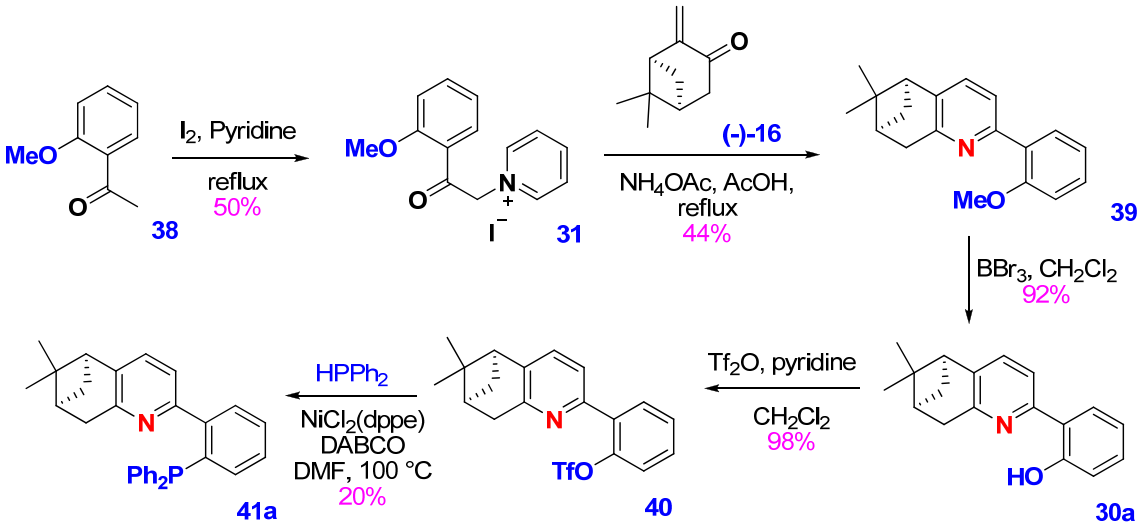
Entry	Ligand	Yield (%)	ee (%)
1	**32a**	90	83 (*R*)
2	**32b**	85	78 (*S*)
3	**34a**	54	20 (*S*)
4	**34b**	0	N.D.
5	**34c**	61	32 (*R*)
6	**36**	0	N.D.

N.D. = Not determined

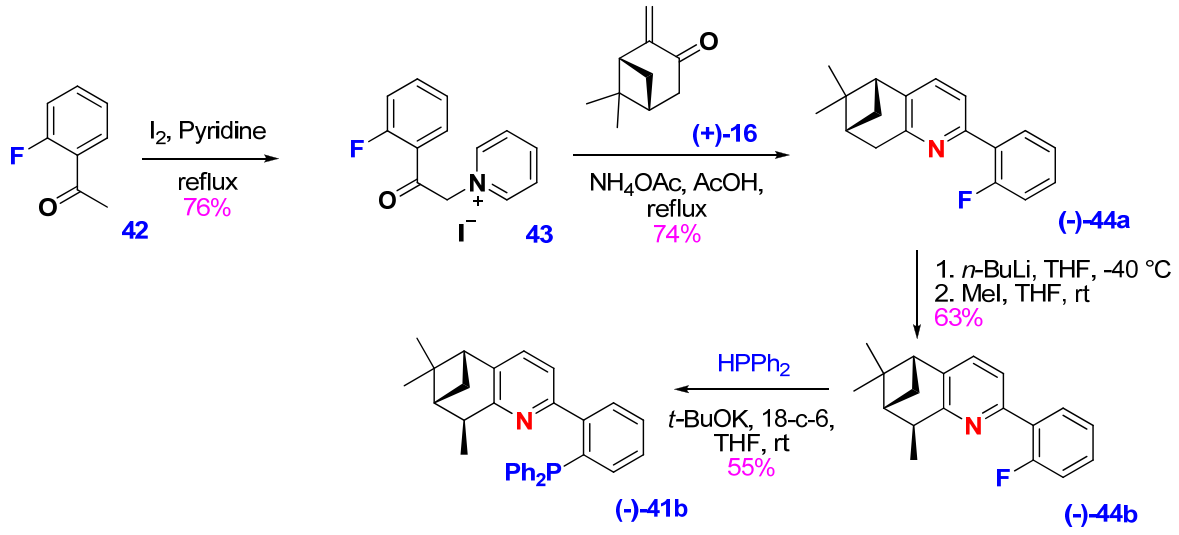
N,*P*-Ligands

A vast number of nonsymmetrical *N*,*P*-ligands have been reported over the past decade, however relatively few examples contained pyridine as a coordinating unit. Chelucci[28] and our group[29] reported independently the use of [5,6]-pinenemonopyridine-phosphine in asymmetric catalysis. Chelucci's strategy to synthesise the *N*,*P*-ligand (+)-**41a** was based on the key nickel-catalysed coupling of the triflate **40** with diphenylphosphine (**Scheme 13**). The manipulations of the hydroxyl group make the synthesis of (+)-**41a** relatively long with poor overall yield (around 4%). Our group employed a different approach. A nucleophilic aromatic substitution of the fluoro derivative **44** was utilised as the key step for the introduction of the diphenylphosphine unit (**Scheme 14**), making the synthesis two steps shorter than the sequence used by Chelucci, with an improved overall yield (31%).

Scheme 13. Chelucci's synthesis of *N*,*P*-ligand (+)-**41a**

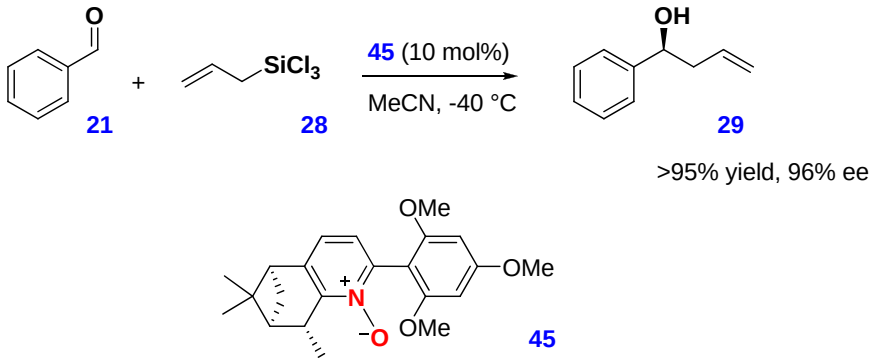


Scheme 14. Approach of our group for the synthesis of *N*,*P*-ligand (–)-**41b**



Our group's continued interest in organocatalysis recently led to development of a series of very active nucleophilic catalysts based on [5,6]-pinenemonopyridine.[30] *N*-Oxide **45** exhibited a very high level of enantioselectivity in the allylation of benzaldehyde with allyl trichlorosilane (up to 96% ee) (**Scheme 15**).

Scheme 15. Allylation of benzaldehyde with (+)-METHOX **45**



1.4 Summary

The [5,6]-pinenemonopyridine framework seems to have all the characteristics required for an efficient chiral backbone of ligands designed for both asymmetric metal- and organo-catalysis. The catalysts are very easy to build (2 steps via Kröhnke annulation), the pinene moiety fused to the pyridine ring makes all the structures extremely rigid; furthermore, the modular character of these structures provides an opportunity for fine-tuning the steric arrangement.

However, it is important to note that the influence of the substitution pattern at the benzylic position on the enantioselective outcome of the catalysed reaction is not easy to predict.

2 Metal-Catalysed Asymmetric Reactions

2.1 Introduction

Over the last 30 years, transition metal catalysis has become an indispensable tool in modern organic synthesis[31] due to high enantioselectivities, reactivity and flexibility of protocols. The importance of transition metal-based catalysis is illustrated by the Nobel Prize award to William S. Knowles and Ryoji Noyori for their work on "chirally catalysed hydrogenation reactions" and to Barry K. Sharpless for the development of "transition metal catalysed oxidation reactions" in 2001.[32] There are, however, a number of transformations for which no practical level of enantioselectivity is obtained, requiring the development of novel catalytic systems.

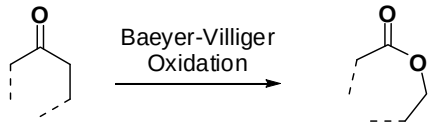
The Baeyer-Villiger oxidation (rearrangement) allows the conversion of ketones (cyclic) into the corresponding esters (lactones).[33] Interestingly, it was only in 1994, more than a century after the reaction discovery, that the first asymmetric Baeyer-Villiger oxidation was reported.[34,35] Although an enormous effort was made over the last decade (a wide range of metals have been screened), the level of enantioselectivity remains unsatisfactory (≤87% ee). In this chapter, the development of the asymmetric metal-catalysed Baeyer-Villiger oxidation will be discussed.

Second part of this chapter deals with asymmetric hydrogenation. Whereas the enantioselective hydrogenation of functionalised olefins with both rhodium and ruthenium has a long history,[31] "largely unfunctionalised alkenes"[36] have been examined only recently. Pfaltz and co-workers have developed complexes[37] of phosphine-oxazolines with iridium which have been used successfully in the asymmetric hydrogenation of arylalkenes. However, the iridium-catalysed asymmetric hydrogenation is still highly substrate dependent, and the development of new efficient chiral ligands that tolerate a broader range of substrates remains a challenge. In this chapter, the asymmetric iridium-catalysed hydrogenation of unfunctionalised olefins will be reviewed.

2.2 Baeyer-Villiger Oxidation (BVO)

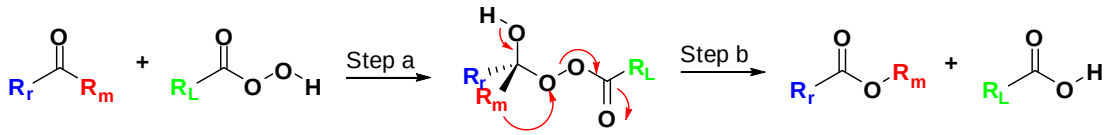
The Baeyer-Villiger conversion of aldehydes and ketones into the corresponding esters by insertion of an oxygen atom into the C-C bond[33] **(Figure 1)** is an established, regioselective and stereospecific synthetic tool.[38]

Figure 1. Baeyer-Villiger oxidation



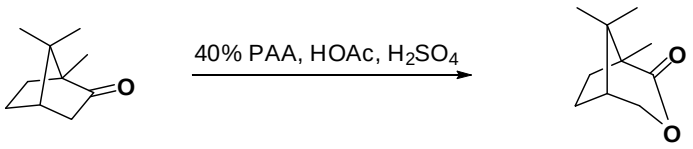
The generally accepted two-step mechanism proposed by Criegee[39] in 1948 was confirmed a few years later with isotopic labelling experiments[40] and kinetic studies. As shown in **Scheme 16**, the stepwise process consists of an initial reversible nucleophilic attack of the peroxy acid on the carbonyl moiety of the ketone (step a). This step is followed by the rearrangement of the tetrahedral intermediate, the Criegee adduct. Subsequent irreversible migration of one of the two substituents and a concomitant cleavage of the O-O bond in a concerted manner leads to ester and acid (step b).

Scheme 16. BVO mechanism

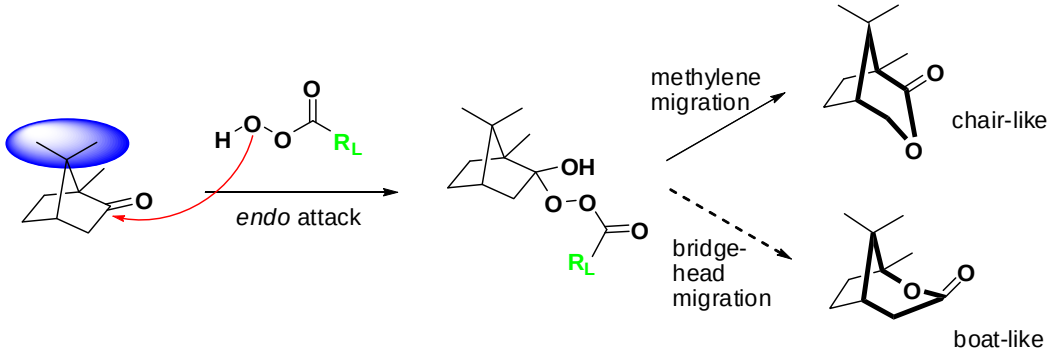


Doering and Speers[41] established that the rearrangement is regioselective with migration of the group that is best able to stabilise the developing positive charge, i.e., a *tert*-butyl substituent is more prone to migrate than a methyl group. Although this rule dictates the behaviour of most of the ketones, there are other electronic and steric effects which can affect the migration step. In the case of polycyclic systems, in particular, steric effects proved to be important. For instance, Baeyer-Villiger rearrangement of camphor remained a mystery in the 1950's as the methylene group rather than the tertiary bridgehead carbon atom was found to migrate preferentially **(Scheme 17)**. Murray, Johnson, Pederson and Ott[42] proposed to take into account the steric effect generated by the two methyl groups at the camphor bridge inducing the attack of the peracid in an *endo*-fashion. Migration of the bridgehead carbon would therefore lead to a boat-like lactone which is much less favourable than the migration of the methylene group affording a chair-like lactone **(Scheme 18)**.

Scheme 17. Camphor mystery



Scheme 18. *endo* attack ruling the regioselectivity



Migration of the substituents is not only regioselective (as discussed above) but also proceeds with retention of configuration,[43] making the Baeyer-Villiger oxidation particularly attractive for stereospecific synthesis.

The choice of oxidant is primordial for several reasons, as it acts both as a nucleophile and a leaving group. A reactivity order of oxidants has been established. Peroxy acids, and especially *m*-CPBA, are the most efficient oxidants, followed by alkyl peroxides. The use of molecular oxygen as the terminal oxidant in the presence of sacrificial aldehyde[44] is a greener and safer alternative to the highly reactive and potentially explosive peracids. Finally, hydrogen peroxide, which is not reactive enough to promote the BVO, can only be used in the presence of carboxylic acids to form peracids *in situ*[45] or in combination with catalysts.[38c,e-f] This is where metal catalysts can play an important role in the development of the asymmetric Baeyer-Villiger Oxidation[38e-f, 46] through selection of appropriate chiral ligands.

2.2.1 Metal-Catalysed Baeyer-Villiger Oxidation

Participation of metals can influence the BVO in several ways. Metals can be used as Lewis acids to activate the carbonyl group of the substrate towards the nucleophilic addition of the peroxy species. They also can increase the nucleophilicity of the peroxy species through

coordination. Finally, metals can facilitate *in situ* formation of peroxy acids from a sacrificial aldehyde and molecular oxygen.

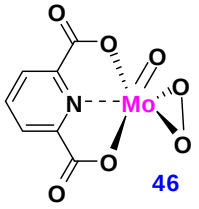
2.2.1.1 Lewis Acids Activation

The use of Lewis acids to accelerate BVO through the activation of the ketone was pioneered by Noyori and co-workers in 1982.[47] A wide range of cyclic ketones were oxidised into the corresponding lactones in moderate to good yields using bis(trimethylsilyl) peroxide as an oxidant and a catalytic amount of trimethylsilyl trifluoromethanesulfonate as a Lewis acid. It is also interesting to note that the oxidation occurred specifically at the carbonyl functionality, while carbon-carbon double bonds were not affected. Takai *et al.*[48] reported similar results using bis(trimethylsilyl) peroxide as an oxidant and Lewis acids such as $SnCl_4$ or $BF_3.Et_2O$. An ingenious fluorous biphasic protocol using tin bis(perfluoroalkanesulfonyl)amide as catalyst[49] and hydrogen peroxide as an oxidant allowed BVO to proceed with excellent yield and selectivity with further advantage of a full recovery of the catalyst without any loss of activity.

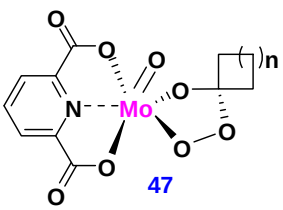
2.2.1.2 Activation of Hydrogen Peroxide

The first report of transition metal catalysed Baeyer-Villiger oxidation is due to Mares and co-workers,[50] who reported in 1978 the use of peroxomolybdenum complex **46** **(Chart 3)** as catalysts and 90% H_2O_2 as an oxidant. Cycloalkanones were oxidised into the corresponding lactones in 10-83% yield. They proposed that the carbonyl group of the ketone inserts into the molybdenum-oxygen bond of the peroxo species to form metallo-ozonide **47** **(Chart 3)**. This work has been re-investigated by Campestrini and Di Furia,[51] who proposed that complex **46** only serves as a Lewis acid catalyst, with hydrogen peroxide as an effective oxidant.

Chart 3. Molybdenum catalyst - 1978



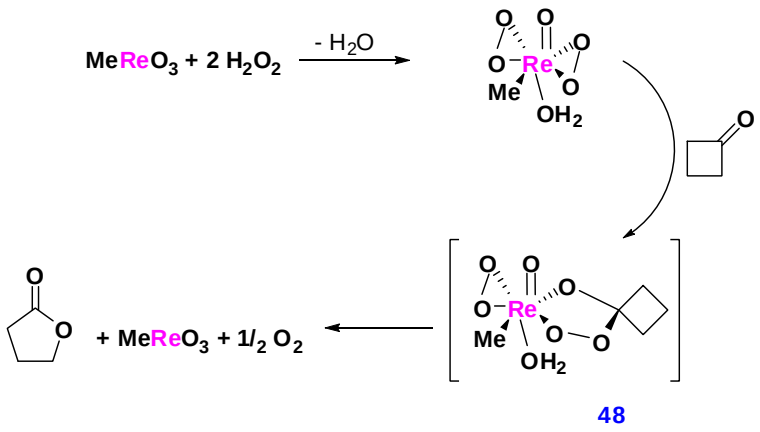
46



47

Rhenium was also employed to activate hydrogen peroxide. Methyltrioxorhenium (MTO) was used as a catalyst in BVO[52] of cyclobutanone with hydrogen peroxide *via* a reactive peroxy intermediate **48** **(Scheme 19)**.

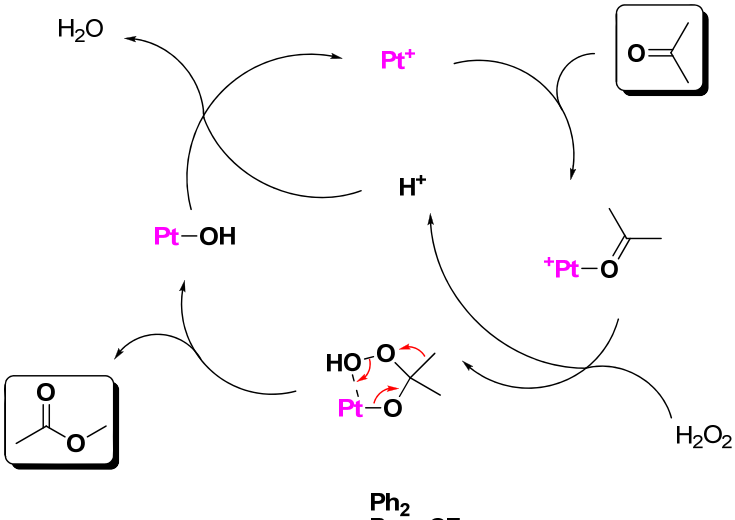
Scheme 19. MTO as H_2O_2 activator



48

Another suitable catalyst for the activation of hydrogen peroxide was found through the use of platinum complexes. Strukul[53] reported that cationic platinum diphosphine complexes of the type $[(P\text{-}P)Pt(CF_3)(CH_2Cl_2)]^+$, such as **49**, catalysed BVO of cyclic ketones with H_2O_2. Detailed studies revealed that the transformation involved coordination of the ketone to a vacant coordination site on the platinum complex, followed by a nucleophilic attack of free hydrogen peroxide on the attached carbonyl group **(Scheme 20)**.

Scheme 20. Mechanism of BVO with Pt catalyst

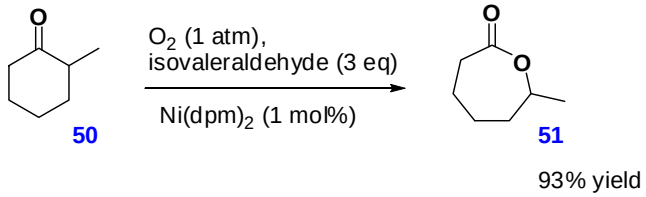


49

2.2.1.3 Dioxygen as Oxidant – The Mukaiyama System

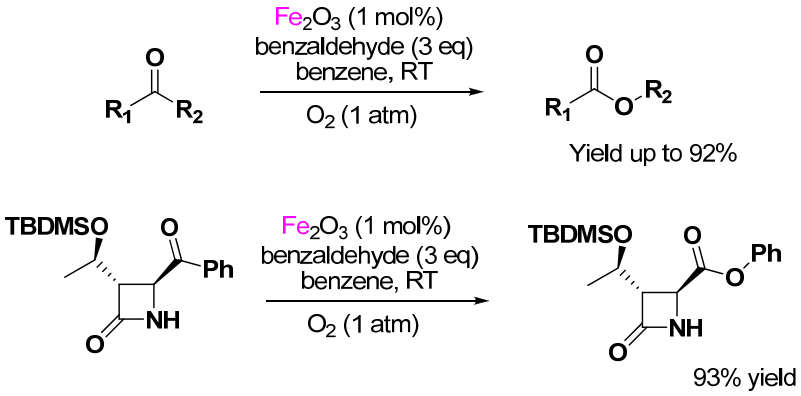
In 1991 Mukaiyama and co-workers[54] described the use of sacrificial aldehydes for the aerobic BVO of ketones such as cyclohexanone **50** in the presence of nickel(II) complexes as catalysts **(Scheme 21)**.

Scheme 21. Mukaiyama system for the BVO



Mechanistic aspects of this catalysis remained largely unknown. However, in 1992, Murahashi *et al.*[55] used iron(III) in the presence of benzaldehyde and molecular oxygen to oxidise a wide range of ketones to the corresponding lactones or esters. 4-Acyloxy β-lactams were also synthesised using the same protocol **(Scheme 22)**. A mechanistic interpretation of the Fe_2O_3-catalysed oxidation was proposed by Murahashi. The catalyst is suggested to be involved in the autoxidation of benzaldehyde with molecular oxygen to produce peroxy benzoic acid *in situ* required for BVO. However, since the Mukaiyama system has also been employed successfully for the asymmetric BVO, it seems that the metal may also play an important role in the oxygen transfer step, although its exact nature is still unclear.

Scheme 22. Murahashi's conditions

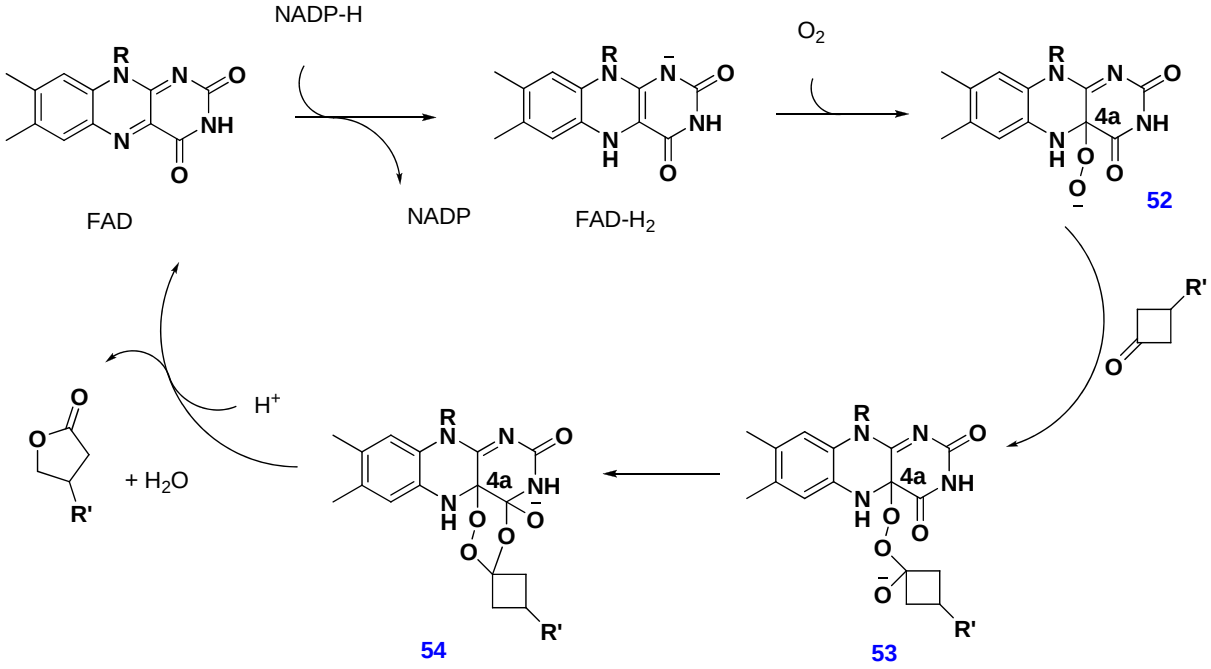


2.2.2 Asymmetric BVO

2.2.2.1 Enzymatic BVO

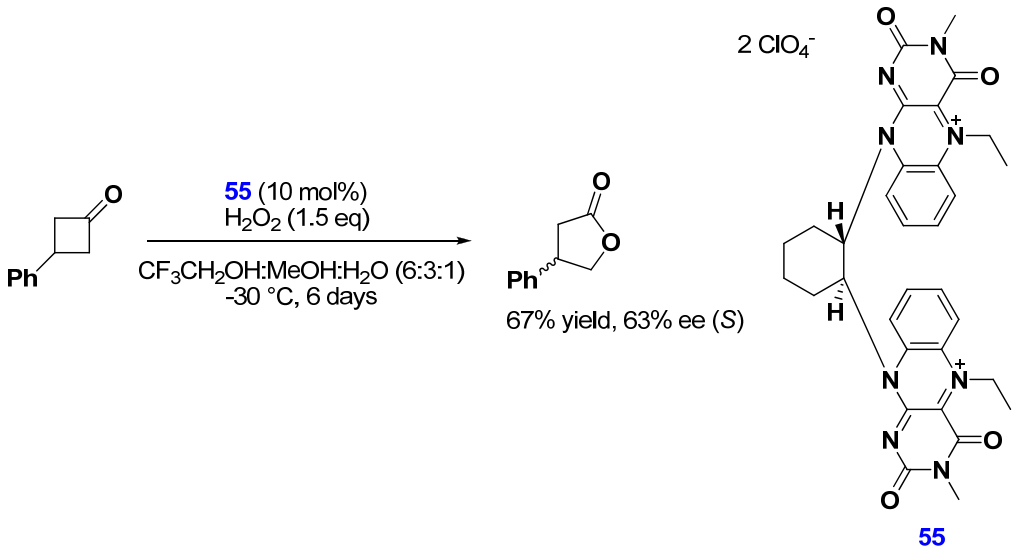
For many years, the only way of carrying enantioselective Baeyer-Villiger oxidation was with the use of microorganisms.[56] Enzymes that catalyse BVO mostly bear a FAD prosthetic group and use NADPH as the reducing agent (**Scheme 23**). Reduced FAD-H_2 reacts with oxygen to give 4a-hydroperoxyflavin **52**, which reacts with a carbonyl compound to give the corresponding Criegee intermediate **53**. Presumably, the Criegee adduct is further converted into the cyclic peroxy intermediate **54** before allowing the rearrangement to take place **(Scheme 23)**.

Scheme 23. Enzymatic BVO



Recently, asymmetric BVO catalysed by an enzyme-mimicking bisflavin **98** was reported **(Scheme 24)**.[57]

Scheme 24. Organocatalyst bisflavin

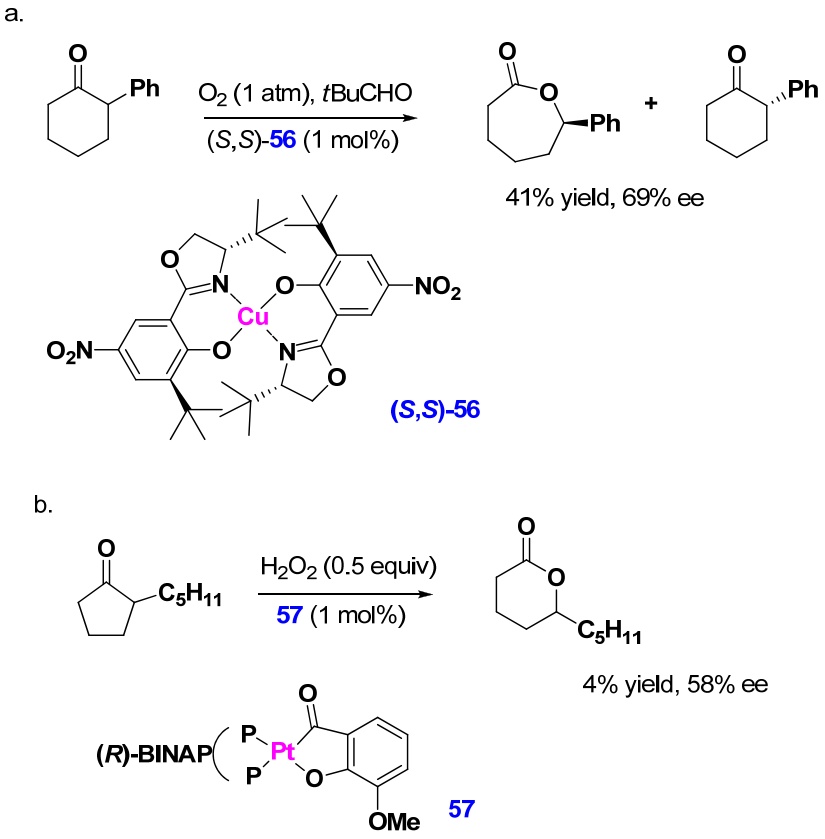


2.2.2.2 Chemical Asymmetric BVO

Despite the long history of the Baeyer-Villiger oxidation, it is only recently that its asymmetric version was reported. In 1994, Bolm[34] and Strukul[35] published independently the first enantioselective kinetic resolution of racemic 2-substituted-cyclohexanones **(Scheme 25)**. Bolm *et al.* used a modified copper catalyst (*S*,*S*)-**56** under classical Mukaiyama conditions (molecular oxygen and sacrificial aldehyde) to afford the corresponding optically active lactone in 41% yield with up to 69% ee **(Scheme 25a)**.

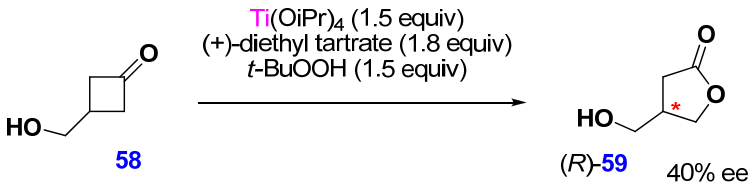
Strukul *et al.* achieved their highest enantiomeric excess (58%) with 2-(*n*-pentyl)cyclopentanone as substrate and BINAP-2-vanillin platinum complex **57** as catalyst **(Scheme 25b)**. Six-membered cyclic ketone, 2-methylcyclohexanone, was converted under identical conditions into the corresponding (*S*)-lactone with 45% ee. The catalytically active cationic complex is formed when complex **57** is treated with a strong acid, such as $HClO_4$. Under these conditions, phenolic oxygen is protonated leading to cleavage of the coordinate Pt-vanillin bond. The non-coordinating anion $[ClO_4]^-$ leaves a vacant coordination site on the metal, thus rendering it catalytically active.

Scheme 25. First chemical asymmetric BVO



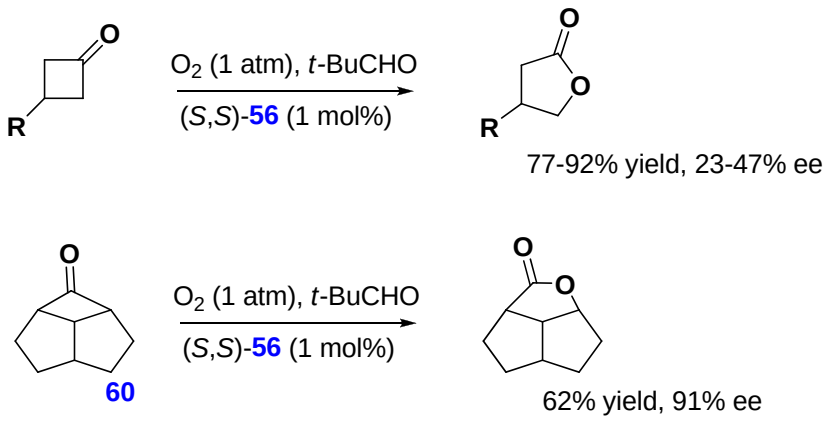
Besides the oxidation of racemic ketones, oxidation of prochiral 3-substituted-cyclobutanones to optically active γ-butyrolactones is an important aspect in the study of asymmetric BVO. In 1996, Lopp[58] was the first to report on oxidation of prochiral cyclobutanone **58** to afford (*R*)-**59** (40% ee) using (*i*-PrO)$_4$Ti, (+)-diethyl tartrate, and *tert*-butyl hydroperoxide, a system originally developed by Sharpless for epoxidation of allylic alcohols **(Scheme 26).**

Scheme 26. Asymmetric Ti-catalysed BVO



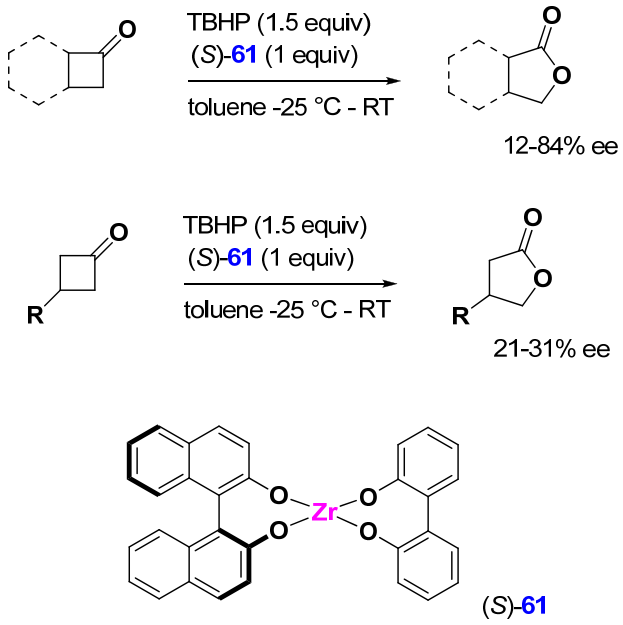
Bolm[59] extended the scope of his copper(II) catalyst (*S*,*S*)-**56** to the oxidation of prochiral cyclobutanones **(Scheme 27)**. However, the achieved enantioselectivity remained moderate (up to 47% ee), only Kelly's tricyclic ketone **60** afforded the corresponding lactone with high enantioselectivity (91% ee).

Scheme 27. Asymmetric Cu-catalysed BVO of prochiral cyclobutanones



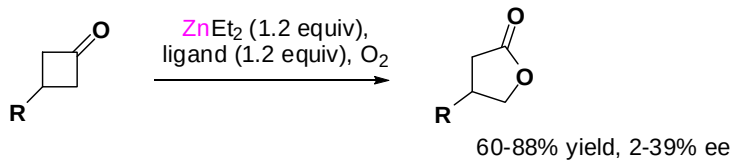
Bolm[60] also developed zirconium-BINOL-BIPOL complex **61** which in combination with *tert*-butyl hydroperoxide (TBHP) proved to be effective in the asymmetric oxidation of bicyclic and monosubstituted cyclobutanones **(Scheme 28)**. However, complex **61** had to be used in stoichiometric equivalent. High enantioselectivity was achieved with bicyclic structures (up to 84% ee), while the monosubstituted cyclobutanones exhibited only moderate selectivity (up to 44% ee).

Scheme 28. Asymmetric Zr-mediated BVO of cyclobutanones



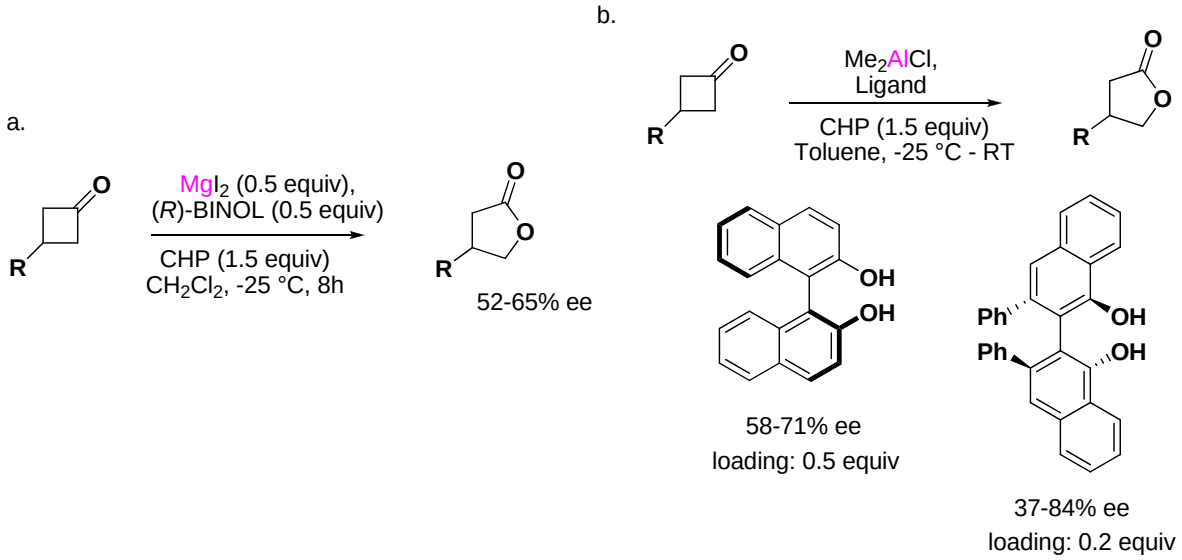
Kotsuki[61] reported oxidation of cyclobutanones with O_2, using a complex generated from Et_2Zn and a chiral amino alcohol but the reaction required high catalyst loading and the enantioselectivities remained moderate (≤39% ee) **(Scheme 29)**.

Scheme 29. Asymmetric Zn-mediated BVO



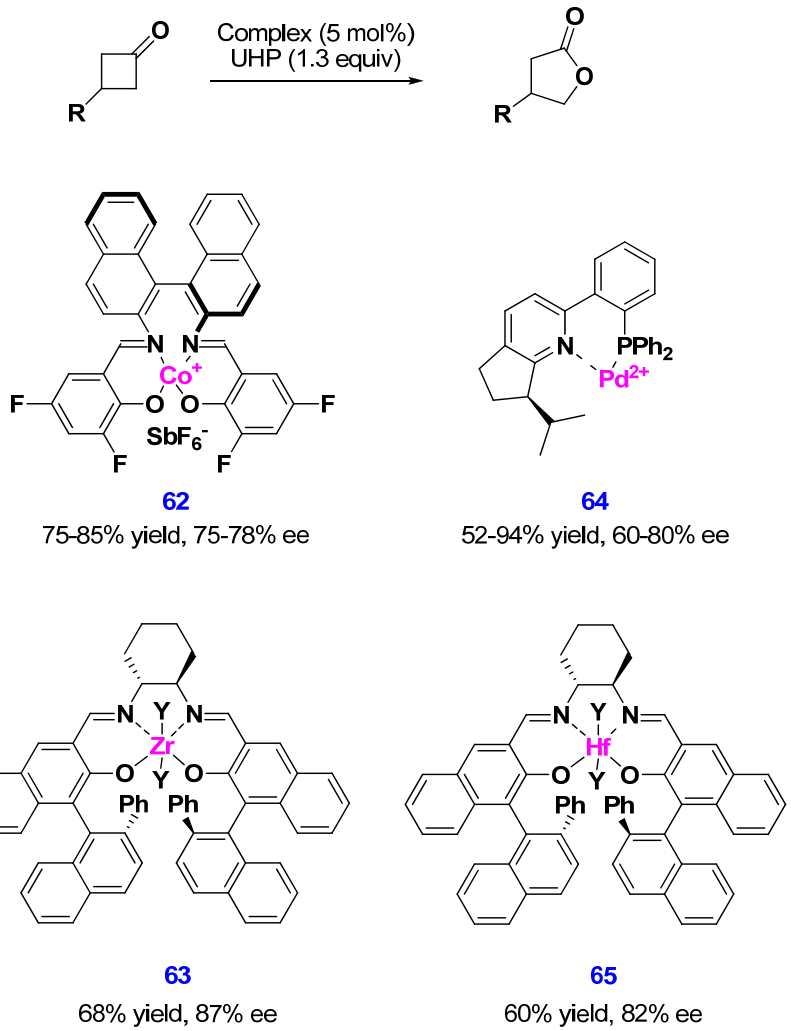
Bolm improved his BINOL system by replacing Zr(IV) with Mg(II): using cumene hydroperoxide and 50 mol% catalyst loading, he obtained a range of lactones in 52-65% ee **(Scheme 30-a)**.[62] A combination of the Lewis-acidic Me_2AlCl and BINOL or vaulted BINOL (VANOL) as chiral ligands resulted in further improvement in enantioselectivity (37-84% ee) and lowering of the catalyst loading to 20 mol% **(Scheme 30-b)**.[63]

Scheme 30. Binaphthol-based system



Katsuki successfully applied three different metal salen complexes and a palladium phosphino-pyridine complex in the asymmetric BVO. The cationic cobalt(III) (salen) complex **62** was reported to be an efficient catalyst (up to 78% ee) for the asymmetric BVO of 3-substituted cyclobutanones using hydrogen peroxide as a terminal oxidant **(Scheme 31)**.[64] The efficiency of this cobalt catalyst was attributed to its *cis*-β-structure, which had two vicinal coordination sites that became vacant during the catalysis. Interestingly, by replacing cobalt with zirconium in the salen complex, Katsuki[65] produced catalyst **63** which is responsible for the best enantioselectivity so far (up to 87% ee). Further modifications, including various metal sources (such as **65**), did not improve the enantioselectivity of the reaction.[66] The Pd(II) complex with the phosphinopyridine ligand **64** gave lactones in 60-80% ee.[67]

Scheme 31. Katsuki's catalysts



62
75-85% yield, 75-78% ee

64
52-94% yield, 60-80% ee

63
68% yield, 87% ee

65
60% yield, 82% ee

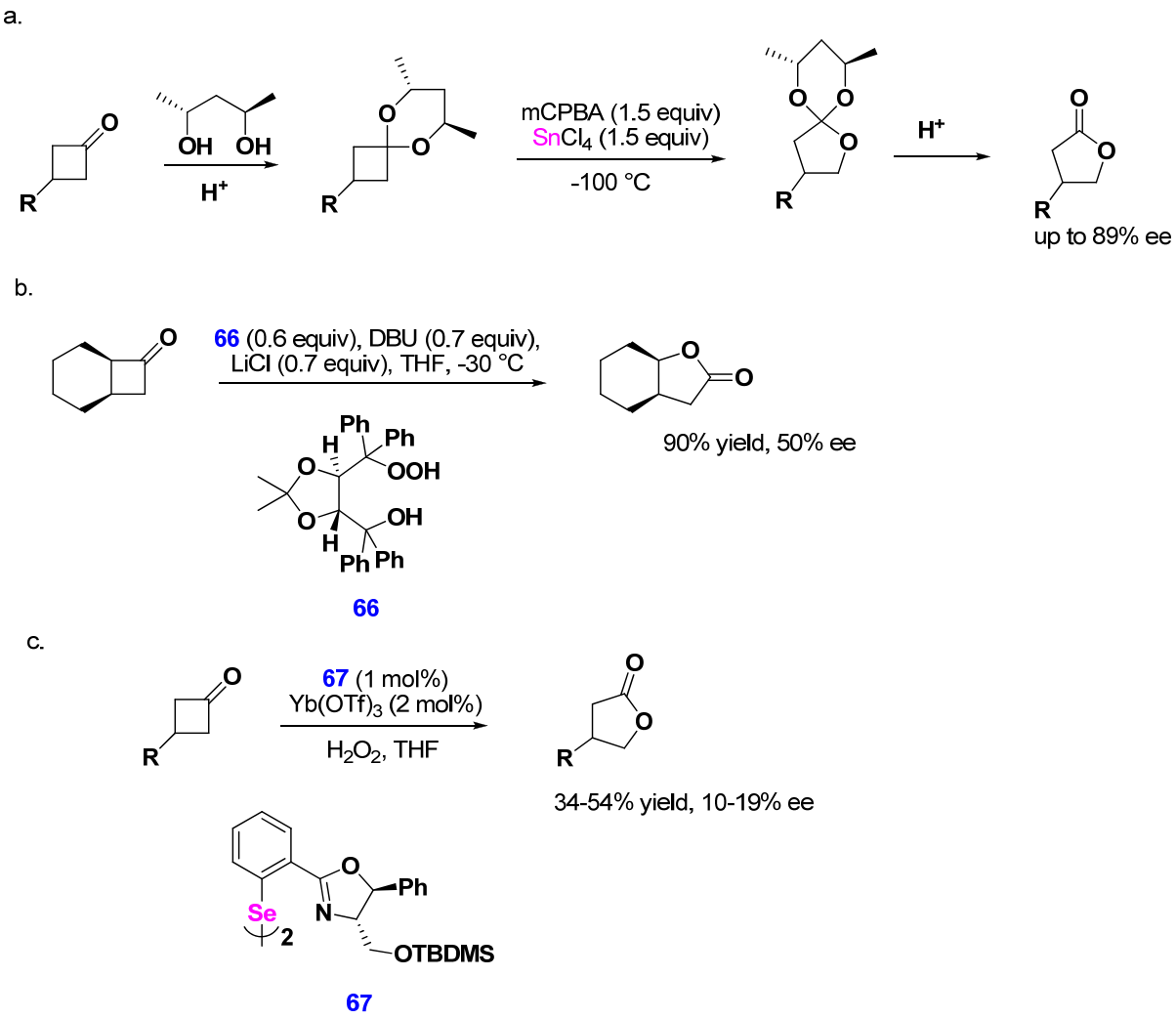
2.2.2.3 Other Approaches

Sugimura[68] introduced a diastereotopic differentiating peracid oxidation of ketals prepared from prochiral ketones with a chiral C_2-symmetrical diol in the presence of tin tetrachloride. High level of enantioselectivity were achieved (up to 89% ee) when the reaction was performed at low temperature (-100°C) **(Scheme 32-a)**.

Seebach *et al.* [69] developed a chiral, nonracemic oxidant which was employed under base catalysis. The readily accessible TADDOL-derived hydroperoxide **66** oxidised bicyclooctanone in 50% ee **(Scheme 32-b)**.

Uemura[70] reported the use of chiral diselenide **67** in combination with ytterbium triflate and hydrogen peroxide which produced γ-butyrolactones with low enantioselectivity (up to 19% ee) **(Scheme 32-c)**.

Scheme 32. Other approaches



2.2.3 BVO Summary

Although the Baeyer-Villiger oxidation was discovered more than a century ago, its asymmetric version has only been recently investigated. Even so, many chiral catalytic systems based on different metals (Cu, Pt, Ti, Zr, Zn, Mg, Al, Co, Pd, Hf) have been tested, only moderate to good enantioselectivity (up to 87% ee) was usually obtained with the very reactive 3-substituted cyclobutanones.

2.3 Hydrogenation of Unfunctionalised Alkenes

In the mid 1960s, the discovery by Wilkinson of the hydrogenation catalyst, $RhCl(PPh_3)_3$,[71] opened the door for developing asymmetric hydrogenation of olefins catalysed by rhodium complexes with a chiral phosphine ligand. The enantioselective efficacy of the chiral ligands has often been evaluated by hydrogenation of methyl acetamidocinnamate **9**. **Figure 2** illustrates typical examples of phosphorus-based chiral ligands, with which Rh(I) catalyst selectively afforded (*S*)-amino acid derivative **10**.[31,72] In the mid 1980s, the discovery of BINAP-Ru(II) complexes[72] significantly expanded the scope of olefinic substrates for asymmetric hydrogenation **(Figure 3)**. Nevertheless, there are still many classes of substrates that these catalysts cannot handle.

Figure 2. Asymmetric hydrogenation of **9** using chiral phosphine-Rh(I) complexes

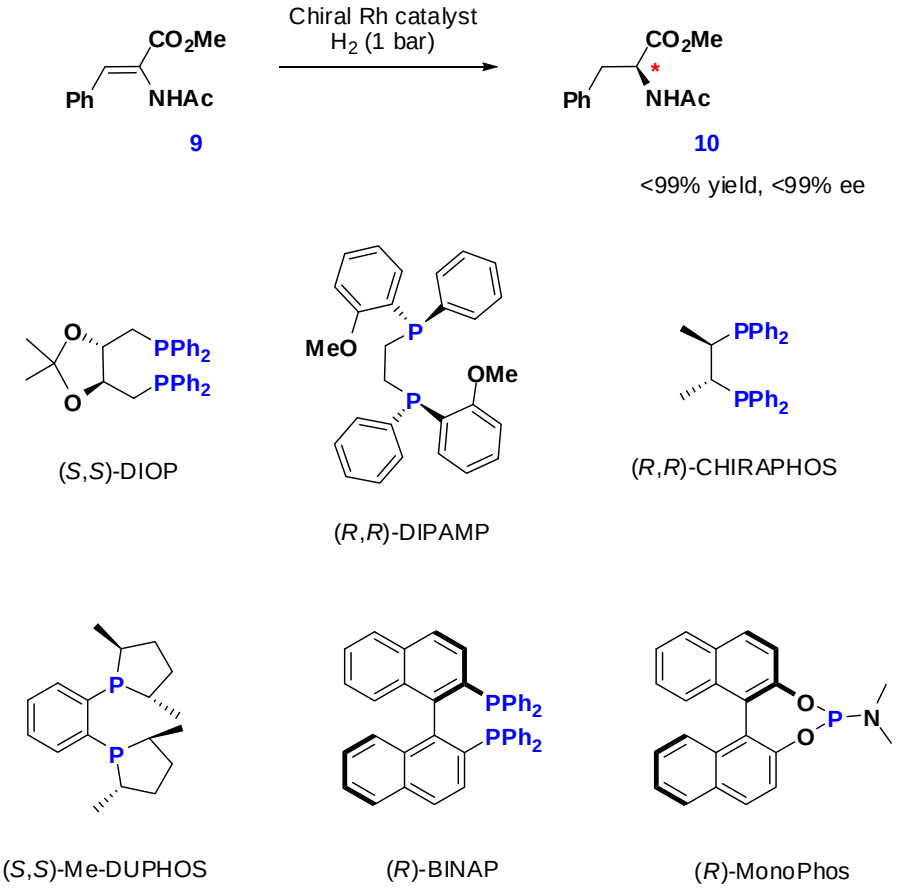
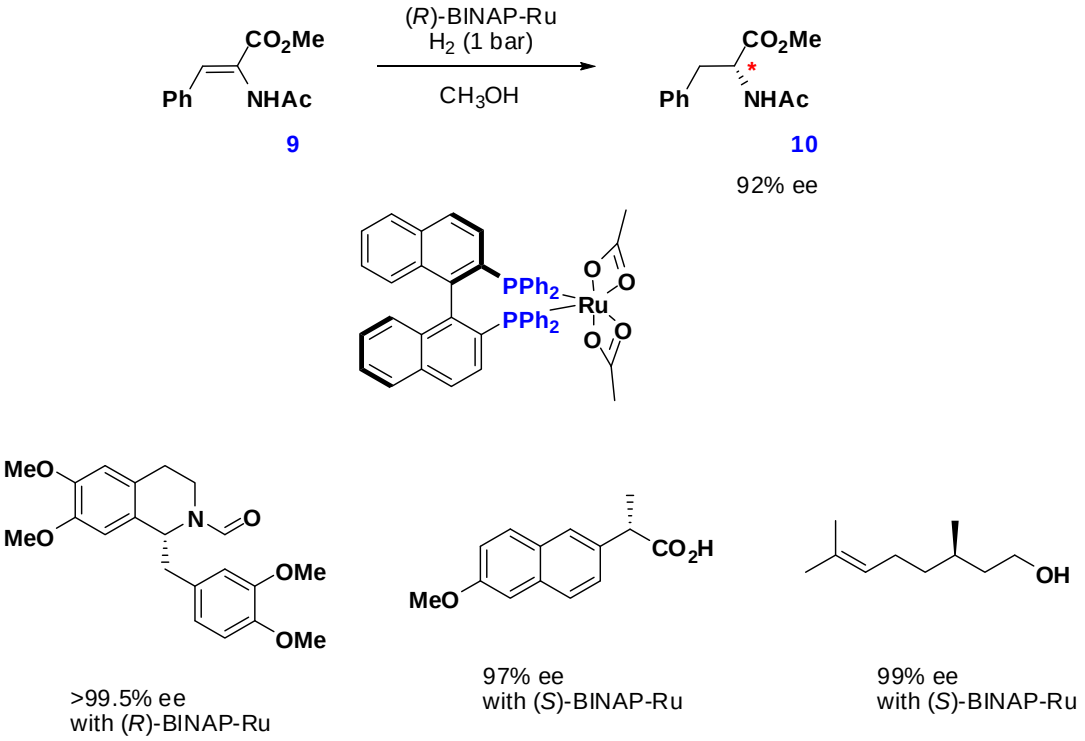
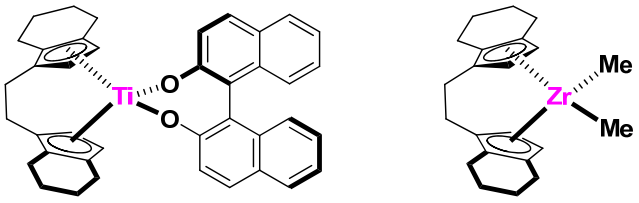


Figure 3. Asymmetric hydrogenation of functionalised olefins catalysed BINAP-Ru complexes



Unfunctionalised olefins are particularly difficult substrates because, in general, a polar group adjacent to the C=C bond, capable of coordinating to the rhodium or ruthenium centre, is required for high catalyst activity and enantioselectivity. There are very few examples of highly enantioselective hydrogenation of olefins lacking such a polar group.[73] Among them, titanocene and zirconocene complexes **(Chart 4)**,[74] developed by Buchwald, have shown high level of reactivity and enantioselectivity in the hydrogenation of various unfunctionalised tri- and tetrasubstituted arylalkenes. However, the complexes are extremely air-sensitive and relatively difficult to prepare. The major breakthrough in the asymmetric hydrogenation of unfunctionalised olefins came with the recent development of relatively air and moisture tolerant cationic iridium complexes, with chiral *N*,*P*-ligands and weakly coordinating counter ions.

Chart 4. Buchwald's titanocene and zirconocene complexes

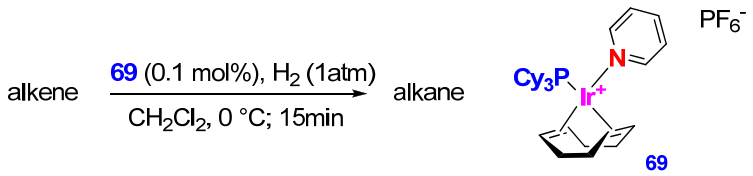


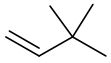
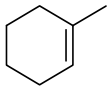
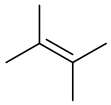
68a **68b**

2.3.1 Iridium-Catalysed Enantioselective Hydrogenation of Olefins

Early work on iridium catalysis was reported by Crabtree in 1977.[75] The [Ir(pyridine)(PCy_3)(COD)]PF_6 complex **69** (often referred to as Crabtree's catalyst) catalysed hydrogenation of a range of unfunctionalised olefins with good turnover frequency (TOF) (up to 4000 h^{-1}, see **Table 3**). This is remarkable considering that tetrasubstituted alkenes are very difficult to hydrogenate due to their steric hindrance. The disadvantage of this catalyst is a competitive degradation leading to inactive dimer or trimer in the presence of H_2. This explains why low conversions were reported in the case of tri- and tetrasubstituted alkenes even though very high initial TOFs were observed.

Table 3. Hydrogenation of unsubstituted alkenes with Crabtree's catalyst **69**



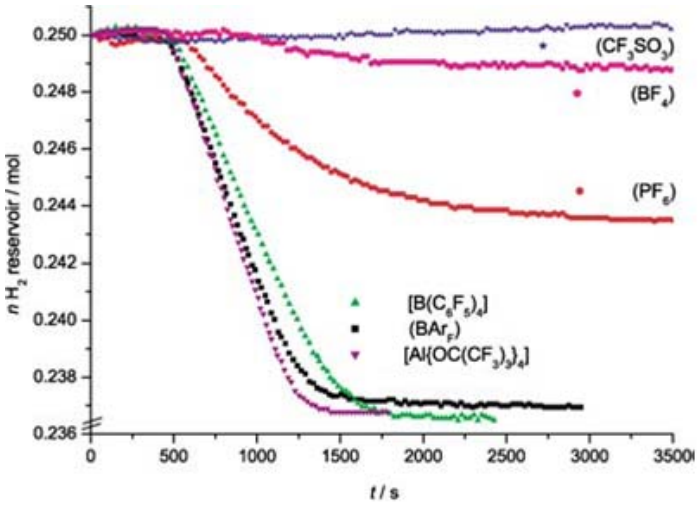
Alkene	Conversion (%)	Max TOF (h^{-1})
	100	8300
	100	4500
	35	3800
	<40	4000

2.3.1.1 Phosphine-Oxazoline Type Ligands

Inspired by Crabtree's catalyst, Pfaltz *et al* in 1998[76] reported on the first asymmetric iridium-catalysed hydrogenation of alkenes using iridium complexes derived from chiral *N*,*P*-phosphinooxazolines **70a-g** (PHOX ligands,[37a] **Chart 3**). The preliminary results obtained by Pfaltz and co-workers were very promising (up to 97% ee for trisubstituted alkenes, see **Table 4**). However, deactivation of the catalyst, similar to the Crabtree's system, was observed in the case of the iridium-PHOX complexes **70a-d** (catalysts having PF_6^- as counterion). Interestingly, replacement of PF_6^- with the bulky and extremely weakly

coordinating anion BAr_F^- (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) allowed the cationic iridium complexes to be more stable towards deactivation and full reduction of various alkenes were routinely obtained with catalyst loading lower than 1 mol%. Recent kinetic study of catalysts with different counterions[77] **(Figure 4)** showed that the catalytic activity of the complexes **70f** strongly depends on the anion and increases in the order $CF_3SO_3^- < BF_4^- << PF_6^- < [B(C_6F_5)_4]^- < BAr_F^- < [Al\{OC(CF_3)_3\}_4]^-$. These early results influenced the development of the future catalysts in two ways. First, (*E*)-1,2-diphenyl-1-propene **78** has become the model substrate for all new ligands. Relatively ineffective catalysts for the hydrogenation of (*E*)-1,2-diphenyl-1-propene **78** are usually not investigated further. That will prove to be unfortunate if those catalysts would have been more suitable for more difficult substrates. Second, and more important, all the chiral catalysts reported in the literature, contain BAr_F^- as the counterion.

Figure 4. Influence of the counterion on the reaction rate of hydrogenation of **78** with **70f**

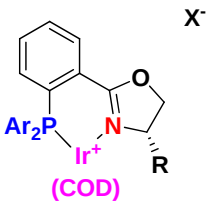


Extensive modifications of the privileged PHOX ligands were realised by Pfaltz and others (**Chart 5**). The influence of the size of the coordinating sphere around the iridium centre and the electronic density of the phosphorous atom on the enantioselectivity was first examined. The phenyl ring linking the oxazoline unit to the phosphine moiety plays a central role in this structure. As an alternative arrangement, other linkers were examined. A series of iridium complexes based on pyrrole-derived phosphinooxazolines (**71**)[78] was developed and showed a clear improvement of the enantioselectivity (particularly for the less sterically-demanding (*E*)- and (*Z*)-2-(4-methoxyphenyl)-2-butene **79** and **80**). Interestingly, when a planar ferrocenyl unit (**72**) was introduced instead of the classical phenyl ring,[79] a slight decrease of enantioselectivity was observed. Gilbertson[80] developed iridium complexes of proline-

derived phosphine–oxazoline ligands (**73**), which afforded good enantioselectivity for trisubstituted alkenes but tetra- and disubstituted alkenes, such as **82** and **83**, were hydrogenated with poor enantioselectivity (6% ee and 38% ee, respectively). Andersson reported on a new iridium catalyst based on 2-aza-norbornane-oxazoline ligand (**77**)[81] which afforded high level of enantioselectivity with trisubstituted olefins such as **79** (up to 99% ee). Zhang developed electron-rich phospholane-oxazoline catalysts,[82] whose iridium complexes (**74**) proved to be particularly efficient for the asymmetric hydrogenation of β-methylcinammic esters (**85**) (up to 99% ee). Although there is no sensible rationale behind the ligand modifications, it is worth to note that the environment (both electronic and steric) around the phosphorous atom clearly plays an important role in the selectivity of hydrogenation.

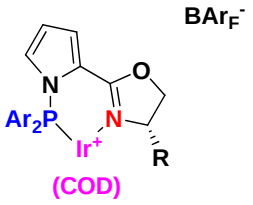
Several groups investigated the influence of the oxazoline ring on the enantioselectivity of the hydrogenation reaction. Zhang developed a new class of conformationally rigid phosphine-oxazolines (**75**)[83] which showed to be highly enantioselective ligands for iridium-catalysed asymmetric hydrogenation of both (*E*)-1,2-diphenyl-1-propene **78** and of β-methylcinammic esters **85** (up to 99% ee). Pfaltz *et al* replaced the oxazoline ring with an imidazoline ring (**76**),[84] the extra nitrogen atom providing a handle for tuning the electronic and conformational properties of the ligand by the appropriate choice of the R^2 group. The results were rather similar to those obtained with the PHOX catalysts family (**70**) but with a slight increase in enantioselectivity for unhindered alkenes, such as **79**.

Chart 5. Chiral iridium-phosphine-oxazoline type catalysts used for the enantioselective hydrogenation of unfunctionalised alkenes



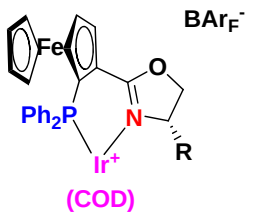
70[76]

70a	Ar=Ph	R=*i*-Pr	X=PF_6
70b	Ar=Ph	R=*t*-Bu	X=PF_6
70c	Ar=*o*-Tol	R=*i*-Pr	X=PF_6
70d	Ar=*o*-Tol	R=*t*-Bu	X=PF_6
70e	Ar=Ph	R=*i*-Pr	X=BAr_F
70f	Ar=*o*-Tol	R=*t*-Bu	X=BAr_F
70g	Ar=Ph	R=CH_2*t*-Bu	X=BAr_F



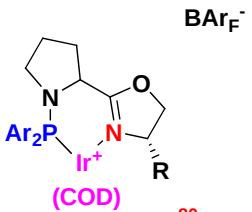
71[78]

71a	Ar=Ph	R=*i*-Pr	
71b	Ar=Ph	R=*t*-Bu	
71c	Ar=*o*-Tol	R=*t*-Bu	
71d	Ar=Cy	R=*t*-Bu	



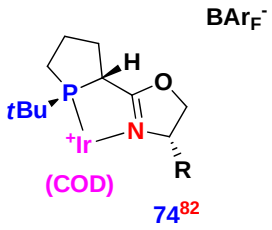
72[79]

72a	R=Me
72b	R=*i*-Pr
72c	R=*t*-Bu
72d	R=Ph
72e	R=Bn



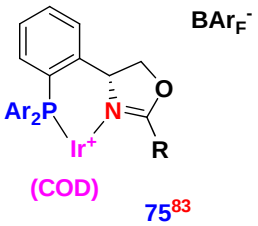
73[80]

73a	Ar=Ph	R=*i*-Pr
73b	Ar=Ph	R=*t*-Bu
73c	Ar=*o*-Tol	R=*t*-Bu
73d	Ar=2-Et-C_6H_4	R=*t*-Bu
73e	Ar=2.3-Me_2-C_6H_3	R=*t*-Bu
73f	Ar=2,4-Me_2-C_6H_3	R=*t*-Bu



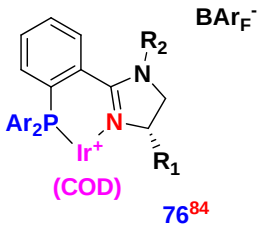
74[82]

74a	R=*i*-Pr
74b	R=*t*-Bu
74c	R=Ph
74d	R=Bn
74e	R=*i*-Bu



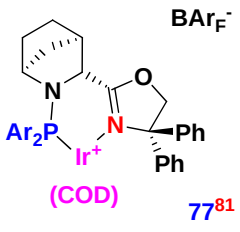
75[83]

75a	R=*t-Bu*	Ar=Ph
75b	R=$CHPh_2$	Ar=Ph
75c	R=3,5-*t*-Bu_2Ph	Ar=Ph
75d	R=ad	Ar=Ph
75e	R=*t*-Bu	Ar=Cy



76[84]

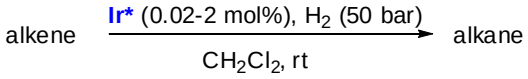
76a	Ar=Ph	R_1=*i*-Pr	R_2=*i*-Pr
76b	Ar=Ph	R_1=*i*-Pr	R_2=Cy
76c	Ar=Ph	R_1=*i*-Pr	R_2=Bn
76d	Ar=Ph	R_1=*i*-Pr	R_2=Ph
76e	Ar=Ph	R_1=*t*-Bu	R_2=Ph
76f	Ar=Ph	R_1=*t*-Bu	R_2=*p*-MeO-C_6H_4
76g	Ar=Ph	R_1=*t*-Bu	R_2=*p*-CF_3-C_6H_4
76h	Ar=Ph	R_1=*t*-Bu	R_2=*p*-Tol
76i	Ar=*o*-Tol	R_1=*t*-Bu	R_2=Ph
76j	Ar=*o*-Tol	R_1=*t*-Bu	R_2=Bn

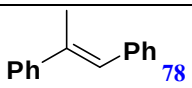
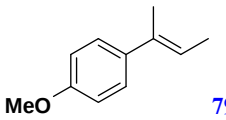
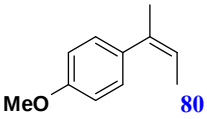
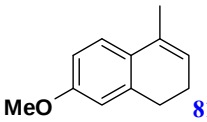
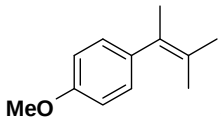
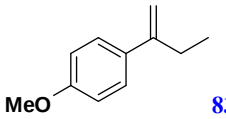
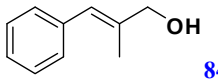
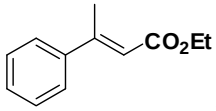


77[81]

For the catalysts synthesis, see the highlighted reference.

Table 4. Hydrogenation of various alkenes using iridium-phosphine-oxazoline type catalysts (**Chart 5**)



Alkene	Iridium complex (conversion %, ee %)							
	70[76]	**71**[78]	**72**[79]	**73**[80]	**74**[82]	**75**[83]	**76**[84]	**77**[81]
 **78**	**f** >99 97	**c** >99 99	**a** >99 90	**d** >99 92	**c** >99 95	**e** >99 99	**i** >99 94	>99 98
 **79**	**f** >99 61	**d** >99 75	-	**d** >99 76	-	-	**j** >99 90	>99 99
 **80**	**f** 97 42	**d** >99 70	-	**d** 97 56	-	-	**i** >99 88	-
 **81**	-	**c** >99 92	**a** 95 89	**d** >99 64	-	-	**i** >99 91	>99 95
 **82**	**g** >99 81	-	-	**d** >52 6	-	-	-	-
 **83**	-	-	**a** >99 22	**d** >99 38	-	-	**j** >99 52	-
 **84**	**d** 95 96	-	**a** >99 99	**d** >99 94	-	-	-	-
 **85**	**d** 96 84	**c** >99 92	**a** >99 82	**d** >99 88	**c** >99 98	**d** >99 99	-	>99 90

2.3.1.2 Other *N*,*P*-Ligands

Although the original Crabtree's catalyst contained pyridine and tricyclohexylphosphine as nitrogen and phosphorous donors, respectively, very few other chiral *N*,*P*-ligands are based on a phosphine-pyridine structure. In 2003, Knochel[85] reported on iridium complexes of pyridine-phosphines derived from camphor (**86**) and pinene (**87**) which were employed as catalysts in the hydrogenation of methyl α-acetamidocinnamate **9** with encouraging enantioselectivities (up to 97% ee). Pfaltz developed two new pyridine- and quinoline-phosphine ligands **88** and **89**.[86] Both classes of ligands were readily prepared using either ethyl picolinate or 2-vinylquinoline. However, the results were rather disappointing for the

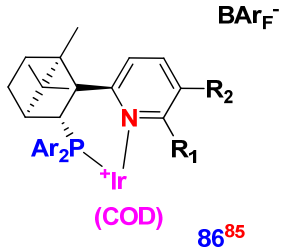
hydrogenation of (*E*)-1,2-diphenyl-1-propene **78** (<90% ee) and the ligands were not investigated further.

Li and co-workers recently reported the use of QUINAP-iridium complex in the asymmetric hydrogenation of a range of unfunctionalised olefins in moderate (33% ee) to high enantioselectivity (95% ee).[87]

Other types of nitrogen-containing heterocycles were also used for the development of novel *N*,*P*-ligands. For instance, Andersson developed chiral bidentate phosphine-thiazoles[88] (**91**) which were successfully applied as ligands in the homogeneous iridium-catalyzed asymmetric hydrogenation of aryl alkenes and aryl alkene esters. It was found that a six-membered ring backbone of the rigid ligand structure was preferred over seven- or five-membered rings. It was shown that the substitution pattern of the ligands had a major effect on the stereochemical outcome of the reactions. Excellent enantioselectivity was obtained for typical substrates. Pfaltz developed an analogue of his PHOX ligands by replacing the oxazoline ring with a benzoxazine motif[89] (5-membered ring replaced by a 6-membered ring). However, their iridium complexes (**92**) catalysed the hydrogenation of trisubstituted alkenes with lower enantioselectivity than the corresponding PHOX ligands.

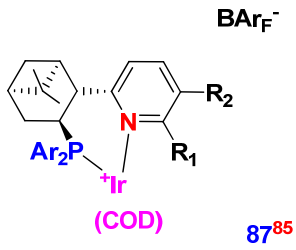
Ellman[90] in 2004 reported on a new class of *P*,*N*-ligands. A variety of sterically and electronically differing chiral sulfinyl imine ligands (**93**) were synthesised and successfully applied in the asymmetric iridium-catalysed hydrogenation (up to 94% ee).

Chart 6. Chiral iridium catalysts used for the enantioselective hydrogenation of unfunctionalised alkenes



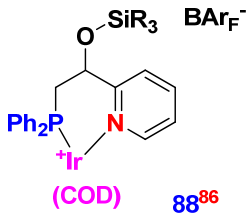
86[85]

86a	Ar=Ph	R_1=R_2=H
86b	Ar=Ph	R_1=Ph, R_2=H
86c	Ar=Cy	R_1=R_2=H
86d	Ar=Ph	R_1-R_2=Ph

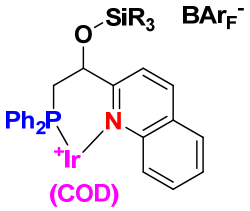


87[85]

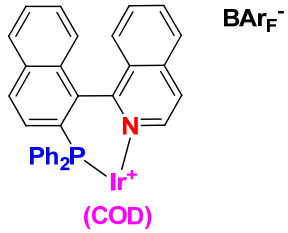
87a	Ar=Ph	R_1=R_2=H
87b	Ar=Ph	R_1=Ph, R_2=H



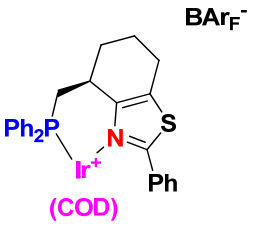
88[86]



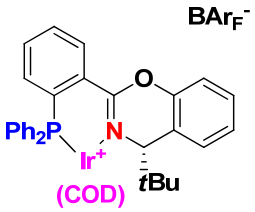
89[86]



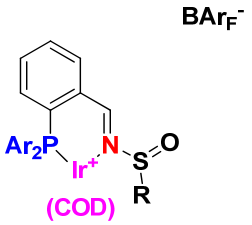
90[87]



91[88]



92[89]

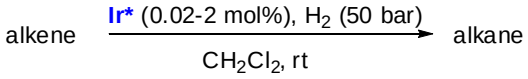


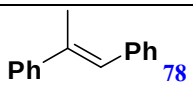
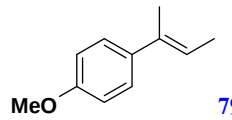
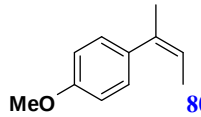
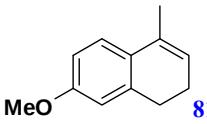
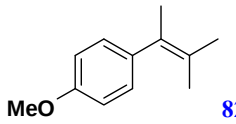
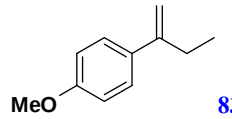
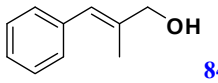
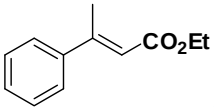
93[90]

93a	R=(*R*) *t*Bu	Ar=*o*-Tol
93b	R=(*S*) ad	Ar=*o*-Tol
93c	R=(*S*) 3-ethylpentane	Ar=*o*-Tol
93d	R=(*S*) *p*-Tol	Ar=*o*-Tol
93e	R=(*S*) mesiltylene	Ar=*o*-Tol
93f	R=(*R*) *t*-Bu	Ar=3,5-Me_2Ph
93g	R=(*R*) *t*-Bu	Ar=Ph
93h	R=(*S*) 2,4,6-(*i*-Pr)$_3$Ph	Ar=*o*-Tol

For the catalysts synthesis, see the highlighted reference.

Table 5. Hydrogenation of various alkenes using iridium catalysts (**Chart 6**)



Alkene	Iridium complex (conversion %, ee %)							
	86[85]	**87**[85]	**88**[86]	**89**[86]	**90**[87]	**91**[88]	**92**[89]	**93**[90]
 **78**	**a** >99 95	**a** 26 80	**a** 93 88	**b** 92 45	**c** >99 95	>99 99	>99 78	**a** >99 94
 **79**	-	-	-	-	-	>99 99	>99 37	-
 **80**	-	-	-	-	-	-	-	-
 **81**	-	-	-	-	-	>99 93	-	-
 **82**	-	-	-	-	-	-	63 10	-
 **83**	-	-	-	-	-	-	>99 9	-
 **84**	-	-	-	-	-	>99 99	13 77	**a** >99 70
 **85**	-	-	-	-	**c** >99 98	>99 98	95 75	**a** >99 65

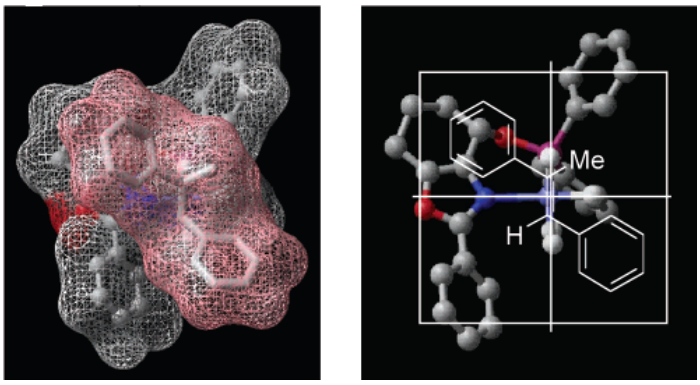
2.3.1.3 Phosphinite Ligands

Continuous development of new ligands for broadening the substrate scope led Pfaltz and co-workers to investigate the use of phosphinite-oxazolines for the enantioselective iridium-catalysed hydrogenation of unfunctionalised olefins. The SimplePHOX catalysts family **94** **(Chart 7 & Table 6)**,[91] readily available from α-hydroxyisobutyric acid and a range of various amino alcohols, was the first generation of a new promising class of ligands for broad application in asymmetric hydrogenations of unfunctionalised alkenes. Trisubstituted alkenes, such as **78-81**, allylic alcohol **84** and β-methylcinammic esters **85** were reduced in high enantioselectivity (<90% ee), even disubstituted alkene **83** was hydrogenated with good

enantioselectivity (78% ee). Pfaltz extended his phosphinite ligands family by developing a more conformationally rigid type of phosphinite-oxazolines based on serine methyl ester[92] (**95**) and threonine methyl ester[93] (**96**) whose iridium complexes induced high enantioselectivity with a wide range of alkenes (alkene **79** was hydrogenated with perfect enantioselectivity (99% ee)). Ligand **96** was found to be generally more selective than its counterpart **95**.

Since phosphinites were clearly more selective and, in particular, tolerated a broader range of substrates, other groups started to develop new types of phosphinite ligands. For instance, Andersson reported on phosphinite-oxazole iridium complexes (**97**),[94] which not only could reduce a wide range of olefins but also produced high enantioselectivity (**Table 6**). The success of these catalysts for enantioselective hydrogenation of substituted styrenes could be rationalised in terms of the selectivity model shown in **Figure 5**. The enantiofacial selectivity is primarily based on discrimination between a larger and a smaller germinal substituent. This also explained why tetrasubstituted alkene **82** afforded racemic product in only 46% conversion.

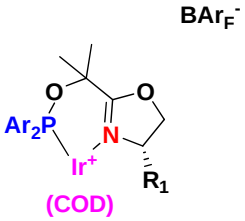
Figure 5. Calculated structure of the couple catalyst-substrate (Left). Selectivity model (Right).



Zhou[95] and Pfaltz[96] reported independently the use of a new class of phosphinite-catalysts (**98** and **99**, respectively). Interestingly, the nitrogen donor atom comes from the pyridine ring which makes **98** and **99** closer to the Crabtree's catalyst structure than the other ligands previously reported. The 5- or 6-membered rings containing the phosphorous coordinating unit are fused to the pyridine ring, increasing the overall rigidity of the ligands. However, these chiral ligands were obtained by resolution of the racemic pyridyl alcohols using preparative chiral HPLC, which makes their large-scale preparation rather difficult. The observed enantioselectivity was clearly dependent on the ligand structure. Introduction of a

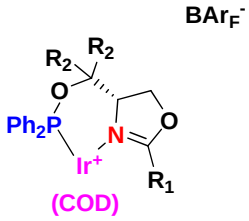
substituent into the 2-position of the pyridine ring strongly increased the ee of the products. Enantioselectivities increased substantially when the *P*-phenyl groups were replaced by *ortho*-tolyl groups. In general, 5-membered ring derivatives exhibited higher enantioselectivities. Even a very difficult tetrasubstituted alkene **82** was hydrogenated in good enantioselectivity (up to 64% ee).

Chart 7. Chiral iridium-phosphinite type catalysts used for the enantioselective hydrogenation of unfunctionalised alkenes



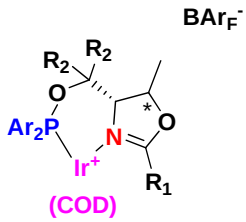
94[91]

94a	R_1=*t*-Bu	Ar=Ph
94b	R_1=*t*-Bu	Ar=*o*-Tol
94c	R_1=*i*-Pr	Ar=Ph
94d	R_1=*i*-Pr	Ar=*o*-Tol



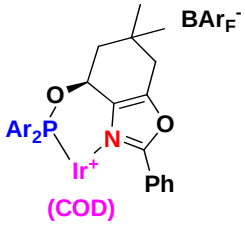
95[92]

95a	R_1=ferrocenyl	R_2=*i*-Pr
95b	R_1=ferrocenyl	R_2=*i*-Bu
95c	R_1=ferrocenyl	R_2=Bn
95d	R_1=3,5-*t*-Bu$_2$C$_6$H$_3$	R_2=*i*-Bu
95e	R_1=3,5-*t*-Bu$_2$C$_6$H$_3$	R_2=Bn
95f	R_1=naphthyl	R_2=*i*-Bu
95g	R_1=biphenyl-4-yl	R_2=*i*-Bu
95h	R_1=Ph	R_2=*i*-Pr
95i	R_1=Ph	R_2=Bn
95j	R_1=*t*-Bu	R_2=Bn



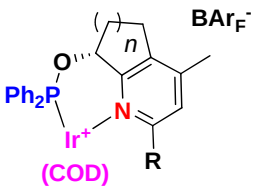
96[93]

96a	R_1=Ph	R_2=Bn	Ar=Ph
96b	R_1=Ph	R_2=Bn	Ar=Ph
96c	R_1=Ph	R_2=Bn	Ar=*o*-Tol
96d	R_1=Ph	R_2=Me	Ar=Ph
96e	R_1=3,5-Me$_2$C$_6$H$_3$	R_2=Bn	Ar=Ph
96f	R_1=3,5-*t*-Bu$_2$C$_6$H$_3$	R_2=Bn	Ar=Ph



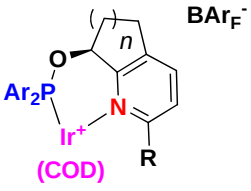
97[94]

97a	Ar=Ph
97b	Ar=*o*-Tol
97c	Ar=3,5-Me$_2$Ph



98[95]

98a	R=H
98b	R=Cl
98c	R=Ph

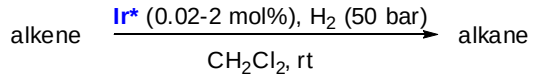


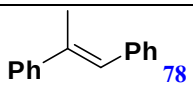
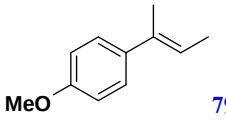
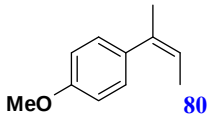
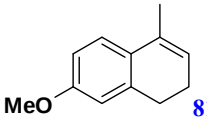
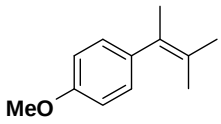
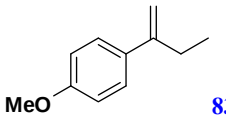
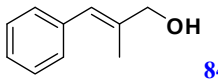
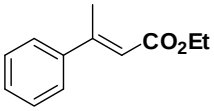
99[96]

n=1 or 2
R=H, Me, Ph
Ar=Ph, *o*-Tol, Cy, *t*-Bu

For the catalysts synthesis, see the highlighted reference.

Table 6. Hydrogenation of various alkenes using iridium-phosphinite type catalysts (Chart 7)



Alkene	Iridium complex (conversion %, ee %)					
	94[91]	**95**[92]	**96**[93]	**97**[94]	**98**[95]	**99**[96]
 **78**	**b** >99 98	**e** >99 98	**a** >99 99	**b** >99 99	**c** >99 99	>99 99
 **79**	**b** >99 91	**c** >99 96	**f** >99 99	**b** >99 96	-	>99 99
 **80**	**b** >99 89	**a** >99 85	**e** >99 92	-	-	>99 98
 **81**	**b** >99 95	**a** >99 85	**b** 95 85	**b** >99 94	-	>99 92
 **82**	-	-	-	**b** >46 0	-	>99 64
 **83**	**b** >99 78	**e** >99 88	**a** >99 89	**b** >99 97	-	>99 80
 **84**	**b** >99 97	-	-	**b** 95 98	**c** >99 86	-
 **85**	**b** >99 94	**b** >99 90	**b** >99 85	**b** >99 93	**c** >99 88	>99 99

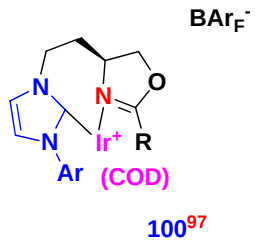
2.3.1.4 *C,N*-Ligands

N-heterocyclic carbenes (NHCs) emerged as useful ligand framework in organometallic chemistry. Their powerful σ-donating and weak π-accepting properties result in the metal centres to be more electron rich compared to the corresponding phosphine complexes. Thus, complexes containing carbene based ligands tend to be more active in oxidative addition reactions and more thermostable than their phosphine analogues which make them attractive alternatives.

Therefore, it is not surprising that chiral iridium catalysts based on heterocyclic carbenes were explored in the asymmetric hydrogenation of alkenes **(Chart 8 & Table 7)**. Burgess[97]

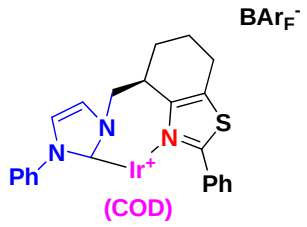
reported a series of chiral NHCs-oxazolines whose iridium complexes (**100**) showed high activity and selectivity in the enantioselective hydrogenation of various arylalkenes (up to 98% ee). Andersson developed an imidazole analogue[98] (**101**) of his chiral phosphine-thiazole ligand (**91**). The catalyst exhibited good level of enantioselectivity (up to 90% ee) but remained less efficient than its phosphine analogue. Finally, Bolm[99] reported the use of iridium catalysts based on planar chiral NHCs **102** and **103** for the enantioselective hydrogenation of arylalkenes, although the results were disappointing (from 15 to 82% ee). However, it is pertinent to note that the phosphine-NHC iridium complex **103** was much more efficient than the NHC-oxazoline iridium complex **102.**

Chart 8. Chiral iridium catalysts based on NHCs used for the enantioselective hydrogenation of unfunctionalised alkenes

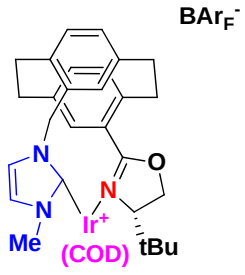


100[97]

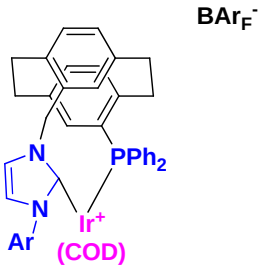
100a R=Ph Ar=2,6-*i*-PrC$_6$H$_3$
100b R=CHPh$_2$
100c R=*t*-Bu
100d R=ad



101[98]



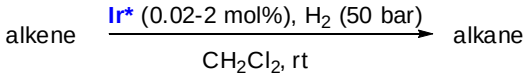
102[99a]

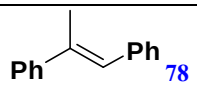
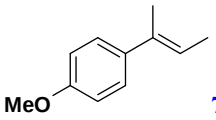
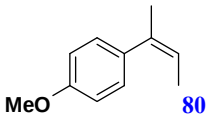
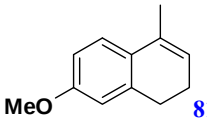
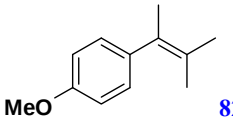
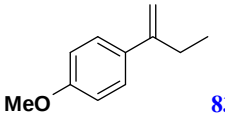
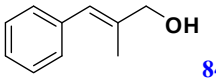
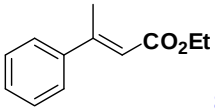


103[99b]

For the catalysts synthesis, see the highlighted reference.

Table 7. Hydrogenation of various alkenes using iridium catalysts based on NHCs (**Chart 8**)

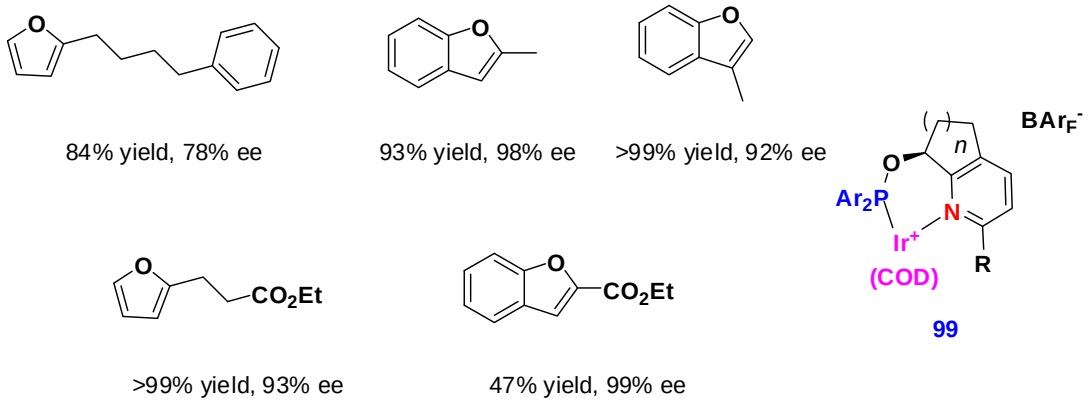


Alkene	Iridium complex (conversion %, ee %)			
	100[97]	**101**[98]	**102**[99a]	**103**[99b]
 **78**	**d** >99 98	>99 90	76 15	89 82
 **79**	**d** >99 91	>99 79	-	>99 37
 **80**	**d** >99 78	-	-	>99 79
 **81**	-	-	-	-
 **82**	-	-	-	-
 **83**	**d** 91 31	-	-	>99 79
 **84**	**d** >99 93	>99 80	-	-
 **85**	-	>99 63	-	>99 53

2.3.1.5 Substrate Scope

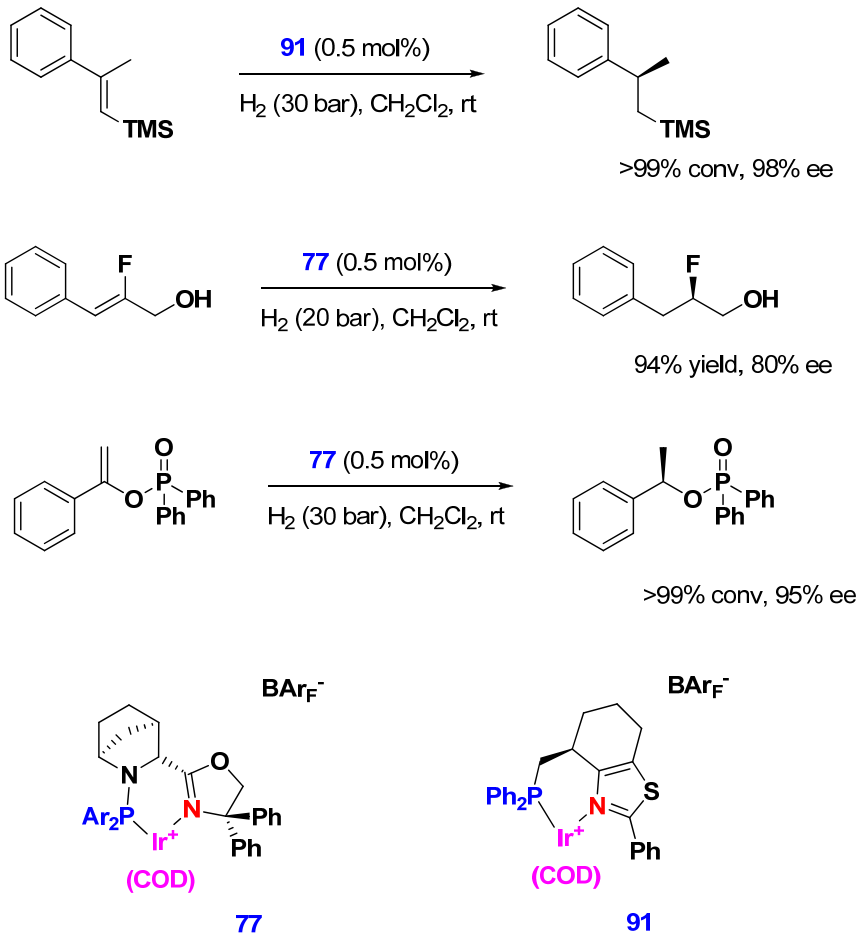
Although the asymmetric iridium-catalysed hydrogenation of arylalkenes has been extensively studied over the past decade (*vide supra*), other types of substrates only recently became the focus of attention. In 2006, Pfaltz reported the use of his champion pyridine-phosphinite iridium catalysts **99** for the enantioselective hydrogenation of a series of substituted furans (**Chart 9**).[96] High enantioselectivities were obtained, particularly when electron-rich (*t*-Bu)$_2$P phosphine was used.

Chart 9. Hydrogenation of furans and benzofurans



Recently, Andersson significantly broadened the substrates scope in the enantioselective iridium-catalysed hydrogenation to vinylsilanes,[100] fluorinated olefins[101] and enol phosphinates[102] (**Scheme 33**).

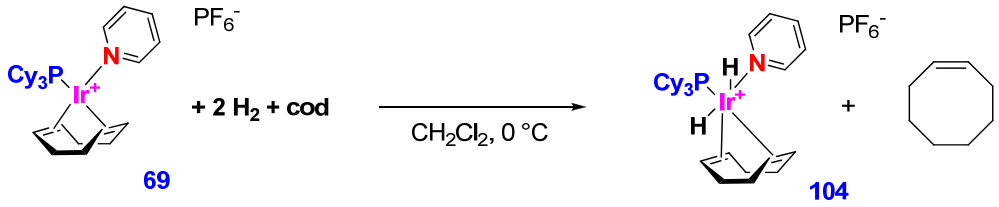
Scheme 33. Hydrogenation of vinylsilanes, fluorinated olefins and enol phosphinates



2.3.2 Mechanistic Considerations

The mechanism of olefin hydrogenation using Crabtree's catalyst and chiral analogues has been studied over several years.[75] The earliest mechanistic study in this area was carried out by Crabtree and co-workers, who employed NMR spectroscopy to detect olefin dihydride intermediate **104** which was formed during hydrogenation of cyclooctadiene using [Ir(pyridine)(PCy_3)COD]PF_6 in dichloromethane at 0 °C (**Scheme 34**).[75]

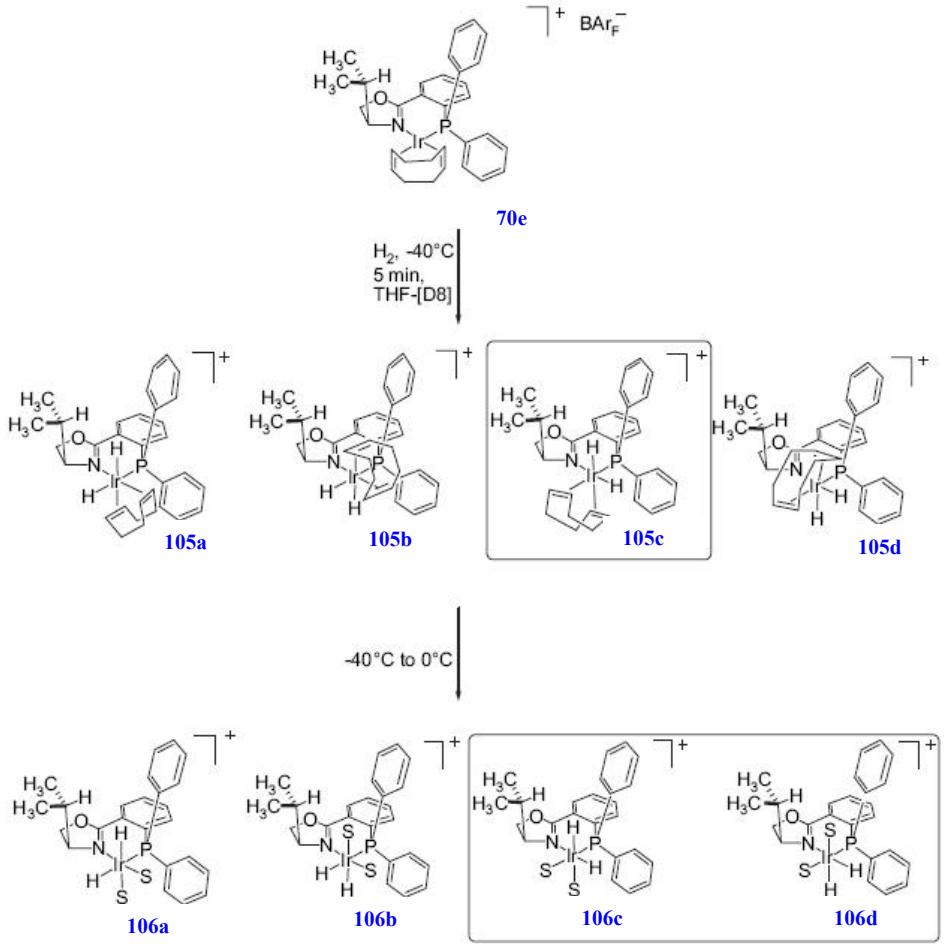
Scheme 34. Crabtree's olefin dihydride intermediate



In a complementary study, Pfaltz and co-workers have recently demonstrated, by combining experimental and computational data, that the stereoselectivity of formation of the isolated dihydride complexes **106c** and **106d** was controlled by a combination of electronic (addition of hydride *trans* to the Ir-N bond) and steric effects (presence of the bulky *i*-Pr group on the PHOX complex) (**Scheme 35**).[103]

The reaction of the $[(PHOX)Ir(COD)]^+$ complex **70e** with dihydrogen was studied by NMR spectroscopy. A single $[(PHOX)Ir(H)_2(COD)]^+$ isomer (**105c**) was formed as the primary product at -40 °C in THF. Subsequent reaction with H_2 at -40 to 0 °C led to a mixture of two diastereoisomeric $[(PHOX)Ir(H)_2(solvent)_2]^+$ complexes **106c** and **106d** with a concomitant loss of cyclooctane. The stereochemistry of the three hydride complexes was assigned from the NMR data. The structures and energies of the observed hydride complexes and the possible stereoisomers were analysed by using density functional theory calculations. The substantial energy differences (up to 39 kcal/mol) between the various stereoisomers demonstrated a strong influence of the nature of the chiral ligand. Consequently, computational studies of the potential reaction pathways should be based on the full catalyst and substrate structures rather than simple model systems.

Scheme 35. Hydrogenation of **70e**



The rest of the mechanism remains unclear. Burgress, Hall and co-workers[104] proposed an Ir^{III}/Ir^{V} cycle (**Figure 6**) based on DFT (density functional theory) calculation which reproduced the correct selectivity order for three different substrates. On the other hand, Chen and Dietiker[105] reported an experimental investigation on the hydrogenation of styrene with **70e** in the gas phase by means of electrospray ionisation tandem mass spectroscopy, which suggests an Ir^{I}/Ir^{III} catalytic cycle (**Figure 7**).

Taking into account the available computational and experimental data, it is still too early to draw definitive conclusions regarding the mechanism of iridium-catalysed hydrogenation of alkenes.

Figure 6. Ir^{III}/Ir^{V} catalytic cycle

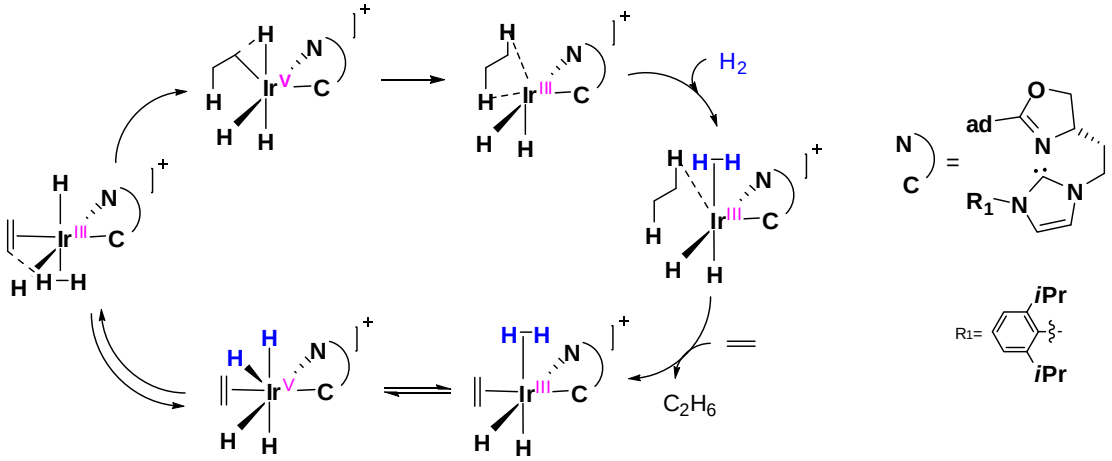
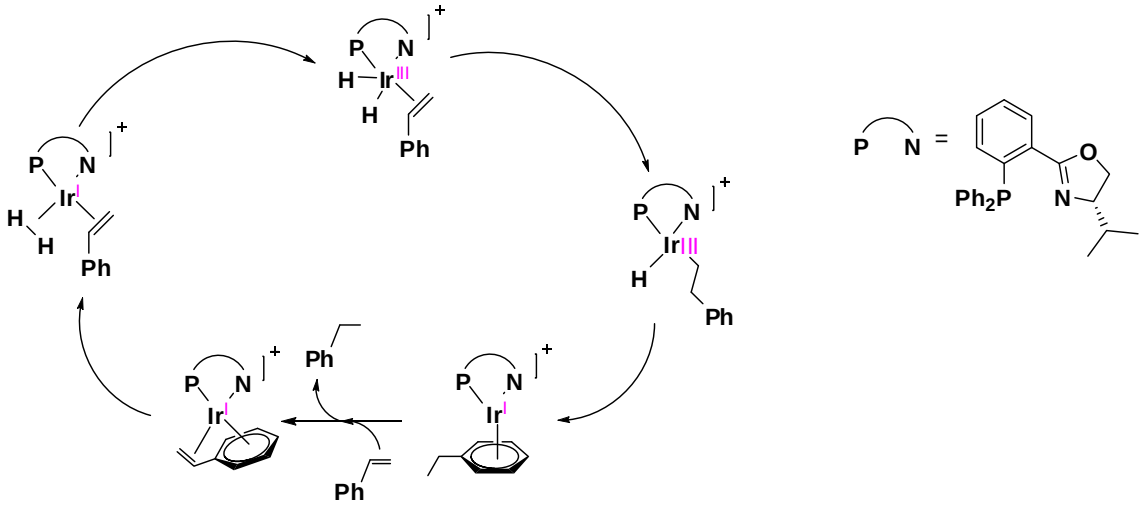


Figure 7. Ir^{I}/Ir^{III} catalytic cycle



2.3.3 Summary of Iridium-Catalysed Hydrogenation

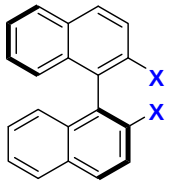
After the discovery in 1977 of the Crabtree's catalyst, allowing the hydrogenation of tetra-substituted olefins with high TOFs, iridium catalysts with chiral *P*,*N*- and *C*,*N*-ligands emerged as a new class of highly efficient catalysts for asymmetric hydrogenation, which are largely complementary to rhodium- and ruthenium-diphosphine catalysts. A variety of unfunctionalised arylalkenes, allylic alcohols and α,β-unsaturated carboxylic esters can now be hydrogenated with excellent enantioselectivity. Chiral pyridine-phosphinites seem to be the most efficient class of ligands reported to date. However, iridium-catalysed asymmetric hydrogenation remains highly substrate dependent and the development of novel chiral ligands with an extended scope seems to be the key factor for further improvement.

3 Synthesis and Application of Pinene-Derivative Pyridines I

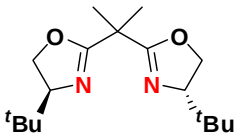
3.1 Introduction

Of the thousands of chiral ligands developed to-date, a relatively small number stands out because of their broad applicability. These "privileged ligands"[106] (**Chart 10**) allow high levels of enantiocontrol in many different metal-catalysed reactions. A survey of their structures reveals an obvious common point. They all possess C_2 symmetry.

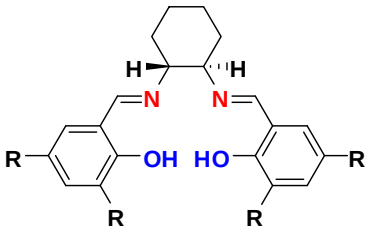
Chart 10. Examples of privileged ligands



X=OH BINOL
X=PPh$_2$ BINAP



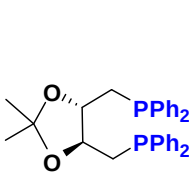
Bis(oxazoline)



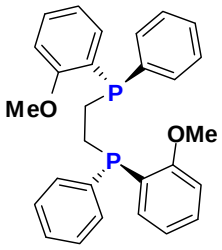
Salen Complexes

The concept of utilising C_2-symmetric ligands was first reported by Dang and Kagan in 1971 with the synthesis of the famous C_2-symmetric diphosphine DIOP for the asymmetric rhodium-catalysed hydrogenation.[107] The reason for choosing a C_2-symmetric ligand with two equivalent phosphorous atoms was to reduce the number of possible isomeric metal complexes, as well as the number of different substrate-catalyst arrangements and reactions pathways. This design principle had a marked influence on the course of research in asymmetric catalysis, and many diphosphine ligands introduced subsequently were patterned after DIOP (**Chart 11**).

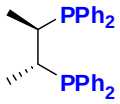
Chart 11. Examples of chiral C_2-symmetric diphosphine ligands



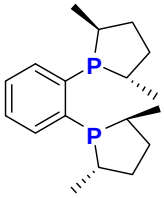
(*S*,*S*)-DIOP



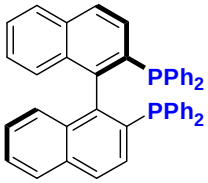
(*R*,*R*)-DIPAMP



(*R*,*R*)-CHIRAPHOS



(*S*,*S*)-Me-DUPHOS



(*R*)-BINAP

Although the concept of C_2 symmetry has been very successful, there is no fundamental reason why C_2-symmetric ligands should necessarily be superior to their nonsymmetrical counterparts. In fact, the ligands can induce asymmetry not only through their steric factors but also by generating electronic differentiation on the metal centre through the presence of different donor atoms. In the family of heterodentate ligands, the most important and widely used are those containing phosphorous and nitrogen as their donor atoms. Chiral *P*,*N*-ligands have already proved to be very efficient in a variety of asymmetric transformations such as palladium-catalysed allylic substitution, copper-catalysed 1,4-addition to enones and iridium-catalysed hydrogenation.[108]

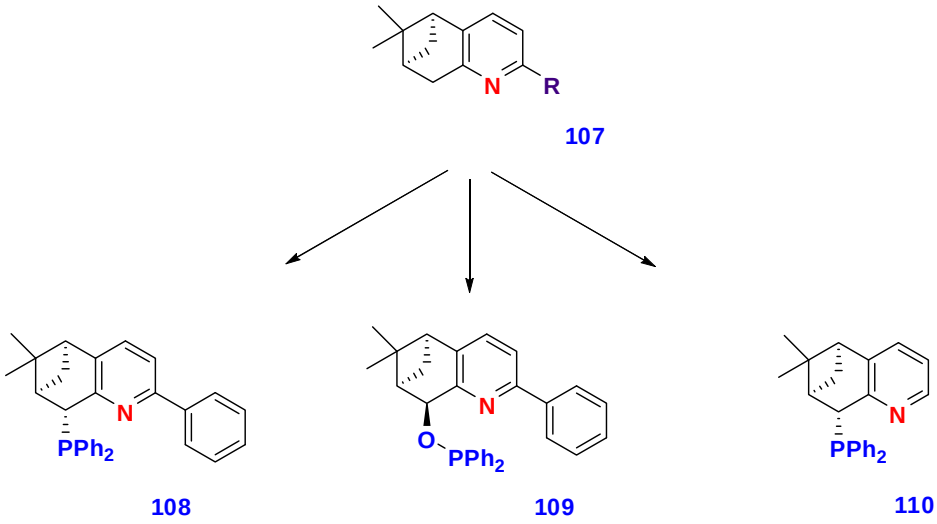
In this chapter, synthesis of novel *P*,*N*-ligands based on pinene will be described. Their application for a rather undeveloped asymmetric palladium-catalysed Baeyer-Villiger oxidation of cyclobutanones will also be discussed. With an attempt to extend the scope of these novel ligands, their iridium complexes were prepared and tested in the asymmetric hydrogenation of olefins and imines.

3.2 Synthesis of the First Generation of *P,N*-Ligands

3.2.1 Target Ligands

The target *P,N*-ligands **109-110** contain a rigid pyridine-pinene fused framework and a chiral phosphine moiety appended to the pinene ring (**Chart 12**). Importantly for the method development and catalyst screening, the ligand structure is modular. On one hand, the steric properties of the pyridine ring can be tuned by varying substitution at position 2. On the other hand, the electronic properties of the ligand can be easily modified through alterations to the phosphine unit.

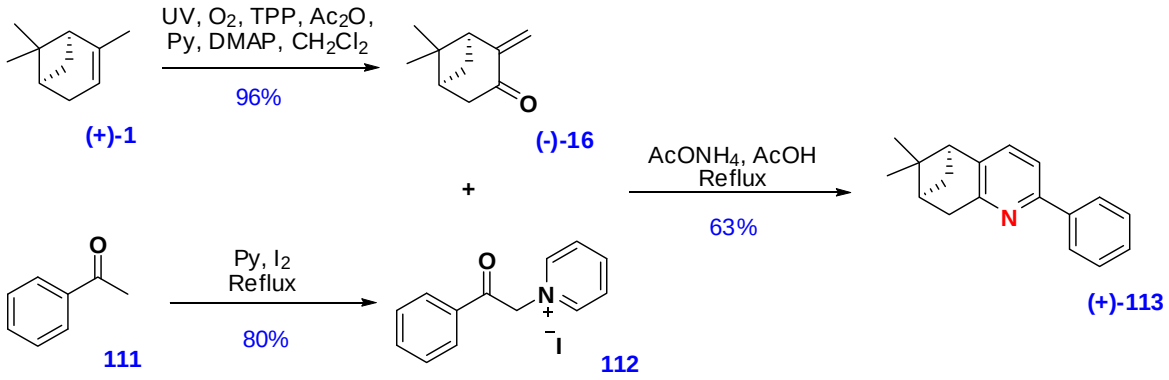
Chart 12. Target *P,N*-ligands – First generation



3.2.2 Chiral Pyridine-Phosphine 108

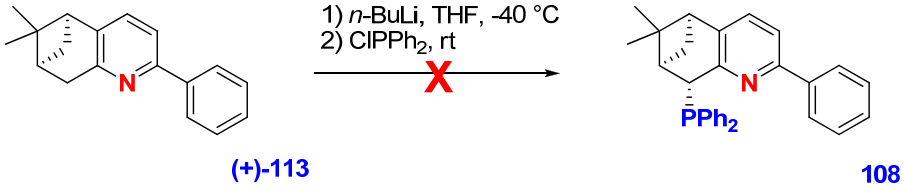
The general synthetic route to the preparation of the chiral pyridine moiety derived from α-pinene (+)-**1** was based on the Kröhnke annulation[109] shown in **Scheme 36**. Commercially available α-pinene (+)-**1** was first converted to pinocarvone (–)-**16** in 96% yield by ene reaction with singlet oxygen $^1O_2$.[110] The reaction of pinocarvone (–)-**16** with the pyridinium salt **112** derived from acetophenone **111** (Kröhnke annulation) furnished the desired chiral pinene-pyridine (+)-**113** as a result of Michael addition and ring closure in one-pot.

Scheme 36. Synthetic route to chiral pyridine based on α-pinene



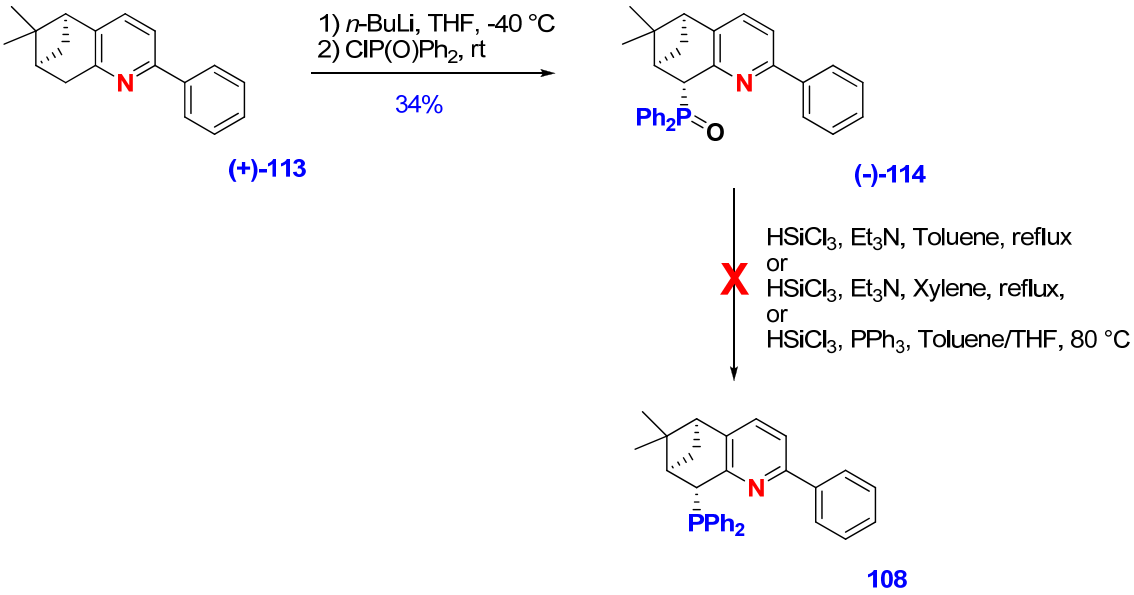
The benzylic CH_2 group of chiral pyridine (+)-**113** is reasonably acidic.[17] As a result, various substituents can be selectively introduced at this position by one-pot deprotonation with strong organic bases, such as LDA or *n*-butyl lithium, followed by treatment with appropriate electrophiles. Therefore, we attempted introduction of the phosphine unit by the use of diphenylphosphine chloride (**Scheme 37**). However, the desired *P*,*N*-ligand **108** was not obtained.

Scheme 37. Attempted introduction of phosphine unit with $ClPPh_2$



Another strategy was then investigated (**Scheme 38**). A very stable pyridine-phosphine oxide (–)-**114** was successfully synthesised by taking advantage of the high electrophilicity of diphenylphosphinic chloride. However, all attempts to reduce the phosphine oxide (–)-**114** with trichlorosilane in boiling toluene[111a] or xylene[111b] failed. An adapted protocol developed by Spencer *et al.*[111c] using triphenylphosphine as an "oxygen trap" was also tried but without any success. The diphenylphosphine oxide (–)-**114** was either extremely stable and the reduction did not occur at all or the targeted diphenylphosphine **108** was too sensitive and suffered reoxidation in the presence of traces of oxygen.

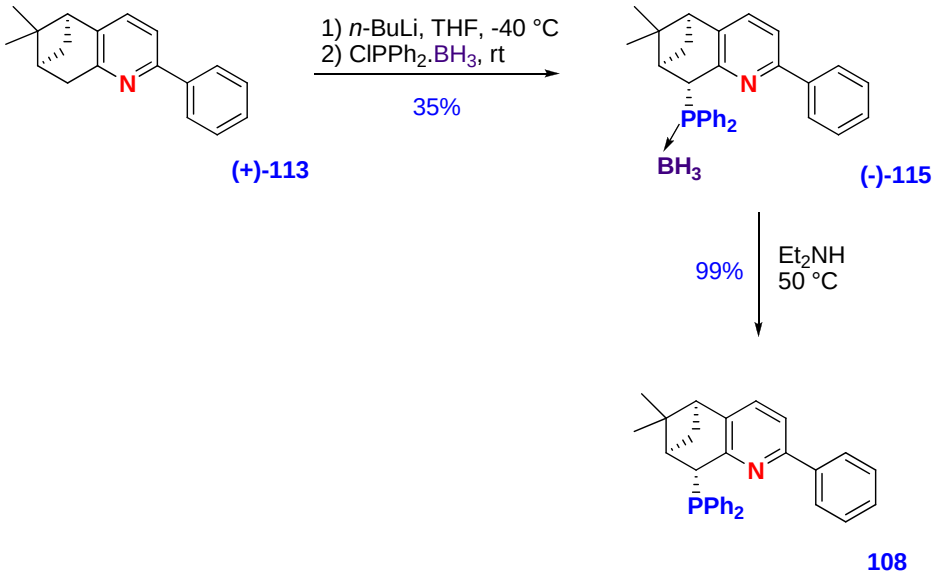
Scheme 38. Attempts to reduce the phosphine oxide (–)-**114**



Protection of trivalent phosphorous with borane has recently proved to be a valuable synthetic tool for the preparation of air-sensitive chiral phosphine ligands.[112] Borane-protected phosphines can resist not only a wide range of reaction conditions but they are also air stable, allowing classical column chromatography for purification and long time storage.

The borane-protected diphenylphosphine-pyridine (–)-**115** was successfully prepared in 35% yield by classical deprotonation of the pyridine (+)-**113** with *n*-BuLi at -40 °C, followed by reaction with the freshly prepared $ClPPh_2.BH_3$ as electrophile (chlorodiphenylphosphine was added to a solution of borane in THF (1M) and stirred for 30 min) (**Scheme 39**).

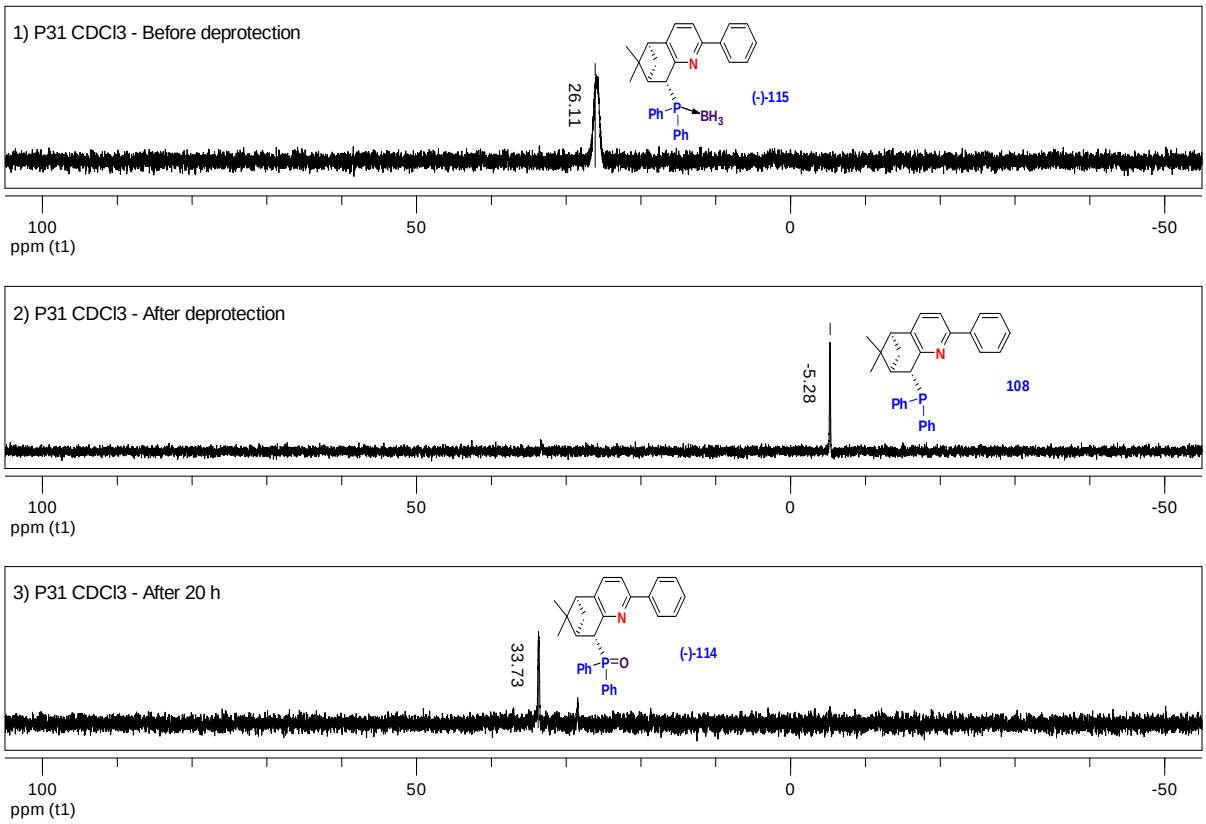
Scheme 39. Formation of the *P*,*N*-ligand **108** *via* its borane-protected form



Deprotection of (–)-**115** to afford the desired *P*,*N*-ligand **108** was accomplished in quantitative yield following standard protocol. The borane-protected diphenylphosphine-pyridine (–)-**115** was heated at 50 °C in the presence of a large excess of distilled diethylamine;[113] the reaction was monitored by TLC.

A ^{31}P-NMR study was carried out to determine stability of the freshly deprotected pyridine-phosphine **108**. To ensure classical anaerobic reaction conditions, the deuterated chloroform used for the study was degassed beforehand and the NMR tube was kept under an argon atmosphere between each measurement. The results from investigation into the oxidative stability of **108** are shown in **Figure 8**.

Figure 8. ^{31}P-NMR study



A ^{31}P-NMR spectrum was recorded before deprotection of (–)-**115** (Figure 8-1) and showed a broad singlet with a chemical shift (26.11 ppm) typical for phosphine-borane adducts. Immediately after deprotection of (–)-**115**, the ^{31}P-NMR exhibited only one singlet at -5.28 ppm (Figure 8-2), representative for diphenylphosphine compounds, showing clearly the quantitative formation of the pure desired chiral pyridine-phosphine **108**. Finally, the ^{31}P NMR experiments were carried out every 2 h to check the stability of **108**. After only 20 h (Figure 8-3), the pyridine-phosphine **108** was fully oxidised into (–)-**114** (singlet at 33.73 ppm).

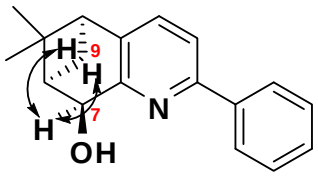
These results clearly demonstrate that the pyridine-phosphine **108** is extremely sensitive to oxygen traces. It is therefore imperative to carry out the complexation step immediately after deprotection.

3.2.3 Chiral Pyridine-Phosphinite 109

Synthesis of the chiral pyridine-phosphinite **109** is outlined in **Scheme 40**. Pyridine (+)-**113** was first *N*-oxidised with *meta*-chloroperoxybenzoic acid and then treated with acetic anhydride to undergo a Boekelheide rearrangement,[114] furnishing alcohols **117a** and **117b** as

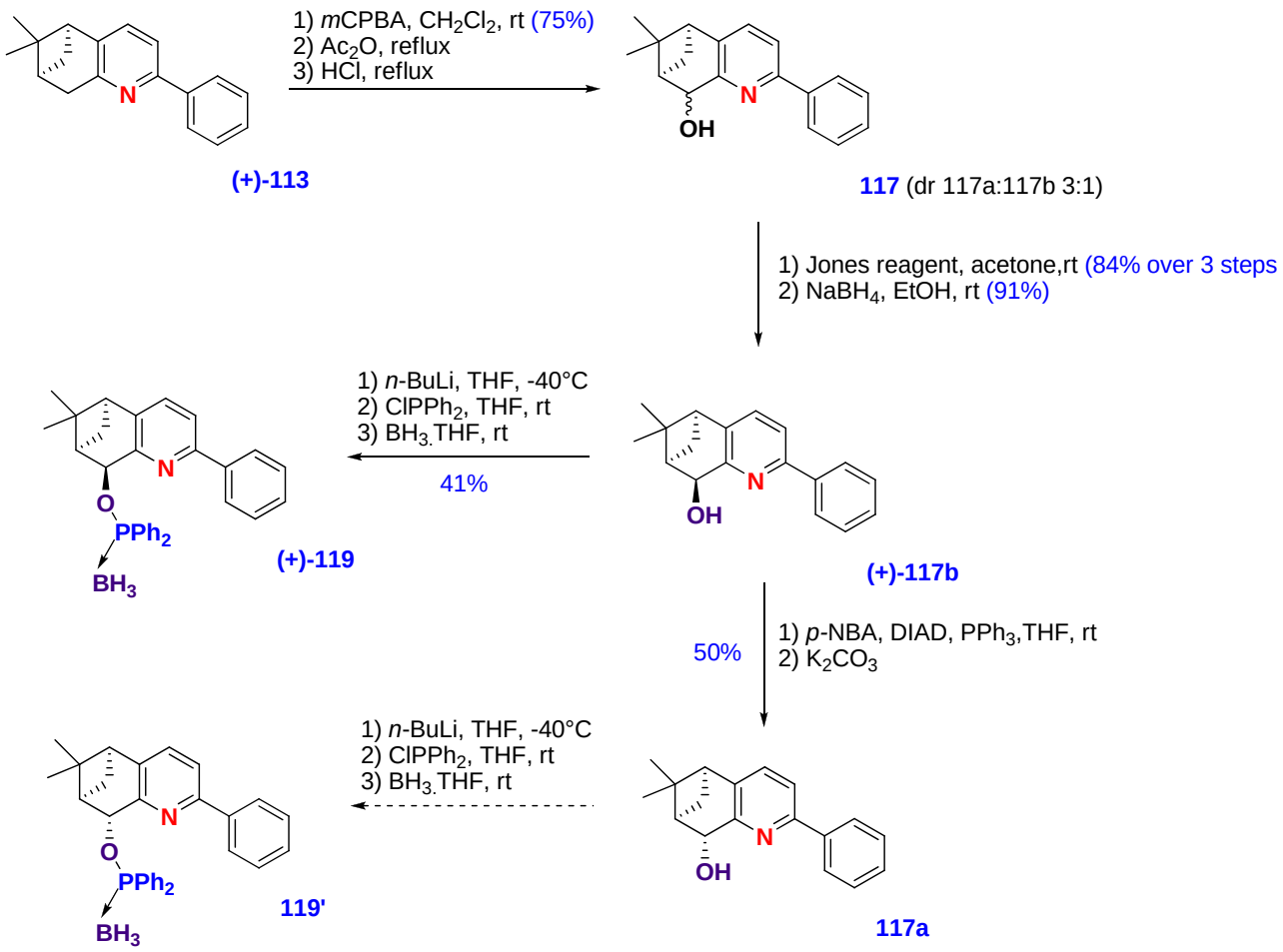
a 3:1 diastereoisomeric mixture in a reasonable yield (53% yield over two steps). Instead of separating the two diastereoisomers, it was considered more advantageous to correct the diastereoselectivity by an oxidation/reduction sequence. First, **117** was oxidised using Jones' reagent and the resulting ketone (+)-**118** was then reduced with sodium borohydride. The hydride is expected to be delivered from the bottom face since the dimethyl bridge of the pinene moiety partially blocks the upper face. Alcohol (+)-**117b** was obtained nearly diastereoisomerically pure (94:6) with the expected configuration. The structure of the alcohol (+)-**117b** was confirmed by NOE experiment (see **Figure 9**): when the benzylic proton was irradiated (7-H, **4.88** ppm), a clear enhancement appeared at **1.50** ppm and **2.50-2.60** ppm, corresponding to the CH_2 bridge (9-H and 9-H').

Figure 9. NOE experiment on the alcohol (+)-**117b**



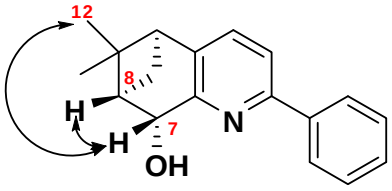
The alcohol (+)-**117b** was deprotonated with *n*-BuLi, then treated with diphenylphosphine chloride and the reaction was finally quenched with a solution of borane in THF to afford the desired air stable chiral borane-protected pyridine-phosphinite (+)-**119** in 41% yield.

Scheme 40. Synthesis of the chiral borane-protected pyridine-phosphinite (+)-**119**



It is interesting to note that **119'**, diastereoisomer of (+)-**119**, is easily accessible *via* standard Mitsunobu[115] inversion of configuration of the alcohol (+)-**117b**. Alcohol (+)-**117b** was first transformed into a *p*-nitrobenzoic ester under classical conditions[116] (use of *p*-nitrobenzoic acid, DIAD and PPh_3 in THF) in moderate yield (52%) due to difficulties associated with the separation of the desired ester from the unreacted alcohol. The ester derivative was then hydrolysed with potassium carbonate in methanol in high yield (93%) to afford the alcohol **117a** with the opposite configuration, as confirmed by the NMR shift of the α-proton of the hydroxyl group and NOE experiment (**Figure 10**): when the benzylic proton was irradiated (7-H, **4.97** ppm), a clear enhancement appeared at **0.70** ppm and **2.53** ppm, corresponding to the endo methyl (12-H) and 8-H, respectively.

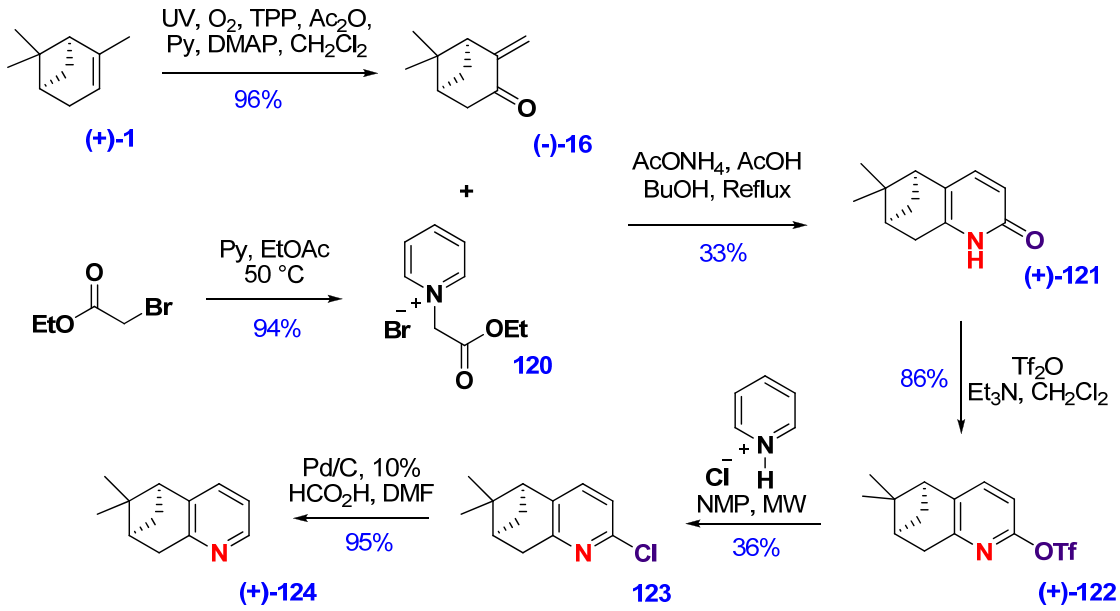
Figure 10. NOE experiment on the alcohol **117a**



3.2.4 Chiral Pyridine-Phosphine 110

In order to vary the steric properties of the pyridine moiety, synthesis of pinene-pyridine unsubstituted at position 2 was required. This was accomplished from the pinene-pyridone intermediate (+)-**121** *via* the synthetic route outlined in **Scheme 41**. (+)-α-Pinene (+)-**1** was oxidised into pinocarvone (–)-**16** in quantitative yield (as described previously), which was followed by Kröhnke annulation with salt **120** (generated from ethyl-α-bromoacetate and pyridine) to afford the desired pyridone (+)-**121** in moderate yield (33%) due to difficulties associated with the isolation of the pure product. First, we attempted to convert pyridone (+)-**121** directly into 2-chloropyridine **123** using standard protocols, such as treatment with phosphoryl chloride[117] or phenyl dichlorophosphate, but without success. Pyridone (+)-**121** was therefore transformed into the triflate derivative (+)-**122** in a quantitative yield using triflic anhydride. Surprisingly, (+)-**122** proved to be extremely resistant toward the displacement of the triflate group by a chlorine anion to give the desired 2-chloropyridine **123**. Both the use of lithium chloride in boiling DMF[118] and tetrabutylammonium chloride in CH_2Cl_2[119] were ineffective. Finally, treatment of the triflate (+)-**122** with pyridinium chloride in *N*-methyl-2-pyrrolidone (NMP) under microwave irradiation at 250 ºC for 15 min allowed formation of the 2-chloropyridine **123** (36%). Chloride **123** was quantitatively reduced (>95%) into the desired unsubstituted pyridine (+)-**124** with a mixture of 10% Pd/C and formic acid in boiling DMF. Since the reduction of 2-chloropyridine **123** by Pd/C and formic acid proved to be efficient, the same conditions were applied to triflate (+)-**122**, however it was not successful.

Scheme 41. Synthesis of the chiral pinene-pyridine (+)-**124**



Convinced that triflate (+)-**122** was a useful substrate for homogeneous palladium catalysis, we decided to investigate its reactivity further (**Table 8**). The use of a mixture of palladium(II) acetate, potassium fluoride and polymethylhydrosiloxane (PMHS) was reported to dehalogenate a wide range of chloropyridines.[120] We decided to try those conditions, using triflate (+)-**122** as substrate (*entry 1*). To our delight, the desired pyridine (+)-**124** was obtained with 50% conversion. Encouraged by the latter result, we replaced PMHS by a more classical hydrogen donor such as formic acid. However, no reaction occurred in boiling THF (*entry 2*). On the other hand, the simple change of solvent, from THF to the higher boiling DMF (*entry 3*), allowed the formation of the desired pyridine (+)-**124** (50% conversion) accompanied by the formation of pyridone (+)-**121** (30% conversion). The addition of 1,1'-bis(diphenylphosphino)ferrocene (dppf) (4 mol%) as a ligand for palladium(II) acetate (2 mol%) (*entry 4*) allowed complete conversion and isolation in reasonable yield (65%) of the desired unsubstituted pyridine (+)-**124**.

Scheme 42. Investigation of the transformation of triflate (+)-**122** into the pyridine (+)-**124**

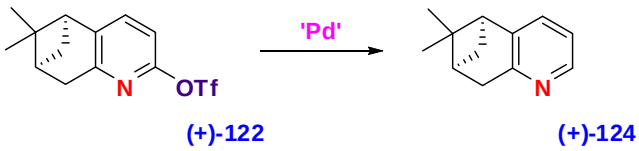


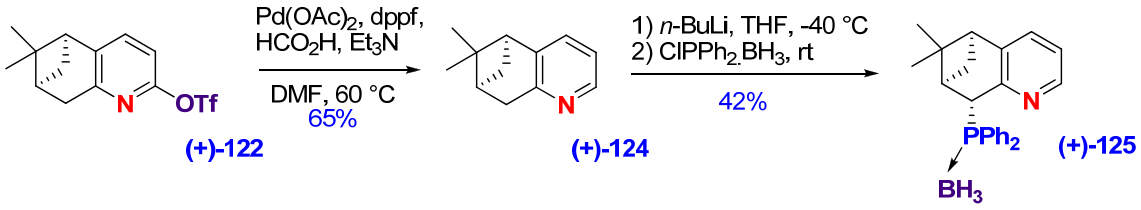
Table 8. Investigation of the transformation of triflate (+)-**122** into the pyridine (+)-**124** (**Scheme 42**)

entry	Reagents	Solvent, T	Conv. of (+)-124[a]	Conv. of (+)-121[a]
1	$Pd(OAc)_2$ – 5mol% KF – 2equiv PMHS – 4equiv	THF, rt	50%	-
2	$Pd(OAc)_2$ – 5mol% HCO_2H – 2equiv	THF, reflux	-	-
3	$Pd(OAc)_2$ – 5mol% HCO_2H – 2equiv	DMF, reflux	50%	30%
4	$Pd(OAc)_2$ – 2mol% dppf – 4mol% HCO_2H – 2equiv Et_3N – 3equiv	DMF, 60°C	100%	-

[a]Determined by ^{1}H-NMR.

Finally, the introduction of the borane-protected diphenylphosphine unit was accomplished as described previously. Chiral pyridine (+)-**124** was deprotonated with *n*-BuLi at -40 °C, followed by reaction with the freshly prepared $ClPPh_2.BH_3$ to afford the desired borane-protected pyridine-phosphine (+)-**125** in a reasonable yield (42%) (**Scheme 43**).

Scheme 43. Formation of the borane-protected pyridine-phosphine (+)-**125**

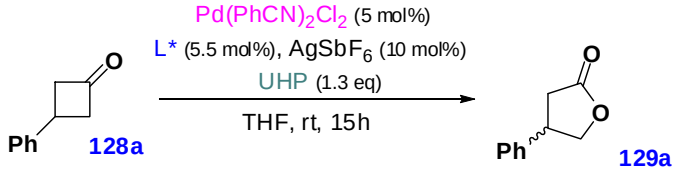


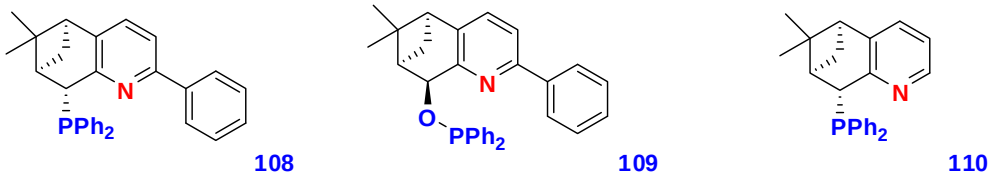
3.3 Preliminary Results for the Baeyer-Villiger Oxidation

Our preliminary investigation focused on the Baeyer-Villiger oxidation of prochiral 3-phenylcyclobutanone **128a** with urea-hydrogen peroxide (UHP) catalysed by a complex of palladium(II) chelated to the first generation of terpene-derived *P*,*N*-ligands (**Scheme 44**). The results were rather disappointing as none of the catalysts allowed the formation of the desired phenyl-γ-butyrolactone **129a**. We assumed that the lack of reactivity observed was due to the presence of $BH_3.Et_2NH$ adduct, resulting from the deprotection step, which reduces palladium(II) into palladium(0), preventing the reaction to proceed further. This assumption

is in agreement with the experimental observation of immediate formation of a black precipitate after addition of the palladium(II) precatalyst to the freshly deprotected ligand solution in THF. In fact, formation of black palladium as a result to complexation of palladium(II) with borane-deprotected phosphines has already been reported in the literature.[121] After numerous unsuccessful attempts to purify the free phosphine from the $BH_3.Et_2NH$ adduct, we decided to develop a second generation of *P*,*N*-ligands which would not require any borane-protection.

Scheme 44. BVO of cyclobutanone **128a** with UHP catalysed by Pd(II)-*P*,*N*-ligand complexes





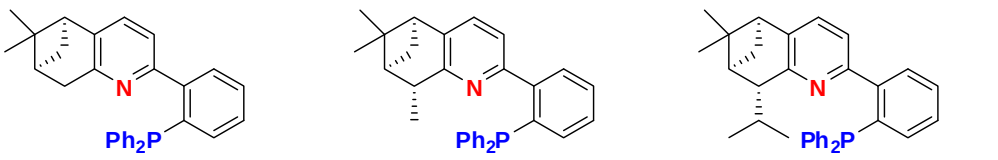
No Conversion *No Conversion* *No Conversion*

3.4 Synthesis of the Second Generation of *P*,*N*-Ligands

3.4.1 Target Ligands

The new generation of *P*,*N*-ligands (**Chart 13**) was designed based on the idea that triarylphosphines are usually more stable than their diaryl analogues. Our experience of the Kröhnke annulation allows us to prepare a variety of chiral 2-arylpyridines, which can serve as points of entry for the phosphine unit. The chiral environment can be controlled by placing various alkyl groups at the "benzylic" position of the pinene fragment.

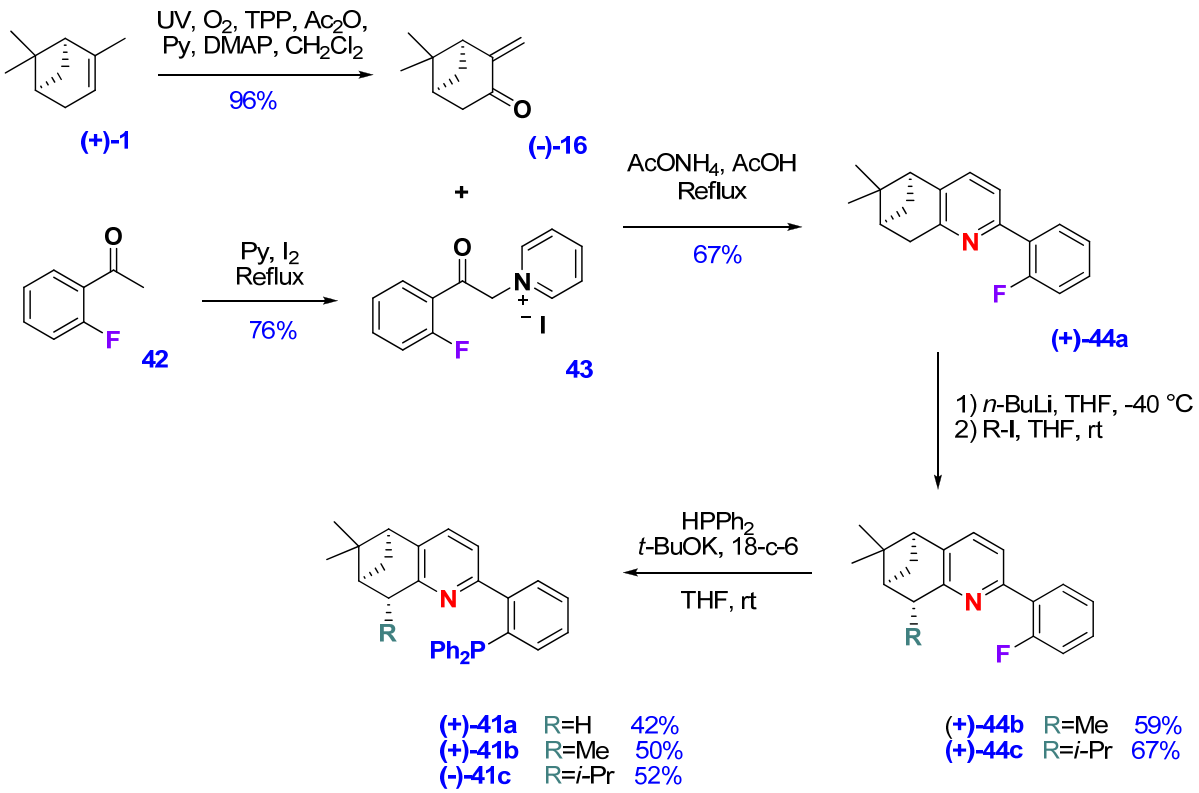
Chart 13. Targeted 2nd generation of *P*,*N*-ligands



3.4.2 Ligand Synthesis

Chiral pyridine-phosphines **41a-c** were prepared as shown in **Scheme 45**. Pinocarvone (–)-**16** reacted with pyridinium salt **43** derived from 2-fluoroacetophenone **42** to afford the desired chiral fluoro-pyridine (+)-**44a** *via* Kröhnke annulation in good yield (67%). Deprotonation of (+)-**44a** at the benzylic position with *n*-BuLi at -40 °C, followed by alkylation with either MeI or *i*-PrI gave (+)-**44b** and (+)-**44c**, respectively. Finally, aromatic nucleophilic substitution of **44a-c** with diphenylphosphine anion[122] (generated in situ from $HPPh_2$, *t*-BuOK and 18-crown-6) led to the formation of the desired chiral pyridine-phosphines **41a-c** in 42%, 50% and 52% yield, respectively.

Scheme 45. Synthesis of chiral pyridine-phosphines **41a-c**



While the synthesis of (+)-**41a** was straightforward, the preparation of (+)-**41b** and (–)-**41c** was complicated by the difficulties associated with isolation of the pure product from the crude mixture. Since phosphines (+)-**41b** and (–)-**41c** could not be fully separated from the unreacted respective fluorides (+)-**44b** and (+)-**44c** and traces of Ph_2PH, the crude mixture was oxidized (H_2O_2, Me_2CO, rt, 10 min) to convert the phosphines into the corresponding phosphine oxides, which were then readily separated from the fluorides (+)-**44b** and (+)-**44c** by column chromatography. However, the phosphine oxides were still contaminated by

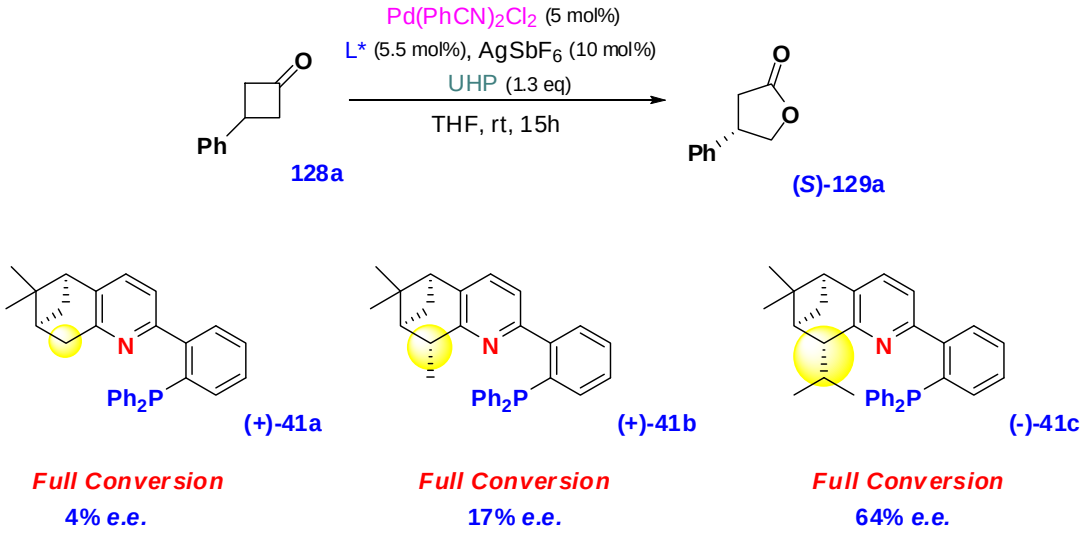
$Ph_2P(O)H$, generated from Ph_2PH. Therefore, the mixture was treated with KOH in ethanol (reflux, 4 h), which generated the water-soluble Ph_2PO_2K,[123] whose separation from the respective phosphine oxides was carried out by partitioning between the aqueous and organic phase. The pure phosphine oxides were then reduced with Cl_3SiH (Et_3N, toluene, reflux, 24 h) to afford the respective phosphines (+)-**41b** and (–)-**41c**. The yields (50 and 52%, respectively) correspond to the overall procedure.

3.5 Application of Triarylphosphine Ligands in Baeyer-Villiger Oxidation

The results employing the second generation of ligands are shown in **Scheme 46**. The pre-catalysts for the oxidation were generated in situ from $(PhCN)_2PdCl_2$ and the respective ligand (**41a-c**) in THF at room temperature. Each of the resulting complexes was then treated with $AgSbF_6$ and the insoluble AgCl was removed by filtration. The solution of the catalyst thus generated, i.e., (Ligand)$Pd(SbF_6)_2$, was used in the individual oxidation reactions.

Compounds **41a-c**, being triarylphosphines, are relatively more stable than the diarylphosphines **108-110** and do not require borane protection. As a result, they were expected to achieve higher level of reactivity compared to the first generation of ligands. We were therefore pleased to note that full conversion of γ-butyrolactone **129a** was achieved with all three ligands of the second generation. Furthermore, it is clear from **Scheme 46** that the bulk of the ligand plays a dramatic role in the enantiocontrol of the reaction. In the absence of a substituent at the benzylic position (ligand **41a**), the resulting γ-butyrolactone **127a** was nearly racemic (4% *ee*). The enantioselectivity of the reaction was slightly improved (17% *ee*) when a methyl group was incorporated into the ligand (ligand **41b**). Finally, replacement of the methyl group by a bulkier isopropyl substituent (ligand **41c**) significantly increased the enantioselectivity (64% *ee*).

Scheme 46. BVO of cyclobutanone **128a** with UHP catalysed by Pd(II)-*P*,*N*-ligand complexes



3.5.1 Solvent Effect

Employing our most efficient ligand, the isopropyl-substituted phosphino-pyridine **41c**, we investigated the effect of the solvent on the reactivity and enantioselectivity of the BVO (**Scheme 47**). The results obtained are shown in **Table 9**. In short, replacing THF with other solvent proved to be detrimental to enantioselectivity. In non-coordinating solvents, such as toluene (*entry 1*), the reaction did not occur. Dichloromethane (*entry 2*) gave full conversion but with moderate enantioselectivity. Finally coordinating solvent, such as acetonitrile and THF (*entries 3 & 4*), gave full conversion, THF exhibiting the highest enantioselectivity (64% *ee*).

Scheme 47. Solvent effect

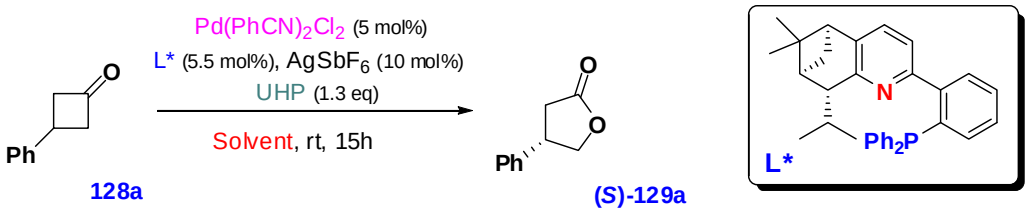


Table 9. Solvent screening (**Scheme 47**)

Entry	Solvent	Conversion (%)[a]	*ee* (%)[a]
1	Toluene	No	N.D.
2	DCM	Full	36 (*S*)
3	CH_3CN	98	46 (*S*)
4	THF	Full	64 (*S*)

[a]Determined by chiral GC (Supelco α-DEX); N.D.=Not determined.

3.5.2 Low Temperature Experiments

In an attempt to increase enantioselectivity of the oxidation, we have investigated the reaction in THF at low temperatures (**Scheme 48**). Lowering the temperature had a beneficial effect on the enantioselectivity (**Table 10**). A considerable increase of enantioselectivity (to 81% *ee*) was observed when the reaction was carried out at -40 °C (*entry 2*). However, below that temperature (*entry 3*), the reactivity was dramatically reduced due to precipitation of the catalyst from the solution.

Scheme 48. Low temperature experiments

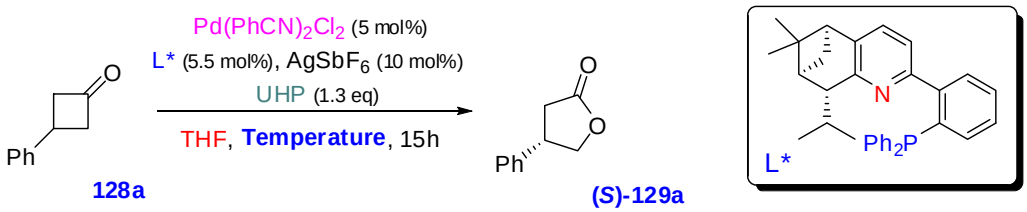


Table 10. Low temperature experiments (**Scheme 48**)

Entry	Temperature (°C)	Conversion (%)[a]	*ee* (%)[a]
1	RT	Full	64 (*S*)
2	-40	Full	81 (*S*)
3	-80	11[b]	N.D.

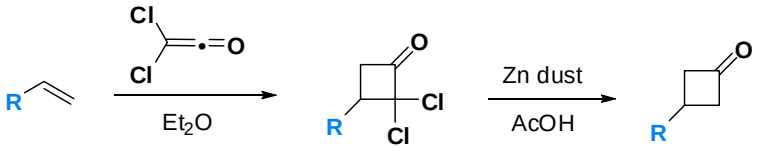
[a]Determined by chiral GC (Supelco α-DEX). [b]After 4 days of reaction. N.D.=Not determined.

3.5.3 Substrate Scope

With the aim of establishing the scope of the BVO, the required cyclobutanones **128a-j** were synthesised in two steps *via* cyclisation of dichloro ketene (generated *in situ* from

trichloroacetyl chloride, Zn-Cu couple, and $POCl_3$) and the vinyl derivative **126a-j**, followed by reduction of the resulting dichloro ketones **127a-j** with zinc in acetic acid (**Scheme 49**).[124] Most of the cyclobutanones **128a-j** were obtained in good yields. However, we failed to prepare *p*-methoxy-phenylcyclobutanone due to the polymerisation of the starting *p*-methoxy styrene under the reaction conditions. It is interesting to note that Imada[57] reported the use of *p*-methoxy-phenylcyclobutanone for his BVO study. However, after contacting Imada, it appeared that *p*-methoxy-phenylcyclobutanone was obtained in very poor yield (0.1%) and large scale distillation was necessary to purify it (100 mol scale reaction).

Scheme 49. Synthesis of 3-substituted cyclobutanones **128a-j**



126a R=C_6H_5	**127a,** 97%	**128a,** 86%
126b R=4-Me-C_6H_4	**127b,** 91%	**128b,** 32%
126c R=4-F-C_6H_4	**127c,** 94%	**128c,** 56%
126d R=4-Cl-C_6H_4	**127d,** 90%	**128d,** 46%
126e R=4-Br-C_6H_4	**127e,** 92%	**128e,** 51%
126f R=2-Br-C_6H_4	**127f,** 94%	**128f,** 52%
126g R=2-Naphth	**127g,** 41%	**128g,** 15%
126h R=4-MeO-$C_6H_4CH_2$	**127h,** 99%	**128h,** 43%
126i R=Cyclohexyl	**127i,** 96%	**128i,** 51%
126j R=*n*-Octyl	**127j,** 85%	**128j,** 46%

The reactivity of cyclobutanones **128a-j** was then investigated under the optimised conditions (THF, –40 °C, (–)-**41c** as ligand) (**Scheme 50**). The results are shown in **Table 11**. All γ-butyrolactones **129a-j** were obtained in high yield. Variation of the substitution pattern in the 4-position of the cyclobutanone (**128b-j**) led to reduction in enantioselectivity to 70-75% ee for the aromatics with electron-withdrawing or neutral groups **128b-g** (*entries 2-7*) and to 58% ee for the *p*-methoxybenzyl derivative **128h** (*entry 8*). Asymmetric induction observed for the cyclohexyl derivative **128i** was in the midrange (*entry 9*), whereas *n*-octyl-cyclobutanone **128j** leaned toward the lower end of the spectrum (*entry 10*).

Scheme 50. Substrate investigation

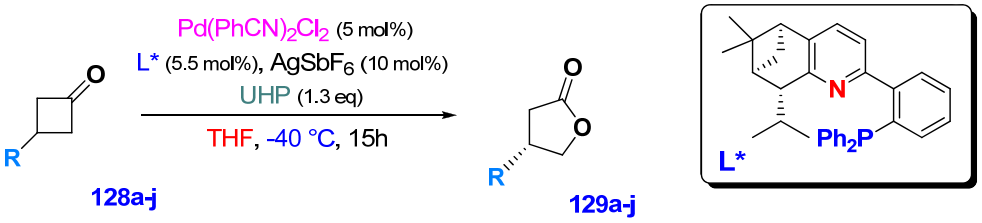


Table 11. Substrate investigation (**Scheme 50**)

entry	Ketone	R	Yield (%)	129 % *ee*[a]
1	**128a**	C_6H_5	97	81 (*S*)[b]
2	**128b**	4-Me-C_6H_5	93	75 (*S*)[b]
3	**128c**	4-F-C_6H_5	96	72 (+)[b]
4	**128d**	4-Cl-C_6H_5	94	73 (*S*)[b]
5	**128e**	4-Br-C_6H_5	95	76 (+)[c]
6	**128f**	2-Br-C_6H_5	92	70 (+)[c]
7	**128g**	2-Naphth	83	71 (+)[c]
8	**128h**	4-MeO-$C_6H_4CH_2$	91	58 (*R*)[d,e]
9	**128i**	Cyclohexyl	89	65 (–)[c]
10	**128j**	*n*-Octyl	83	55 (*R*)[c]

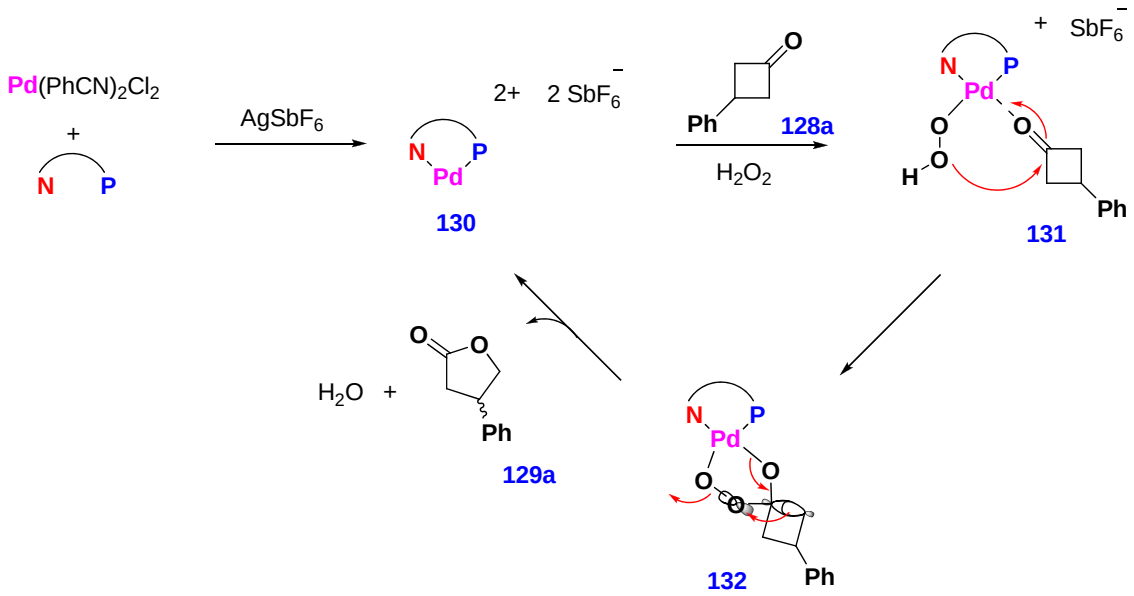
[a]The absolute configuration was established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Experimental). Lactones **129a**, **129b**, and **129d** were (*S*)-configured; the configuration of **129c** and **129e-g** is assumed to be (*S*) in analogy with the rest of the series. [b]Determined by chiral GC. [c]Determined by chiral HPLC (Chiralpak IB) after conversion into the corresponding hydroxy benzylamide derivative.[64] [d]Determined by optical rotation.[125] [e]Note the change in the substituent priorities in the Cahn-Ingold-Prelog system.

Our study indicates that the enantioselectivity of the oxidation is not only dependent on the steric size of the alkyl group in the benzylic position of the *P*,*N*-ligand but also on the nature of the substituent in the cyclobutanone ring.

3.5.4 Mode of Action

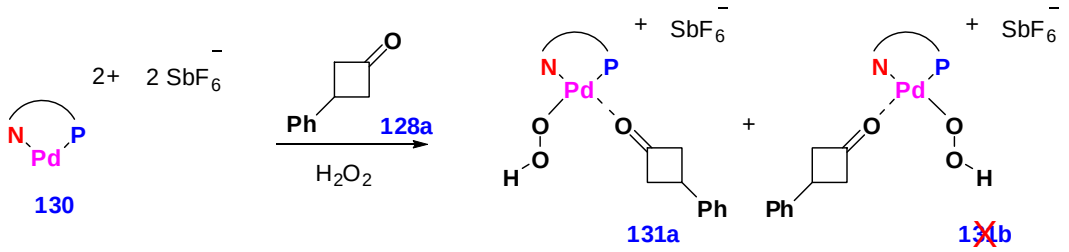
Based on our experimental data, we can tentatively rationalise the high selectivity of the ligand (–)-**41c**. *P*,*N*-chelation of palladium by ligand (–)-**41c** and treatment with $AgSbF_6$ generates the palladium complex **130** with two vacant coordination sites (**Scheme 51**). Subsequent coordination of the carbonyl group and hydrogen peroxide (**131**) can be assumed to activate the keto group towards intramolecular nucleophilic attack of the peroxide moiety, generating the Criegee adduct **132**. Finally, the C-C bond antiperiplanar to the O-O bond migrates to give the lactone and regenerates the active palladium species **130**.

Scheme 51. Possible mechanism of Pd(II)-catalysed BVO of cyclobutanone



However, it is important to note that several factors have to be controlled along the catalytic cycle to reach high enantioselectivity. First, depending on the nature of the coordination, two intermediates **131a** and **131b** can be generated (**Scheme 52**). The electronic asymmetry of the *P*,*N*-ligand will presumably determines the mode of coordination. The oxygen atom of hydrogen peroxide, being electronically richer than the oxygen atom of the carbonyl group, is expected to coordinate *trans* to the phosphine moiety, leading to **131a** as favoured intermediate.

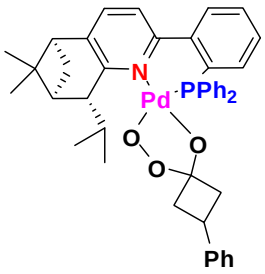
Scheme 52. Electronic control



Once the intramolecular nucleophilic attack has occurred, the spacial arrangement of the Criegee intermediate **132** and its subsequent rearrangement is supposed to be dictated by the chiral environment generated by the ligand. As shown in **Figure 11**, the presence of the *i*-propyl group at the benzylic position of the ligand **41c**, relatively close to the metal centre,

can influence the configuration of the Criegee adduct **132c** and therefore the absolute configuration of the product.

Figure 11. Possible mode of action



132c

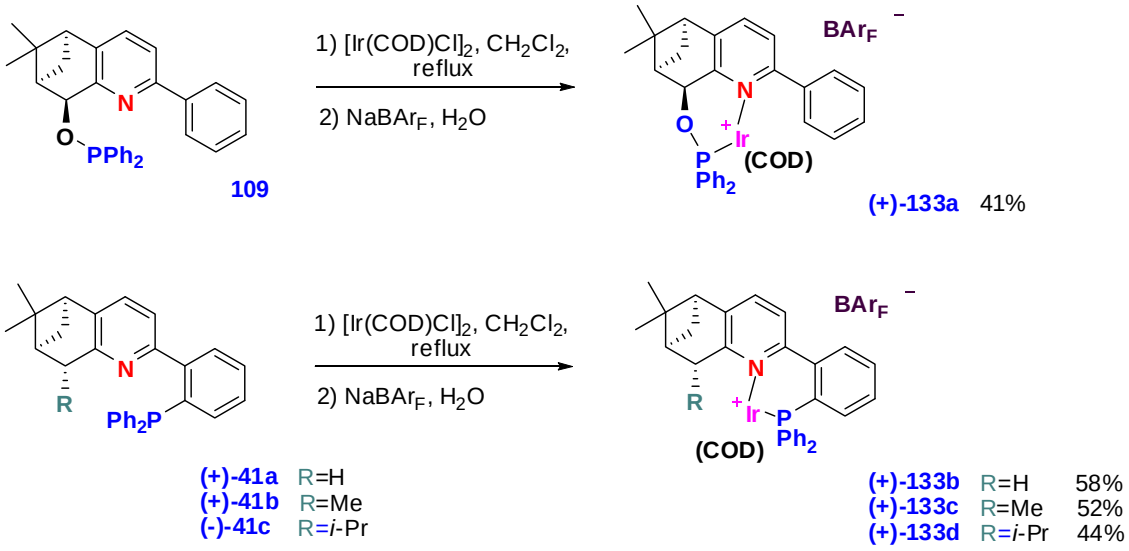
3.6 Application of the New *P*,*N*-Ligands in the Iridium-Catalysed Hydrogenation

With the aim of extending the scope of application of our chiral *P*,*N*-ligands family, the asymmetric iridium-catalysed hydrogenation of unfunctionalised olefins was investigated.

3.6.1 Iridium Catalysts Synthesis

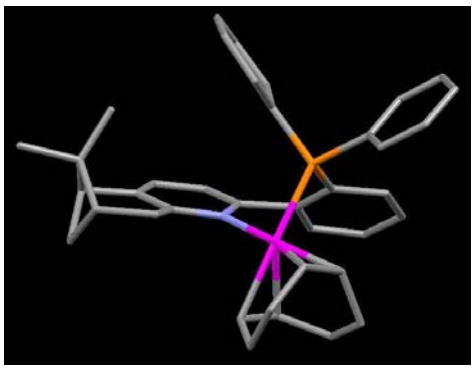
The ligands **109** and **41a-c** were complexed to iridium metal according to the standard protocol. The pyridine-phosphines were first refluxed in CH_2Cl_2 in the presence of $[Ir(COD)Cl]_2$ dimer, and subsequently treated with $NaBAr_F$ to afford the air and moisture stable chiral iridium complexes **133a-d** (**Scheme 53**). All iridium catalysts were easily purified by flash column chromatography and isolated in moderate yield (≤ 58%). However, we failed to prepare catalysts based on pyridine-phosphines **108** and **110**.

Scheme 53. Iridium catalysts preparation



The single crystal X-ray structure of the cationic iridium complex (+)-**133b** is shown in **Figure 12**.[126] Single-crystals of complex (+)-**133b** were obtained from a mixture of hexane and diethyl ether (1:1) at low temperature (0 °C). The structure is depicted without the BAr_F anion. Hydrogen atoms were also omitted for clarity.

Figure 12. X-ray structure of iridium complex (+)-**133b**



3.6.2 Application of Iridium Catalysts

3.6.2.1 Hydrogenation of *trans*-α-Methylstilbene 78

Iridium complexes **133a-d** were first evaluated as catalysts for asymmetric hydrogenation of the unfunctionalised *trans*-α-methylstilbene **78** under 10 bar hydrogen pressure (**Scheme 54**).

The reactions were performed at room temperature over two days with 2 mol% catalyst loading. The results are shown in **Table 12**. Structure of the catalyst proved to have a great influence on the reactivity and enantioselectivity of the reaction.

Scheme 54. Hydrogenation of trans-α-methylstilbene **78**

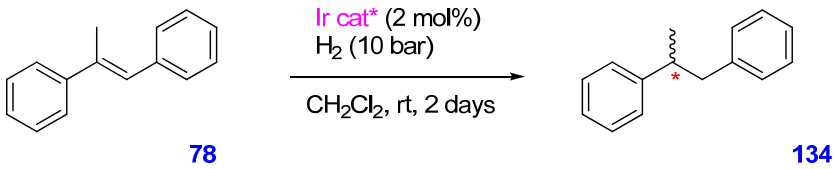
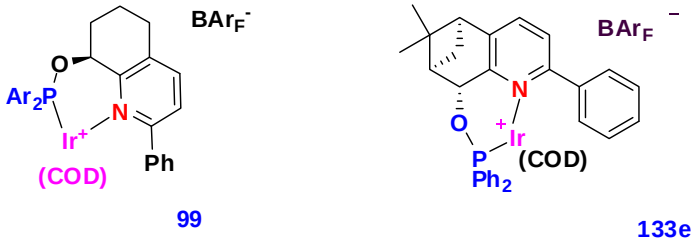


Table 12. Hydrogenation of *trans*-α-methylstilbene **78** (see **Scheme 54** for exp. cond.)

Entry	Catalyst	Conversion (%)[a]	% *ee*[b]
1	**99**	99	99
2	**133e**	11	41 (*R*)[c]
3	**133a**	30	12 (*S*)[c]
4	**133a**	50	80 (*S*)[d]
5	**133b**	96	21 (*R*)[d]
6	**133c**	7	N.D.
7	**133d**	No conversion	N.D.

[a]Determined by ^{1}H NMR. [b]Determined by chiral HPLC (OJ-H, 0.5 mL.min^{-1}, 99:1 (Hexane:^{i}PrOH)). [c]Reaction carried out with 0.5 mol% catalyst loading under 30 bar hydrogen pressure.[127] [d]Absolute configurations were assigned by comparison of the HPLC retention times with literature values.[81] N.D.=Not determined.

Chart 14. Reported catalyst analogues to **133a**



Iridium catalyst **133a** resembles the tertahydroquinoline-based phosphinite-iridium complex **99** recently developed by Pfaltz and co-workers (**Chart 14**). Since catalyst **99** (*entry 1*) exhibited high reactivity (99% conversion) and enantioselectivity (99% ee),[96] complex **133a** was expected to be an effective catalyst for hydrogenation. However, the results were clearly not comparable. Catalyst **133a** showed only moderate reactivity (50% conversion) and good enantioselectivity (80% ee). Andersson reported recently the synthesis of complex **133a** and

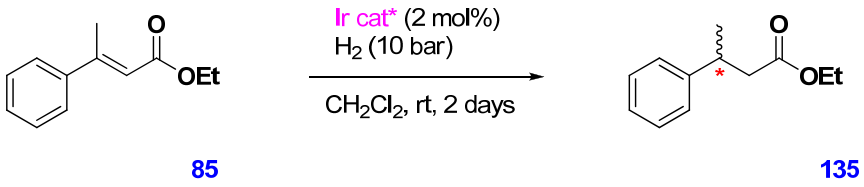
its diastereoisomer **133e** (**Chart 14**) and their application in asymmetric hydrogenation of olefins.[127] The hydrogenation was performed under 30 bar hydrogen pressure and 0.5 mol% catalyst loading. First, **133e** (*entry 2 and 3*) proved to be less effective but more selective than **133a**. But more interestingly, **133a** seemed to be a more reactive and selective catalyst (*entry 3 and 4*) under our experimental conditions (10 bar of hydrogen pressure with 2 mol% catalyst loading), clearly showing that slight modifications of the catalyst structure or of the reaction conditions can have a big influence on the outcome of the hydrogenation.

The second generation of catalysts **133b-d** also exhibited a high dependence on the catalyst structure. Complex **133b** showed high reactivity (*entry 5*); however, its benzylic substituted analogues **133c-d** did not prove to be effective catalysts (*entry 6 and 7*).

3.6.2.2 Hydrogenation of Ethyl *trans*-β-Methylcinnamate 85

Iridium complexes **133a-d** were then tested as catalysts for asymmetric hydrogenation of ethyl *trans*-β-methylcinnamate **85** under 10 bar hydrogen pressure and 2 mol% catalyst loading (**Scheme 55**). The results are shown in **Table 13**.

Scheme 55. Hydrogenation of Ethyl *trans*-β-methylcinnamate **85**



85 **135**

Table 13. Hydrogenation of ethyl *trans*-β-methylcinnamate **85** (see **Scheme 55** for exp. cond.)

Entry	Catalyst	Conversion (%)[a]	e.e. (%)[b]
1	**133e**	10	16 (*S*)[c]
2	**133a**	15	9 (*S*)[c]
3	**133a**	15	N.D.
4	**133b**	>99	20 (*S*)[d]
5	**133c**	>99	83 (*S*)[d]
6	**133d**	>99	57 (*S*)[d]

[a]Determined by ^{1}H NMR. [b]Determined by chiral HPLC (IB, 0.75 mL.min^{-1}, 99:1 (Hexane:^{i}PrOH)). [c]Reaction carried out with 0.5 mol% catalyst loading under 30 bar hydrogen pressure.[127] [d]Absolute configuration obtained from optical rotation and comparison with literature data.[128] N.D.=Not determined.

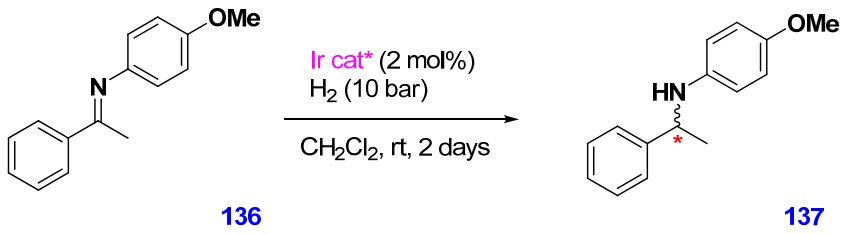
Iridium catalysts based on the chiral pyridine-phosphinite (**133a** and **133e**) showed very low reactivity (*entries 1-3*). However, the second generation of iridium catalysts **133b-d** were more suitable for this type of substrate. High level of reactivity was achieved for the three catalysts (full conversion) and the enantioselectivity was clearly controlled by the steric hindrance generated by the alkyl groups in the benzylic position of the ligand (*entries 4-6*). The enantiomeric excess varied from 20% (ligand with no substituent **41a**, *entry 4*) to 83% (methyl-substituted ligand **41b**, *entry 5*). Unfortunately, the *i*-propyl substituted ligand **41c** did not improve the enantioselectivity (57% ee, *entry 6*).

3.6.2.3 Hydrogenation of Arylimine 136

Although, iridium-catalysed hydrogenation of unfunctionalised olefins has been extensively studied over the last decade, the iridium-catalysed hydrogenation of imines was only scarcely evaluated.[129] We therefore decided to apply our chiral iridium catalysts **133a-d** for the asymmetric hydrogenation of arylimine **136** under 10 bar hydrogen pressure (**Scheme 56**). Arylimine **136** is sterically very similar to *trans*-α-methylstilbene **78**. It is therefore not surprising that comparable results were obtained (**Table 14**). Iridium complex **133a** exhibited the best results of the whole catalysts family (*entry 1*) with full conversion and moderate enantioselectivity (48% ee). Reactivity of the second generation of catalysts **133b-d** was, as previously observed, very sensitive to the steric bulk of the substituent at the benzylic position in the ligand. Complex **133b** with unsubstituted ligand afforded full conversion into the hydrogenated product but as a racemate (*entry 2*), whereas the reactivity

quickly diminished for the substituted analogues (Me, 31% conversion, *entry 3*. *i*-Pr, 6% conversion, *entry 4*).

Scheme 56. Hydrogenation of arylimine **136**



136 **137**

Table 14. Hydrogenation of arylimine **136** (see **Scheme 56** for exp. cond.)

Entry	Catalyst	Conversion (%)[a]	e.e. (%)[b]
1	**133a**	>99	48 (*S*)[c]
2	**133b**	>99	0[c]
3	**133c**	31	32 (*S*)[c]
4	**133d**	6	N.D.

[a]Determined by ^{1}H NMR. [b]Determined by chiral HPLC (IB, 0.75 mL.min^{-1}, 99:1 (Hexane:^{i}PrOH)). [c]Absolute configurations were assigned by comparison of the HPLC retention times with literature values.[130] N.D.=Not determined.

3.7 Summary

Two generations of chiral *P*,*N*-ligands have been developed. The first generation, containing chiral phosphine moiety, had to be synthesised *via* borane protection due to their high oxygen sensitivity. The second generation was based on the more stable triarylphosphines. The chiral environment was then controlled by the size of the alkyl substituent in the benzylic position of the pyridine fragment.

Chiral pyridine-phosphines of the second generation can act as efficient *P*,*N*-ligands for the enantioselective palladium(II)-catalysed Baeyer-Villiger oxidation of prochiral 3-substituted cyclobutanones to furnish chiral γ-butyrolactones in up to 81% ee. As well as the ligand structure, the enantioselectivity of the oxidation is dependent on the reaction temperature, solvent and the substrate structure. High enantioselectivity was observed for cyclobutanones with aromatic substituent, the optimal conditions were identifies as –40 °C in THF.

Complexes of the developed ligands with iridium can also promote asymmetric hydrogenation of olefins and imines. Hydrogenation has been shown to be very sensitive to the ligand structure, the experimental conditions, as well as to the olefin structure. Chiral pyridine-phosphines of second generation have proved to be particularly suitable for the enantioselective hydrogenation of ethyl *trans*-β-methylcinnamate in up to 83% ee.

4 Organocatalysis – Activation of Silicon with Lewis Bases

4.1 Introduction

Due to some drawbacks inherent to transition metals such as their cost, toxicity and the difficulty to remove their traces from the desired product, pharmaceutical companies try to avoid metal-based catalysts. Recently, considerable attention has become focused on the development of metal-free asymmetric protocols promoted by simple chiral small molecules. Over the past five years, *organocatalysis* has undergone an exponential development. Many enantioselective transformations can now be catalysed without metal.[6,7]

Transition metal complexes translate chirality from the ligands coordinated to the metal centre to the newly formed stereogenic atom or group of atoms *via* organised transition states, resulting from a strong association between the metal centre and the reactants. Organocatalytic mechanisms often take advantage of weaker interactions such as hydrogen-bonding and arene-arene interactions, as well as covalent interactions to activate and bring substrates together in an organised fashion as required for asymmetric induction. A wide array of organic molecules ranging from natural product derived organic bases to synthetic Brønsted acids has been employed as organocatalysts.[6,7]

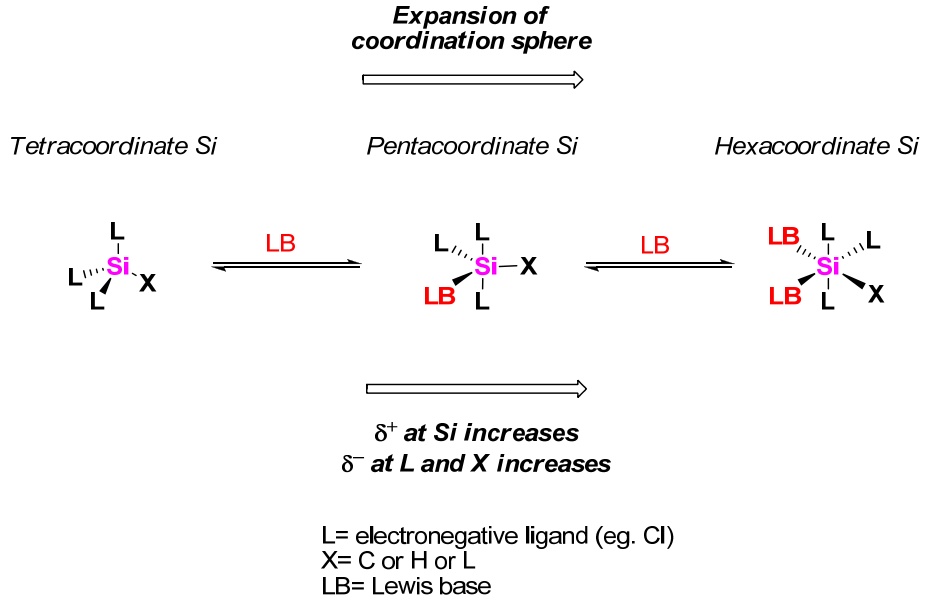
The enantioselective metal-free Lewis base catalysis[131] of reactions mediated by silicon reagents has been pioneered by the groups of Denmark and Kobayashi, as well as our own group, and represents a powerful tool in asymmetric catalysis.[132] In this chapter, organocatalytic allylation based on the activation of allyltrichlorosilane with chiral Lewis bases catalysts will be reviewed.

4.2 Activation of Silicon Reagents

One of the most striking differences between carbon and silicon is the ability of the latter to expand its coordination shell. Strong Lewis bases such as DMF and HMPA are capable of generating neutral hypervalent silanes that possess enhanced nucleophilicity at the peripheral groups (**X**) (a consequence of the changes in the electron distribution caused by the formation

of hypervalent bonds) (**Figure 13**) and an increase of the positive charge on silicon, thus providing opportunities for the development of new reactions *via* double activation (nucleophilic and electrophilic).[133] This enhanced polarisation of hypervalent silicon species is the central point to the development of enantioselective organocatalytic transformations employing silicon reagents such as allylation of aromatic aldehydes with allyltrichlorosilane.

Figure 13. Formation of hypervalent silicon species



4.3 Allylation of Carbonyl Groups

Asymmetric allylation of carbonyl compounds is a useful synthetic method to prepare optically active secondary homoallylic alcohols. It has been employed as a key-step in the synthesis of numerous natural products.[134] The most common strategies to accomplish stereoselective introduction of an allyl group is the use of allylic organometallic reagents in which the metal is ligated by chiral modifiers. Excellent results have been obtained with chirally modified allylic borane or allylic titanium reagents,[135] but they required a stoichiometric amount of chiral controller group or chiral ligand.

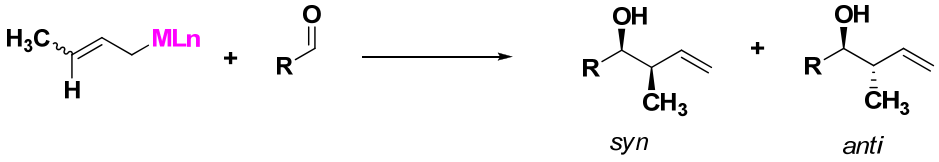
More recently, allylic stannanes and allylic silanes extended the field toward catalytic processes.[132a] Allylation can be divided into three categories that reflect the stereochemical outcome of the reaction:[136]

Type 1: reactions wherein the *syn/anti* (**Scheme 57**) ratio reflects the (*E*/*Z*) ratio of the starting allylmetal;

Type 2: reactions wherein the product is predominantly *syn*, independent of the geometry of the allylmetal;

Type 3: reactions wherein the product is predominantly *anti*, independent of the geometry of the allylmetal.

Scheme 57. Allylation reaction



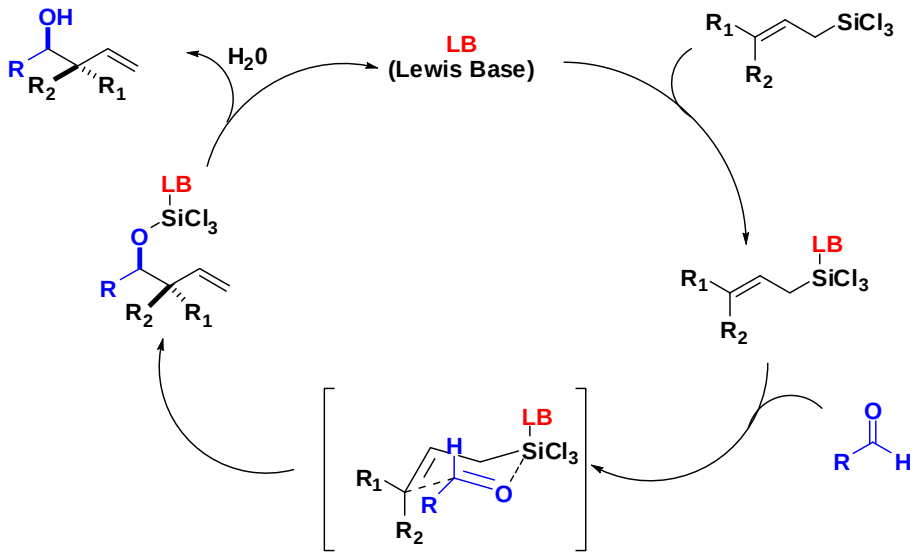
The type 1 includes the addition of allylic trichlorosilanes catalysed by chiral Lewis bases, the type 2 reflects the addition of allylmetals (Si, Sn, B) catalysed by chiral Lewis acids and the type 3 relates more to the addition of allylmetals (Cr, Zn, In) generated in situ from the corresponding allylic halides catalysed by chelating ligands. In this review we only concentrate on the type 1 transformations.

4.3.1 Generality Concerning Lewis Base-Promoted Allylation

The allylation of aldehydes with allyltrialkyl silanes in the presence of chiral Lewis acids (Sakurai-Hosomi reaction) (type 2) made a considerable impact on asymmetric synthesis.[137] The complementary activation with chiral Lewis bases is less common but offers high diastereo- and enantiocontrol that can be explained by a different reaction mechanism compared to the one operating in the Lewis acids activation.

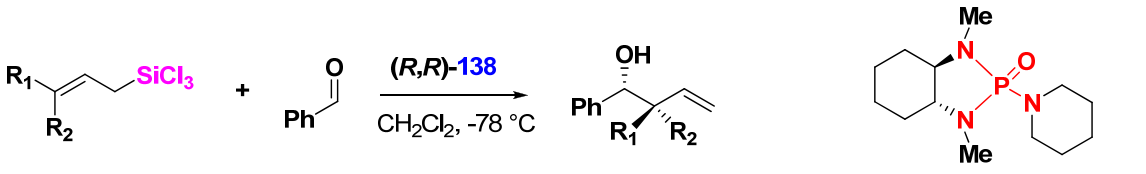
The Lewis base (LB) first coordinates to the silicon atom (**Scheme 58**). The resulting complex possesses a highly electrophilic silicon atom allowing coordination and therefore activation of the aldehyde. The enhanced nucleophilicity of the allyl fragment (due to the hypervalency of the silicon species) permits reaction with the activated aldehyde through a closed chair-like transition structure. Finally, the dissociation of the LB from the product completes the catalytic cycle.

Scheme 58. Lewis base-promoted allylation mechanism



LB-activation of allyltrichlorosilane was pioneered by Kobayashi[138] by the use of dimethylformamide. However, the first asymmetric allylation reaction was carried out by Denmark, in 1994, by employing a chiral phosphoramide (*R*,*R*)-**138** as a chiral Lewis base promoter (**Scheme 59** & **Table 15**).[139] Using either a stoichiometric amount or 10 mol % of the activator (*R*,*R*)-**138**, addition of allyltrichlorosilane **139** to benzaldehyde provided the homoallylic alcohol with modest enantioselectivity (from 53 to 66% ee) in good chemical yield (*entries 1 & 4*). However, it is important to note that the geometry of C=C double bond in the starting allylsilanes is completely transferred into the product *anti/syn* ratio (*entries 2 and 3*).

Scheme 59. Addition of allylic trichlorosilanes to benzaldehyde promoted by (*R*,*R*)-**138**



139 R_1=H, R_2=H
(*E*)-**140** R_1=Me, R_2=H
(*Z*)-**140** R_1=H, R_2=Me

141 R_1=H, R_2=H
142a R_1=Me, R_2=H
142b R_1=H, R_2=Me

(*R*,*R*)-**138**

Table 15. Addition of allylic trichlorosilanes to benzaldehyde promoted by (*R*,*R*)-**138** (**Scheme 59**)

entry	Silane	(*R*,*R*)-**138** (equiv)	Yield (%)	anti/syn	*ee* (%)
1	**139**	1.0	80	-	60 (*R*)
2	(*E*)-**140**	1.0	68	98/2	66 (*R*,*R*)
3	(*Z*)-**140**	1.0	72	2/98	60 (*R*,*S*)
4	**139**	0.1	40	-	53 (*R*)

Since then, three major categories of chiral Lewis basic activators of allyl trichlorosilanes and related reagents dominated the field: phosphoramides, formamides, and more recently *N*-oxides.

4.3.2 Chiral Phosphoramide-Catalysed Allylation Reaction

In 1996, Iseki reported an improvement in enantioselectivity when phosphoramides derived from (*S*)-proline (**143-145**) were employed (**Scheme 60**).[140] The results are detailed in **Table 16**. The loading of the chiral Lewis base had a considerable influence on the conversions. A reduction in loading from 1 equivalent to 10 mol% of the Lewis base dramatically slowed down the reaction (*entries 1 & 4*). On the other hand, the enantioselectivity of the allylation seemed to be controlled by the configuration of the phosphorus atom and the substituents on the nitrogen (*entries 1-3*).

Scheme 60. Addition of allylic trichlorosilanes to benzaldehyde promoted by **143-145**

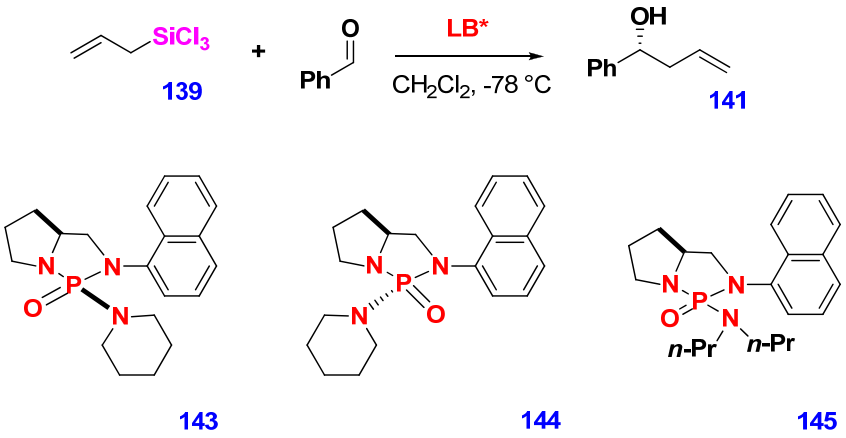
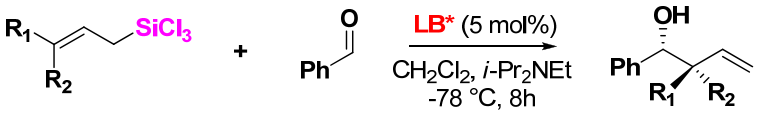


Table 16. Addition of allylic trichlorosilanes to benzaldehyde promoted by **143-145** (**Scheme 60**)

entry	LB*	Loading (equiv)	Time (h)	Yield (%)	*ee* (%)
1	**143**	1.0	6	74	71 (*R*)
2	**144**	1.0	6	5	29 (*R*)
3	**145**	1.0	6	84	85 (*S*)
4	**143**	0.1	168	67	85 (*R*)

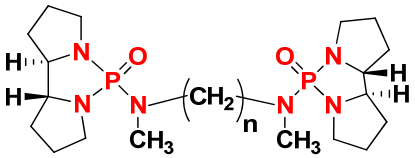
Extensive mechanistic study carried out by Denmark revealed that the reaction was second order in phosphoramide catalyst.[141] This led to the design of bisphosphoramides **146a-c** with varying tether length (**Scheme 61**).[142] The results are shown in **Table 17**. The optimal length of the spacer between the two phosphoramide units was found to be five carbon atoms (*entry 2*). Catalyst **146b** allowed high reactivity (85% yield) and enantioselectivity (87% ee). The addition of crotylsilanes catalysed by **146b** again was found to be highly diastereoselective (*entries 4 & 5*), the enantioselectivity remaining very high (up to 94% ee). Under optimised conditions, *N*,*N*-diisopropylethylamine was employed as an additive. Hünig's base was reported to dramatically enhance the reactivity of the allylation reaction and it was postulated that the additive could increase the rate of catalyst turnover by facilitating cleavage of the catalyst-silicon bond.[143]

Scheme 61. Addition of allylic trichlorosilanes to benzaldehyde promoted by bisphosphoramides **148**



139 R_1=H, R_2=H
(*E*)-140 R_1=Me, R_2=H
(*Z*)-140 R_1=H, R_2=Me

141 R_1=H, R_2=H
142a R_1=Me, R_2=H
142b R_1=H, R_2=Me



148a: n=4; **148b**: n=5; **148c**: n=6

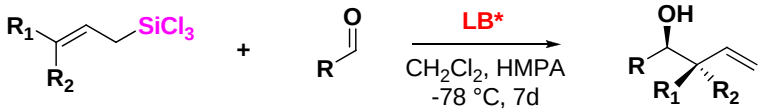
Table 17. Addition of allylic trichlorosilanes to benzaldehyde promoted by bisphosphoramides **148** (**Scheme 61**)

entry	LB*	Silane	Yield (%)	anti/syn	*ee* (%)
1	**148a**	**139**	54	-	18 (*S*)
2	**148b**	**139**	85	-	87 (*S*)
3	**148c**	**139**	58	-	67 (*S*)
4	**148b**	(*E*)-**140**	57	99/1	80 (*S*,*S*)
5	**148b**	(*Z*)-**140**	89	1/99	94 (*S*,*R*)

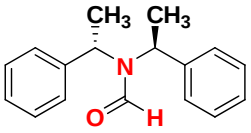
4.3.3 Chiral Formamide-Catalysed Allylation Reaction

Following on the original observation by Kobayashi that DMF (as solvent) promoted the allylation of aldehydes with allyltrichlorosilane; Iseki introduced a "chiral version" of DMF (**Scheme 62**).[144] The results are shown in **Table 18**. In the presence of one equivalent of chiral formamide (*S*,*S*)-**149** (*entry 1*), allylation of cyclohexanecarboxaldehyde with allyltrichlorosilane after 7 days at -78 °C afforded the corresponding homoallylic alcohol in good yield (81%) and reasonable ee (68%). However, if the chiral promoter was used in substoichiometric amount (*entry 2*), both reactivity and enantioselectivity dropped. According to the mechanistic insight reported by Denmark, coordination of two molecules of the Lewis base to the silicon atom is probably needed. Use of hexamethyl phosphoramide (HMPA) (1.0 equiv) as an additive was therefore found to be beneficial for the enantioselectivity (*entry 3 & 4*). Unfortunately, HMPA also catalysed non-chiral background reaction leading to poor enantioselectivity when aromatic aldehydes were used (*entry 5*). The addition of crotylsilanes to cyclohexylcarboxaldehyde catalysed by (*S*,*S*)-**149** was again found to be highly diastereoselective (*entries 6 & 7*).

Scheme 62. Addition of allylic trichlorosilanes to aldehydes promoted by chiral formamide (*S*,*S*)-**149**



139 R_1=H, R_2=H
(***E***)-**140** R_1=Me, R_2=H
(***Z***)-**140** R_1=H, R_2=Me



(***S*,*S***)-**149**

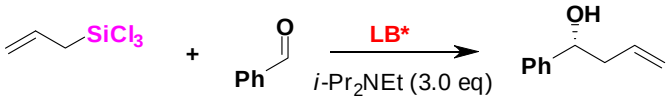
Table 18. Addition of allylic trichlorosilanes to aldehydes promoted by chiral formamide (*S*,*S*)-**149** (**Scheme 62**)

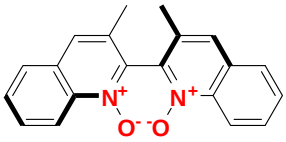
entry	LB* (equiv)	R	Silane	HMPA (equiv)	*anti/syn*	Yield (%)	*ee* (%)
1	1.0	Cy	**139**	-	-	81	68 (*R*)
2	0.1	Cy	**139**	-	-	12	32 (*S*)
3	1.0	Cy	**139**	1.0	-	89	96 (*R*)
4	0.2	Cy	**139**	1.0	-	34	94 (*R*)
5	0.2	Ph	**139**	1.0	-	94	8 (*R*)
6	0.4	Cy	(*E*)-**140**	2.0	99/1	92	98 (*S*,*R*)
7	0.4	Cy	(*Z*)-**140**	2.0	5/95	34	3 (*R*,*R*)

4.3.4 Chiral Pyridine-*N*-Oxide-Catalysed Allylation Reaction

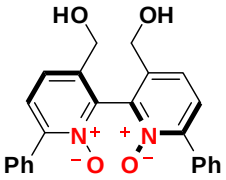
Pyridine-*N*-oxides were shown to be highly effective Lewis base catalysts for the allylation of aromatic aldehydes with allyltrichlorosilane. In 1998, Nakajima reported on the use of bisquinoline-*N*,*N*'-dioxide (*S*)-**150** as a chiral promoter for this reaction (**Scheme 63**).[143] High level of reactivity and enantioselectivity were obtained (**Table 19**). The allylation reaction was very fast even at -78 °C (85% yield in 6 h) with only 10 mol % of the axially chiral catalyst **150** (*entry 1*).

Scheme 63. Addition of allyltrichlorosilane to benzaldehyde promoted by chiral *N*-oxides **150-151**





(*S*)-**150**



151

Table 19. Addition of allyltrichlorosilane to benzaldehyde promoted by chiral *N*-oxides **150-151** (**Scheme 63**)

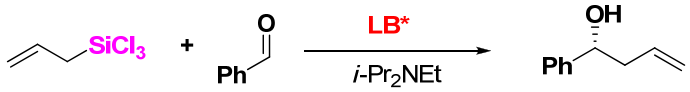
entry	LB* (mol%)	Solvent	T (°C)	Time (h)	Yield (%)	*ee* (%)
1	**150** (10)	CH_2Cl_2	-78	6	85	88 (*R*)
2	**151** (1)	CH_3CN	-45	0.25	96	94 (*S*)
3	**151** (0.1)	CH_3CN	-45	2.5	96	94 (*S*)
4	**151** (0.01)	CH_3CN	-45	12	68	94 (*S*)

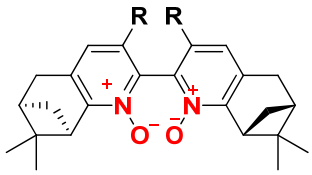
In 2002, Hayashi described a very reactive bis-*N*-oxide **151**.[145] Homoallylic alcohols were obtained in high yield and enantioselectivity (up to 94% ee) even with as low as 0.01 mol % catalyst loading (*entry 2-4*). The enantioselectivity was found highly dependent on the electronic nature of the aromatic aldehyde, suggesting participation of π-π interactions. Electron-rich aldehydes afforded enantiomeric excess up to 94% whereas electron-poor aldehydes gave only 56% ee.

Prior to Hayashi's report, Malkov and Kočovský developed bipyridine- *N,N'*-dioxide **152** derived from β-pinene (**Scheme 64**).[146] Although **152** afforded the homoallylic alcohol in low yield (18%) and modest enantiomeric excess (41% ee), the corresponding monoxide PINDOX **153a** was more reactive and enantioselective (78% yield, 90% ee). Me_2PINDOX **153b**, combining both central an axial chirality, showed even higher enantioselectivity (up to 98% ee). Mechanistic analysis suggested that while the *N*-oxide unit activates the trichlorosilyl functionality, the role of other nitrogen atom in stabilising the closed, chair-like transition state was less clear. As a further extension of this family of catalysts, Malkov and Kočovský reported new bipyridine-*N*-monoxides derived from α-pinene (**Scheme 64**). Due to extreme steric hindrance, *iso*-PINDOX **154** showed a reduction in the reaction rate; however,

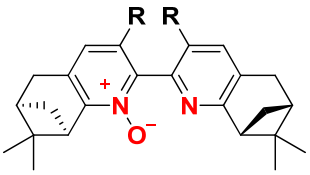
a high level of enantioselectivity was still obtained (96% ee).[146] Interestingly, monopyridine *N*-oxide METHOX **45**,[30b] lacking the second pyridine ring, still allowed formation of the homoallylic alcohol in high yield (95%) and enantioselectivity (96% ee), suggesting that coordination to nitrogen in **153** and **154** may not play an important role. Instead, arene-arene interactions between the catalyst and the substrate have been suggested to account for the high reactivity and selectivity.

Scheme 64. Addition of allyltrichlorosilane to benzaldehyde promoted by chiral *N*-oxides **45** and **152-154**

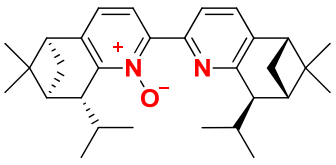




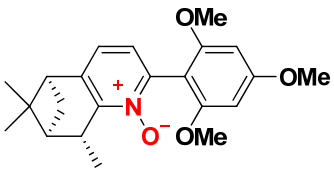
152 (18% yield, (*R*) 41% ee)



153a R=H (78% yield, (*S*) 90% ee)
153b R=Me (72% yield, (*S*) 98% ee)



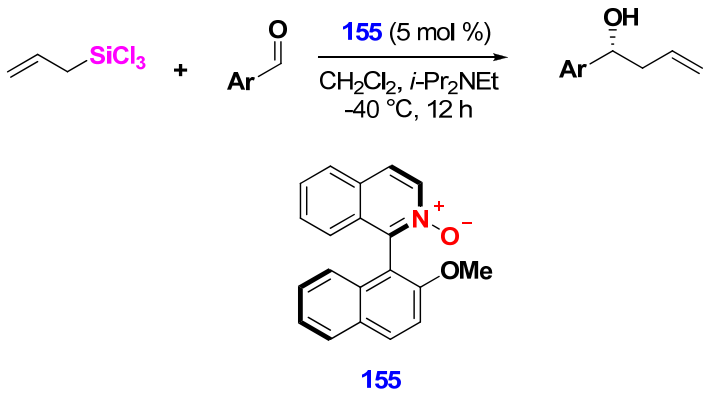
154 (75% yield, (*S*) 96% ee)



45 (95% yield, (*S*) 96% ee)

Malkov and Kočovský have also reported that quinoline-*N*-oxide QUINOX **155** catalysed the enantioselective allylation of aromatic and heteroaromatic aldehydes (**Scheme 65**).[147] The results are shown in **Table 20**. Although all the homoallylic alcohols were obtained in reasonable yields, their enantiopurity strongly depended on their electronic character; electron poor aldehydes exhibiting high level of enantioselectivity (*entries 5 & 6*) compared to electron rich aldehydes (*entries 2-4*). This effect was attributed to the enhanced π-π interactions between the catalyst and the incoming electron poor aldehyde.[147]

Scheme 65. Addition of allyltrichlorosilane to aromatic aldehydes promoted by QUINOX **155**



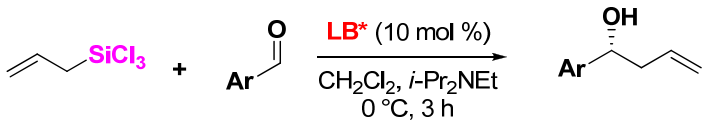
155

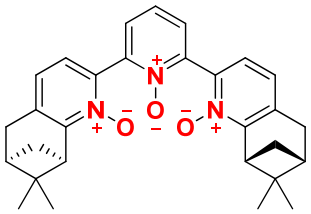
Table 20. Addition of allyltrichlorosilane to aromatic aldehydes promoted by QUINOX **155** (**Scheme 65**)

entry	Ar	Yield (%)	*ee* (%)
1	Ph	60	87 (*R*)
2	4-MeO-C_6H_4	70	16 (*R*)
3	2-Furyl	68	5 (*R*)
4	2-Thiophenyl	59	6 (*R*)
5	4-NO_2-C_6H_4	73	89 (*R*)
6	4-CF_3-C_6H_4	85	96 (*R*)

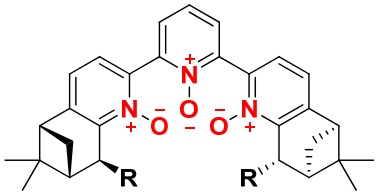
Terpyridine tri-*N*-oxides have also been reported to catalyse the allylation of aromatic aldehydes with allyltrichlorosilane. Kwong and co-workers developed a series of terpene derived terpyridine tri-*N*-oxides **157a-d** which proved to be effective catalysts for the allylation of electron poor aldehyde (up to 86% ee) (**Scheme 66, Table 21**).[148]

Scheme 66. Addition of allyltrichlorosilane to aromatic aldehydes promoted by **156-157a-d**





156



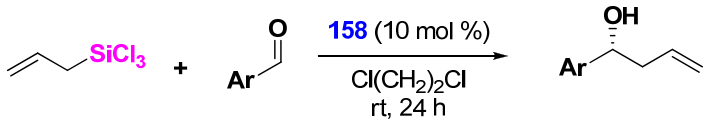
157a R= Bn
157b R= Me
157c R= *n*-Bu
157d R= *i*-Pr

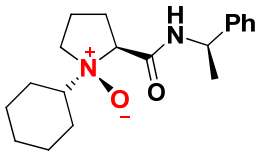
Table 21. Addition of allyltrichlorosilane to aromatic aldehydes promoted by **156-157a-d** (**Scheme 66**)

entry	LB*	Ar	Yield (%)	*ee* (%)
1	**156**	Ph	85	34 (*R*)
2	**157a**	Ph	89	74 (*R*)
3	**157b**	Ph	97	64 (*R*)
4	**157c**	Ph	87	67 (*R*)
5	**157d**	Ph	85	44 (*R*)
6	**157a**	4-MeO-C_6H_4	94	65 (*R*)
7	**157a**	4-CF_3-C_6H_4	91	86 (*R*)

Snapper *et al.* have reported that chiral-at-nitrogen *N*-oxides can also be effective organocatalysts for the allylation of aromatic aldehydes (**Scheme 67**).[149]

Scheme 67. Addition of allyltrichlorosilane to aromatic aldehydes promoted by **158**





158

Chiral *N*-oxides derived from proline and (*R*)-α-methylbenzylamine **158** proved to be an efficient activator for the enantioselective allylation of a variety of aromatic aldehydes with allyltrichlorosilane at room temperature (**Table 22**). Electron rich and electron poor substrates gave rise to appreciable levels of asymmetric induction; the highest enantiopurity was observed with electron rich 3,4-dimethoxybenzaldehyde (92% ee, *entry 4*).

Table 22. Addition of allyltrichlorosilane to aromatic aldehydes promoted by **158** (**Scheme 67**)

Entry	Ar	Yield (%)	*ee* (%)
1	Ph	82	87 (*R*)
2	4-MeO-C_6H_4	81	88 (*R*)
3	4-Cl-C_6H_4	74	85 (*R*)
4	3,4-$(MeO)_2$-C_6H_3	73	92 (*R*)

4.4 Summary

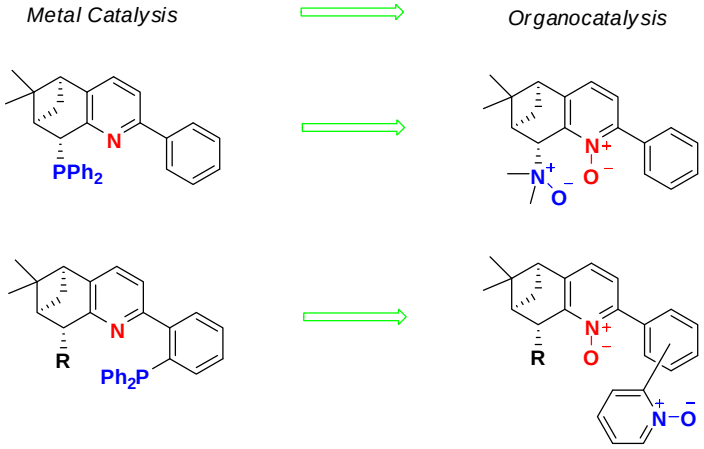
Chiral Lewis bases, such as phosphoramides, formamides and *N*-oxides, were found to be effective organocatalysts for the enantioselective allylation of aromatic aldehydes with allyl trichlorosilane. The good diastereoselectivity observed for the Lewis base-catalysed crotylation is dictated by a closed chair-like transition state.

5 Synthesis and Application of Pinene-Derivative Pyridine II

5.1 Introduction

Since chiral pyridine *N*-oxides were found to be effective organocatalysts for the enantioselective allylation of aromatic aldehydes with allyltrichlorosilane, we decided to develop novel pyridine *N*-oxides derived from α-pinene. Their design was based on the privileged pinene-pyridine fused structure which already allowed creating a successful chiral environment for metal-based catalysis (**Figure 14**).

Figure 14. Novel pyridine *N*-oxides design



5.2 Chiral Pyridine-Dimethylamine-*N*,*N*'-bisoxide

5.2.1 Synthesis

The synthetic strategy for preparation of the chiral bis-*N*-oxide (–)-**162** from alcohol (+)-**117b** is shown in **Scheme 68**. Initially, we attempted to convert alcohol (+)-**117b** (for the synthesis, see chapter 3) into azide (+)-**159** *via* one-pot mesylation of the hydroxyl functionality and subsequent displacement with azide anion,[150] however without success. One of the possible explanations is that the approach of the azide anion may be impeded by the bulky pinene moiety. Eventually, alcohol (+)-**117b** was successfully transformed into azide (+)-**159** (80% yield) with inversion of configuration *via* a Mitsunobu-like reaction using diphenylphosphorylazide (DPPA).[151] The structure of azide (+)-**159** was confirmed by NOE

experiment (**Figure 15**). When the benzylic proton was irradiated (7-H, **4.91** ppm), a clear enhancement appeared at **0.70** ppm and **2.44** ppm corresponding to endo-methyl group (12-H) and 8-H, respectively. Hydrogenation of azide (+)-**159** over Pd/C was not very efficient (35%), whereas reduction with lithium aluminium hydride afforded the desired amine (+)-**160** in 98% yield.

Scheme 68. Formation of the chiral bis-*N*-oxide (–)-**162**

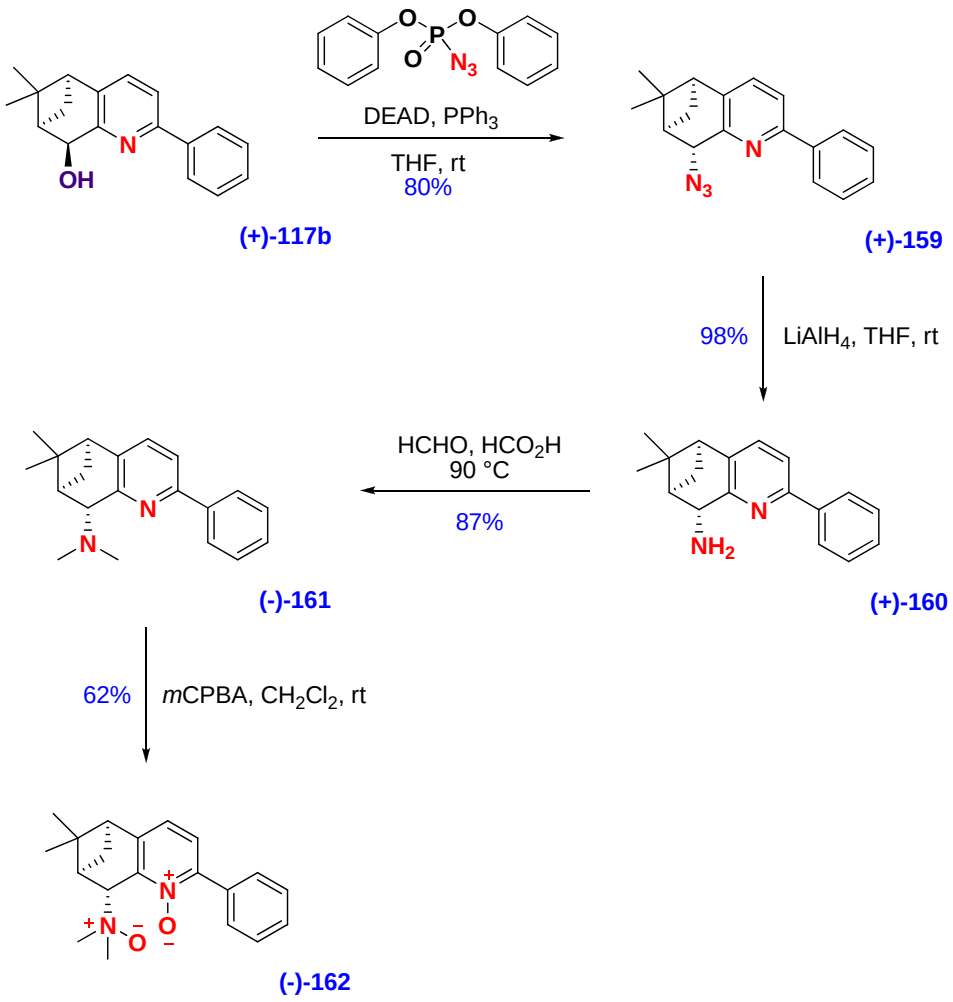
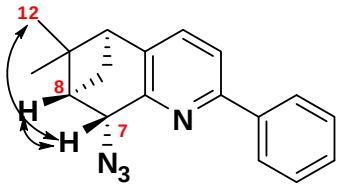


Figure 15. NOE experiment on the azide (+)-**159**



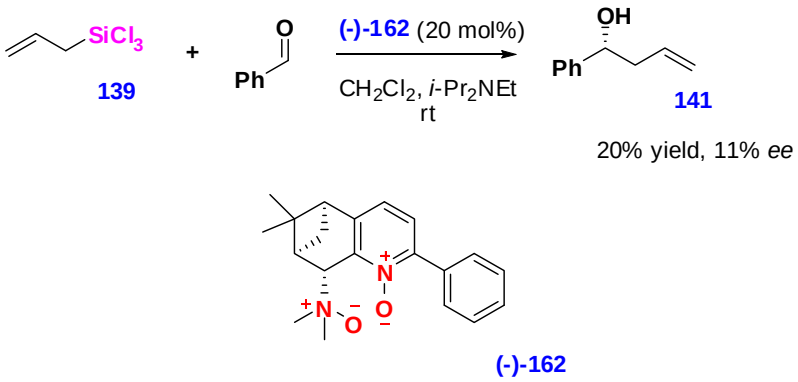
Dimethylation of amine (+)-**160** *via* a classical reductive amination protocol (e.g. paraformaldehyde, sodium borohydride and TFA in THF[152]) resulted only in low conversion to the desired dimethylamine (–)-**161**. However, the Eschweiler-Clarke methylation[153] of

amine (+)-**160** (using formaldehyde in formic acid) was more successful, leading to dimethylamine (−)-**161** in high yield (87%). Dimethylamine (–)-**161** was finally treated with *m*CPBA to give the desired bis-*N*-oxide (–)-**162** in moderate yield (62%).

5.2.2 Allylation of Benzaldehyde Catalysed by (–)-162

Bis-*N*-oxide (–)-**162** was tested as catalyst in the model asymmetric allylation of benzaldehyde with allyltrichlorosilane (**Scheme 69**). Unfortunately, even at room temperature, the conversion remained very low (20% yield). Due to the lack of flexibility, bis-*N*-oxide (–)-**162** may encounter some difficulties to coordinate to the silicon atom, resulting in a poor activation of allyl trichlorosilane.

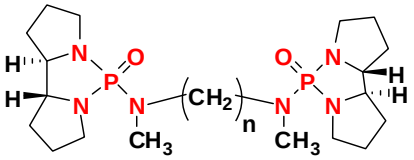
Scheme 69. Allylation of benzaldehyde catalysed by the bis-*N*-oxide (–)-**162**



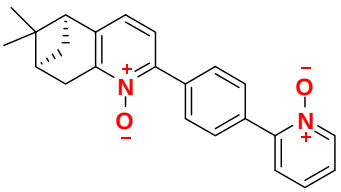
5.3 Chiral Pinene-Bipyridine-*N*,*N*'-dioxides

The mechanistic study carried out by Denmark indicated that the allylation reaction was second order in phosphoramide catalyst[141] which led to the design of bisphosphoramides **148a-c** with varying tether length (see chapter 4).[142] Therefore, we decided to develop a series of chiral bipyridine-*N*,*N*'-dioxides with varying spacers (**Chart 15**).

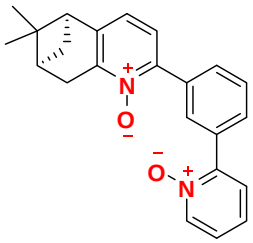
Chart 15. Targeted chiral bipyridine-*N*,*N*'-dioxides



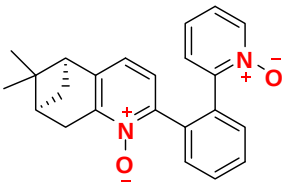
148a: n=4; **148b:** n=5; **148c**: n=6



167a



167b

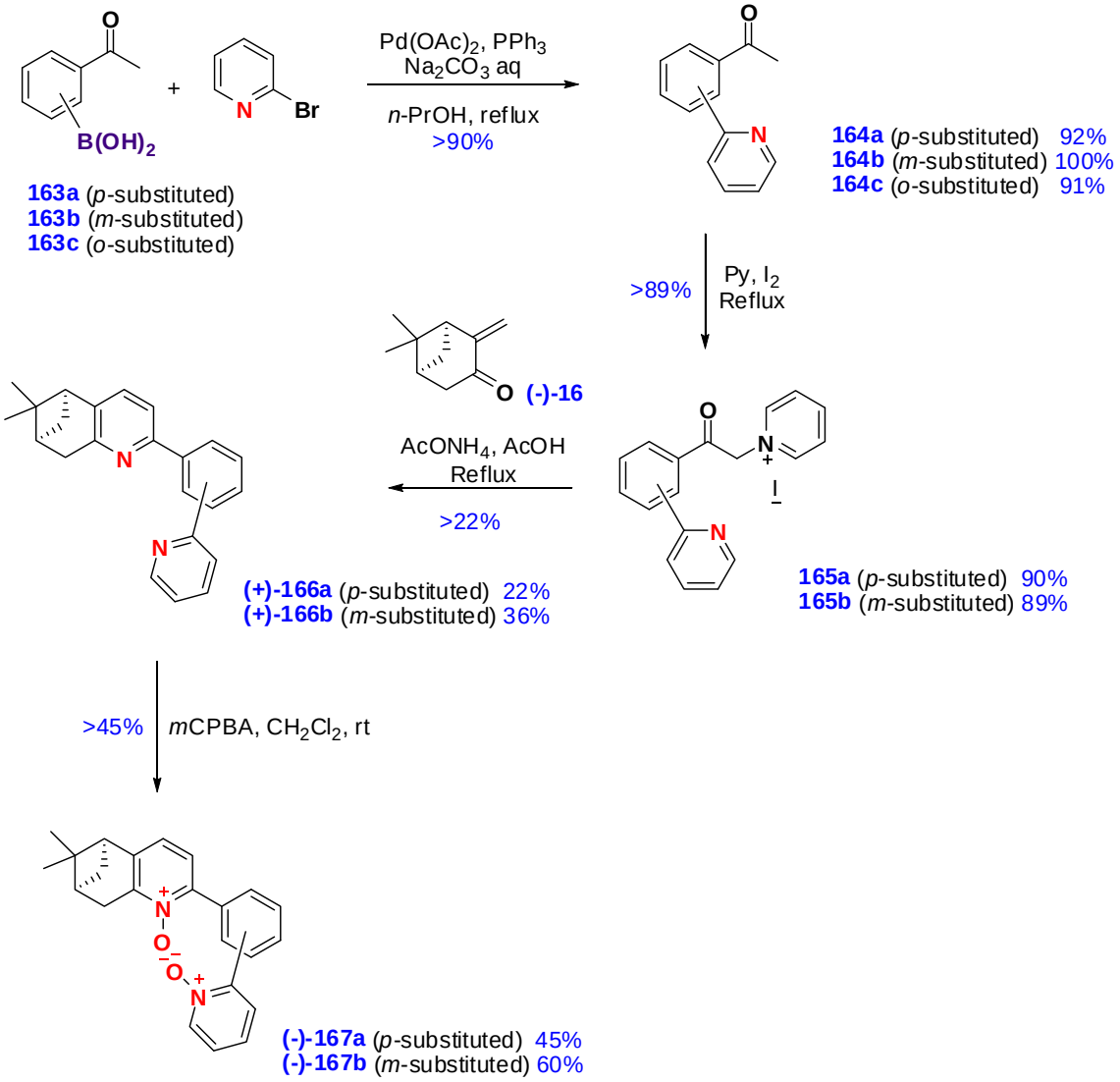


167c

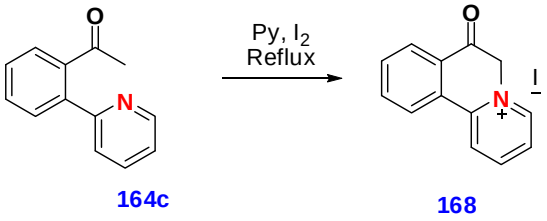
5.3.1 Synthesis of the Bipyridine-*N*,*N*'-dioxides 167a-b

Chiral bipyridine-*N*,*N*'-dioxides **167a-b** were synthesised as shown in **Scheme 70**. The desired substituted-2-pyridine-acetophenones **164a-c** were obtained in high yield by Suzuki-Miyaura coupling between 2-bromopyridine and the substituted acetylphenylboronic acid **163a-c**.[154] Substituted acetophenones **164a-c** were then heated in pyridine with iodine to afford the corresponding Kröhnke salts **165a-c**. The desired salts **165a-b** were obtained in high yield, whereas the pyridinium salt **168** was formed (as a result of intramolecular nucleophilic substitution) instead of **165c** (**Scheme 71**). Subsequent Kröhnke annulation of the pyridinium salts **165a-b** with pinocarvone (–)-**16** afforded bipyridines **166a-b** in moderate yields (22% and 36% yield, respectively). Bipyridines **166a-b** were finally treated with *m*CPBA to give the desired chiral pinene-bipyridine-*N*,*N*'-dioxides **167a-b** in reasonable yield.

Scheme 70. Synthesis of the chiral bipyridine-*N*,*N*'-dioxides **167a-b**



Scheme 71. Formation of the pyridinium salt **168**



5.3.2 Preliminary Results for the Allylation of Benzaldehyde

Chiral bipyridine-*N*,*N*'-dioxides **167a-b** were tested in the enantioselective allylation of benzaldehyde with allyltrichlorosilane (**Scheme 72**). The results are shown in **Table 23**.

Bipyridine-*N*,*N*'-dioxides **167a-b** catalysed formation of homoallylic alcohol **141** in high yield (*entries 1 and 2*), however, enantioselectivity in both cases was very low (3% and 12% ee, respectively, *entries 1 and 2*). It was not surprising to find that *para*-substituted catalyst (–)-**167a** led to a racemic alcohol, since the bidentate coordination to silicon seems improbable. On the other hand, bis-*N*-oxide (–)-**167b** appears to have enough flexibility to chelate silicon, leading to a slight increase in enantioselectivity.

Scheme 72. Allylation of benzaldehyde catalysed by the bipyridine-*N*,*N*'-dioxides **167a-b**

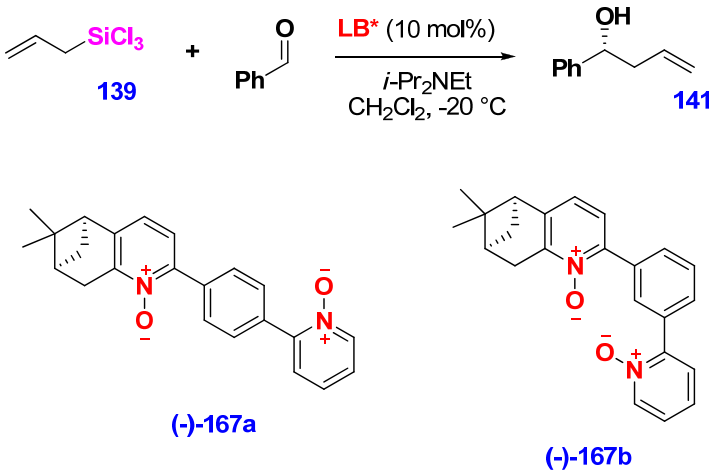


Table 23. Allylation of benzaldehyde catalysed by the bipyridine-*N*,*N*'-dioxides **167a-b** (**Scheme 72**)

entry	LB*	Yield (%)	*ee* (%)[a]
1	(–)-**167a**	84	3 (*R*)[b]
2	(–)-**167b**	83	12 (*R*)[b]

[a]Determined by chiral HPLC (IB, 0.75 mL.min^{-1}, hexane/2-propanol, 97.5:2.5).

[b]Absolute configuration obtained from the HPLC retention times and comparison with literature data. [155]

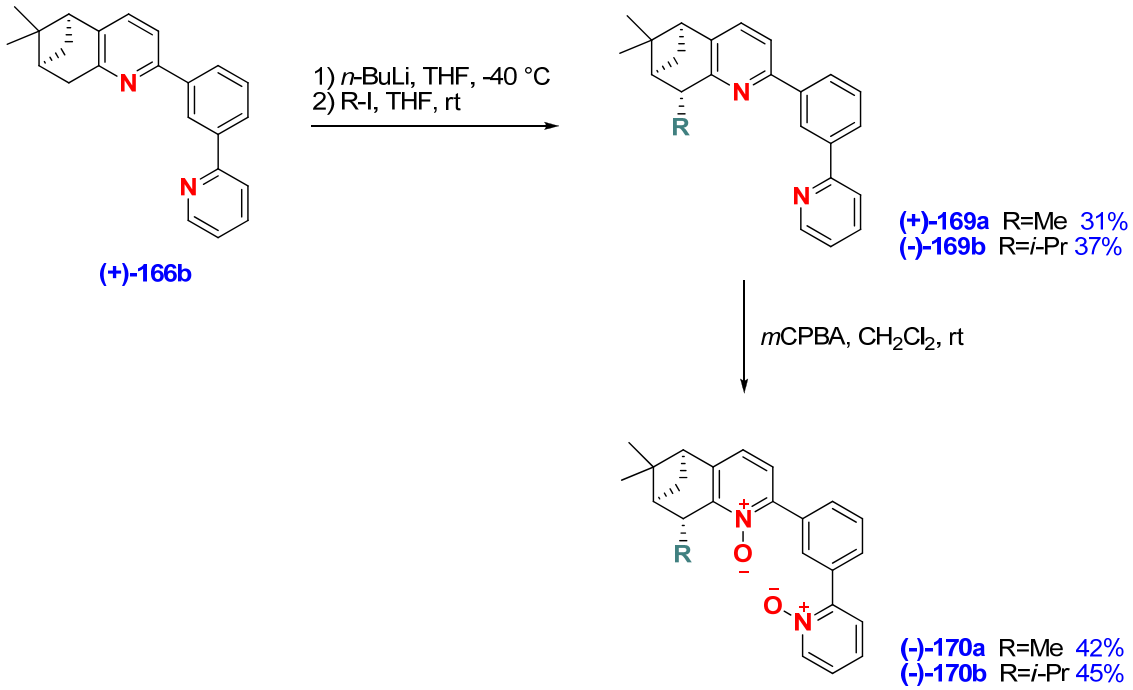
5.3.3 Synthesis of Bipyridine-*N*,*N*'-dioxides 170a-b

In an attempt to improve the enantioselectivity of the allylation reaction, we decided to tune the promising bis-*N*-oxide (–)-**167b** by substituting the benzylic position of the pyridine ring with various alkyl groups.

Chiral bipyridine-*N*,*N*'-dioxides **170a-b** were prepared as shown in **Scheme 73**. Deprotonation of the bipyridine (+)-**166b** in the benzylic position with *n*-BuLi at -40 °C, followed by alkylation with either MeI or *i*-PrI gave (+)-**169a** and (–)-**169b**, respectively.

Subsequent treatment with *m*CPBA finally afforded the desired chiral bipyridine-*N*,*N*'-dioxides **170a-b** in moderate yield.

Scheme 73. Formation of the bipyridine-*N*,*N*'-dioxides **170a-b**



5.3.4 Enantioselective Allylation of Benzaldehyde

The results obtained employing bis-*N*-oxides (–)-**170a** and (–)-**170b** are shown in **Table 24** below. Again, both compounds showed good reactivity but the enantioselectivity was negligible (*entries 1 and 2*). We can only assume that the presence of the alkyl groups impedes the chelation of silicon by the two *N*-oxide functionalities.

Scheme 74. Allylation of benzaldehyde catalysed by the bipyridine-*N*,*N*'-dioxides **170a-b**

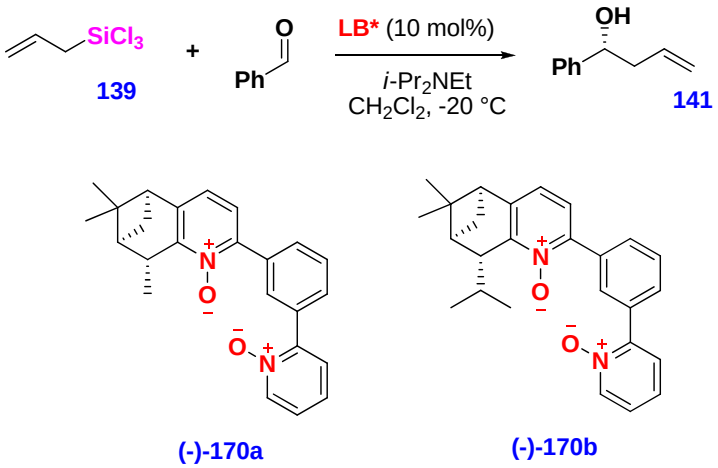


Table 24. Allylation of benzaldehyde catalysed by the bipyridine-*N*,*N*'-dioxides **170a-b** (**Scheme 74**)

entry	LB*	Yield (%)	*ee* (%)[a]
1	(–)-**170a**	87	2 (*R*)
2	(–)-**170b**	85	3 (*R*)

[a]Determined by chiral HPLC (IB, 0.75 mL.min^{-1}, hexane/2-propanol, 97.5:2.5).
[b]Absolute configuration obtained from the HPLC retention times and comparison with literature data.[155]

5.4 Summary

Novel bis-*N*-oxide compounds **167a-b** and **170a-b** were synthesised from α-pinene and a range of 2-pyridine-acetophenones **164a-c** by employing Kröhnke annulation reaction as the key cyclisation step. Although poor enantioselectivity was achieved (up to 12% ee), high reactivity of the prepared catalysts is, however, promising. Better tuning of the chiral environment may lead to an improvement of the enantioselectivity.

6 Experimental

6.1 General Methods

All reactions were carried out under an inert atmosphere in oven-dried glassware unless otherwise stated. Room temperature refers to ambient room temperature (20-22 °C); 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by Thin Layer Chromatography (TLC) using aluminium backed silica gel 60 (F_{254}) plates, visualised using UV_{254nm} and potassium permanganate, PMA, Drangendorf and ninhydrin dips as appropriate. Flash chromatography was carried out routinely using 60Å silica gel (Fischer) as the stationary phase unless otherwise stated. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ at 20 °C unless otherwise indicated with an error of $<\pm 0.1$. The $[\alpha]_D$ values are given in 10^{-1} deg.cm^2.g^{-1}. The NMR spectra were recorded on a Bruker Spectrospin 400 (400 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million (ppm) downfield from TMS. Coupling constants (*J*) are measured in Hertz (Hz) and are unadjusted; therefore, due to limits in resolution, in some cases there are small differences (<1 Hz) in the measured *J* value of the same coupling constant determined from different signals. Splitting patterns are designed as follows: s – singlet, d – doublet, t – triplet, dd – doublet of doublets, dt – doublet of triplets, td – triplet of doublets, ddd – doublet of doublet of doublets, tt – triplet of triplets, sp – septet, m – multiplet, br – broad. Various 2D techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded on a JASCO FT-IR spectrophotometer for a thin film between NaCl plates, or as a KBr disc. The mass spectra (EI and/or CI) were measured on a Joel JMS700 spectrometer. Enantiomeric excess was determined by chiral GC analysis (using a Hewlett Packard 6890 Series GC system, Hewlett Packard 3395 integrator and Supelco α-DEX^{TM} 120 fused capillary column 30 m × 0.25 mm × 0.25 μm film thickness) or by chiral HPLC analysis (using a Hewlett Packard Agilent 1100 Series quaternary pump, vacuum degasser, diode array detector, manual injector and Hewlett Packard ChemStation and a Diacel Chiracel IB or OJ-H 0.46 cm × 25 cm column) as stated. The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures. Autoclave reactions were accomplished in a stainless steel autoclave manufactured by HEL Ltd.

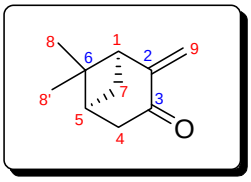
6.2 Materials

All solvents were of reagent grade and were dried and distilled under argon or nitrogen immediately before use as follows: tetrahydrofuran, diethyl ether and toluene from sodium/benzophenone, dichloromethane from calcium hydride. Petroleum ether refers to the fraction boiling in the range 40-60°C. Methanol and ethanol were distilled over magnesium turnings and stored over molecular sieves. Triethylamine was distilled immediately before use from calcium hydride. Yields are given for isolated products showing one spot on a TLC plate and with no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR spectra and TLC behaviour. (R)-(+)-α-Pinene was purchased from Aldrich with a 98% ee.

6.3 Synthesis and Application of Pinene-Derivative *P*,*N*-Ligands

6.3.1 Synthesis of the First Generation of Ligands

(1*R*,5*R*)-(–)-6,6-Dimethyl-2-methylenebicyclo[3.1.1]heptan-3-one (–)-16

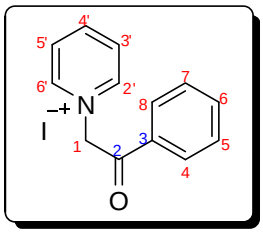


$C_{10}H_{14}O$
Mol. Wt.: 150.22

(*R*)-(+)-α-Pinene **1** (7.5 g, 55 mmol, 1.0 equiv), acetic anhydride (6.24 mL, 66 mmol, 1.2 equiv), pyridine (2.20 mL, 27 mmol, 0.5 equiv), TPP (catalytic amount) and DMAP (catalytic amount) were introduced into a UV reactor with CH_2Cl_2 (100 mL). A stream of oxygen was bubbled through the latter solution accompanied by UV irradiation (546 nm). The solution was stirred at room temperature until completion of the reaction, as determined by TLC (hexane / ethyl acetate: 95:5), typically 20 h. The reaction mixture was then diluted with CH_2Cl_2 (60 mL). The organic layer was successively washed with a saturated aqueous solution of $NaHCO_3$ (60 mL), 10% aqueous solution of HCl (2 × 40 mL), 0.5M aqueous solution of $CuSO_4$ (40 mL), brine (40 mL) and finally dried over $MgSO_4$. The solvent was then removed under vacuum to afford pure pinocarvone (–)-**16** as a purple oil (7.92 g, 96%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.76 (s, 3H, 8-H), 1.25 (d, *J* = 10.3 Hz, 1H, 7a-H), 1.32 (s,

3H, 8'-H), 2.16 (tt, *J* = 6.2, 3.0 Hz, 1H, 5-H), 2.48 (m, 1H, 7b-H), 2.58-2.68 (m, 2H, 4-H), 2.72 (t, *J* = 6.2 Hz, 1H, 1-H), 4.97 (d, *J* = 1.7 Hz, 1H, 9a-H), 5.92 (d, *J* = 1.7 Hz, 1H, 9b-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.4 (CH_3-8), 25.9 (CH_3-8'), 32.3 (CH_2-7), 38.4 (CH-5), 40.7 (C-6), 42.4 (CH_2-4), 48.1 (CH-1), 117.3 (CH_2-9), 149.0 (C-2), 199.8 (C=O-3) in agreement with the literature data.[110]

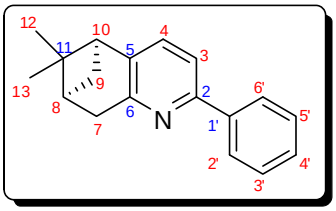
1-(2-Oxo-2-phenylethyl)pyridinium iodide 112



$C_{13}H_{12}INO$
Mol. Wt.: 325.14

A solution of acetophenone **111** (2.40 g, 20 mmol) and iodine (5.08 g, 20 mmol, 1.0 equiv) in pyridine (10 mL) was refluxed overnight. The reaction mixture was cooled to room temperature, inducing the precipitation of a solid which was filtered off and washed with diethyl eher (3×20 mL). The remaining solid was then stirred overnight in diethyl ether (50 mL). After filtration, the brown solid **112** was isolated (5.21 g, 80%): **^{1}H NMR** (400 MHz, d_6-DMSO) δ 6.51 (s, 2H, 1–H), 7.67 (t, *J* = 7.6 Hz, 2H, 5–H, 7–H), 7.80 (t, *J* = 7.5 Hz, 1H, 6–H), 8.05-8.09 (m, 2H, 4–H, 8–H), 8.29 (dd, *J* = 7.8, 6.7 Hz, 2H, 3'–H, 5'–H), 8.75 (tt, *J* = 7.8, 1.3 Hz, 1H, 4'–H), 9.01 (dd, *J* = 6.7, 1.3 Hz, 2H, 2'–H, 6'–H) in agreement with the literature data.[30a]

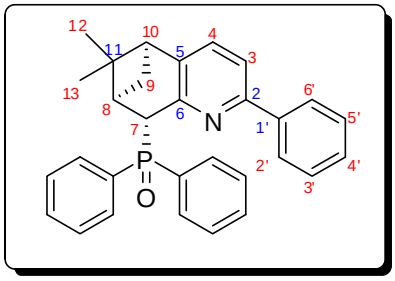
(8*S*,10*S*)-(+)-2-Phenyl-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene (+)-113



$C_{18}H_{19}N$
Mol. Wt.: 249,35

A solution of pinocarvone (–)-**16** (1.05 g, 7.0 mmol, 1.0 equiv) with the Kröhnke salt **112** (2.28 g, 7.0 mmol, 1.0 equiv) and ammonium acetate (9.25 g) in acetic acid (12 mL) was refluxed for 6 h. The mixture was then diluted with water (25 mL), made neutral by addition of an aqueous solution of sodium hydroxide (2M) and extracted with ethyl acetate (3×50 mL). The organic phase was successively washed with water (3×50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvent was removed under vacuum to afford pure (+)-**113** as a brown solid (1.10 g, 63%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.69 (s, 3H, 12-H), 1.32 (d, *J* = 9.6 Hz, 1H, 9-H), 1.42 (s, 3H, 13-H), 2.40 (tt, *J* = 5.8, 3.0 Hz, 1H, 8-H), 2.71 (dt, *J* = 9.6, 5.8 Hz, 1H, 9-H'), 2.80 (t, *J* = 5.8 Hz, 1H, 10-H), 3.21 (d, *J* = 3.1 Hz, 2H, 7-H), 7.28 (d, *J* = 7.8 Hz, 1H, 3-H), 7.37 (tt, *J* = 7.3, 1.3 Hz, 1H, 4'-H), 7.41 (d, *J* = 7.8 Hz, 1H, 4-H), 7.45 (td, *J* = 7.3, 1.3 Hz, 2H, 3'-H, 5'-H), 7.96 (d, *J* = 7.2 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.3 (CH_3-12), 26.1 (CH_3-13), 32.0 (CH_2-9), 36.8 (CH_2-7), 39.5 (C-11), 40.3 (CH-8), 46.3 (CH-10), 117.2 (CH-4), 126.7 (2×CH-2',6'), 128.2 (CH-4'), 128.6 (2×CH-3',5'), 133.5 (CH-3), 140.0 (C-1'), 140.3 (C-5), 154.8 (C-2), 156.8 (C-6) in accordance with the literature data.[30a]

(7*R*,8*R*,10*S*)-(–)-2-Phenyl-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-trien-7-yl(diphenyl)phosphine oxide (–)-114

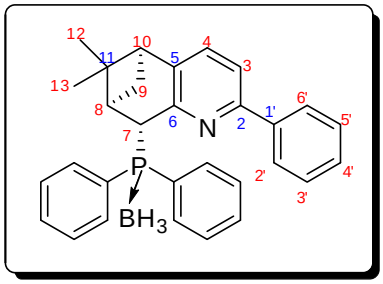


$C_{30}H_{28}NOP$
Mol. Wt.: 449.52

A 2.5M solution of *n*-butyllithium in hexane (0.8 mL, 2.0 mmol, 1.0 equiv) was added dropwise to a solution of (+)-**113** (0.50 g, 2.0 mmol, 1.0 equiv) in anhydrous THF (5 mL) under an argon atmosphere at –40 °C. The red colour of the mixture turned darker and darker. The solution was stirred at that temperature for 1 h and then a solution of diphenylphosphinic chloride (0.40 mL, 2.0 mmol, 1.0 equiv) in THF (2 mL) was added dropwise at –40 °C. The solution was then gradually warmed up to room temperature and stirred overnight. The reaction was then quenched by addition of water (20 mL), the mixture was extracted with CH_2Cl_2 (3×20 mL), the organic solution was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (30 g) using a mixture of petroleum ether and ethyl acetate (1:1) at the beginning, followed by a regular increase of the ethyl acetate ratio to pure ethyl acetate to give pure (–)-**114** as a white solid (307 mg, 34%): **mp** 104-106 °C (hexane); **[α]$_D^{25}$** –54.0 (*c* 1.0, $CHCl_3$); **IR** (KBr) ν 3016 (s, C-H), 1596 (m, C=Car), 1525 (m, C=Car), 1432 (m, C=Car), 1216 (s, P=O), 771 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.63 (s, 3H, 12-H), 1.32 (s, 3H, 13-H), 1.54 (d, *J* = 10.2 Hz, 1H, 9-H), 2.45 (dt, *J* = 10.2, 5.8 Hz, 1H, 9-H'), 2.60-2.65 (m, 2H, 8-H, 10-H), 4.32 (dd, $J^2_{H,P}$ = 13.9 Hz, *J* = 1.0 Hz, 1H, 7-H), 7.10 (td, *J* = 7.2, 1.5 Hz, 2H, 3'-H, 5'-H), 7.14-7.20 (m, 4H, 4-H, 4'-H, 2'-H, 4'-H), 7.30 (td, *J* = 7.4, 3.0 Hz, 2H, aromH), 7.35-7.51 (m, 5H, 3-H, aromH), 7.69-7.75 (m, 2H, aromH), 7.82-7.89 (m, 2H, aromH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.8 (CH_3-12), 25.7 (CH_3-13), 28.4 (CH_2-9), 41.1 (CH-8), 41.9 (C-11), 45.3 (d, *J* = 21 Hz, CH-7), 45.9 (CH-10), 116.9 (CH-3), 126.0 (2×CH-2',6'), 128.1 (d, *J* = 12 Hz, 2×aromCH), 128.2 (2×CH-3',5'), 128.22 (CH-4'), 128.5 (d, *J* = 12 Hz, 2× aromCH), 130.9 (d, *J* = 3 Hz, aromCH), 131.0 (d, *J* = 3 Hz, aromCH), 131.15 (d, *J* = 9 Hz, 2× aromCH), 131.85 (d, *J* = 9 Hz, 2× aromCH), 133.0 (d, *J* = 97 Hz, C), 134.2 (CH-4), 134.6 (d, *J* = 97 Hz, C), 138.4 (C-1'), 141.0 (d, *J* = 5 Hz, C-5),

152.0 (d, J = 7 Hz, C-6), 153.3 (C-2); **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ 33.4 (P=O); **MS** (EI) *m/z* (%) 449 ($M^{\bullet+}$, 15), 248 ($M^{\bullet+}$-$P(O)Ph_2$, 100), 206 ($M^{\bullet+}$-$P(O)Ph_2$-C_3H_6, 18); **HRMS** (EI) 449.1906 ($C_{30}H_{28}NOP$ requires 449.1909).

Borane-protected (7*R*,8*R*,10*S*)-(–)-2-Phenyl-7-(diphenylphosphino)-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene (–)-115

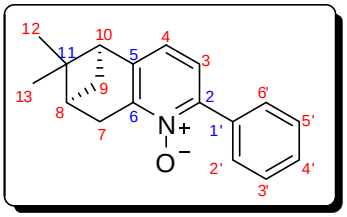


$C_{30}H_{31}BNP$
Mol. Wt.: 447,36

A solution of *n*-buthyllithium in hexane (2.5M; 0.4 mL, 1.0 mmol, 1.0 equiv) was added dropwise to a solution of (+)-**113** (0.25 g, 1.0 mmol, 1.0 equiv) in THF (2 mL) at –40 °C. The solution was stirred at that temperature for 1 h and then a solution of $Ph_2PCl.BH_3$ (3.0 mmol, 3.0 equiv) was added dropwise at –40 °C [the $Ph_2PCl.BH_3$ solution was prepared by stirring for 30 min a mixture of borane in THF (1M, 3 mL, 3 mmol, 1.0 equiv) and chlorodiphenylphosphine (0.54 mL, 3 mmol, 1.0 equiv) in diethyl ether (2 mL) at room temperature]. The resulting solution was then gradually warmed up to room temperature and stirred overnight. A saturated aqueous solution of NH_4Cl (2 mL) was then added to quench the reaction, the mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (20 g) using a mixture of hexane and diethyl ether (20:1) to give pure (–)-**115** as a white solid (154 mg, 35%): **mp** 190-192 °C (MeOH); **$[\alpha]_D^{25}$** –112.4 (*c* 1.0, $CHCl_3$); **IR** (KBr) ν 3050-2950 (s, C-H), 2397 (m, B-H), 1560 (m, C=Car), 1425 (m, C=Car), 771 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.74 (s, 3H, 12-H), 1.21 (d, J = 10.3 Hz, 1H, 9-H), 1.41 (s, 3H, 13-H), 1.54 (s, 3H, BH_3), 2.45 (dt, J = 10.3, 5.8 Hz, 1H, 9-H'), 2.66 (t, J = 5.8 Hz, 1H, 10-H), 2.77 (qd, J = 6.2, 2.0 Hz, 1H, 8-H), 4.43 (dd, $J^2_{H,P}$ = 13.4 Hz, J = 2.0 Hz, 1H, 7-H), 7.19-7.23 (m, 3H, 4-H, 3'-H, 5'-H), 7.25-7.29 (m, 3H, 4'-H, 2×aromH), 7.35-7.43 (m, 3H, 2'-H, 6'-H, aromH), 7.47-7.57 (m, 4H, 3-H, 3×aromH), 7.68-7.73 (m, 2H, aromH), 7.83-7.88 (m, 2H, aromH);

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (CH_3-12), 25.9 (CH_3-13), 28.3 (CH_2-9), 42.4 (CH-8), 42.5 (C-11), 42.7 (d, *J* = 29 Hz, CH-7), 45.8 (CH-10), 117.1 (CH-3), 126.1 (2×CH-2',6'), 128.2 (d, *J* = 10 Hz, 2×aromCH), 128.33 (2×CH-3',5'), 128.39 (CH-4'), 128.45 (d, *J* = 55 Hz, C), 128.5 (d, *J* = 10 Hz, 2×aromCH), 130.1 (d, *J* = 2 Hz, aromCH), 131.0 (d, *J* = 2 Hz, aromCH), 131.7 (d, *J* = 55 Hz, C), 132.5 (d, *J* = 9 Hz, 2×aromCH), 134.2 (CH-4), 134.4 (d, *J* = 9 Hz, 2×aromCH), 138.5 (C-1'), 140.8 (d, *J* = 4 Hz, C-5), 153.1 (d, *J* = 7 Hz, C-6), 153.3 (C-2); **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ 25.8 (m); **MS** (EI) *m/z* (%) 447 ($M^{\bullet+}$, 14), 433 ($M^{\bullet+}$-BH_3, 58), 248 ($M^{\bullet+}$-$PPh_2.BH_3$, 57), 206 ($M^{\bullet+}$- $PPh_2.BH_3$-C_3H_6, 100), 91 (73); **HRMS** (EI) 447.2286 ($C_{30}H_{31}BNP$ requires 447.2293).

(8*S*,10*S*)-(+)-2-Phenyl-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene 1-oxide (+)-116

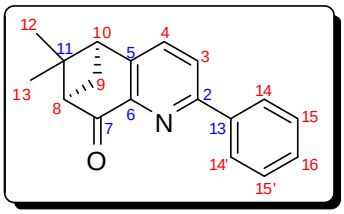


$C_{18}H_{19}NO$
Mol. Wt.: 265,35

m-Chloroperoxybenzoic acid (70%, 0.7 g, 4 mmol, 2.0 equiv) was added portion-wise to a cooled (0 °C) solution of (+)-**113** (0.5 g, 2 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL). The mixture was then allowed to warm up to room temperature and stirred overnight. The mixture was washed with an aqueous solution of $NaHCO_3$ (10%; 1×20 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (25 g) using ethyl acetate to remove the unreacted starting material and some by-products, followed by methanol to afford pure (+)-**116** as a white solid (394 mg, 75%): **mp** 128-130 °C (hexane); **$[\alpha]_D^{20}$** +100.2 (*c* 0.6, $CHCl_3$); **IR** (KBr) ν 3051 (m, C-H), 2938 (s, C-H), 1662 (m, C=Car), 1477 (s, C=Car), 1447 (m, C=Car), 1265 (s, N-O), 770 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.73 (s, 3H, 12-H), 1.32 (d, *J* = 9.8 Hz, 1H, 9-H), 1.42 (s, 3H, 13-H), 2.45 (m, 1H, 8-H), 2.69 (dt, *J* = 9.8, 5.7 Hz, 1H, 9-H'), 2.81 (t, *J* = 5.7 Hz, 1H, 10-H), 3.05-3.24 (m, 2H, 7-H), 6.92 (d, *J* = 7.8 Hz, 1H, 3-H), 7.19 (d, *J* = 7.8 Hz, 1H, 4-H), 7.42 (t, *J* = 6.9 Hz, 1H, 4'-H), 7.45 (t, *J* = 6.9 Hz, 2H, 3'-H, 5'-H), 7.79 (d, *J* = 6.9 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.1 (CH_3-12), 25.8 (CH_3-13), 31.2 (CH_2-7), 31.5 (CH_2-9),

39.31 (CH-8), 39.32 (C-11), 46.1 (CH-10), 122.9 (CH-3), 123.7 (CH-4), 128.0 (2×CH-3',5'), 128.9 (CH-4'), 129.5 (2×CH-2',6'), 133.3 (C-1'), 144.2 (C-5), 146.8 (C-2), 147.1 (C-6); **MS** (EI) *m/z* (%) 265 ($M^{\bullet+}$, 50), 248 ($M^{\bullet+}$-OH, 65), 206 ($M^{\bullet+}$-OH-C_3H_6, 100), 83 (62); **HRMS** (EI) 265.1466 ($C_{18}H_{19}NO$ requires 265.1467).

(8*R*,10*S*)-(+)-2-Phenyl-11,11-dimethyl-1-azatricyclo[7.1.1.$0^{5,6}$]undeca-2,4,6-trien-7-one (+)-118

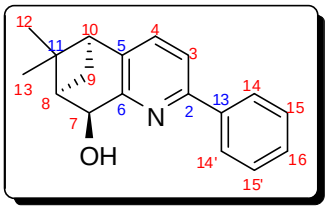


$C_{18}H_{17}NO$
Mol. Wt.: 263,33

A mixture of the *N*-oxide derivative (+)-**116** (105.2 mg, 0.40 mmol) and acetic anhydride (5 mL) was stirred at 110 °C for 2 h under argon. The reaction mixture was then cooled to room temperature and acetic anhydride was removed under vacuum. An aqueous solution of hydrochloric acid (3M, 10 mL) was added to the residue and the resulting mixture was refluxed for 1.5 h., then cooled to room temperature and chilled with an ice bath. The solution was made alkaline (pH≈12-13) by a slow addition of an aqueous solution of sodium hydroxide (2M). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic solutions were dried over $MgSO_4$ and concentrated under vacuum to obtain a diastereoisomeric mixture of benzylic alcohol derivatives **117a** and **117b** (ratio 3:1) (74.2 mg, 70%). The latter mixture of alcohols **117** (74.2 mg, 0.28 mmol, 1.0 equiv) was dissolved in acetone (2 mL) and Jones' reagent (70 µL, 0.28 mmol, 1.0 equiv) was added and the mixture was stirred at room temperature for 30 min. The reaction was then quenched by addition of propan-2-ol (10 drops) and the mixture was filtered over a silica pad. The filtrate was then made alkaline by addition of an aqueous solution of sodium hydroxide (2M). CH_2Cl_2 (10 mL) was then added, the two layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic solutions were dried over $MgSO_4$ and concentrated under vacuum to give pure (+)-**118** as a white solid (62 mg, 84%): **mp** 155-157 °C; **$[\alpha]_D^{20}$** +163.7 (*c* 0.6, $CHCl_3$); **IR** (KBr) ν 2975 (m, C-H), 1705 (s, C=O), 1585 (m, C=Car), 1558 (s, C=Car), 1455 (m, C=Car), 779 (m, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz,

$CDCl_3$) δ 0.83 (s, 3H, 12-H), 1.62 (s, 3H, 13-H), 2.18 (dt, *J* = 8.2, 5.0 Hz, 1H, 9-H), 3.09-3.13 (m, 3H, 8-H, 9-H', 10-H), 7.41 (tt, *J* = 7.2, 1.3 Hz, 1H, 4'-H), 7.47 (t, *J* = 7.2 Hz, 2H, 3'-H, 5'-H), 7.64 (d, *J* = 7.9 Hz, 1H, 3-H), 7.78 (d, *J* = 7.9 Hz, 1H, 4-H), 8.08 (d, *J* = 7.2 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 22.7 (CH_3-12), 26.7 (CH_3-13), 39.3 (CH_2-9), 47.1 (CH-10), 52.7 (C-11), 58.2 (CH-8), 123.2 (CH-4), 127.1 (2×CH-2',6'), 128.7 (2×CH-3',5'), 129.1 (CH-4'), 134.9 (CH-3), 138.5 (C-2'), 144.8 (C-5), 147.9 (C-2), 156.6 (C-6), 199.9 (C=O); **MS** (CI-isobutane) *m/z* (%) 264 ($(M+H)^+$, 100), **HRMS** (CI-isobutane) 264.1389 ($C_{18}H_{18}NO$ $(M+H)^+$ requires 264.1388).

(7*S*,8*R*,10*S*)-(+)-2-Phenyl-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-trien-7-ol (+)-117b

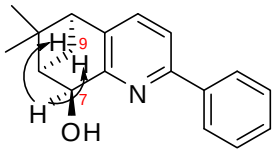


$C_{18}H_{19}NO$
Mol. Wt.: 265,35

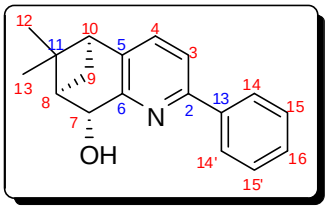
Sodium borohydride (4 mg, 0.103 mmol, 1.0 equiv) was added portion-wise to a solution of ketone (+)-**118** (27 mg, 0.103 mmol, 1.0 equiv) in ethanol (1 mL) and the reaction mixture was stirred at room temperature for 20 min. Water (2 mL) was then added to quench the remaining sodium borohydride and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to afford pure (+)-**117b** as a white solid (25 mg, 91%): **mp** 85-87 °C; **$[\alpha]_D^{20}$** +86.9 (*c* 1.5, $CHCl_3$); **IR** (KBr) ν 3430 (s, OH), 2933 (s, C-H), 1586 (m, C=Car), 1568 (m, C=Car), 1441 (m, C=Car), 772 (m, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.61 (s, 3H, 12-H), 1.39 (s, 3H, 13-H), 1.50 (d, *J* = 9.9 Hz, 1H, 9-H), 2.44 (td, *J* = 5.8, 3.3 Hz, 1H, 8-H), 2.50-2.60 (m, 1H, 9-H'), 2.74 (t, *J* = 5.8 Hz, 1H, 10-H), 3.42 (br s, 1H, OH), 4.88 (d, *J* = 3.3 Hz, 1H, 7-H), 7.29 (d, *J* = 7.8 Hz, 1H, 4-H), 7.33 (t, *J* = 7.0 Hz, 1H, 4'-H), 7.39 (t, *J* = 7.0 Hz, 2H, 3'-H, 5'-H), 7.47 (d, *J* = 7.8 Hz, 1H, 3-H), 7.95 (d, *J* = 7.0 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 22.0 (CH_3-12), 25.7 (CH_3-13), 33.0 (CH_2-9), 39.5 (C-11), 45.1 (CH-8), 45.9 (CH-10), 73.2 (CH-7), 117.8 (CH-3), 125.64 (2×CH-2',6'), 125.69 (CH-4'), 127.7 (2×CH-3',5'), 132.9 (CH-4), 137.9 (C-1'), 138.4 (C-5), 153.9 (C-2), 156.9 (C-6); **MS** (EI)

m/z (%) 265 ($M^{\bullet+}$, 50), 248 ($M^{\bullet+}$-OH, 26), 206 ($M^{\bullet+}$-OH-C_3H_6, 50), 196 (100), 28 (39); **HRMS** (EI) 265.1469 ($C_{18}H_{19}NO$ requires 265.1467).

NOE: Irradiation on **4.88** 7-H enhanced **1.50** 9-H and **2.50-2.60** 9-H'



(7*R*,8*R*,10*S*)-2-Phenyl-11,11-dimethyl-1-azatricyclo[7.1.1.$0^{5,6}$]undeca-2,4,6-trien-7-ol 117a

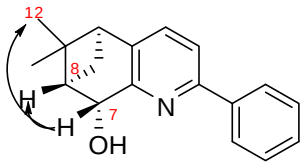


$C_{18}H_{19}NO$
Mol. Wt.: 265,35

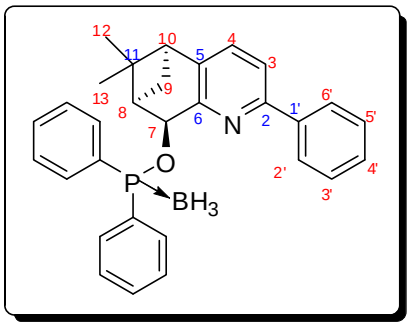
Diisopropyl azodicarboxylate (0.62 mL, 3.12 mmol, 4 equiv) was added dropwise to a cold (0 ºC) solution of alcohol (+)-**117b** (200 mg, 0.78 mmol, 1 equiv), *p*-nitrobenzoic acid (520 mg, 3.12 mmol, 4 equiv), and triphenylphosphine (820 mg, 3.12 mmol, 4 equiv) in dry THF (6 mL). After completion of the addition, the reaction mixture was allowed to warm to room temperature and was stirred overnight at that temperature. The mixture was then diluted with ether (10 mL) and the organic layer was washed with a saturated aqueous solution of sodium carbonate (2×15 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude material was dissolved in methanol (3 mL) and potassium carbonate (570 mg, 4.1 mmol, 10 equiv) was added portion-wise and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure, the residue was diluted with water (5 mL) and made alkaline by addition of an aqueous solution of 2M sodium hydroxide. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the organic extract was dried over $MgSO_4$, and concentrated under vacuum to provide pure alcohol **117a** as a colourless oil (100.3 mg, 50%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.70 (s, 3H, 12-H), 1.48 (s, 3H, 13-H), 1.59 (d, *J* = 9.9 Hz, 1H, 9-H), 2.53 (td, *J* = 5.8, 3.2 Hz, 1H, 8-H), 2.64 (dt, *J* = 9.9, 5.8 Hz, 1H, 9-H'), 2.83 (t, *J* = 5.8 Hz, 1H, 10-H), 3.51 (br s, 1H, OH), 4.97 (d, *J* = 3.2 Hz, 1H, 7-H), 7.35

(d, *J* = 7.8 Hz, 1H, 3-H), 7.38 (t, *J* = 7.4 Hz, 1H, 4'-H), 7.45 (t, *J* = 7.4 Hz, 2H, 3'-H, 5'-H), 7.52 (d, *J* = 7.8 Hz, 1H, 4-H), 8.00 (d, *J* = 7.4 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0 (CH_3-12), 26.6 (CH_3-13), 29.6 (CH_2-9), 44.9 (C-11), 45.5 (CH-8), 46.6 (CH-10), 71.5 (CH-7), 118.9 (CH-4), 126.7 (2×CH-2',6'), 128.5 (CH-4'), 128.6 (2×CH-3',5'), 133.8 (CH-3), 139.2 (C-1'), 139.8 (C-5), 155.0 (C-2), 157.2 (C-6); **HRMS** (EI) 265.1469 ($C_{18}H_{19}NO$ requires 265.1467).

NOE: Irradiation on **4.97** 7-H enhanced **0.70** 12-H and **2.53** 8-H



Borane-protected (7*S*,8*R*,10*S*)-(+)-2-Phenyl-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-trien-7- yl diphenylphosphinite (+)-119

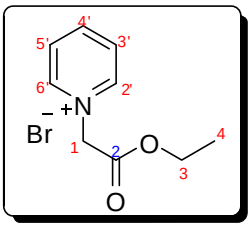


$C_{30}H_{31}BNOP$
Mol. Wt.: 463,36

A solution of *n*-butyllithium in hexane (2.5M; 0.38 mL, 0.94 mmol, 1.0 equiv) was added dropwise to a solution of (+)-**117b** (250 mg, 0.94 mmol, 1.0 equiv) in anhydrous THF (2 mL) under argon at –40 °C. The solution was stirred at that temperature for 30 min and then allowed to gradually warm to 0 °C. Diphenylphosphine chloride (0.20 mL, 1.04 mmol, 1.1 equiv) was then added dropwise and the reaction mixture was warmed up to room temperature and stirred for 3 h. A solution of borane in THF (1M, 0.94 mL, 0.94 mmol, 1.0 equiv) was added dropwise to the latter solution and the reaction mixture was stirred overnight. The reaction was then quenched by addition of water (15 mL), the aqueous phase was extracted with CH_2Cl_2 (3×20 mL), and the combined organic extracts were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by chromatography on a column of silica gel (13 g) using a mixture of

petroleum ether and AcOEt (95:5) to give pure (+)-**119** (176 mg, 41%) as a white solid: **mp** 117-120 °C (hexane); $[\alpha]_D^{19}$ +170.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.82 (s, 3H, 12-H), 1.42 (s, 3H, 13-H), 1.48 (d, *J* = 9.7 Hz, 1H, 9-H), 1.54 (br s, 3H, BH_3), 2.73-2.79 (m, 2H, 10-H, 9-H'), 2.84 (td, *J* = 6.4, 3.3 Hz, 1H, 8-H), 5.78 (dd, $J^2_{H,P}$ = 10.0 Hz, *J* = 3.3 Hz, 1H, 7-H), 7.33 (d, *J* = 7.8 Hz, 1H, 4-H), 7.35-7.49 (m, 9H, 3'-H, 5'-H, 4'-H, 6×aromH), 7.55 (d, *J* = 7.8 Hz, 1H, 3-H), 7.72-7.77 (m, 2H, aromH), 7.90 (dd, *J* = 8.0, 1.6 Hz, 2H, 2'-H, 6'-H), 8.02-8.07 (m, 2H, aromH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 23.5 (CH_3-12), 26.6 (CH_3-13), 35.1 (CH_2-9), 40.6 (C-11), 46.6 (CH-10), 47.0 (CH-8), 80.1 (CH-7), 118.6 (CH-3), 126.6 (2×CH-2',6'), 128.3 (d, *J* = 10 Hz, 2×aromCH), 128.4 (d, *J* = 10 Hz, 2×aromCH), 128.49 (CH-4'), 128.51 (2×CH-3',5'), 131.2 (d, *J* = 11 Hz, 2×aromCH), 131.37 (d, *J* = 2 Hz, aromCH), 131.46 (d, *J* = 2 Hz, aromCH), 132.1 (d, *J* = 11 Hz, 2×aromCH), 133.0 (d, *J* = 65 Hz, C), 133.7 (CH-4), 133.9 (d, *J* = 65 Hz, C), 139.1 (C-1'), 140.2 (C-5), 154.0 (d, *J* = 6 Hz, C-6), 155.0 (C-2); **^{31}P NMR** (162.0 MHz, CDCl3) δ 105.9 (m); **Anal. Calcd**. for $C_{30}H_{31}BNOP$: C, 77.76; H, 6.74; N, 3.02. Found: C, 77.30; H, 6.69; N, 3.22.

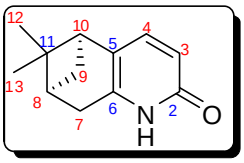
1-(2-Ethoxy-2-oxoethyl)pyridinium bromide 120



$C_9H_{12}BrNO_2$
Mol. Wt.: 246,10

Ethyl α-bromoacetate (11.1 mL, 100 mmol, 1.0 equiv) was added dropwise to a solution of pyridine (7 mL, 100 mmol, 1.0 equiv) in ethyl acetate (20 mL). The reaction mixture was heated at 50 °C for 1 h and then cooled to room temperature. The yellow precipitate was filtered off and washed with ethyl acetate (20 mL) to yield pure **120** as a clear brown solid (23.1 g, 94%): **^{1}H NMR** (400 MHz, d_6-DMSO) δ 1.24 (t, *J* = 7.1 Hz, 3H, 4–H), 4.22 (q, *J* = 7.1 Hz, 2H, 3–H), 5.79 (s, 2H, 1–H), 8.27 (dd, *J* = 7.6, 6.8 Hz, 2H, 3'–H, 5'–H), 8.74 (t, *J* = 7.6 Hz, 1H, 4'–H), 9.15 (d, *J* = 6.8 Hz, 2H, 2'–H, 6'–H) in accordance with the literature data.[24]

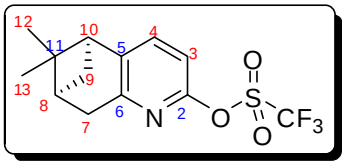
(8*S*,10*S*)-(+)-11,11-Dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-3,5-dien-2-one (+)-121



$C_{12}H_{15}NO$
Mol. Wt.: 189,25

Piperidine (0.13 mL) was added dropwise to a solution of pinocarvone (–)-**16** (1.30 g, 8.65 mmol, 1.0 equiv), Kröhnke salt **120** (2.30 g, 9.34 mmol, 1.1 equiv) and ammonium acetate (6.40 g, 83 mmol, 9.6 equiv) in butanol (15 mL). The reaction mixture was refluxed for 2 h, then acetic acid (0.88 mL) was added, and the mixture was refluxed for an additional 48 h. The reaction mixture was then cooled to room temperature and quenched by addition of an aqueous solution of sodium hydroxide (2M). The mixture was extracted with ethyl acetate (3×20 mL), washed with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The resulting brown oil was then purified by ion-exchange low pKa sorbent column (SCX). Two column volume of MeOH were used to wash impurities. A solution of ammonia in MeOH (2M) was then used to release the pure pyridone (+)-**121** from the column, as a brown solid (540 mg, 33%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.70 (s, 3H, 12-H), 1.24 (d, *J* = 9.2 Hz, 1H, 9-H), 1.37 (s, 3H, 13-H), 2.28 (m, 1H, 8-H), 2.56 (t, *J* = 5.5 Hz, 1H, 10-H), 2.63 (dt, *J* = 9.2, 5.5 Hz, 1H, 9-H'), 2.85-3.00 (m, 2H, 7-H), 6.32 (d, *J* = 8.9 Hz, 1H, 3-H), 7.14 (d, *J* = 8.9 Hz, 1H, 4-H), 13.52 (br s, 1H, N-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.1 (CH_3-12), 26.0 (CH_3-13), 31.5 (CH_2-7), 32.8 (CH_2-9), 39.6 (CH-8), 40.3 (C-11), 44.2 (CH-10), 115.0 (CH-3), 124.9 (C-5), 141.3 (CH-4), 142.2 (C-6), 165.4 (C=O) in accordance with the literature data.[24]

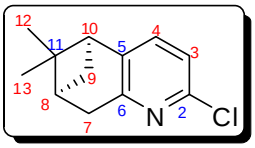
(8*S*,10*S*)-(+)-11,11-Dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-3,5-dien-2-yl trifluoromethanesulfonate (+)-122



$C_{13}H_{14}F_3NO_3S$
Mol. Wt.: 321,32

Triflic anhydride (0.32 mL, 2 mmol, 2.0 equiv) was added dropwise to a solution of pyridone (+)-**121** (194 mg, 1 mmol, 1.0 equiv) and triethylamine (0.21 mL, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 at –45 ºC. The resulting mixture was stirred at this temperature for 1 h., followed by an additional 1 h at 0 ºC and finally allowed to reach room temperature. The reaction was quenched by addition of an aqueous solution of sodium carbonate (1M). The mixture was extracted with CH_2Cl_2 (3×20 mL), the organic extract was washed with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum to afford the pure triflate (+)-**122** (277 mg, 86%) as a brown oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.63 (s, 3H, 12-H), 1.27 (d, *J* = 9.9 Hz, 1H, 9-H), 1.41 (s, 3H, 13-H), 2.37 (tt, *J* = 5.8, 2.9 Hz, 1H, 8-H), 2.71 (dt, *J* = 9.9, 5.8 Hz, 1H, 9-H'), 2.82 (t, *J* = 5.8 Hz, 1H, 10-H), 3.08 (d, *J* = 2.9 Hz, 2H, 7-H), 6.86 (d, *J* = 8.0 Hz, 1H, 3-H), 7.36 (d, *J* = 8.0 Hz, 1H, 4-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.2 (CH_3-12), 25.8 (CH_3-13), 31.6 (CH_2-9), 36.1 (CH_2-7), 39.3 (C-11), 39.7 (CH-8), 45.7 (CH-10), 111.3 (CH-3), 118.9 (q, *J* = 276 Hz, CF_3), 137.1 (CH-4), 143.0 (C-5), 153.8 (C-6), 157.1 (C-2) in accordance with the literature data.[24]

(8*S*,10*S*)-2-Chloro-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene 123

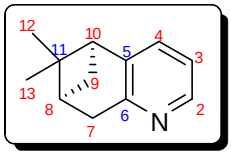


$C_{12}H_{14}ClN$
Mol. Wt.: 207,7

Pyridinium chloride (100 mg, 0.864 mmol, 2 equiv) was added to a solution of triflate (+)-**122** (139 mg, 0.431 mmol, 1 equiv) in *N*-methyl-2-pyrrolidone (2.6 mL) and the mixture was stirred under microwave irradiation (250 ºC) for 15 min. The resulting mixture was diluted with ethyl acetate (4 mL), the organic layer was washed with water (2×10 mL), dried over

$MgSO_4$, and concentrated under vacuum. The resulting brownish oil was purified by column chromatography on silica gel (4 g) using a mixture of hexane and ethyl acetate (1:1) to give pure **123** (32 mg, 36%) as a colourless oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.63 (s, 3H, 12-H), 1.27 (d, *J* = 9.8 Hz, 1H, 9-H), 1.40 (s, 3H, 13-H), 2.38 (m, 1H, 8-H), 2.69 (dt, *J* = 9.8, 5.7 Hz, 1H, 9-H'), 2.75 (t, *J* = 5.7 Hz, 1H, 10-H), 3.08 (d, *J* = 2.1 Hz, 2H, 7-H), 7.01 (d, *J* = 8.9 Hz, 1H, 3-H), 7.17 (d, *J* = 8.9 Hz, 1H, 4-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0 (CH_3-12), 25.9 (CH_3-13), 31.9 (CH_2-7), 36.2 (CH_2-9), 39.3 (C-11), 39.9 (CH-8), 45.8 (CH-10), 120.5 (CH-3), 135.7 (CH-4), 140.7 (C-5), 147.8 (C-6), 157.8 (C-2); **LCMS** (GSK-gold) 3.31 min – *mass* 208.1.

(8*S*,10*S*)-(+)-11,11-Dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene (+)-124



$C_{12}H_{15}N$
Mol. Wt.: 173,25

Procedure A: from chloropyridine

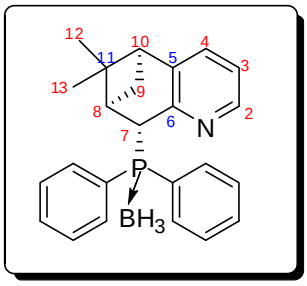
A mixture of 10% Pd/C (10 mg, 0.0077 mmol, 0.05 equiv) and 2-chloropyridine derivative **123** (32 mg, 0.155 mmol, 1.00 equiv) in formic acid 99% (0.25 mL) and DMF (1.25 mL) was heated at 60 ºC for 5 h. The mixture was then cooled to room temperature, diluted with CH_2Cl_2 (4 mL) and filtered through a plug of celite. The filtrate was made alkaline by addition of an aqueous solution of sodium hydroxide (2M). The mixture was then extracted with CH_2Cl_2 (3×20 mL), dried over $MgSO_4$, and concentrated under vacuum to afford the pure pyridine (+)-**124** (25.4 mg, 95%).

Procedure B: from triflate

Formic acid 99% (38 µL, 1.00 mmol, 2.00 equiv) was added dropwise to a solution of the triflate derivative (+)-**122** (160 mg, 0.50 mmol, 1.00 equiv), triethylamine (0.21 mL, 1.50 mmol, 3.00 equiv), palladium(II) acetate (2.3 mg, 0.01 mmol, 0.02 equiv) and 1,1'-bis(diphenylphosphino)ferrocene (12 mg, 0.02 mmol, 0.04 equiv) in DMF (1 mL). The

reaction mixture was stirred at 60 ºC for 2 h under argon, then cooled to room temperature and diluted with water (4 mL). The resulting mixture was extracted with ether (3×10 mL) and the combined organic layers were washed successively with a saturated aqueous solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4, and evaporated. The brown residue was then purified by column chromatography on silica gel (4 g) using a mixture of hexane and ethyl acetate (9:1), to afford pure (+)-**124** (55.6 mg, 65%) as a colourless oil: $[\alpha]_D^{20}$ +51.8 (*c* 1.0, $CHCl_3$); **IR** (KBr) ν 3020 (m, C-H), 1573 (m, C=Car), 1524 (m, C=Car), 1430 (m, C=Car), 758 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.61 (s, 3H, 12-H), 1.24 (d, *J* = 9.5 Hz, 1H, 9-H), 1.37 (s, 3H, 13-H), 2.33 (tt, *J* = 5.8, 2.8 Hz, 1H, 8-H), 2.64 (dt, *J* = 9.5, 5.8 Hz, 1H, 9-H'), 2.71 (t, *J* = 5.8 Hz, 1H, 10-H), 3.08 (d, *J* = 2.8 Hz, 2H, 7-H), 6.93 (dd, *J* = 7.4, 5.0 Hz, 1H, 3-H), 7.15 (dd, *J* = 7.4, 1.3 Hz, 1H, 4-H), 8.31 (dd, *J* = 5.0, 1.4 Hz, 1H, 2-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.1 (CH_3-12), 26.0 (CH_3-13), 31.8 (CH_2-9), 36.4 (CH_2-7), 39.3 (C-11), 40.1 (CH-8), 46.4 (CH-10), 120.2 (CH-3), 132.8 (CH-4), 141.7 (C-5), 146.6 (CH-2), 156.8 (C-6); **MS** (CI-isobutane) *m/z* (%) 174 ($(M+H)^+$, 100), 95 (11), 69 (61); **HRMS** (CI-isobutane) 174.1284 ($C_{12}H_{16}N$ $(M+H)^+$ requires 174.1283).

Borane-protected (7*R*,8*S*,10*S*)-(+)-7-(diphenylphosphino)-11,11-Dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene (+)-125

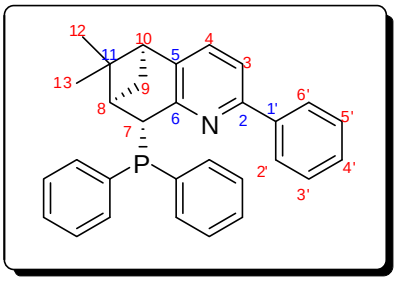


$C_{24}H_{27}BNP$
Mol. Wt.: 371.26

A solution of *n*-buthyllithium in hexane (1.6M; 0.42 mL, 0.67 mmol, 1.0 equiv) was added dropwise to a solution of (+)-**124** (120 mg, 0.67 mmol, 1.0 equiv) in THF (2 mL) at –40 °C. The solution was stirred at that temperature for 1 h and then a solution of $Ph_2PCl.BH_3$ (1.0 mmol, 1.5 equiv) was added dropwise at –40 °C [the $Ph_2PCl.BH_3$ solution was prepared by stirring for 30 min a mixture of borane in THF (1M, 1 mL, 1.0 mmol, 1.0 equiv) and chlorodiphenylphosphine (0.18 mL, 1.0 mmol, 1.0 equiv) in diethyl ether (2 mL) at room temperature]. The resulting solution was then gradually warmed up to room temperature and

stirred overnight. A saturated aqueous solution of NH_4Cl (2 mL) was then added to quench the reaction, the mixture was extracted with CH_2Cl_2 (3×20 mL), and the combined organic extracts were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (20 g) using a mixture of hexane and ether (20:1) to give pure **(+)-125** as a white solid (103 mg, 42%): **$[\alpha]_D^{26}$** +45.7 (*c* 1.0, $CHCl_3$); **IR** (KBr) ν 3018 (m, C-H), 2389 (m, B-H), 1576 (m, C=Car), 1525 (m, C=Car), 1432 (m, C=Car), 1213 (s, P-BH_3), 758 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.69 (s, 3H, 12-H), 1.40 (s, 3H, 13-H), 1.50 (d, *J* = 10.3 Hz, 1H, 9-H), 2.53 (dt, *J* = 10.3, 5.8 Hz, 1H, 9-H'), 2.67 (t, *J* = 5.8 Hz, 1H, 10-H), 2.70 (qd, *J* = 6.2, 2.1 Hz, 1H, 8-H), 4.33 (dd, $J^2_{H,P}$ = 13.8 Hz, *J* = 2.0 Hz, 1H, 7-H), 7.91-6.96 (m, 1H, 3-H), 7.15 (dd, *J* = 7.5, 1.5 Hz, 1H, 4-H), 7.29 (td, *J* = 7.6, 2.0 Hz, 2H, aromH), 7.38 (td, *J* = 7.6, 1.4 Hz, 1H, aromH), 7.45-7.52 (m, 3H, 3×aromH), 7.74 (ddd, *J* = 10.7, 8.0, 1.2 Hz, 2H, 2×aromH), 7.92 (ddd, *J* = 10.3, 7.7, 1.8 Hz, 2H, 2×aromH), 8.23 (dd, *J* = 4.9, 1.7 Hz, 1H, 2-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.7 (CH_3-12), 25.8 (CH_3-13), 28.4 (CH_2-9), 42.0 (d, *J* = 10 Hz, C-11), 42.4 (d, *J* = 29 Hz, CH-7), 42.7 (CH-8), 45.8 (d, *J* = 2 Hz, CH-10), 121.1 (CH-3), 127.8 (d, *J* = 10 Hz, 2×aromCH), 128.3 (d, *J* = 10 Hz, 2×aromCH), 129.3 (d, *J* = 53 Hz, C), 130.5 (d, *J* = 2 Hz, aromCH), 130.6 (d, *J* = 2 Hz, aromCH), 130.9 (d, *J* = 55 Hz, C), 133.2 (CH-4), 133.21 (d, *J* = 9 Hz, 2×aromCH), 134.2 (d, *J* = 9 Hz, 2×aromCH), 141.8 (d, *J* = 4 Hz, C-5), 146.4 (d, *J* = 2 Hz, CH-2), 153.6 (d, *J* = 6 Hz, C-6); **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ 26.7 (m); **MS** (EI) *m/z* (%) 371 ($M^{\bullet+}$, 22), 357 ($M^{\bullet+}$-BH_3, 100), 172 ($M^{\bullet+}$-$PPh_2.BH_3$, 86), 130 ($M^{\bullet+}$-PPh_2•BH_3-C_3H_6, 100); **HRMS** (EI) 371.1653 ($C_{24}H_{27}BNP$ requires 371.1646); **Anal. Calcd**. for $C_{24}H_{27}BNP$: C, 77.64; H, 7.33; N, 3.77. Found: C, 77.74; H, 7.44; N, 3.71.

(7*R*,8*R*,10*S*)-2-Phenyl-7-(diphenylphosphino)-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene 108

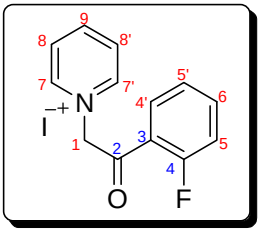


$C_{30}H_{28}NP$
Mol. Wt.: 433.52

Borane-protected diphenylphosphine (–)-**115** was dissolved in diethylamine (1-2 mL) and stirred for 6 h. The conversion was monitored by TLC. After completion of the reaction all volatiles were removed under high-vacuum at 60 °C to afford **108**: **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ -5.28 (s). No other experimental data were recorded because of rapid oxidation of phosphine **108**.

6.3.2 Synthesis of the Second Generation of Ligands

1-[2-(2'-Fluorophenyl)-2-oxoethyl]pyridinium iodide 43

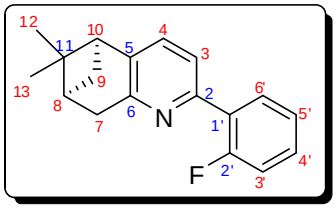


$C_{13}H_{11}FINO$
Mol. Wt.: 343,14

A solution of 2'-fluoroacetophenone **42** (2.76 g, 20 mmol) and iodine (5.08 g, 20 mmol, 1.0 equiv) in pyridine (10 mL) was refluxed overnight. The reaction mixture was cooled to room temperature, inducing the precipitation of a solid which was filtered off and washed with eher (3×20 mL). The remaining solid was then stirred overnight in diethyl ether (50 mL). After filtration, the salt **43** was isolated as a brown solid (5.22 g, 76%): **^{1}H NMR** (400 MHz, *d*$_4$-MeOD) δ 6.30 (s, 2H, 1–H), 7.38-7.43 (m, 2H, 5–H, 5'–H), 7.75-7.82 (m, 1H, 6–H), 8.06

(dd, *J* = 7.3, 1.7 Hz, 1H, 4'–H), 8.20-8.24 (m, 2H, 8–H, 8'–H), 8.73 (tt, *J* = 7.9, 1.3 Hz, 1H, 9–H), 8.95 (dd, *J* = 6.5, 1.3 Hz, 2H, 7–H, 7'–H) in agreement with the literature data.[30a]

(8*S*,10*S*)-(+)-2-(2'-Fluorophenyl)-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene (+)-44a



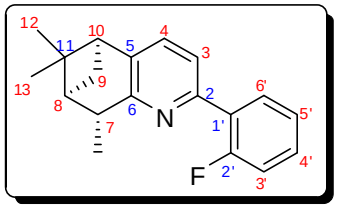
$C_{18}H_{18}FN$
Mol. Wt.: 267,34

A solution of pinocarvone (–)-**16** (1.05 g, 7.0 mmol, 1.0 equiv), the Kröhnke salt **43** (2.41 g, 7.0 mmol, 1.0 equiv), and ammonium acetate (9.25 g) in acetic acid (12 mL) was refluxed for 6 h. The mixture was then cooled to room temperature, diluted with water (25 mL), made neutral by addition of an aqueous solution of sodium hydroxide (2M), and extracted with ethyl acetate (3×50 mL). The organic phase was successively washed with water (3×50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvent was removed under vacuum to afford pure (+)-**44a** as a red oil (1.25 g, 67%): **[α]$_D^{19}$** +68.8 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2939 (s, C-H), 1588 (s, C=Car), 1595 (s, C=Car), 1440 (s, C=Car), 1225 (m, C-H methyl), 1108 (s, C-F), 752 (m, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.69 (s, 3H, 12-H), 1.32 (d, *J* = 9.6 Hz, 1H, 9-H), 1.41 (s, 3H, 13-H), 2.39 (tt, *J* = 5.8, 2.9 Hz, 1H, 8-H), 2.71 (dt, *J* = 9.6, 5.8 Hz, 1H, 9-H'), 2.79 (t, *J* = 5.8 Hz, 1H, 10-H), 3.18 (d, *J* = 2.9 Hz, 2H, 7-H), 7.12 (ddd, *J* = 11.3, 8.1, 1.2 Hz, 1H, 3'-H), 7.23 (td, *J* = 7.9, 1.3 Hz, 1H, 5'-H), 7.25 (d, *J* = 7.8 Hz, 1H, 4-H), 7.31 (m, 1H, 4'-H), 7.46 (dd, *J* = 7.8, 2.4 Hz, 1H, 3-H), 7.96 (td, *J* = 7.9, 1.9 Hz, 1H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.3 (CH_3-12), 26.0 (CH_3-13), 31.9 (CH_2-9), 36.7 (CH_2-7), 39.5 (C-11), 40.2 (CH-8), 46.3 (CH-10), 116.0 (d, *J* = 23 Hz, CH-3'), 121.1 (d, *J* = 9 Hz, CH-3), 124.4 (d, *J* = 4 Hz, CH-5'), 127.9 (d, *J* = 12 Hz, C-1'), 129.6 (d, *J* = 8 Hz, CH-4'), 130.9 (d, *J* = 3 Hz, CH-6'), 133.1 (CH-4), 140.7 (C-5), 150.3 (d, *J* = 2 Hz, C-2), 156.9 (C-6), 160.3 (d, *J* = 249 Hz, C-2'); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –117.4 (s); **MS** (EI) *m/z* (%) 267 ($M^{\bullet+}$, 68), 252 ($M^{\bullet+}$-CH_3, 52), 224 (100), 83 (38); **HRMS** (EI) 267.1427 ($C_{18}H_{18}FN$ requires 267.1423).

General Procedure for the Benzylic Alkylation of (+)-44a

A solution of *n*-butyllithium in hexane (2.5M; 0.6 mL, 1.5 mmol, 1 equiv) was added dropwise to a solution of (+)-**44a** (400 mg, 1.5 mmol, 1 equiv) in anhydrous THF (2 mL) under argon at –40 °C. The solution was stirred at that temperature for 1 h, then the respective electrophile, iodomethane (0.1 mL, 1.5 mmol, 1 equiv) or 2-iodopropane (0.15 mL, 1.5 mmol, 1 equiv) was added dropwise at –40 °C. The solution was then gradually warmed up to room temperature and stirred overnight. The reaction was quenched by addition of water (15 mL), the aqueous phase was extracted with CH_2Cl_2 (3×20 mL), and the combined organic extracts were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (15 g) using a mixture of petroleum ether and ethyl acetate (97:3) to give, respectively, pure (+)-**44b** as a colourless oil, or pure (+)-**44c** as a colourless oil.

(7*R*,8*S*,10*S*)-(+)-2-(2'-Fluorophenyl)-7,11,11-trimethyl-1-azatricyclo[7.1.1.$0^{5,6}$]undeca-2,4,6-triene (+)-44b

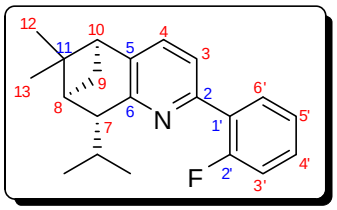


$C_{19}H_{20}FN$
Mol. Wt.: 281,37

(+)-44b (246 mg, 59%): **[α]$_D^{20}$** +38.4 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2945 (s, C-H), 1586 (m, C=Car), 1488 (m, C=Car), 1437 (m, C=Car), 1206 (m, C-H methyl), 1031 (s, C-F), 754 (m, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.65 (s, 3H, 12-H), 1.31 (d, *J* = 9.8 Hz, 1H, 9-H), 1.38 (s, 3H, 13-H), 1.44 (d, *J* = 7.1 Hz, 3H, CH_3C(7)), 2.13 (td, *J* = 5.8, 2.5 Hz, 1H, 8-H), 2.53 (dt, *J* = 9.8, 5.8 Hz, 1H, 9-H'), 2.74 (t, *J* = 5.8 Hz, 1H, 10-H), 3.24 (qd, *J* = 7.1, 2.5 Hz, 1H, 7-H), 7.09 (ddd, *J* = 11.5, 8.1, 1.3 Hz, 1H, 3'-H), 7.18 (d, *J* = 7.8 Hz, 1H, 4-H), 7.20 (td, *J* = 7.6, 1.3 Hz, 1H, 5'-H), 7.24-7.29 (m, 1H, 4'-H), 7.48 (dd, *J* = 7.8, 2.0 Hz, 1H, 3-H), 7.96 (td, *J* = 7.9, 1.9 Hz, 1H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.2 (CH_3C(7)), 20.8 (CH_3-12), 26.2 (CH_3-13), 28.5 (CH_2-9), 38.8 (CH-7), 41.3 (C-11), 46.7 (CH-8), 46.9 (CH-10), 115.9 (d, *J* = 23 Hz, CH-3'), 121.0 (d, *J* = 9 Hz, CH-3), 124.2 (d, *J* = 4 Hz, CH-5'), 127.8 (d, *J* = 12 Hz, C-1'), 129.5 (d, *J* = 9 Hz, CH-4'), 130.9 (d, *J* = 4 Hz, CH-6'), 132.8 (CH-4), 140.4 (C-5), 149.9 (d, *J* = 3 Hz, C-2), 160.4 (d, *J* = 249 Hz, C-2'), 160.6 (C-6); **^{19}F**

NMR (376 MHz, $CDCl_3$) δ –116.9 (s); **MS** (EI) *m/z* (%) 281 ($M^{\bullet+}$, 19), 266 ($M^{\bullet+}$-CH_3, 50), 238 (62), 224 (12), 83 (100); **HRMS** (EI) 281.1583 ($C_{19}H_{20}FN$ requires 281.1580).

(7*R*,8*S*,10*S*)-(+)-2-(2'-Fluorophenyl)-7-isopropyl-11,11-dimethyl-1-azatricyclo[7.1.1.$0^{5,6}$]undeca-2,4,6-triene (+)-44c.



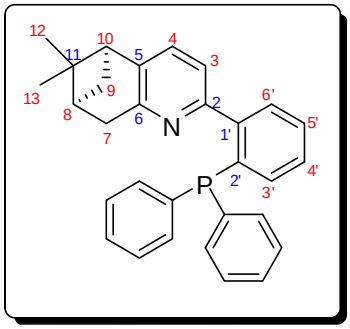
$C_{21}H_{24}FN$
Mol. Wt.: 309,42

(+)-44c (309 mg, 67%): $[\alpha]_D^{25}$ +15.8 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2942 (s, C-H), 1587 (m, C=Car), 1483 (m, C=Car), 1432 (m, C=Car), 1213 (m, C-H methyl), 1056 (s, C-F), 752 (m, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.59 (s, 3H, 12-H), 0.81 (d, *J* = 7.0 Hz, 3H, CH_3CH), 1.17 (d, *J* = 7.0 Hz, 3H, CH_3'CH), 1.35 (d, *J* = 9.7 Hz, 1H, 9-H), 1.36 (s, 3H, 13-H), 2.32 (td, *J* = 5.7, 2.0 Hz, 1H, 8-H), 2.52 (dt, *J* = 9.7, 5.7 Hz, 1H, 9-H'), 2.68 (t, *J* = 5.7 Hz, 1H, 10-H), 2.83 (spd, *J* = 7.0, 4.7 Hz, 1H, $(CH_3)_2CH$), 2.93 (dd, *J* = 4.7, 2.0 Hz, 1H, 7-H), 7.06 (ddd, *J* = 11.5, 8.1, 1.3 Hz, 1H, 3'-H), 7.17 (d, *J* = 7.8 Hz, 1H, 4-H), 7.18 (td, *J* = 7.5, 1.4 Hz, 1H, 5'-H), 7.22-7.27 (m, 1H, 4'-H), 7.47 (dd, *J* = 7.8, 2.0 Hz, 1H, 3-H), 8.04 (td, *J* = 7.9, 2.0 Hz, 1H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.0 (CH_3CH), 21.0 (CH_3-12), 22.2 (C'H_3CH), 26.3 (CH_3-13), 29.4 (CH_2-9), 30.3 (CH_3CHCH_3), 41.2 (CH-8), 41.9 (C-11), 46.5 (CH-10), 49.1 (CH-7), 116.0 (d, *J* = 23 Hz, CH-3'), 121.0 (d, *J* = 10 Hz, CH-3), 124.3 (d, *J* = 4 Hz, CH-5'), 127.9 (d, *J* = 12 Hz, C-1'), 129.5 (d, *J* = 9 Hz, CH-4'), 130.9 (d, *J* = 3 Hz, CH-6'), 132.9 (CH-4), 141.1 (C-5), 149.6 (d, *J* = 3 Hz, C-2), 159.2 (C-6), 160.5 (d, *J* = 249 Hz, C-2'); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –116.9 (s); **MS** (EI) *m/z* (%) 309 ($M^{\bullet+}$, 17), 294 ($M^{\bullet+}$-CH_3, 15), 266 ($M^{\bullet+}$-$CH(CH_3)_2$, 84), 224 (100), 83 (78); **HRMS** (EI) 309.1897 ($C_{21}H_{24}FN$ requires 309.1893).

General Procedure for the Reaction of Fluoro Derivatives 44a-c with Ph_2PK

Diphenylphosphine (0.32 mL, 1.86 mmol, 2 equiv) was added to a suspension of potassium *tert*-butoxide (210 mg, 1.86 mmol, 2 equiv) and 18-crown-6 (490 mg, 1.86 mmol, 2 equiv) in THF (10 mL) at 0 °C and the resulting deep red solution was stirred at this temperature for 1 h. A solution of the respective fluoro derivative **44a** (250 mg, 0.93 mmol, 1 equiv), **44b** (262 mg, 0.93 mmol, 1 equiv), and **44c** (287 mg, 0.93 mmol) in THF (2 mL) was then added dropwise and the mixture was stirred at room temperature for 48 h. Methanol (2 mL) was then added and the solvent was removed *in vacuo* to afford an oil that was purified *via* flash chromatography on silica gel (25 g) with use of petroleum ether followed by a 9:1 mixture of petroleum ether and ethyl acetate to give pure (+)-**41a** (167 mg, 42%) as a white solid. In the case of (+)-**41b** and (–)-**41c**, after evaporation of the solvent, the residue was dissolved in acetone (20 mL) and a 30% aqueous solution of hydrogene peroxide (3 mL) was added. The resulting mixture was stirred at room temperature for 10 min, and then partitioned between water and CH_2Cl_2. The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3×10 mL), and the combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude mixture was then purified via flash chromatography on silica gel (17 g) with a 1:1 mixture of petroleum ether and ethyl acetate, followed by pure methanol. The methanolic fraction was concentrated *in vacuo* and the residue was dissolved in ethanol (1.5 mL). Potassium hydroxide (1.3 mmol, 56.1 mg, 1.3 equiv) was added to the latter solution and the reaction mixture was refluxed for 4 h. The latter mixture was then cooled to room temperature and diluted with water (20 mL). The aqueous phase was extracted with ethyl acetate (3×20 mL) and the combined organic extracts were then washed with a saturated aqueous solution of $NaHCO_3$ (3×20 mL), dried over $MgSO_4$, and concentrated under vacuum. Finally, the residue was dissolved in toluene (10 mL), triethylamine (2.1 mL, 15 mmol, 15 equiv) and trichlorosilane (1 mL, 10 mmol, 10 equiv) were added, and the resulting reaction mixture was refluxed for 24 h. The mixture was then diluted with an aqueous solution of sodium hydroxide (2M, 10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL) and dried over $MgSO_4$ and concentrated under vacuum to afford pure (+)-**41b** (208 mg, 50%) and (–)-**41c** (230 mg, 52%), respectively.

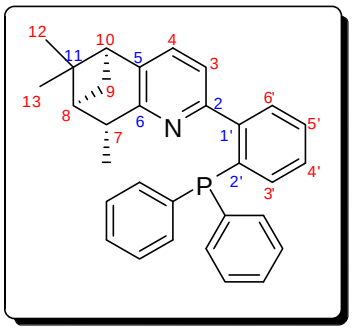
(8*S*,10*S*)-(+)-2-[2'-(Diphenylphosphino)phenyl]-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene (+)-41a



$C_{30}H_{28}NP$
Mol. Wt.: 433.52

(+)-41a (167 mg, 42%): **[α]$_D^{19}$** +58.5 (*c* 1.0, $CHCl_3$); **IR** (KBr) ν 2936 (m, C-H), 1576 (m, C=Car), 1445 (m, C=Car), 1432 (m, C=Car), 1213 (m), 757 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.46 (s, 3H, 12-H), 1.13 (d, *J* = 9.4 Hz, 1H, 9-H), 1.27 (s, 3H, 13-H), 2.18 (tt, *J* = 5.7, 2.9 Hz, 1H, 8-H), 2.52 (dt, *J* = 9.4, 5.7 Hz, 1H, 9-H'), 2.60 (t, *J* = 5.7 Hz, 1H, 10-H), 2.75 (d, *J* = 2.9 Hz, 2H, 7-H), 6.92 (ddd, *J* = 7.7, 4.1, 1.1 Hz, 1H, 3'-H), 7.02 (d, *J* = 7.7 Hz, 1H, 4-H), 7.08 (d, *J* = 7.7 Hz, 1H, 5-H), 7.12-7.22 (m, 11H, aromH), 7.31 (td, *J* = 7.6, 1.3 Hz, 1H, 5'-H), 7.51 (ddd, *J* = 7.6, 4.2, 1.2 Hz, 1H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.3 (CH_3-12), 26.0 (CH_3-13), 31.7 (CH_2-9), 36.0 (CH_2-7), 39.4 (C-11), 40.1 (CH-8), 46.2 (CH-10), 120.14 (d, *J* = 3.7 Hz, CH-3), 127.7, (CH-4'), 128.0-128.2 (6×aromCH), 128.5 (CH-5'), 129.3 (d, *J* = 4 Hz, CH-6'), 132.6 (CH-4), 133.9 (d, *J* = 6.4 Hz, 2×aromCH), 134.1 (d, *J* = 6.4 Hz, 2×aromCH), 134.2 (d, *J* = 30.5 Hz, CH-3'), 136.6 (d, *J* = 18 Hz, C-1'), 138.6 (d, *J* = 11 Hz, *C*PAr$_2$), 138.7 (d, *J* = 11 Hz, *C*'PAr$_2$), 139.7 (C-5), 145.9 (d, *J* = 24 Hz, C-2'), 155.6 (C-6), 155.8 (d, *J* = 2 Hz, C-2); **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ –9.3 (s); **MS** (EI) *m/z* (%) 433 ($M^{\bullet+}$, 10), 356 ($M^{\bullet+}$-C_6H_5, 100), 248 ($M^{\bullet+}$-PPh_2, 5), 91 (12), 44 (76); **HRMS** (EI) 433.1953 ($C_{30}H_{28}NP$ requires 433.1959).

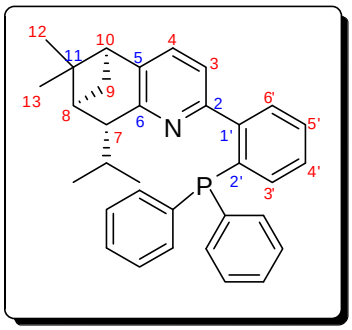
(7*R*,8*S*,10*S*)-(+)-2-[2'-(Diphenylphosphino)phenyl]-7,11,11-trimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene (+)-41b



$C_{31}H_{30}NP$
Mol. Wt.: 447.55

(+)-41b (208 mg, 50%): **[α]$_D^{26}$** +3.4 (*c* 1.0, $CHCl_3$); **IR** (KBr) ν 2942 (m, C-H), 1573 (m, C=Car), 1452 (m, C=Car), 1431 (m, C=Car), 1217 (m), 755 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.51 (s, 3H, 12-H), 0.90 (d, *J* = 7.0 Hz, 3H, CH_3C(7)), 1.17 (d, *J* = 9.9 Hz, 1H, 9-H), 1.31 (s, 3H, 13-H), 1.97 (td, *J* = 5.7, 2.4 Hz, 1H, 8-H), 2.41 (dt, *J* = 9.9, 5.7 Hz, 1H, 9-H'), 2.63 (t, *J* = 5.7 Hz, 1H, 10-H), 2.90 (qd, *J* = 7.0, 2.4 Hz, 1H, 7-H), 6.96 (dd, *J* = 7.5, 3.8 Hz, 1H, 3'-H), 7.06 (d, *J* = 7.7 Hz, 1H, 4-H), 7.11 (d, *J* = 7.7 Hz, 1H, 3-H), 7.15-7.25 (m, 11H, aromH), 7.34 (td, *J* = 7.5, 1.0 Hz, 1H, 5'-H), 7.55 (ddd, *J* = 7.5, 4.3, 1.1 Hz, 1H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.7 (CH_3C(7)), 20.9 (CH_3-12), 26.2 (CH_3-13), 28.5 (CH_2-9), 38.7 (CH-7), 41.3 (C-11), 46.8 (CH-8), 46.9 (CH-10), 120.2 (d, *J* = 3.0 Hz, CH-3), 127.7, (CH-4'), 128.0-128.2 (6×aromCH), 128.4 (CH-5'), 129.4 (d, *J* = 4.2 Hz, CH-6'), 132.5 (CH-4), 133.7 (d, *J* = 15.1 Hz, 2×aromCH), 134.9 (d, *J* = 14.8 Hz, 2×aromCH), 134.4 (d, *J* = 21.4 Hz, CH-3'), 136.1 (d, *J* = 18 Hz, C-1'), 139.0 (d, *J* = 11 Hz, *C*PAr$_2$), 139.2 (d, *J* = 11 Hz, *C*'PAr$_2$), 139.5 (C-5), 146.4 (d, *J* = 23 Hz, C-2'), 156.0 (d, *J* = 2 Hz, C-2), 159.6 (C-6); **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ –9.9 (s); **MS** (EI) *m/z* (%) 447 ($M^{\bullet+}$, 14), 370 ($M^{\bullet+}$-C_6H_5, 100); **HRMS** (EI) 447.2118 ($C_{31}H_{30}NP$ requires 447.2116).

(7*R*,8*S*,10*S*)-(–)-2-[2'-(Diphenylphosphino)phenyl]-7-isopropyl-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene (–)-41c



$C_{33}H_{34}NP$
Mol. Wt.: 475.60

(–)-41c (230 mg, 52%): **[α]$_D^{26}$** –15.0 (*c* 1.0, $CHCl_3$); **IR** (KBr) ν 2951 (m, C-H), 1571 (m, C=Car), 1449 (m, C=Car), 1433 (m, C=Car), 1215 (m), 752 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.49 (s, 3H, 12-H), 0.53 (d, *J* = 7.0 Hz, 3H, CH_3CH), 0.73 (d, *J* = 7.0 Hz, 3H, CH_3'CH), 1.30 (d, *J* = 9.9 Hz, 1H, 9-H), 1.31 (s, 3H, 13-H), 2.15-2.25 (m, 2H, 8-H, CH_3CHCH_3), 2.44 (dt, *J* = 9.9, 5.6 Hz, 1H, 9-H'), 2.60 (t, *J* = 5.6 Hz, 1H, 10-H), 2.63-2.67 (m, 1H, 7-H), 6.99 (dd, *J* = 7.2, 3.8 Hz, 1H, 3'-H), 7.09 (d, *J* = 7.7 Hz, 1H, 4-H), 7.12 (d, *J* = 7.7 Hz, 1H, 3-H), 7.14-7.26 (m, 11H, aromH), 7.33 (t, *J* = 7.2 Hz, 1H, 5'-H), 7.54 (dd, *J* = 7.2, 4.4 Hz, 1H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.7 (CH_3CH), 21.1 (CH_3-12), 22.0 (*C*'H_3CH), 26.3 (CH_3-13), 29.1 (*C*H(CH_3)$_2$), 29.5 (CH_2-9), 40.4 (CH-8), 41.9 (C-11), 46.6 (CH-10), 48.9 (CH-7), 120.4 (d, *J* = 3.1 Hz, CH-3), 127.7-128.2 (7×aromCH), 128.6 (CH-5'), 129.6 (d, *J* = 5.0 Hz, CH-6'), 132.5 (CH-4), 133.6 (d, *J* = 18.8 Hz, 2×aromCH), 133.8 (d, *J* = 18.8 Hz, 2×aromCH), 135.2 (d, *J* = 22.2 Hz, CH-3'), 135.8 (d, *J* = 18 Hz, C-1'), 139.0 (d, *J* = 12.8 Hz, *C*PAr$_2$), 139.3 (d, *J* = 12.6 Hz, *C*'PAr$_2$), 140.3 (C-5), 147.4 (d, *J* = 25.7 Hz, C-2'), 156.2 (d, *J* = 2.7 Hz, C-2), 158.2 (C-6); **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ –11.2 (s); **MS** (EI) *m/z* (%) 475 ($M^{\bullet+}$, 39), 398 ($M^{\bullet+}$-C_6H_5, 100), 355 ($M^{\bullet+}$-C_6H_5-$(CH_3)_2CH$, 32), 194 (60); **HRMS** (EI) 475.2428 ($C_{33}H_{34}NP$ requires 475.2429).

6.3.3 Asymmetric Palladium-Catalysed Baeyer-Villiger Oxidation

Zinc-copper couple preparation

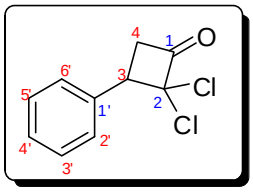
A solution of copper sulfate ($CuSO_4 \cdot 5H_2O$, 0.76 g) in water (5 mL) was added in two portions at 30-s intervals to a stirred mixture of zinc dust (6.5 g, 0.1 mol) in water (10 mL).

After 1 min the mixture was filtered through a sintered-glass Büchner funnel and the zinc–copper couple was washed with water (2×5 mL), acetone (2×5 mL), ether (5 mL). The resulting dark-gray powder was dried at 100 °C under vacuum for 6 h and then stored under argon.

General Procedure for the Formation of 2,2-Dichloro-Cyclobutanones 127a-j

A solution of trichloroacetyl chloride (1.12 mL, 10.0 mmol, 2.0 equiv) and phosphorus oxychloride (0.51 mL, 5.5 mmol, 1.1 equiv) in ether (5 mL) was added dropwise to a solution of the vinyl derivative **126a-j** (5.0 mmol, 1.0 equiv) and zinc-copper couple (0.98 g, 15.0 mmol, 3.0 equiv) in ether (10 mL). The resulting solution was heated at 40 °C for 2 h and then stirred at room temperature overnight. The resulting mixture was filtered over Celite and the Celite was washed with ether (12 mL). Hexane (40 mL) was added to the filtrate, which was then gently stirred to help zinc dichloride to precipitate. The supernatant solution was successively washed with water (20 mL), a saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under vacuum to afford pure **127a-j** which were used directly in the next step without further purification.

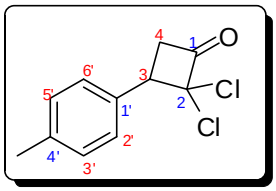
2,2-Dichloro-3-phenylcyclobutanone 127a



$C_{10}H_8Cl_2O$
Mol. Wt.: 215,08

127a: (1.042 g, 97%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.55 (dd, *J* = 17.6, 10.3 Hz, 1H, 4-H), 3.73 (dd, *J* = 17.6, 10.3 Hz, 1H, 4-H'), 4.26 (t, *J* = 10.3 Hz, 1H, 3-H), 7.33 (d, *J* = 7.2 Hz, 2H, 2'-H, 6'-H), 7.40 (t, *J* = 7.2 Hz, 1H, 4'-H), 7.45 (t, *J* = 7.2 Hz, 2H, 3'-H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 45.7 (CH_2-4), 50.5 (CH-3), 89.5 (C-2), 128.0 (2×CH-2',6'), 128.3 (CH-4'), 128.6 (2×CH-3',5'), 134.4 (C-1'), 191.9 (C=O-1) in agreement with the literature data.[124a]

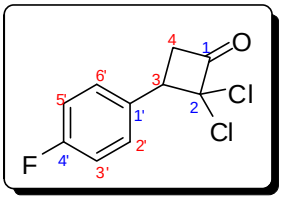
2,2-Dichloro-3-(4'-toluyl)cyclobutanone 127b



$C_{11}H_{10}Cl_2O$
Mol. Wt.: 229.10

127b: (1.040 g, 91%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.33 (s, 3H, CH_3), 3.41 (dd, *J* = 17.7, 10.3 Hz, 1H, 4-H), 3.59 (dd, *J* = 17.7, 10.3 Hz, 1H, 4-H'), 4.13 (t, *J* = 10.3 Hz, 1H, 3-H), 7.14 (d, *J* = 8.2 Hz, 2H, 3'-H, 5'-H), 7.18 (dd, *J* = 8.2 Hz, 2H, 2'-H, 6'-H) in agreement with the literature data.[156]

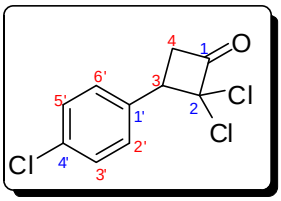
2,2-Dichloro-3-(4'-fluorophenyl)cyclobutanone 127c



$C_{10}H_7Cl_2FO$
Mol. Wt.: 233.07

127c: (1.092 g, 94%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.75 (dd, *J* = 17.7, 10.3 Hz, 1H, 4-H), 3.55 (dd, *J* = 17.7, 10.3 Hz, 1H, 4-H'), 4.10 (t, *J* = 10.3 Hz, 1H, 3-H), 6.97 (t, *J* = 8.7 Hz, 2H, 3'-H, 5'-H), 7.17 (dd, *J* = 8.7, 5.2 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 45.8 (CH_2-4), 49.8 (CH-3), 89.4 (C-2), 115.5 (d, *J* = 21.6 Hz, 2×CH-3',5'), 129.7 (d, *J* = 8.2 Hz, 2×CH-2',6'), 130.2 (d, *J* = 3.3 Hz, C-1'), 162.4 (d, *J* = 247.4 Hz, CF-4'), 191.5 (C=O-1); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –113.2 (s).

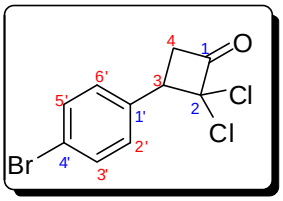
2,2-Dichloro-3-(4'-chlorophenyl)cyclobutanone 127d



$C_{10}H_7Cl_3O$
Mol. Wt.: 249.52

127d: (1.121 g, 90%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.49 (dd, *J* = 17.7, 10.3 Hz, 1H, 4-H), 3.61 (dd, *J* = 17.7, 10.3 Hz, 1H, 4-H'), 4.14 (t, *J* = 10.3 Hz, 1H, 3-H), 7.18 (d, *J* = 8.9 Hz, 2H, 3'-H, 5'-H), 7.34 (dd, *J* = 8.9 Hz, 2H, 2'-H, 6'-H) in agreement with the literature data.[157]

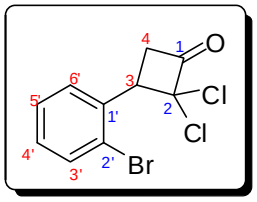
2,2-Dichloro-3-(4'-bromophenyl)cyclobutanone 127e



$C_{10}H_7BrCl_2O$
Mol. Wt.: 293.97

127e: (1.352 g, 92%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.55 (dd, *J* = 17.6, 10.3 Hz, 1H, 4-H), 3.67 (dd, *J* = 17.6, 10.3 Hz, 1H, 4-H'), 4.19 (t, *J* = 10.3 Hz, 1H, 3-H), 7.19 (d, *J* = 8.5 Hz, 2H, 3'-H, 5'-H), 7.56 (dd, *J* = 8.5 Hz, 2H, 2'-H, 6'-H) in agreement with the literature data.[158]

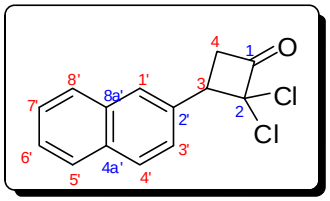
2,2-Dichloro-3-(2'-bromophenyl)cyclobutanone 127f



$C_{10}H_7BrCl_2O$
Mol. Wt.: 293.97

127f: (1.314 g, 94%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.60 (d, *J* = 9.8 Hz, 2H, 4H), 4.67 (t, *J* = 9.8 Hz, 1H, 3-H), 7.13 (td, *J* = 7.7, 1,5 Hz, 1H, 4'-H), 7.17 (dd, *J* = 7.7, 1,5 Hz, 1H, 6'-H), 7.28 (td, *J* = 7.7, 1.1 Hz, 1H, 5'-H), 7.58 (dd, *J* = 7.7, 1.1 Hz, 1H, 3'-H). Used without further purification.

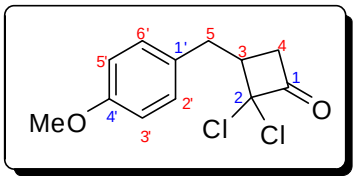
2,2-Dichloro-3-(2'-naphthyl)cyclobutanone 127g



$C_{14}H_{10}Cl_2O$
Mol. Wt.: 265.13

127g (547 mg, 41%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.35 (dd, *J* = 17.7, 10.3 Hz, 1H, 4-H), 3.63 (dd, *J* = 17.7, 10.3 Hz, 1H, 4-H'), 4.17 (t, *J* = 10.3 Hz, 1H, 3-H), 7.33 (dd, *J* = 8.5, 1.8 Hz, 1H, 3'-H), 7.37-7.45 (m, 2H, 6'-H, 7'-H), 7.63-7.67 (m, 1H, 1'-H), 7.72-7.80 (m, 3H, 4'-H, 8'-H, 5'-H). Used without further purification.

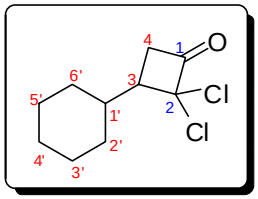
2,2-Dichloro-3-(4'-methoxybenzyl)cyclobutanone 127h



$C_{12}H_{12}Cl_2O_2$
Mol. Wt.: 259.13

127h (1.287 g, 99%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.75 (dd, *J* = 14.0, 8.7 Hz, 1H, 4-H), 3.03 (dd, *J* = 16.7, 8.0 Hz, 1H, 4-H'), 3.10-3.30 (m, 3H, CH_2CH), 3.77 (s, 3H, CH_3O), 6.86 (d, *J* = 8.7 Hz, 2H, 3'-H, 5'-H), 7.15 (dd, *J* = 8.7, 2H, 2'-H, 6'-H). Used without further purification.

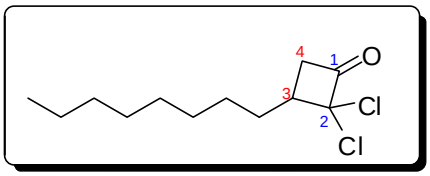
2,2-Dichloro-3-(cyclohexyl)cyclobutanone 127i



$C_{10}H_{14}Cl_2O$
Mol. Wt.: 221.12

127i: (1.062 g, 96%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.92-1.35 (m, 5H), 1.51-1.79 (m, 5H), 2.00-2.12 (m, 1H, 1'-H), 2.54 (q, *J* = 10.3 Hz, 1H, 3-H), 3.03 (dd, *J* = 17.4, 10.3 Hz, 1H, 4-H), 3.13 (dd, *J* = 17.4, 10.3 Hz, 1H, 4-H'). Used without further purification.

2,2-Dichloro-3-octylcyclobutanone 127j



$C_{12}H_{20}Cl_2O$
Mol. Wt.: 251.19

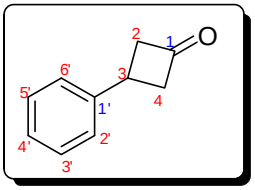
127j (1.062 g, 85%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 6.8 Hz, 3H, CH_3CH_2), 1.16-1.46 (m, 12H, 6×CH_2), 1.50-1.62 (m, 1H, CH_2CH_2CH), 1.80-1.90 (m, 1H, CH_2CH_2'CH),

2.78-2.87 (m, 1H, 3-H), 2.91 (dd, *J* = 17.1, 9.2 Hz, 1H, 4-H), 3.30 (dd, *J* = 17.1, 9.2 Hz, 1H, 4-H') in agreement with the literature data.[159]

General Procedure for the Formation of Cyclobutanones 128a-j

A mixture of dichloro ketone **127a-j** (4 mmol, 1.0 equiv) and zinc dust (1.05 g, 16 mmol, 4.0 equiv) in acetic acid (15 mL) was stirred at room temperature for 2 h and then refluxed for 5 h. The resulting mixture was diluted with water (20 mL) and extracted with ether (2×30 mL). The organic phase was washed successively with a saturated solution of aqueous $NaHCO_3$ (3×20 mL), water (30 mL) and brine (30 mL), and dried over $MgSO_4$ and concentrated under vacuum. The crude material was then purified by flash chromatography on silica gel (20 g) with a mixture of petroleum ether and ethyl acetate (5:1) to afford **128a-j** as colourless oils.

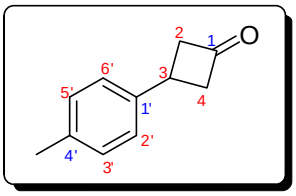
3-Phenylcyclobutanone 128a



$C_{10}H_{10}O$
Mol. Wt.: 146,19

128a: (503 mg, 86%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.10-3.19 (m, 2H, 2-H, 4-H), 3.34-3.43 (m, 2H, 2-H', 4-H'), 3.57 (pent, *J* = 8.2 Hz, 1H, 3-H), 7.16 (t, *J* = 7.1 Hz, 1H, 4'-H), 7.20 (d, *J* = 7.1 Hz, 2H, 2'-H, 6'-H), 7.26 (t, *J* = 7.1 Hz, 2H, 3'-H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.3 (CH-3), 54.6 (2×CH_2-2,4), 126.4 (2×CH-2',6'), 126.5 (CH-4'), 128.6 (2×CH-3',5'), 143.5 (C-1'), 206.5 (C=O-1) in agreement with the literature data.[160]

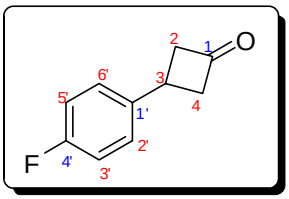
3-(4'-Toluyl)cyclobutanone 128b



$C_{11}H_{12}O$
Mol. Wt.: 160.21

128b (205 mg, 32%): **IR** (NaCl) ν 2922 (w, C-H), 1783 (s, C=O), 1608 (m, C=Car), 1570 (m, C=Car), 1515 (m, C=Car), 1161 (m), 1019 (m), 813 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.28 (s, 3H, CH_3), 3.08-3.17 (m, 2H, 2-H, 4-H), 3.33-3.42 (m, 2H, 2-H', 4-H'), 3.54 (pent, *J* = 8.6 Hz, 1H, 3-H), 7.09 (d, *J* = 8.4 Hz, 2H, 3'-H, 5'-H), 7.12 (dd, *J* = 8.4 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.7 (CH_3), 27.7 (CH-3), 54.4 (2×CH_2-2,4), 126.1 (2×CH-2',6'), 129.0 (2×CH-3',5'), 135.8 (C-4'), 140.3 (C-1'), 206.5 (C=O-1); **MS** (EI) *m/z* (%) 160 ($M^{\bullet+}$, 12), 118 ($M^{\bullet+}$-CH_2C=O, 100), 91 ($M^{\bullet+}$-C_3H_5C=O, 26), 83 (32); **HRMS** (EI) 160.0889 ($C_{11}H_{12}O$ requires 160.0888).

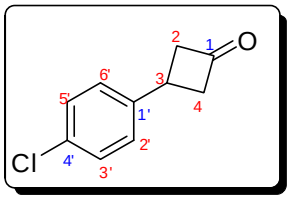
3-(4'-Fluorophenyl)cyclobutanone 128c



$C_{10}H_9FO$
Mol. Wt.: 164.18

128c: (368 mg, 56%): **IR** (NaCl) ν 2977 (w, C-H), 1785 (s, C=O), 1604 (m, C=Car), 1511 (m, C=Car), 1431 (m, C=Car), 1226 (s), 1103 (m, C-F), 829 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.07-3.18 (m, 2H, 2-H, 4-H), 3.35-3.47 (m, 2H, 2-H', 4-H'), 3.58 (pent, *J* = 8.3 Hz, 1H, 3-H), 6.95 (t, *J* = 8.6 Hz, 2H, 3'-H, 5'-H), 7.19 (dd, *J* = 8.6, 5.4 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 27.5 (CH-3), 54.5 (2×CH_2-2,4), 115.2 (d, *J* = 21.3 Hz, 2×CH-3',5'), 127.8 (d, *J* = 8.0 Hz, 2×CH-2',6'), 139.1 (d, *J* = 3.1 Hz, C-1'), 161.3 (d, *J* = 244.7 Hz, CF-4'), 206.0 (C=O-1); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –116.3 (s); **MS** (EI) *m/z* (%) 164 ($M^{\bullet+}$, 4), 122 ($M^{\bullet+}$-CH_2C=O, 100), 84 (61), 49 (86); **HRMS** (EI) 164.0638 ($C_{10}H_9FO$ requires 164.0637).

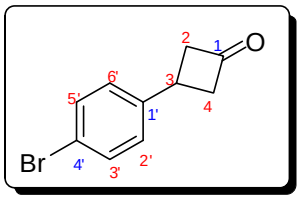
3-(4'-Chlorophenyl)cyclobutanone 128d



$C_{10}H_9ClO$
Mol. Wt.: 180.63

128d: (332 mg, 46%): **IR** (NaCl) ν 2974 (w, C-H), 1786 (s, C=O), 1593 (m, C=Car), 1493 (m, C=Car), 1092 (s, C-Cl), 1013 (m), 821 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.13-3.23 (m, 2H, 2-H, 4-H), 3.42-3.53 (m, 2H, 2-H', 4-H'), 3.63 (pent, *J* = 8.3 Hz, 1H, 3-H), 7.21 (d, *J* = 8.4 Hz, 2H, 2'-H, 6'-H), 7.29 (d, *J* = 8.4 Hz, 2H, 3'-H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 27.7 (CH-3), 54.5 (2×CH_2-2,4), 127.7 (2×CH-3',5'), 128.5 (2×CH-2',6'), 132.1 (C-4'), 141.9 (C-1), 205.8 (C=O-1) in agreement with the literature data.[161]

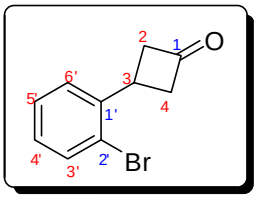
3-(4'-Bromophenyl)cyclobutanone 128e



$C_{10}H_9BrO$
Mol. Wt.: 225.08

128e (459 mg, 51%): **IR** (NaCl) ν 2976 (w, C-H), 1786 (s, C=O), 1589 (m, C=Car), 1489 (m, C=Car), 1073 (s), 1009 (m), 817 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.16-3.25 (m, 2H, 2-H, 4-H), 3.45-3.55 (m, 2H, 2-H', 4-H'), 3.64 (pent, *J* = 8.4 Hz, 1H, 3-H), 7.17 (d, *J* = 8.3 Hz, 2H, 2'-H, 6'-H), 7.47 (d, *J* = 8.3 Hz, 2H, 3'-H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.0 (CH-3), 54.6 (2×CH_2-2,4), 120.4 (C-4'), 128.2 (2×CH-2',6'), 131.7 (2×CH-3',5'), 142.5 (C-1'), 206.0 (C=O-1); **MS** (EI) *m/z* (%) 224/226 ($M^{\bullet+}$, 7/7), 183 ($M^{\bullet+}$-CH_2C=O, 100), 115 (17), 103 ($M^{\bullet+}$-CH_2C=O-Br, 60), 77 (42); **HRMS** (EI) 223.9835 ($C_{10}H_9{}^{79}BrO$ requires 223.9837).

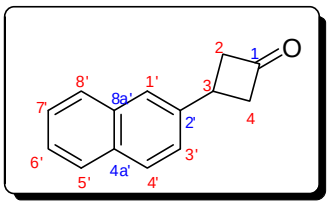
3-(2'-Bromophenyl)cyclobutanone 128f



$C_{10}H_9BrO$
Mol. Wt.: 225.08

128f (468 mg, 52%): **IR** (NaCl) ν 2981 (w, C-H), 1786 (s, C=O), 1590 (m, C=Car), 1566 (m, C=Car), 1472 (m, C=Car), 1102 (s), 1026 (s), 754 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.18-3.27 (m, 2H, 2-H, 4-H), 3.49-3.58 (m, 2H, 2-H', 4-H'), 3.95 (pent, *J* = 8.3 Hz, 1H, 3-H), 7.14 (ddd, *J* = 8.4, 6.1, 3.0 Hz, 1H, 4'-H), 7.32-7.38 (m, 2H, 5'-H, 6'-H), 7.61 (d, *J* = 8.4 Hz, 1H, 3'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.9 (CH-3), 52.9 (2×CH_2-2,4), 124.7 (C-2'), 126.4 (CH-5'), 127.5 (CH-4'), 128.2 (CH-6'), 133.0 (CH-3'), 141.5 (C-1'), 205.9 (C=O-1); **MS** (CI-Isobutane) *m/z* (%) 225/227 ($M^{\bullet+}$, 100/98), 183 ($M^{\bullet+}$-CH_2C=O, 30), 147 (28), 103 ($M^{\bullet+}$-CH_2C=O-Br, 25); **HRMS** (CI-Isobutane) 224.9912 ($C_{10}H_{10}{}^{79}BrO$ $(M+H)^+$ requires 224.9915).

3-(2'-Naphthyl)cyclobutanone 128g

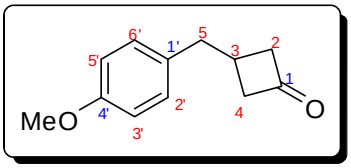


$C_{14}H_{12}O$
Mol. Wt.: 196.24

128g: (60.8 mg, 15%): **IR** (NaCl) ν 3050 (w, Car-H), 1781 (s, C=O), 1623 (m, C=Car), 1511 (m, C=Car), 1430 (m, C=Car), 1226 (s), 817 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.22-3.32 (m, 2H, 2a-H, 4a-H), 3.43-3.52 (m, 2H, 2-H', 4-H'), 3.74 (pent, *J* = 8.3 Hz, 1H, 3-H), 7.33 (dd, *J* = 8.5, 1.8 Hz, 1H, 3'-H), 7.37-7.45 (m, 2H, 6'-H, 7'-H), 7.64 (br s, 1H, 1'-H), 7.72-7.80 (m, 3H, 4'-H, 8'-H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.5 (CH-3), 54.5 (2×CH_2-2,4), 124.7 (CH-1'), 124.8 (CH-3'), 125.7 (CH-6'), 126.3 (CH-7'), 127.48 (CH-4'), 127.54 (CH-8'), 128.5 (CH-5'), 132.1 (C-8a'), 133.2 (C-4a'), 140.7 (C-2'), 206.6

(C=O-1); **MS** (CI-Isobutane) *m/z* (%) 197 ($(M+H)^+$, 95), 154 ($(M+H)^+$-CH_2C=O, 12), 85 (72), 69 (100); **HRMS** (CI-isobutane) 197.0967 ($C_{14}H_{13}O$ $(M+H)^+$ requires 197.0966).

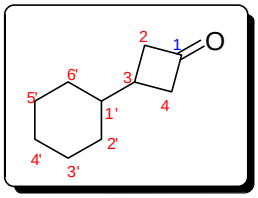
3-(4'-Methoxybenzyl)cyclobutanone 128h



$C_{12}H_{14}O_2$
Mol. Wt.: 190.24

128h: (400 mg, 43%): **IR** (NaCl) ν 2957 (w, Car-H), 1777 (s, C=O), 1612 (m, C=Car), 1590 (m, C=Car), 1512 (m, C=Car), 1247 (s, C-O), 836 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.51-2.61 (m, 1H, 3-H), 2.62-2.71 (m, 2H, 2-H, 4-H), 2.75 (d, *J* = 7.5 Hz, 2H, CH_2CH), 2.96-3.05 (m, 2H, 2-H', 4-H'), 3.70 (s, 3H, CH_3O), 6.80 (d, *J* = 8.6 Hz, 2H, 3'-H, 5'-H), 7.05 (d, *J* = 8.6 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 24.7 (CH-3), 40.4 (CH_2CH), 51.6 (2×CH_2-2,4), 54.7 (CH_3), 113.5 (2×CH-3',5'), 129.0 (2×CH-2',6'), 131.6 (C-1'), 157.7 (C-4'), 207.1 (C=O-1); **MS** (EI) *m/z* (%) 190 ($M^{\bullet+}$, 56), 148 ($M^{\bullet+}$-CH_2C=O, 96), 121 ($M^{\bullet+}$-C_3H_5C=O, 100), 77 (32); **HRMS** (EI) 190.0997 ($C_{12}H_{14}O_2$ requires 190.0994).

3-(Cyclohexyl)cyclobutanone 128i

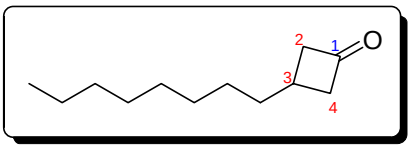


$C_{10}H_{16}O$
Mol. Wt.: 152.23

128i: (371 mg, 51%): **IR** (NaCl) ν 2923 (s, C-H), 2851 (s, C-H), 1786 (s, C=O), 1448 (m, CH_2), 1108 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.78-0.92 (m, 2H), 1.02-1.22 (m, 4H), 1.54-1.74 (m, 5H), 1.90-2.03 (m, 1H, 3-H), 2.60-2.70 (m, 2H, 2-H, 4-H), 2.89-3.00 (m, 2H, 2-H', 4-H'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 25.7 (2× CH_2), 25.9 (CH_2-4'), 29.6 (CH-3), 30.6 (2×CH_2), 43.4 (CH-1'), 50.5 (2×CH_2-2,4), 207.9 (C=O-1); **MS** (CI-Isobutane) *m/z* (%) 153

($(M+H)^+$, 100), 135 ($(M+H)^+$-H_2O, 15), 71 (10); **HRMS** (CI-Isobutane) 153.1281 ($C_{10}H_{17}O$ $(M+H)^+$ requires 153.1279).

3-Octylcyclobutanone 128j



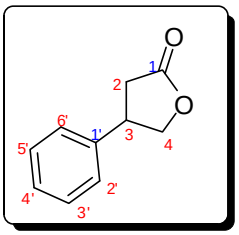
$C_{12}H_{22}O$
Mol. Wt.: 182.30

128j: (354 mg, 46%): **IR** (NaCl) ν 2923 (s, C-H), 2854 (m, C-H), 1785 (s, C=O), 1461 (w), 1380 (w), 1095 (w) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 6.8 Hz, 3H, CH_3CH_2), 1.16-1.31 (m, 12H, 6×CH_2), 1.48-1.56 (m, 2H, CH_2CH), 2.29 (pent, *J* = 7.5, 1.2 Hz, 1H, 3-H), 2.55-2.65 (m, 2H, 2-H, 4-H), 3.01-3.12 (m, 2H, 2-H', 4-H'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9 (CH_3CH_2), 22.5 (CH_2), 23.7 (CH-3), 28.1 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.7 (CH_2), 36.2 (CH_2CH), 52.3 (2×CH_2-2,4), 208.1 (C=O-1); **MS** (CI-Isobutane) *m/z* (%) 183 ($(M+H)^+$, 100), 165 ($(M+H)^+$-H_2O, 9), 71 (18); **HRMS** (CI-Isobutane) 183.1747 ($C_{12}H_{23}O$ $(M+H)^+$ requires 183.1749).

General Procedure for the Formation of γ-Butyrolactones 129a-j

A mixture of dichlorobis(benzonitrile)palladium(II) (9.5 mg, 0.025 mmol, 5.0 mol%) and ligand (–)-**41c** (13 mg, 0.0275 mmol, 5.5 mol%) in THF (2 mL) was stirred at room temperature for 1 h. Silver hexafluoroantimonate (17 mg, 0.05 mmol, 10 mol%) was then added and the reaction mixture was stirred for an additional 1 h. The mixture was then filtered over a Celite pad, cyclobutanone **128a-j** (0.5 mmol, 1 equiv) was then added to the filtrate, and the solution was cooled to -40 °C. Urea-hydrogen peroxide (61 mg, 0.65 mmol, 1.3 equiv) was then added and the mixture was stirred at -40 °C overnight. Concentration *in vacuo*, followed by flash chromatography on silica gel (15 g), using a mixture of petroleum ether and ethyl acetate (9:1) afforded pure γ-butyrolactones **129a-j**.

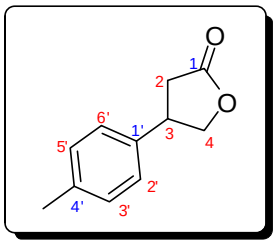
(*S*)-(+)-3-Phenyl-γ-butyrolactone (*S*)-(+)-129a



$C_{10}H_{10}O_2$
Mol. Wt.: 162.19

(+)-129a: (78.6 mg, 97%): **$[\alpha]_D^{24}$** +38.4 (*c* 1.0, $CHCl_3$, 81% *ee*), [lit.[162] gives $[\alpha]_D$ +46.0 (*c* 0.95, $CHCl_3$, 96% *ee*)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.58 (dd, *J* = 17.5, 8.9 Hz, 1H, 2-H), 2.83 (dd, *J* = 17.5, 8.9 Hz, 1H, 2-H'), 3.70 (pent, *J* = 8.9 Hz, 1H, 3-H), 4.18 (dd, *J* = 8.9, 8.1 Hz, 1H, 4-H), 4.57 (dd, *J* = 8.9, 8.1 Hz, 1H, 4-H'), 7.14 (d, *J* = 7.3 Hz, 2H, 2'-H, 6'-H), 7.21 (t, *J* = 7.3 Hz, 1H, 4'-H), 7.28 (t, *J* = 7.3 Hz, 2H, 3'-H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 35.6 (CH_2-2), 41.0 (CH-3), 74.0 (CH_2-4), 126.6 (2×CH-2',6'), 127.6 (CH-4'), 129.1 (2×CH-3',5'), 139.3 (C-1'), 176.3 (C=O-1) in agreement with the literature data;[163] **Chiral GC** (Supelco α-DEX), carrier gas, He (flow 2 mL.min^{-1}), injection temp 200 °C, initial column temp 110 °C for 3 min, rate 1deg.min^{-1}, final temp 220°C, t_R = 56.11 min, t_S = 56.58 min.

(*S*)-(+)-3-(4'-Toluyl)-γ-butyrolactone (*S*)-(+)-129b

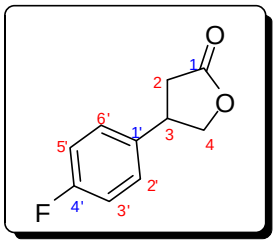


$C_{11}H_{12}O_2$
Mol. Wt.: 176.21

(+)-129b: (81.9 mg, 93%): **$[\alpha]_D^{24}$** +36.9 (*c* 1.0, $CHCl_3$, 75% *ee*); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 2.65 (dd, *J* = 17.5, 8.9 Hz, 1H, 2-H), 2.90 (dd, *J* = 17.5, 8.9 Hz, 1H, 2-H'), 3.75 (pent, *J* = 8.9 Hz, 1H, 3-H), 4.23 (dd, *J* = 8.9, 8.0 Hz, 1H, 4-H), 4.64 (dd, *J* = 8.9, 8.0 Hz, 1H, 4-H'), 7.11 (d, *J* = 8.1 Hz, 2H, 3'-H, 5'-H), 7.17 (dd, *J* = 8.1 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 35.7 (CH_2-2), 40.8 (CH-3), 74.1 (CH_2-4), 126.5 (2×CH-3',5'), 129.7 (2×CH-2',6'), 136.3 (C-1'), 137.4 (C-4'), 176.4 (C=O-1) in agreement

with the literature data;[164] **Chiral GC** (Supelco α-DEX), carrier gas, He (flow 2 mL.min^{-1}), injection temp 200 °C, initial column temp 110 °C for 3 min, rate 1 deg.min^{-1}, final temp 220 °C, t_R = 66.18 min, t_S = 66.67 min.

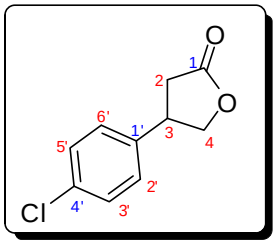
(+)-3-(4'-Fluorophenyl)-γ-butyrolactone (+)-129c



$C_{10}H_9FO_2$
Mol. Wt.: 180.18

(+)-129c: (86.5 mg, 96%): **[α]$_D^{24}$** +29.8 (*c* 1.0, $CHCl_3$, 72% *ee*); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.61 (dd, *J* = 17.5, 8.9 Hz, 1H, 2-H), 2.90 (dd, *J* = 17.5, 8.9 Hz, 1H, 2-H'), 3.77 (pent, *J* = 8.9 Hz, 1H, 3-H), 4.21 (t, *J* = 8.9 Hz, 1H, 4-H), 4.64 (t, *J* = 8.9 Hz, 1H, 4-H'), 7.04 (t, *J* = 8.6 Hz, 2H, 3'-H, 5'-H), 7.20 (dd, *J* = 8.6, 5.2 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 35.6 (CH_2-2), 40.2 (CH-3), 73.8 (CH_2-4), 115.9 (d, *J* = 21.5 Hz, 2×CH-3',5'), 128.2 (d, *J* = 8.1 Hz, 2×CH-2',6'), 135.1 (d, *J* = 3.2 Hz, C-1'), 161.9 (d, *J* = 246.4 Hz, C-4'), 176.1 (C=O-1); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –114.5 (s) in agreement with the literature data;[163] **Chiral GC** (Supelco α-DEX), carrier gas, He (flow 2 mL.min^{-1}), injection temp 200 °C, initial column temp 110 °C for 3 min, rate 1 deg.min^{-1}, final temp 220°C, t_{minor} = 58.06 min, t_{major} = 58.64 min.

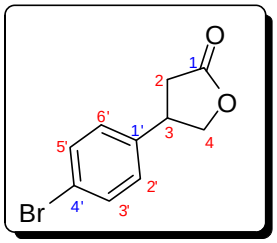
(*S*)-(+)-3-(4'-Chlorophenyl)-γ-butyrolactone (*S*)-(+)-129d



$C_{10}H_9ClO_2$
Mol. Wt.: 196.63

(+)-129d: (92.6 mg, 94%): **$[\alpha]_D^{24}$** +36.5 (*c* 1.0, $CHCl_3$, 73% *ee*); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.62 (dd, *J* = 17.5, 8.8 Hz, 1H, 2-H), 2.93 (dd, *J* = 17.5, 8.8 Hz, 1H, 2-H'), 3.77 (pent, *J* = 8.8 Hz, 1H, 3-H), 4.23 (dd, *J* = 8.8, 7.8 Hz, 1H, 4-H), 4.65 (dd, *J* = 8.8, 7.8 Hz, 1H, 4-H'), 7.17 (d, *J* = 8.3 Hz, 2H, 2'-H, 6'-H), 7.34 (d, *J* = 8.3 Hz, 2H, 3'-H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 35.6 (CH_2-2), 40.5 (CH-3), 73.7 (CH_2-4), 128.0 (2×CH-2',6'), 129.2 (2×CH-3',5'), 133.5 (C-4'), 137.9 (C-1'), 175.8 (C=O-1); in agreement with the literature data;[163] **Chiral GC** (Supelco α-DEX), carrier gas, He (flow 2 mL.min^{-1}), injection temp 200 °C, initial column temp 110 °C for 3 min, rate 1 deg.min^{-1}, final temp 220°C, t_R = 81.43 min, t_S = 81.90 min.

(+)-3-(4'-Bromophenyl)-γ-butyrolactone (+)-129e

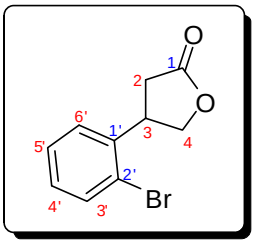


$C_{10}H_9BrO_2$
Mol. Wt.: 241.08

(+)-129e: (114.5 mg, 95%): **mp** 60-62 °C (hexane); **$[\alpha]_D^{25}$** +28.6 (*c* 1.0, $CHCl_3$, 76% *ee*); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.61 (dd, *J* = 17.5, 8.8 Hz, 1H, 2-H), 2.92 (dd, *J* = 17.5, 8.8 Hz, 1H, 2-H'), 3.75 (pent, *J* = 8.8 Hz, 1H, 3-H), 4.22 (dd, *J* = 8.8, 7.7 Hz, 1H, 4-H), 4.65 (dd, *J* = 8.8, 7.7 Hz, 1H, 4-H'), 7.11 (d, *J* = 8.3 Hz, 2H, 2'-H, 6'-H), 7.48 (d, *J* = 8.3 Hz, 2H, 3'-H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 35.5 (CH_2-2), 40.5 (CH-3), 73.6 (CH_2-4), 121.5 (C-4'), 128.3 (2×CH-2',6'), 132.1 (2×CH-3',5'), 138.4 (C-1'), 175.8 (C=O-1); **MS** (EI) *m/z* (%)

240/242 ($M^{\bullet+}$, 31/32), 183 ($M^{\bullet+}$-CH_2CO_2, 100), 103 ($M^{\bullet+}$-CH_2CO_2-Br, 40); **HRMS** (EI) 239.9792 ($C_{10}H_9{}^{79}BrO_2$ requires 239.9786); **Chiral HPLC** (Chiracel IB, 0.75 mL.min^{-1}, hexane/2-propanol, 92:8) t_{major} = 33.4 min, t_{minor} = 39.1 min after derivatisation into the hydroxyl benzylamide derivative.[64b]

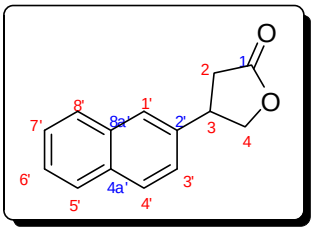
(+)-3-(2'-Bromophenyl)-γ-butyrolactone (+)-129f



$C_{10}H_9BrO_2$
Mol. Wt.: 241.08

(+)-129f: (110.9 mg, 92%): **mp** 41-43 °C (hexane); **[α]$_D^{25}$** +26.6 (*c* 1.0, $CHCl_3$, 70% *ee*); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.67 (dd, *J* = 17.6, 8.7 Hz, 1H, 2-H), 2.98 (dd, *J* = 17.6, 8.7 Hz, 1H, 2-H'), 4.23 (pent, *J* = 8.7 Hz, 1H, 3-H), 4.31 (dd, *J* = 8.7, 6.7 Hz, 1H, 4-H), 4.71 (dd, *J* = 8.7, 6.7 Hz, 1H, 4-H'), 7.17 (td, *J* = 7.7, 1.7 Hz, 1H, 4'-H), 7.28 (dd, *J* = 7.7, 1.7 Hz, 1H, 6'-H), 7.35 (td, *J* = 7.7, 1.2 Hz, 1H, 5'-H), 7.61 (dd, *J* = 7.7, 1.2 Hz, 1H, 3'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 34.6 (CH_2-2), 40.0 (CH-3), 72.8 (CH_2-4), 124.3 (C-2'), 126.6 (CH-6'), 128.2 (CH-5'), 129.1 (CH-4'), 133.4 (CH-3'), 138.6 (C-1'), 176.0 (C=O-1); **MS** (EI) *m/z* (%) 240/242 ($M^{\bullet+}$, 29/28), 183 ($M^{\bullet+}$-CH_2CO_2, 100), 103 ($M^{\bullet+}$-CH_2CO_2-Br, 67); **HRMS** (EI) 239.9787 ($C_{10}H_9{}^{79}BrO_2$ requires 239.9786); **Chiral HPLC** (Chiracel OJ-H, 0.75 mL.min^{-1}, hexane/2-propanol, 75:25) t_{minor} = 9.1 min, t_{major} = 10.4 min after derivatisation into the hydroxyl benzylamide derivative.[64b]

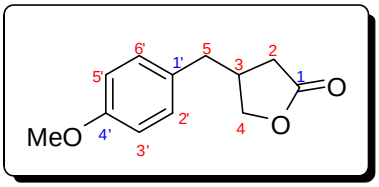
(+)-3-(2'-Naphthyl)-γ-butyrolactone (+)-129g



$C_{14}H_{12}O_2$
Mol. Wt.: 212.24

(+)-129g: (88.1 mg, 83%): **$[\alpha]_D^{24}$** +43.6 (*c* 1.0, $CHCl_3$, 71% *ee*); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.79 (dd, *J* = 17.5, 8.9 Hz, 1H, 2-H), 3.00 (dd, *J* = 17.5, 8.9 Hz, 1H, 2-H), 3.95 (pent, *J* = 8.9 Hz, 1H, 3-H), 4.37 (dd, *J* = 8.9, 7.9 Hz, 1H, 4-H'), 4.74 (dd, *J* = 8.9, 7.9 Hz, 1H, 4-H'), 7.34 (dd, *J* = 8.5, 1.8 Hz, 1H, 3'-H), 7.47-7.55 (m, 2H, 7'-H, 6'-H), 7.67 (br s, 1H, 1'-H), 7.80-7.90 (m, 3H, 4'-H, 8'-H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 35.6 (CH_2-2), 41.1 (CH-3), 73.9 (CH_2-4), 124.4 (CH-3'), 125.4 (CH-1'), 126.2 (CH-6'), 126.6 (CH-7'), 127.60 (CH-4'), 127.63 (CH-8'), 129.0 (CH-5'), 132.6 (C-8a'), 133.3 (C-4a'), 136.6 (C-2'), 176.4 (C=O-1) in agreement with the literature data;[163] **Chiral HPLC** (Chiracel IB, 0.75 mL.min^{-1}, hexane/2-propanol, 90:10) t_{major} = 31.5 min, t_{minor} = 34.7 min after derivatisation into the hydroxyl benzylamide derivative.[64b]

(*R*)-(+)-3-(4'-Methoxybenzyl)-γ-butyrolactone (*R*)-(+)-129h

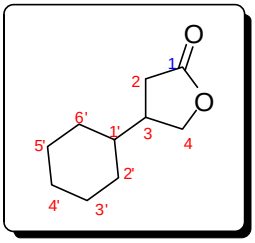


$C_{12}H_{14}O_3$
Mol. Wt.: 206.24

(+)-129h: (93.8 mg, 91%): **$[\alpha]_D^{23}$** +3.2 (*c* 0.5, $CHCl_3$, 58% *ee*), [lit.[125] gives $[\alpha]_D$ +5.4 (*c* 6.8, $CHCl_3$, 98% *ee*)]; **^{1}H NMR** (400 MHz, $CDCl_3$) 2.56 (dd, *J* = 17.5, 8.0 Hz, 1H, 2-H), 2.57 (dd, *J* = 17.5, 8.0 Hz, 1H, 2-H'), 2.70 (dd, *J* = 7.6, 3.3 Hz, 2H, CH_2CH), 2.72-2.86 (m, 1H, 3-H), 3.78 (s, 3H, CH_3O), 4.00 (dd, *J* = 9.1, 6.5 Hz, 1H, 4-H), 4.30 (dd, *J* = 9.1, 6.5 Hz, 1H, 4-H'), 6.84 (d, *J* = 8.6 Hz, 2H, 3'-H, 5'-H), 7.06 (d, *J* = 8.6 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 34.1 (CH_2-2), 37.2 (CH-3), 37.9 (CH_2CH), 55.2 (CH_3), 72.5 (CH_2-4),

114.0 (2×CH-3',5'), 129.5 (2×CH-2',6'), 130.1 (C-1'), 158.3 (C-4'), 176.8 (C=O-1) in agreement with the literature data. [64b]

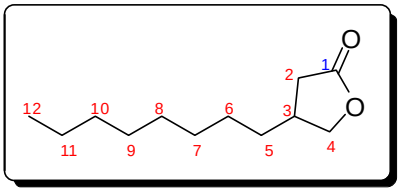
(–)-3-Cyclohexyl-γ-butyrolactone (–)-129j



$C_{10}H_{16}O_2$
Mol. Wt.: 168.23

(–)-129j: (74.8 mg, 89%): $[\alpha]_D^{24}$ –6.8 (*c* 0.5, $CHCl_3$, 65% *ee*); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.89-1.02 (m, 2H), 1.09-1.35 (m, 4H), 1.56-1.77 (m, 5H), 2.20 (dd, *J* = 16.6, 8.0 Hz, 1H, 2-H), 2.30 (pent, *J* = 9.8 Hz, 1H, 3-H), 2.53 (dd, *J* = 16.6, 8.0 Hz, 1H, 2-H'), 3.96 (dd, *J* = 8.9, 8.0 Hz, 1H, 4-H), 4.39 (dd, *J* = 8.9, 8.0 Hz, 1H, 4-H'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 25.7 (CH_2), 25.8 (CH_2), 26.1 (CH_2), 30.4 (CH_2), 31.1 (CH_2), 32.7 (CH_2-2), 41.3 (CH-1'), 41.6 (CH-3), 72.1 (CH_2-4), 177.3 (C=O-1); **MS** (EI) *m/z* (%) 168 ($M^{\bullet+}$, 49), 150 (21), 137 (66), 86 (100), 83 (95); **HRMS** (EI) 168.1153 ($C_{10}H_{16}O_2$ requires 168.1150); **Chiral HPLC** (Chiracel IB, 0.75 mL.min^{-1}, hexane/2-propanol, 90:10) t_{major} = 14.0 min, t_{minor} = 17.5 min after derivatisation into the hydroxyl benzylamide derivative. [64b]

(*R*)-(+)-3-Octyl-γ-butyrolactone (*R*)-(+)-129j



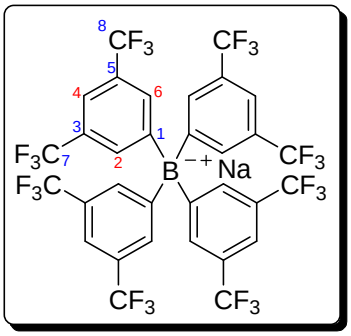
$C_{12}H_{22}O_2$
Mol. Wt.: 198.30

(+)-129j: (82.5 mg, 83%): $[\alpha]_D^{24}$ +0.6 (*c* 1.0, $CHCl_3$, 55% *ee*); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.9 Hz, 3H, CH_3CH_2), 1.19-1.30 (m, 12H, 6×CH_2), 1.40-1.48 (m, 2H, CH_2CH), 2.14 (dd, *J* = 16.7, 7.7 Hz, 1H, 2-H), 2.46-2.56 (m, 1H, 3-H), 2.58 (dd, *J* = 16.7, 8.3 Hz, 1H,

2-H'), 3.89 (dd, *J* = 8.9, 7.1 Hz, 1H, 4-H), 4.38 (dd, *J* = 8.9, 7.4 Hz, 1H, 4-H'); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9 (CH_3CH_2), 22.5 (CH_2), 27.2 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 32.9 (CH_2CH), 34.4 (CH_2-2), 35.5 (CH-3), 73.3 (CH_2-4), 177.2 (C=O-1) in agreement with literature data;[163] **Chiral HPLC** (Chiracel IB, 0.75 mL.min^{-1}, hexane/2-propanol, 95:5) t_R = 30.1 min, t_S = 33.7 min after derivatisation into the hydroxyl benzylamide derivative.[64b]

6.3.4 Asymmetric Iridum-Catalysed Hydrogenation

Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate NaBAr$_F$



$C_{32}H_{12}BF_{24}Na$
Mol. Wt.: 886,2

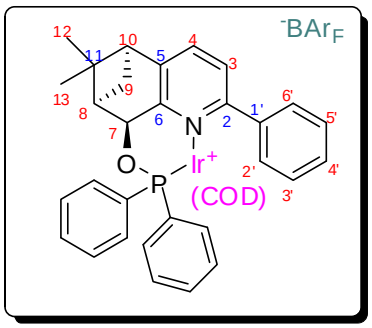
A mixture of magnesium turnings (1.01 g, 41.7 mmol, 6.5 equiv), sodium tetrafluoroborate (0.70 g, 6.4 mmol, 1.0 equiv) (previously dried at 120 °C under vacuum) and 1,2-dibromoethane (0.49 mL, 5.7 mmol, 0.9 equiv) in ether (150 mL) was slightly heated to obtain a gentle reflux. A solution of 1-bromo-3,5-bis(trifluoromethyl)benzene (6.2 mL, 36 mmol, 5.6 equiv) in ether (50 mL) was then added dropwise to keep refluxing the latter solution without external heating. When the addition was over, the mixture was refluxed for an additional 30 min and stirred overnight at room temperature. The reaction mixture was then poured into a solution of sodium carbonate (16 g) in water (200 mL), and the mixture was stirred for 30 min and then filtered. The ethereal layer was separated and the aqueous phase was extracted with ether (3×50 mL). The organic layers were combined, dried over Na_2SO_4, treated with charcoal (2 g), filtered, and concentrated under vacuum. The remaining oily solid was suspended in benzene (200 mL). The remaining water was removed by Dean&Stark azeotrope distillation for 2 h. The solution was then cooled down to room temperature and the solvent was removed by cannula filtration. The residual solid was then

dried overnight under vacuum to afford pure **NaBAr$_F$** as a tan solid (5 g, 88%): **^{1}H NMR** (400 MHz, d_6-DMSO) δ 7.67 (m, 8H, 4-H, 6-H), 7.72 (m, 4H, 2-H); **^{13}C NMR** (100 MHz, d_6-DMSO) δ 117.4 (CH-2), 123.9 (q, J = 272.4 Hz, 2×CF_3-7,8), 128.4 (q, J = 31.4 Hz, 2×C-3,5), 134.0 (2×CH-4,6), 160.9 (q, J = 49.8 Hz, C-1); **^{19}F NMR** (376.5 MHz, d_6-DMSO) δ –61.9 (CF_3).

General Procedure for the Preparation of Iridium(I) Catalysts 133a-d

[Ir(COD)Cl]$_2$ (33.58 mg, 0.05 mmol, 0.5 equiv) and the respective *P*,*N*-ligand (0.10 mmol, 1.0 equiv) were dissolved in CH_2Cl_2 (2 mL). The resulting red solution was heated at 50 °C until disappearance of the starting *P*,*N*-ligand (TLC monitoring). The solution was then cooled to room temperature and Na[BAr$_F$] (133 mg, 0.15 mmol, 1.5 equiv) was added, followed by water (2 mL), and the resulting mixture was stirred vigorously for 30 min. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×3 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by flash chromatography on silica gel (15 g) using a mixture of hexane and CH_2Cl_2 (1:1) to give **133a-d** as orange solids.

(7*S*,8*R*,10*S*)-(+)-2-Phenyl-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-trien-7- yl diphenylphosphinite-η^4-(1,5-cyclooctadiene) iridium(I) tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (+)-133a

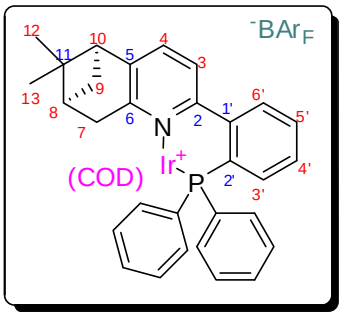


$C_{70}H_{52}BF_{24}IrNOP$
Mol. Wt.: 1613.13

(+)-133a (66.2 mg, 41%): **mp** 69-71 °C (Et_2O:CH_2Cl_2 1:1); **[α]$_D^{25}$** +32.3 (*c* 0.25, $CHCl_3$); **IR** (KBr) ν 3020 (s, C-H), 1638 (brm, C=Car), 1279 (m), 1215 (s, P-O), 770 (s, C-Har) cm^{-1}; **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 0.68 (s, 3H, 12-H), 1.46 (m, 4H, 9-H, 13-H), 1.50-1.52 (m, 2H, CH_2(COD)), 1.66-1.76 (m, 1H, CH_2(COD)), 1.80-1.90 (m, 2H, CH_2(COD)), 1.91-2.12 (m, 3H, CH_2(COD)), 2.72-2.80 (m, 1H, CH(COD)), 2.82-2.94 (m, 3H, 8-H, 9-H', 10-H), 3.00-3.60 (m, 1H, CH(COD)), 4.27-4.35 (m, 2H, CH(COD)), 6.30 (dd, J = 8.6, 3.7 Hz, 1H, 7-H), 7.16-7.20 (m, 2H, aromH), 7.31-7.39 (m, 5H, aromH), 7.40-7.42 (m, 7H, aromH), 7.43-7.50 (m, 5H, aromH), 7.56-7.70 (m, 10H, aromH); **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ 99.2 (s); **MS** (FAB) *m/z* (%) 750 ($M^{\bullet+}$, 100), 642 ($M^{\bullet+}$-COD, 28), 462 (48); **HRMS** (FAB) 750.2498 ($C_{38}H_{40}NOPIr$ requires 750.2479); **Anal. Calcd**. for $C_{70}H_{52}BF_{24}NOPIr$: C, 52.12; H, 3.25; N, 0.87. Found: C, 52.21; H, 3.32; N, 0.81.

(8*S*,10*S*)-(+)-2-[2'-(Diphenylphosphino)phenyl]-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene -η^4-(1,5-cyclooctadiene) iridium(I) tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (+)-133b

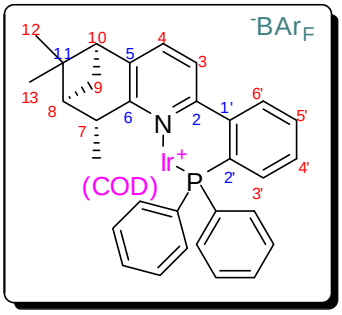


$C_{70}H_{52}BF_{24}IrNP$
Mol. Wt.: 1597.13

(+)-133b (92.6 mg, 58%): **mp** 65-67 °C (hexane:Et_2O 1:1); **[α]$_D^{26}$** +7.8 (*c* 1.0, $CHCl_3$); **IR** (KBr) ν 3022 (s, C-H), 1424 (m, C=Car), 1353 (m, C=Car), 1277 (m, C=Car), 772 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.29 (d, J = 10.0 Hz, 1H, 9-H), 0.52 (s, 3H, 12-H), 0.95-1.00 (m, 1H, CH_2(COD)), 1.17-1.22 (m, 1H, CH_2(COD)), 1.24 (s, 3H, 13-H), 1.27-1.34 (m, 1H, CH_2(COD)), 1.58-1.70 (m, 2H, CH_2(COD)), 1.93-2.03 (m, 1H, CH_2(COD)), 2.25-2.34 (m, 1H, CH_2(COD)), 2.36-2.61 (m, 4H, CH_2(COD), 8-H, 9-H', 10-H), 3.25 (dd, J = 18.0, 2.7 Hz, 1H, 7-H), 3.32 (dd, J = 18.0, 2.7 Hz, 1H, 7-H'), 3.44-3.62 (m, 1H, CH(COD)), 3.85-3.95 (m, 1H, CH(COD)), 4.32-4.51 (m, 1H, CH(COD)), 5.11-5.17 (m, 1H, CH(COD)), 7.02-7.14 (m, 7H, aromH), 7.17-7.30 (m, 3H, aromH), 7.34-7.53 (m, 9H, aromH), 7.57-7.65 (m, 9H, aromH); **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ 19.2 (s); **MS** (FAB) *m/z* (%) 734 ($M^{\bullet+}$, 100), 626

($M^{\bullet+}$-COD, 16), 450 (42); **HRMS** (FAB) 734.2529 ($C_{38}H_{40}NPIr$ requires 734.2530); **Anal. Calcd**. for $C_{70}H_{52}BF_{24}NPIr$: C, 52.64; H, 3.28; N, 0.88. Found: C, 52.38; H, 3.23; N, 1.01.

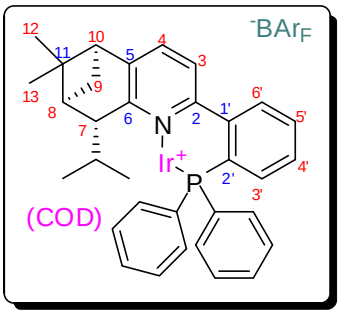
(7*R*,8*S*,10*S*)-(+)-2-[2'-(Diphenylphosphino)phenyl]-7,11,11-trimethyl-1-azatricyclo[7.1.1.$0^{5,6}$]undeca-2,4,6-triene -η^4-(1,5-cyclooctadiene) iridium(I) tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (+)-133c



$C_{71}H_{54}BF_{24}IrNP$
Mol. Wt.: 1611.16

(+)-133c (83.8 mg, 52%): **mp** 61-63 °C (hexane:CH_2Cl_2 1:1); **$[\alpha]_D^{25}$** +2.8 (*c* 0.25, $CHCl_3$); **IR** (KBr) ν 3020 (s, C-H), 1428 (m, C=Car), 1354 (m, C=Car), 1279 (m, C=Car), 770 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.51 (s, 3H, 12-H), 0.55 (d, *J* = 10.2 Hz, 1H, 9-H), 0.80-0.85 (m, 1H, CH_2(COD)), 1.00-1.10 (m, 2H, CH_2(COD)), 1.34 (s, 3H, 13-H), 1.36-1.44 (m, 1H, CH_2(COD)), 1.60-1.70 (m, 1H, CH_2(COD)), 1.85 (d, *J* = 7.1 Hz, 3H, CH_3C(7)), 2.02-2.04 (m, 1H, CH_2(COD)), 2.08-2.12 (m, 1H, CH_2(COD)), 2.40 (m, 1H, 9-H'), 2.52-2.62 (m, 2H, CH_2(COD), 8-H), 2.67 (t, *J* = 5.9 Hz, 1H, 10-H), 3.33-3.41 (m, 2H, CH(COD), 7-H), 4.10-4.15 (m, 1H, CH(COD)), 4.24-4.29 (m, 1H, CH(COD)), 5.27-5.33 (m, 1H, CH(COD)), 6.98-7.09 (m, 3H, aromH), 7.15-7.25 (m, 2H, aromH), 7.31-7.53 (m, 10H, aromH), 7.54-7.63 (m, 3H, aromH), 7.66-7.74 (m, 10H, aromH); **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ 11.1 (s); **MS** (FAB) *m/z* (%) 748 ($M^{\bullet+}$, 100), 636 (48), 558 (22); **HRMS** (FAB) 748.2685 ($C_{39}H_{42}NPIr$ requires 748.2687); **Anal. Calcd**. for $C_{71}H_{54}BF_{24}NPIr$: C, 52.93; H, 3.38; N, 0.87. Found: C, 52.88; H, 3.26; N, 0.98.

(7*R*,8*S*,10*S*)-(+)-2-[2'-(Diphenylphosphino)phenyl]-7-isopropyl-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene -η^4-(1,5-cyclooctadiene) iridium(I) tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (+)-133d



$C_{73}H_{58}BF_{24}IrNP$
Mol. Wt.: 1639.21

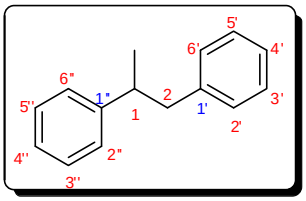
(+)-133d (71 mg, 44%): **mp** 64-66 °C (hexane:Et_2O 2:1); **[α]$_D^{22}$** +28.8 (*c* 0.5, $CHCl_3$); **IR** (KBr) ν 3020 (s, C-H), 1426 (m, C=Car), 1353 (m, C=Car), 1272 (m, C=Car), 770 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.35 (d, *J* = 6.6 Hz, 3H, CH_3CH), 0.38 (s, 3H, 12-H), 0.66-0.76 (m, 1H, CH_2(COD)), 0.83 (d, *J* = 10.2 Hz, 1H, 9-H), 0.96-1.09 (m, 2H, CH_2(COD)), 1.18-1.22 (m, 1H, CH_2(COD)), 1.26 (s, 3H, 13-H), 1.35 (d, *J* = 6.6 Hz, 3H, CH_3'CH), 1.45-1.51 (m, 1H, CH_2(COD)), 1.90-2.00 (m, 1H, CH_2(COD)), 2.22 (td, *J* = 6.1, 1.8 Hz, 1H, 8-H), 2.30-2.38 (m, 2H, CH_2(COD), 9-H'), 2.57 (t, *J* = 6.1 Hz, 1H, 10-H), 2.58-2.66 (m, 1H, CH_2(COD)), 3.06 (brs, 1H, 7-H), 3.16 (td, *J* = 6.6, 3.5 Hz, 1H, CH_3CHCH_3), 3.55-3.43 (m, 1H, CH(COD)), 3.90-3.96 (m, 1H, CH(COD)), 3.97-4.04 (m, 1H, CH(COD)), 5.05-5.11 (m, 1H, CH(COD)), 6.84-6.90 (m, 2H, aromH), 6.91-6.97 (m, 2H, aromH), 7.04 (tq, J = 7.1, 1.5 Hz, 1H, aromH), 7.20-7.28 (m, 3H, aromH), 7.30-7.50 (m, 10H, aromH), 7.52-7.66 (m, 10H, aromH); **^{31}P NMR** (162.0 MHz, $CDCl_3$) δ 8.9 (s); **MS** (FAB) *m/z* (%) 776 ($M^{\bullet+}$, 100), 668 ($M^{\bullet+}$-COD, 5), 262 (58); **HRMS** (FAB) 776.3004 ($C_{41}H_{46}NPIr$ requires 776.3000); **Anal. Calcd**. for $C_{73}H_{58}BF_{24}NPIr$: C, 53.49; H, 3.57; N, 0.85. Found: C, 53.12; H, 3.38; N, 0.97.

General Procedure for the Hydrogenation of Alkenes 78, 85 and Imine 136

α-Methylstilbene **78** (39 mg, 0.2 mmol, 1 equiv), or ethyl trans-β-methylcinnamate **85** (38 mg, 0.2 mmol, 1 equiv), or imine **136** (45 g, 0.2 mmol, 1 equiv) and the appropriate iridium catalyst (4.0 μmol, 2 mol%) were dissolved in CH_2Cl_2 (2 mL). The autoclave was then sealed and the hydrogenation was performed at room temperature under 10 bar of H_2 for 2 d. After

releasing the hydrogen, the reaction mixture was directly passed through a short silica gel plug and flashed with a mixture of petroleum ether and ethyl acetate (4:1). The filtrate was evaporated and the residue was analysed by ^{1}H-NMR to obtain the conversion of the reaction; chiral HPLC was used to determine the enantiomeric excess.

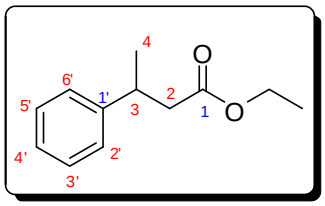
1,2-Diphenylpropane 134



$C_{15}H_{16}$
Mol. Wt.: 196.29

134: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.8 Hz, 3H, CH_3CH), 2.71 (dd, *J* = 12.9, 8.0 Hz, 1H, 2-H), 2.86-3.00 (m, 2H, 1-H, 2-H'), 7.02 (d, *J* = 7.0 Hz, 2H, aromH), 7.10-7.25 (m, 8H, aromH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 41.8 (CH-1), 45.0 (CH_2-2), 125.8 (CH-4'), 126.0 (CH-4''), 127.0 (2×aromCH), 128.0 (2×aromCH), 128.3 (2×aromCH), 129.1 (2×aromCH), 140.8 (C-1'), 146.9 (C-1'') in agreement with the literature data;[95a] **Chiral HPLC** (Chiracel OJ-H, 0.5 mL.min^{-1}, hexane/2-propanol, 99:1) t_R = 13.2 min, t_S = 19.3 min.

Ethyl 3-phenylbutanoate 135

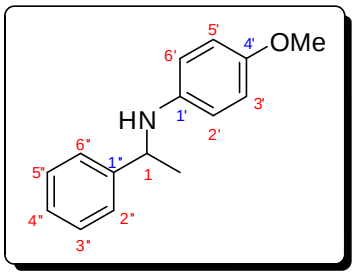


$C_{12}H_{16}O_2$
Mol. Wt.: 192.25

135: **$[\alpha]_D^{26}$** +6.4 (*c* 1.4, $CHCl_3$, 83% *ee*); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.11 (t, *J* = 7.1 Hz, 3H, CH_3CH_2), 1.23 (d, *J* = 7.2 Hz, 3H, 4-H), 2.46 (dd, *J* = 15.0, 7.2 Hz, 1H, 2-H), 2.54 (dd, *J* = 15.0, 7.2 Hz, 1H, 2-H'), 3.20 (q, *J* = 7.2 Hz, 1H, 3-H), 4.00 (q, *J* = 7.2 Hz, 2H, CH_3CH_2), 7.13 (t, *J* = 7.1 Hz, 1H, 4'-H), 7.15 (d, *J* = 6.9 Hz, 2H, 2'-H, 6'-H), 7.22 (t, *J* = 7.1, 2H, 3'-H, 5'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.1 (CH_3CH_2), 21.8 (CH_3-4), 36.5 (CH-3), 43.0

(CH_2CH_3), 60.2 (CH_2-2), 126.3 (CH-4'), 126.7 (2×CH-2', 6'), 128.4 (2×CH-3', 5'), 145.7 (C-1'), 172.4 (C=O-1) in agreement with the literature data;[165] **Chiral HPLC** (IB, 0.75 mL.min^{-1}, hexane/2-propanol, 99:1) t_R = 6.8 min, t_S = 9.8 min.

4-Methoxy-*N*-(1'-phenylethyl)aniline 137



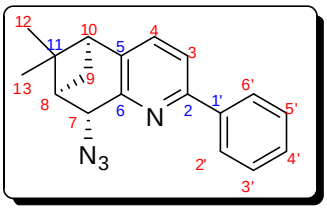
$C_{15}H_{17}NO$
Mol. Wt.: 227.30

137: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.42 (d, J = 6.7 Hz, 3H, CH_3), 3.61 (s, 3H, OCH_3), 4.34 (q, J = 6.7 Hz, 1H, 1-H), 6.40 (d, J = 8.9 Hz, 2H, 2'-H, 6'-H), 6.61 (d, J = 8.9 Hz, 2H, 3'-H, 5'-H), 7.13 (tt, J = 7.3, 1.5 Hz, 1H, 4''-H), 7.23 (td, J = 7.3, 2.0 Hz, 2H, 3''-H, 5''-H), 7.29 (dd, J = 7.3, 1.5 Hz, 2H, 2''-H, 6''-H) in agreement with the literature data;[130] **Chiral HPLC** (IB, 0.75 mL.min^{-1}, hexane/2-propanol, 99:1) t_R = 13.2 min, t_S = 19.3 min.

6.4 Synthesis and Application of Pinene-Derived *N*-Oxides

6.4.1 Synthesis of the First Generation of Catalysts

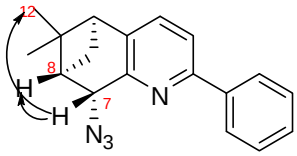
(7*R*,8*R*,10*S*)-(+)-2-Phenyl-7-azido-11,11-dimethyl-1-azatricyclo[7.1.1.$0^{5,6}$]undeca-2,4,6-triene (+)-159



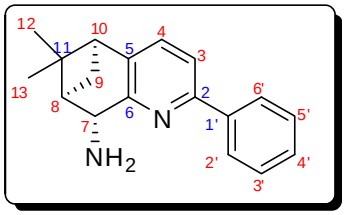
$C_{18}H_{18}N_4$
Mol. Wt.: 290,36

Diethyl azidocarboxylate (47 µL, 0.30 mmol, 1.3 equiv) was slowly added to an ice-cooled stirred solution of alcohol (+)-**117b** (59 mg, 0.22 mmol, 1.0 equiv) and triphenylphosphine (78 mg, 0.30 mmol, 1.3 equiv) in dry THF (3 mL). Diphenylphosphoryl azide (65 µL, 0.30 mmol, 1.3 equiv) was then added dropwise, the reaction mixture was allowed to warm to room temperature and stirred for 24 h. The volatiles were then evaporated under vacuum. The residue was purified by chromatography on silica gel (25 g) using a mixture of petroleum ether and ethyl acetate (20:1) to yield (+)-**159** as a colourless oil (51 mg, 80%): $[\alpha]_D^{20}$ +42.3 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2936 (s, C-H), 2096 (s, N_3), 1586 (m, C=Car), 1456 (m, C=Car), 1441 (m, C=Car), 1251 (m, C-H methyl), 751 (m, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.70 (s, 3H, 12-H), 1.47 (s, 3H, 13-H), 1.55 (d, *J* = 10.2 Hz, 1H, 9-H), 2.44 (td, *J* = 5.9, 3.3 Hz, 1H, 8-H), 2.64 (dt, *J* = 10.2, 5.9 Hz, 1H, 9-H'), 2.83 (t, *J* = 5.9 Hz, 1H, 10-H), 4.91 (d, *J* = 3.3 Hz, 1H, 7-H), 7.36 (d, *J* = 7.9 Hz, 1H, 3-H), 7.39 (tt, *J* = 7.4, 1.3 Hz, 1H, 4'-H), 7.48 (td, *J* = 7.4, 1.3 Hz, 2H, 3'-H, 5'-H), 7.59 (d, *J* = 7.9 Hz, 1H, 4-H), 8.06 (dd, *J* = 7.4, 1.3 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0 (CH_3-12), 26.3 (CH_3-13), 29.8 (CH_2-9), 44.0 (C-11), 45.1 (CH-8), 45.9 (CH-10), 63.0 (CH-7), 118.9 (CH-4), 126.7 (2×CH-2',6'), 128.72 (CH-4'), 128.75 (2×CH-3',5'), 134.1 (CH-3), 139.0 (C-1'), 139.7 (C-5), 154.2 (C-2), 155.2 (C-6); **MS** (EI) *m/z* (%) 290 ($M^{\bullet+}$, 24), 262 ($M^{\bullet+}$-N_2, 96), 248 ($M^{\bullet+}$-N_3, 85), 206 ($M^{\bullet+}$-N3-C_3H_6, 97), 149 (100); **HRMS** (EI) 290.1530 ($C_{18}H_{18}N_4$ requires 290.1531).

NOE: Irradiation on **4.91** 7-H enhanced **0.70** 12-H and **2.44** 8-H



(7*R*,8*R*,10*S*)-(+)-2-Phenyl-11,11-dimethyl-1-azatricyclo[7.1.1.$0^{5,6}$]undeca-2,4,6-trien-7-amine (+)-160



$C_{18}H_{20}N_2$
Mol. Wt.: 264,36

Procedure A: Hydrogenation

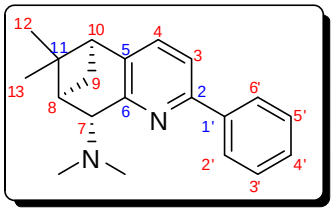
A mixture of Pd/charcoal (3.2 mg, 10 w/w %) and azide (+)-**159** (32 mg, 0.11 mmol) in ethanol (1 mL) was stirred at room temperature overnight under a H_2 atmosphere. The catalyst was removed by filtration through a celite pad. The filtrate was concentrated under vacuum and purified by flash chromatography on silica gel (5 g) using CH_2Cl_2 to remove the unreacted starting material, followed by methanol to afford (+)-**160** as a colourless oil (10 mg, 35%).

Procedure B: Reduction with $LiAlH_4$

Lithium aluminum hydride (27 mg, 0.66 mmol, 2 equiv) was added portion-wise to an ice-cooled solution of azide (+)-**159** (96 mg, 0.33 mmol, 1 equiv) in THF (1 mL). The reaction mixture was allowed to warm to room temperature and stirred overnight. The excess of lithium aluminum hydride was quenched by addition of sodium sulfate decahydrate and the mixture was stirred at room temperature for 30 min. The precipitate was filtered off through a celite pad and washed with ethanol (20 mL). The filtrate was concentrated under vacuum and purified by flash chromatography on silica gel (5 g) using CH_2Cl_2 to remove the unreacted starting material, followed by methanol to afford (+)-**160** as a colourless oil (86 mg, 98%): **$[\alpha]_D^{20}$** +7.9 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 3369 (m, N-H), 2954 (s, C-H), 1583 (m, C=Car),

1570 (s, NH_2), 1453 (m, C=Car), 1439 (m, C=Car), 1216 (m, C-N), 755 (m, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.69 (s, 3H, 12-H), 1.41 (d, *J* = 10.0 Hz, 1H, 9-H), 1.46 (s, 3H, 13-H), 2.01 (br s, 2H, N*H*$_2$), 2.39 (td, *J* = 5.9, 2.9 Hz, 1H, 8-H), 2.63 (dt, *J* = 10.0, 5.9 Hz, 1H, 9-H'), 2.81 (t, *J* = 5.9 Hz, 1H, 10-H), 4.20 (d, *J* = 2.9 Hz, 1H, 7-H), 7.29 (d, *J* = 7.8 Hz, 1H, 3-H), 7.38 (tt, *J* = 7.3, 1.3 Hz, 1H, 4'-H), 7.43-7.50 (m, 3H, 4-H, 3'-H, 5'-H), 8.01 (d, *J* = 7.3 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.9 (CH_3-12), 26.4 (CH_3-13), 29.0 (CH_2-9), 43.5 (C-11), 46.6 (CH-8), 46.7 (CH-10), 54.2 (CH-7), 118.0 (CH-4), 126.5 (2×CH-2',6'), 128.4 (CH-4'), 128.6 (2×CH-3',5'), 133.5 (CH-3), 139.47 (C-1'), 139.53 (C-5), 154.8 (C-2), 159.2 (C-6); **MS** (EI) *m/z* (%) 264 ($M^{\bullet+}$, 43), 262 ($M^{\bullet+}$-NH_3, 46), 206 ($M^{\bullet+}$-NH_2-C_3H_6, 42), 195 (100); **HRMS** (EI) 264.1624 ($C_{18}H_{20}N_2$ requires 264.1626).

(7*R*,8*R*,10*S*)-(–)-*N*,*N*,11,11-Tetramethyl-2-phenyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-trien-7-amine (–)-161

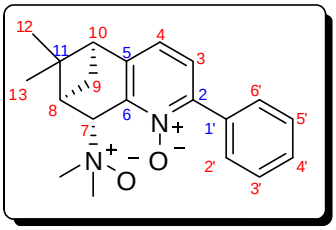


$C_{20}H_{24}N_2$
Mol. Wt.: 292,42

A solution of formaldehyde in water (37% w/w, 1 mL) was added to a cold (0 ºC) solution of amine (+)-**160** (276 mg, 1.04 mmol) in formic acid (1 mL). The resulting mixture was stirred at 0 ºC for 1 h and then at 90 ºC for 4 h. The reaction mixture was cooled to room temperature and the volatiles were removed under vacuum. The residue was diluted with water (5 mL) and made alkaline by addition of an aqueous solution of sodium hydroxide (2M). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, and concentrated under vacuum. The crude material was then purified by column chromatography on silica gel (10 g) using a mixture of petroleum ether and ethyl acetate (2:1) to afford (–)-**161** as a colourless oil (266 mg, 87%): **[α]$_D^{20}$** –28.9 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2932 (s, C-H), 1566 (m, C=Car), 1451 (m, C=Car), 1437 (m, C=Car), 1275 (m, C-H methyl), 775 (m, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.65 (s, 3H, 12-H), 1.44 (s, 3H, 13-H), 1.62 (d, *J* = 9.7 Hz, 1H, 9-H), 2.55 (td, *J* = 5.8, 2.7 Hz, 1H, 8-H), 2.61-2.67 (m, 7H, 9-H', N(CH_3)$_2$), 2.75 (t, *J* = 5.8 Hz, 1H, 10-H), 3.89 (d, *J* = 2.7 Hz,

1H, 7-H), 7.29 (d, *J* = 7.8 Hz, 1H, 3-H), 7.36 (t, *J* = 7.3 Hz, 1H, 4'-H), 7.45 (t, *J* = 7.3 Hz, 2H, 3'-H, 5'-H), 7.48 (d, *J* = 7.8 Hz, 1H, 4-H), 8.01 (d, *J* = 7.3 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.8 (CH_3-12), 26.4 (CH_3-13), 29.2 (CH_2-9), 43.4 (CH-8), 44.0 (C-11), 44.1 (2×CH_3-$N(CH_3)_2$), 46.3 (CH-10), 66.0 (CH-7), 117.9 (CH-4), 126.7 (2×CH-2',6'), 128.2 (CH-4'), 128.5 (2×CH-3',5'), 133.6 (CH-3), 139.8 (C-1'), 140.5 (C-5), 154.5 (C-2), 156.6 (C-6); **MS** (CI-isobutane) *m/z* (%) 293 ($(M+H)^+$, 100), 249 ($(M+H)^+$-$N(Me)_2$, 54), 206 ($(M+H)^+$-$N(Me)_2$-C_3H_6, 8); **HRMS** (CI-isobutane) 293.2011 ($C_{20}H_{25}N_2$ $(M+H)^+$ requires 293.2018).

(7*R*,8*R*,10*S*)-(–)-11,11-Dimethyl-1-2-phenyl-1-azatricyclo[7.1.1.0^{2,7}]undeca-2,4,6-trien-7-yl(dimethyl)amine-*N*,*N*'-bisoxide (–)-162



$C_{20}H_{24}N_2O_2$
Mol. Wt.: 324,42

*m*CPBA (627 mg, 3.65 mmol, 4 equiv) was added portion-wise to a cold solution (0 °C) of the *N*,*N*-dimethylamine (–)-**161** (265 mg, 0.91 mmol, 1 equiv) in CH_2Cl_2 (5 mL). The resulting mixture was allowed to warm up to room temperature and then stirred overnight. The organic layer was washed with a saturated aqueous solution of sodium carbonate (10 mL), dried over $MgSO_4$, and concentrated under vaccum. The crude material was then purified by column chromatography on silica gel (10 g) using pure ethyl acetate to remove the unreacted starting amine, followed by methanol to obtain (–)-**162** as a colourless oil (183 mg, 62%): **$[\alpha]_D^{20}$** –59.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.69 (s, 3H, 12-H), 1.50 (s, 3H, 13-H), 1.60 (d, *J* = 10.0 Hz, 1H, 9-H), 2.76-2.85 (m, 2H, 10-H, 9-H'), 3.05 (s, 3H, NCH_3), 3.78 (td, *J* = 6.0, 1.9 Hz, 1H, 8-H), 4.12 (s, 3H, NCH'_3), 4.47 (d, *J* = 1.9 Hz, 1H, 7-H), 7.40 (t, *J* = 7.1 Hz, 1H, 4'-H), 7.43 (d, *J* = 7.9 Hz, 1H, 3-H), 7.47 (t, *J* = 7.1 Hz, 2H, 3'-H, 5'-H), 7.61 (d, *J* = 7.9 Hz, 1H, 4-H), 7.92 (d, *J* = 7.1 Hz, 2H, 2'-H, 6'-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.8 (CH_3-12), 26.1 (CH_3-13), 29.5 (CH_2-9), 41.4 (CH-8), 45.9 (C-11), 46.5 (CH-10), 55.2 (NCH_3), 64.7 ($NC'H_3$), 80.0 (CH-7), 119.5 (CH-4), 126.4 (2×CH-2',6'), 128.8 (2×CH-3',5'), 129.0 (CH-4'), 135.0 (CH-3), 138.7 (C-1'), 142.3 (C-5), 150.6 (C-2),

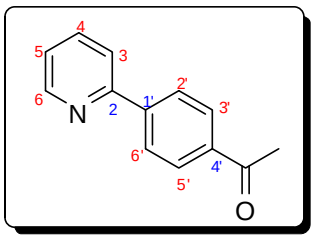
154.6 (C-6). Product synthesised at GSK, Harlow where no high resolution mass spectrometer was available.

6.4.2 Synthesis of the Second Generation of Catalysts

General Procedure for the Formation of 2-(acetoxyphenyl)pyridines 164a-c

A mixture of 2-bromopyridine (0.96 mL, 10.0 mmol, 1.0 equiv) and the respective acetylphenylboronic acid **163a-c** (2.07 g, 12.6 mmol, 1.3 equiv) was stirred in *n*-propanol (24 mL) at room temperature for 15 min. Palladium(II) acetate (8.8 mg, 38.8 µmol, 0.4 mol%), triphenylphosphine (31.2 mg, 120 µmol, 1.2 mol%), an aqueous solution of Na_2CO_3 (2M, 3.9 mL) and water (5 mL) were then added and the resulting mixture was refluxed overnight. The mixture was then cooled to room temperature, water (10 mL) was added, and the mixture was stirred for an additional 15 min. The mixture was made acidic by addition of an aqueous solution of hydrochloric acid (2M) and was extracted with ethyl acetate (3×20 mL). The remaining aqueous layer was made alkaline by addition of an aqueous solution of sodium hydroxide (2M). and was finally extracted with ethyl acetate (3×20 mL). The combined organic extracts from the second extraction were dried over $MgSO_4$, filtered and concentrated under vacuum, affording pure **164a**, **164b** and **164c**, respectively.

2-(4'-Acetoxyphenyl)pyridine 164a

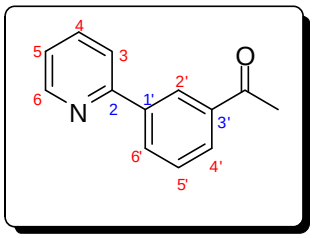


$C_{13}H_{11}NO$
Mol. Wt.: 197.23

164a: (1.82 g, 92%): **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 2.62 (s, 3H, CH_3), 7.30 (ddd, *J* = 6.7, 4.8, 2.0 Hz, 1H, 5-H), 7.81 (ddd, *J* = 8.0, 6.7, 1.7 Hz, 1H, 4-H), 7.83 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H, 3-H), 8.05 (d, *J* = 8.7 Hz, 2H, 3'-H, 5'-H), 8.14 (d, *J* = 8.7 Hz, 2H, 2'-H, 6'-H), 8.71 (ddd, *J* = 4.8, 1.7, 1.1 Hz, 1H, 6-H); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 26.6 (CH_3), 120.9 (CH-

3), 123.0 (CH-5), 126.9 (2×CH-2',6'), 128.6 (2×CH-3',5'), 136.9 (CH-4), 137.3 (C-4'), 143.4 (C-1'), 149.8 (CH-6), 155.8 (C-2), 197.5 (C=O) in agreement the with literature data.[154]

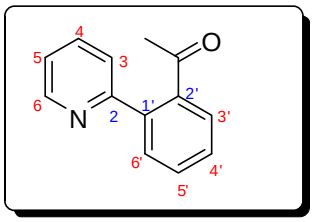
2-(3'-Acetoxyphenyl)pyridine 164b



$C_{13}H_{11}NO$
Mol. Wt.: 197.23

164b: (1.973 g, 100%): **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 2.66 (s, 3H, CH_3), 7.28 (ddd, *J* = 6.8, 4.8, 1.8 Hz, 1H, 5-H), 7.58 (td, *J* = 7.8, 0.5 Hz, 1H, 5'-H), 7.80 (ddd, *J* = 8.0, 6.8, 1.8 Hz, 1H, 4-H), 7.83 (ddd, *J* = 8.0, 1.8, 1.0 Hz, 1H, 3-H), 7.99 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H, 6'-H), 8.24 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H, 4'-H), 8.61 (td, *J* = 1.8, 0.5 Hz, 1H, 2'-H), 8.70 (ddd, *J* = 4.8, 1.7, 1.1 Hz, 1H, 6-H); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 26.6 (CH_3), 120.4 (CH-3), 122.6 (CH-5), 126.6 (CH-2'), 128.5 (CH-6'), 129.0 (CH-5'), 131.2 (CH-4'), 136.9 (CH-4), 137.7 (C-3'), 139.8 (C-1'), 149.7 (CH-6), 156.1 (C-2), 197.7 (C=O) in agreement with the literature data. [154]

2-(2'-Acetoxyphenyl)pyridine 164c



$C_{13}H_{11}NO$
Mol. Wt.: 197.23

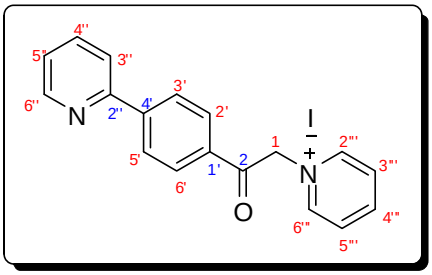
164c: (1.785 g, 91%): **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 2.17 (s, 3H, CH_3), 7.28 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H, 5-H), 7.45-7.51 (m, 2H, 4'-H, 5'-H), 7.55 (dd, *J* = 6.2, 2.6 Hz, 1H, 3'-H), 7.62-7.66 (m, 2H, 3-H, 6'-H), 7.81 (td, *J* = 7.4, 1.8 Hz, 1H, 4-H), 8.61 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H, 6-H); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 30.3 (CH_3), 122.37 (CH-5), 122.39 (CH-6'),

127.5 (CH-5'), 128.6 (CH-4'), 129.1 (CH-3), 130.1 (CH-3'), 136.9 (CH-4), 138.7 (C-1'), 141.9 (C-2'), 149.1 (CH-6), 157.4 (C-2), 203.8 (C=O) in agreement with the literature data.[154]

General Procedure for the Synthesis of Kröhnke Salts 165a,b

A solution of the respective substituted acetophenone **164a,b** (1.97 g, 10 mmol, 1.0 equiv) and iodine (2.53 g, 10 mmol, 1.0 equiv) in pyridine (6 mL) was refluxed overnight. The reaction mixture was then cooled to room temperature, inducing the precipitation of a solid which was filtered off and washed with eher (3×20 mL). The remaining solid was then stirred overnight in ether (20 mL). The salts **165a** and **165b** were then isolated by filtration.

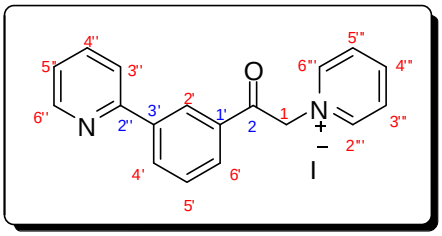
1-{2-Oxo-2-[4'-(2''-pyridinyl)phenyl]ethyl}pyridinium iodide 165a



$C_{18}H_{15}IN_2O$
Mol. Wt.: 402.23

165a: (3.62 g, 90%): **^{1}H NMR** (400 MHz, d_6-DMSO) δ 6.57 (s, 2H, 1-H), 7.50 (ddd, J = 7.7, 4.8, 1.0 Hz, 1H, 5''-H), 7.81 (ddd, J = 7.9, 7.7, 1.8 Hz, 1H, 4''-H), 8.15-8.22 (m, 3H, 3''-H, 2'-H, 6'-H), 8.31 (dd, J = 7.7, 6.1 Hz, 2H, 3'''-H, 5'''-H), 8.38 (d, J = 8.6 Hz, 2H, 3'-H, 5'-H), 8.74-8.79 (m, 2H, 6''-H, 4'''-H), 9.05 (dd, J = 6.1, 1.0 Hz, 2H, 2'''-H, 6'''-H); **^{13}C NMR** (100 MHz, , d_6-DMSO) δ 66.3 (CH_2-1), 121.4 (CH-3''), 123.8 (CH-5''), 126.9 (2×CH-3',5'), 127.8 (2×CH-3''',5'''), 128.7 (2×CH-2',6'), 133.5 (C-1'), 137.9 (CH-4''), 143.5 (C-4'), 146.1 (2×CH-2''',6'''), 146.3 (CH-4'''), 149.4 (CH-6), 154.0 (C-2''), 190.1 (C=O-2); **MS** (FAB) *m/z* (%) 275 ($M^{\bullet+}$, 100), 155 (18), 139 (22), 108 (17), 91 (18), 79 (14); **HRMS** (FAB) 275.1187 ($C_{18}H_{15}N_2O$ requires 275.1184).

1-{2-Oxo-2-[3'-(2''-pyridinyl)phenyl]ethyl}pyridinium iodide 165b



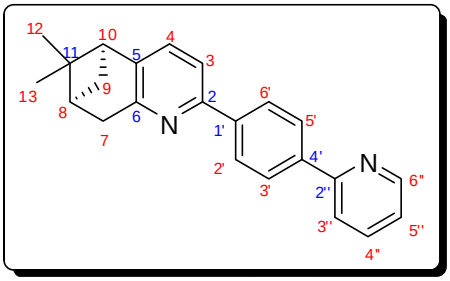
$C_{18}H_{15}IN_2O$
Mol. Wt.: 402.23

165b: (3.58 g, 89%): **^{1}H NMR** (400 MHz, d_6-DMSO) δ 6.63 (s, 2H, 1-H), 7.48 (dd, J = 7.2, 5.1 Hz, 1H, 5''-H), 7.81 (t, J = 7.8 Hz, 1H, 5'-H), 8.02 (t, J = 7.2 Hz, 1H, 4''-H), 8.13 (s, 1H, 2'-H), 8.16 (d, J = 7.8 Hz, 1H, 4'-H), 8.32 (t, J = 7.0 Hz, 2H, 3'''-H, 5'''-H), 8.48 (d, J = 7.8 Hz, 1H, 6'-H), 8.74-8.80 (m, 3H, 3''-H, 6''-H, 4'''-H), 9.05 (d, J = 7.0 Hz, 2H, 2'''-H, 6'''-H); **^{13}C NMR** (100 MHz, d_6-DMSO) δ 66.3 (CH_2-1), 120.8 (CH-4'), 123.4 (CH-5''), 126.1 (CH-3''), 127.8 (2×CH-3''',5'''), 128.7 (CH-2'), 129.7 (CH-5'), 132.3 (C-6'), 134.1 (C-1'), 138.0 (CH-4''), 138.9 (C-3'), 146.1 (2×CH-2''',6'''), 146.3 (CH-4'''), 149.3 (CH-6''), 154.1 (C-2''), 190.5 (C=O-2); **MS** (FAB) *m/z* (%) 275 ($M^{\bullet+}$, 82), 241 (33), 136 (37), 122 (100), 101 (82), 82 (75); **HRMS** (FAB) 275.1181 ($C_{18}H_{15}N_2O$ requires 275.1184).

General Procedure for the Kröhnke Annulation 166a,b

A solution of pinocarvone (–)-**16** (1.05 g, 7.0 mmol, 1.0 equiv), the respective Kröhnke salt **165a** (2.82 g, 7.0 mmol, 1.0 equiv) or **165b** (2.82 g, 7.0 mmol, 1.0 equiv), and ammonium acetate (9.25 g) in acetic acid (12 mL) was refluxed for 6 h. The mixture was then cooled to room temperature, diluted with water (25 mL), made neutral by addition of an aqueous solution of sodium hydroxide (2M), and extracted with ethyl acetate (3×50 mL). The organic phase was successively washed with water (3×50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the crude product was purified by flash chromatography on silica gel (20 g) using a mixture of petroleum ether and ethyl acetate (3:1) to afford pure (+)-**166a** and (+)-**166b**, respectively.

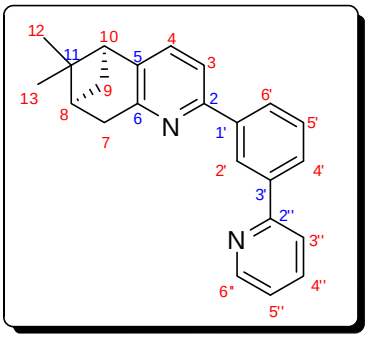
(8*S*,10*S*)-(+)-2-[4'-(2''-Pyridinyl)phenyl]-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene (+)-166a



$C_{23}H_{22}N_2$
Mol. Wt.: 326.43

(+)-166a (484 mg, 22%): **[α]$_D^{25}$** +79.6 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2922 (m, C-H), 1583 (m, C=Car), 1465 (m, C=Car), 1435 (m, C=Car), 821 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.70 (s, 3H, 12-H), 1.32 (d, *J* = 9.5 Hz, 1H, 9-H), 1.43 (s, 3H, 13-H), 2.41 (tt, *J* = 5.8, 2.8 Hz, 1H, 8-H), 2.71 (dt, *J* = 9.5, 5.8 Hz, 1H, 9-H'), 2.80 (t, *J* = 5.8 Hz, 1H, 10-H), 3.21 (d, *J* = 2.8 Hz, 2H, 7-H), 7.23 (ddd, *J* = 7.0, 4.8, 1.5 Hz, 1H, 5''-H), 7.27 (d, *J* = 7.8 Hz, 1H, 3-H), 7.47 (d, *J* = 7.8 Hz, 1H, 4-H), 7.75 (td, *J* = 7.0 ,1.7 Hz, 1H, 4''-H), 7.79 (ddd, *J* = 7.0, 1.5, 1.0 Hz, 1H, 3''-H), 8.10 (s, 4H, 2'-H, 3'-H, 5'-H, 6'-H), 8.71 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H, 6''-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.4 (CH_3-12), 26.1 (CH_3-13), 32.1 (CH_2-9), 36.8 (CH_2-7), 39.6 (C-11), 40.3 (CH-8), 46.4 (CH-10), 117.4 (CH-4), 120.6 (CH-3''), 122.2 (CH-5''), 127.1 (2×CH-2',6'), 127.2 (2×CH-3',5'), 133.6 (CH-3), 136.8 (CH-4''), 139.1 (C-1'), 140.5 (C-5), 140.7 (C-4'), 149.7 (CH-6''), 154.2 (C-2''), 157.0 (C-2), 157.1 (C-6); **MS** (CI-isobutane) *m/z* (%) 327 ($(M+H)^+$, 100); **HRMS** (CI-isobutane) 327.1860 ($C_{23}H_{23}N_2$ $(M+H)^+$ requires 327.1861).

(8*S*,10*S*)-(+)-2-[3'-(2''-Pyridinyl)phenyl]-11,11-dimethyl-1-azatricyclo[7.1.1.$0^{5,6}$]undeca-2,4,6-triene (+)-166b



$C_{23}H_{22}N_2$
Mol. Wt.: 326.43

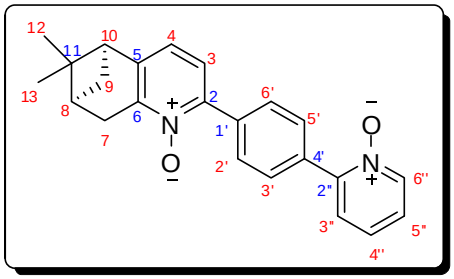
(+)-166b (820 mg, 36%): $[\alpha]_D^{18}$ +58.7 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2936 (m, C-H), 1587 (m, C=Car), 1466 (m, C=Car), 1437 (m, C=Car), 761 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.63 (s, 3H, 12-H), 1.24 (d, *J* = 9.5 Hz, 1H, 9-H), 1.33 (s, 3H, 13-H), 2.32 (tt, *J* = 5.8, 2.8 Hz, 1H, 8-H), 2.61 (dt, *J* = 9.5, 5.8 Hz, 1H, 9-H'), 2.70 (t, *J* = 5.8 Hz, 1H, 10-H), 3.16 (d, *J* = 2.8 Hz, 2H, 7-H), 7.11 (ddd, *J* = 7.4, 4.8, 1.0 Hz, 1H, 5''-H), 7.18 (d, *J* = 7.8 Hz, 1H, 3-H), 7.44 (d, *J* = 7.8 Hz, 1H, 4-H), 7.49 (t, *J* = 7.8 Hz, 1H, 5'-H), 7.62 (td, *J* = 7.4 ,1.8 Hz, 1H, 4''-H), 7.74 (dt, *J* = 7.4, 1.0 Hz, 1H, 3''-H), 7.97 (ddd, *J* = 7.8, 2.8, 1.6 Hz, 1H, 6'-H), 8.00 (ddd, *J* = 7.8, 2.8, 1.6 Hz, 1H, 4'-H), 8.59 (t, *J* = 1.6 Hz, 1H, 2'-H), 8.64 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H, 6''-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0 (CH_3-12), 25.8 (CH_3-13), 31.7 (CH_2-9), 36.5 (CH_2-7), 39.2 (C-11), 39.9 (CH-8), 45.9 (CH-10), 117.0 (CH-4), 120.3 (CH-3''), 121.8 (CH-5''), 125.0 (CH-2'), 126.5 (CH-6'), 127.0 (CH-4'), 128.8 (CH-5'), 133.2 (CH-3), 136.3 (CH-4''), 139.4 (C-5), 140.2 (2×C-1', 3'), 149.3 (CH-6''), 154.1 (C-2''), 156.5 (C-2), 157.0 (C-6); **MS** (EI) *m/z* (%) 326 ($M^{\bullet+}$, 100), 283 (66); **HRMS** (EI) 326.1780 ($C_{23}H_{22}N_2$ requires 326.1783).

General Procedure for the *N*-Oxidation of Pyridine Derivatives 166a-b

m-Chloroperoxybenzoic acid (70%, 106 mg, 0.60 mmol, 4.0 equiv) was added portion-wise to a respective cool (0 °C) solution of (+)-166a (50 mg, 0.15 mmol, 1.0 equiv) or (+)-166b (50 mg, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL). The mixture was then allowed to warm up to room temperature and stirred overnight. The mixture was washed with an aqueous solution of $NaHCO_3$ (10%; 5 mL) and dried over $MgSO_4$. The solvent was removed under vacuum

and the residue was purified by chromatography on silica gel (10 g) using ethyl acetate to remove the unreacted starting material and some by-products, followed by methanol to afford pure (–)-**167a** and (–)-**167b** respectively.

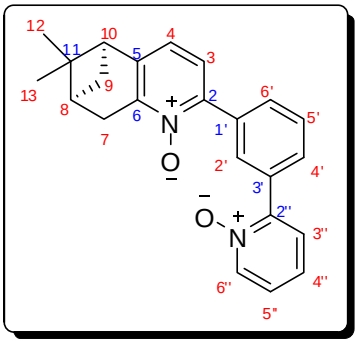
(8*S*,10*S*)-(–)-2-[4'-(1''-oxido-2''-pyridinyl)phenyl]-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene-1-oxide (–)-167a



$C_{23}H_{22}N_2O_2$
Mol. Wt.: 358.43

(–)-167a (25 mg, 45%): **[α]$_D^{20}$** –24.2 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2932 (m, C-H), 1584 (m, C=Car), 1461 (m, C=Car), 1430 (m, C=Car), 1215 (m, N^+-O^-), 761 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.65 (s, 3H, 12-H), 1.23 (d, *J* = 9.8 Hz, 1H, 9-H), 1.34 (s, 3H, 13-H), 2.36 (tt, *J* = 5.7, 2.8 Hz, 1H, 8-H), 2.61 (dt, *J* = 9.8, 5.7 Hz, 1H, 9-H'), 2.74 (t, *J* = 5.7 Hz, 1H, 10-H), 3.03 (dd, *J* = 19.1, 2.0 Hz, 1H, 7-H), 3.11 (dd, *J* = 19.1, 2.0 Hz, 1H, 7-H'), 6.88 (d, *J* = 7.8 Hz, 1H, 4-H), 7.15 (d, *J* = 7.8 Hz, 1H, 3-H), 7.16-7.21 (m, 1H, 5''-H), 7.26 (td, *J* = 7.7 ,1.0 Hz, 1H, 4''-H), 7.40 (dd, *J* = 7.7, 1.8 Hz, 1H, 3''-H), 7.83 (s, 4H, 2'-H, 3'-H, 5'-H, 6'-H), 8.26 (dd, *J* = 6.4, 1.0 Hz, 1H, 6''-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.0 (CH_3-12), 25.7 (CH_3-13), 31.0 (CH_2-7), 31.3 (CH_2-9), 39.1 (C-11), 39.2 (CH-8), 46.0 (CH-10), 123.2 (CH-4), 123.8 (CH-3), 124.7 (CH-5''), 126.1 (CH-4''), 127.4 (CH-3''), 128.8 (2×CH-2',6'), 129.3 (2×CH-3',5'), 132.8 (C-1'), 134.3 (C-5), 140.3 (CH-6''), 144.6 (C-4'), 146.2 (C-2''), 146.8 (C-2), 148.7 (C-6); **MS** (FAB) *m/z* (%) 359 ($(M+H)^+$, 100); **HRMS** (FAB) 359.1829 ($C_{23}H_{23}N_2O_2$ $(M+H)^+$ requires 359.1827).

(8*S*,10*S*)-(–)-2-[3'-(1''-oxido-2''-pyridinyl)phenyl]-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene-1-oxide (–)-167b



$C_{23}H_{22}N_2O_2$
Mol. Wt.: 358.43

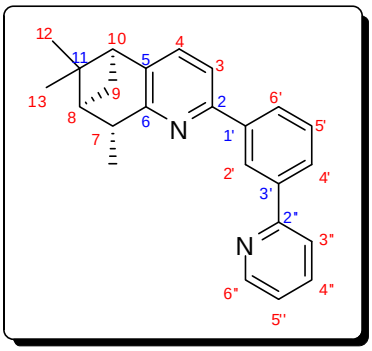
(–)-167b (32 mg, 60%): **[α]$_D^{21}$** –22.3 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2933 (m, C-H), 1586 (m, C=Car), 1463 (m, C=Car), 1430 (m, C=Car), 1215 (m, N^+-O^-), 760 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.72 (s, 3H, 12-H), 1.31 (d, *J* = 9.8 Hz, 1H, 9-H), 1.42 (s, 3H, 13-H), 2.44 (tt, *J* = 5.9, 2.9 Hz, 1H, 8-H), 2.69 (dt, *J* = 9.8, 5.9 Hz, 1H, 9-H'), 2.81 (t, *J* = 5.9 Hz, 1H, 10-H), 3.10 (dd, *J* = 19.2, 5.9 Hz, 1H, 7-H), 3.18 (dd, *J* = 19.2, 5.9 Hz, 1H, 7-H'), 6.93 (d, *J* = 7.8 Hz, 1H, 4-H), 7.22 (ddd, *J* = 7.6, 6.5, 2.0 Hz, 1H, 5''-H), 7.27 (d, *J* = 7.8 Hz, 1H, 3-H), 7.30 (td, *J* = 7.6, 1.3 Hz, 1H, 4''-H), 7.52 (dd, *J* = 7.6, 2.0 Hz, 1H, 3''-H), 7.56 (t, *J* = 7.9 Hz, 1H, 5'-H), 7.87 (ddd, *J* = 7.9, 1.7, 1.2 Hz, 1H, 6'-H), 7.90 (ddd, *J* = 7.9, 1.7, 1.2 Hz, 1H, 4'-H), 8.25 (t, *J* = 1.7 Hz, 1H, 2'-H), 8.31 (dd, *J* = 6.5, 1.3 Hz, 1H, 6''-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.1 (CH_3-12), 25.8 (CH_3-13), 31.1 (CH_2-7), 31.5 (CH_2-9), 39.3 (CH-8, C-11), 46.1 (CH-10), 123.1 (CH-4), 124.0 (CH-3), 124.6 (CH-5''), 125.8 (CH-4''), 127.7 (CH-3''), 128.0 (CH-5'), 129.8 (CH-4'), 130.5 (CH-6'), 130.7 (CH-2'), 132.3 (C-5), 133.3 (C-1'), 140.3 (CH-6''), 144.6 (C-3'), 146.4 (C-2''), 146.8 (C-2), 149.0 (C-6); **MS** (FAB) *m/z* (%) 359 ($(M+H)^+$, 100); **HRMS** (FAB) 359.1829 ($C_{23}H_{23}N_2O_2$ $(M+H)^+$ requires 359.1827).

General Procedure for the Benzylic Alkylation of (+)-166b

A solution of *n*-butyllithium in hexane (1.6M, 0.4 mL, 0.61 mmol, 1.0 equiv) was added dropwise to a solution of (+)-**166b** (200 mg, 0.61 mmol, 1.0 equiv) in anhydrous THF (2 mL) under argon at –40 °C. The solution was stirred at that temperature for 1 h, then the respective electrophile, iodomethane (40 µL, 0.61 mmol, 1.0 equiv) or 2-iodopropane (62 µL, 0.61 mmol, 1.0 equiv) was added dropwise at –40 °C. The solution was then gradually

warmed up to room temperature and stirred overnight. The reaction was quenched by addition of water (10 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (15 g) with a mixture of petroleum ether and ethyl acetate (6:1) to give, respectively, pure (+)-**169a**, or pure (–)-**169b**.

(7*R*,8*S*,10*S*)-(+)-2-[3'-(2''-Pyridinyl)phenyl]-7,11,11-trimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene (+)-169a

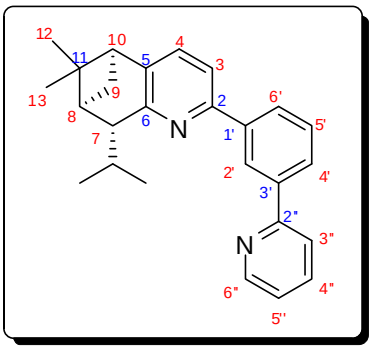


$C_{24}H_{24}N_2$
Mol. Wt.: 340.46

(+)-169a (64 mg, 31%): **[α]$_D^{23}$** +7.1 (*c* 1.0, CH_2Cl_2); **IR** (NaCl) ν 2926 (m, C-H), 1637 (m, C=Car), 1585 (m, C=Car), 1460 (m, C=Car), 773 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.61 (s, 3H, 12-H), 1.27 (d, *J* = 9.8 Hz, 1H, 9-H), 1.35 (s, 3H, 13-H), 1.41 (d, *J* = 7.1 Hz, 3H, C*H*$_3$C(7)), 2.10 (td, *J* = 5.7, 2.5 Hz, 1H, 8-H), 2.50 (dt, *J* = 9.8, 5.7 Hz, 1H, 9-H'), 2.71 (t, *J* = 5.7 Hz, 1H, 10-H), 3.20 (qd, *J* = 7.1, 2.5 Hz, 1H, 7-H), 7.15 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H, 5''-H), 7.18 (d, *J* = 7.8 Hz, 1H, 3-H), 7.44 (d, *J* = 7.8 Hz, 1H, 4-H), 7.48 (t, *J* = 7.7 Hz, 1H, 5'-H), 7.68 (td, *J* = 7.6 ,1.8 Hz, 1H, 4''-H), 7.75 (dt, *J* = 7.6, 1.1 Hz, 1H, 3''-H), 7.93 (ddd, *J* = 7.7, 1.7, 1.2 Hz, 1H, 6'-H), 8.02 (ddd, *J* = 7.7, 1.7, 1.2 Hz, 1H, 4'-H), 8.53 (t, *J* = 1.7 Hz, 1H, 2'-H), 8.64 (ddd, *J* = 4.8, 1.8, 1.1 Hz, 1H, 6''-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.3 (*C*H$_3$C(7)), 20.9 (CH$_3$-12), 26.3 (CH$_3$-13), 28.7 (CH$_2$-9), 38.9 (CH-7), 41.4 (C-11), 46.8 (CH-8), 47.0 (CH-10), 117.2 (CH-4), 120.7 (CH-3''), 122.1 (CH-5''), 125.2 (CH-2'), 126.8 (CH-6'), 127.3 (CH-4'), 129.0 (CH-5'), 133.3 (CH-3), 136.7 (CH-4''), 139.7 (C-5), 140.4 (C-1'), 140.5 (C-3'), 149.6 (CH-6''), 154.1 (C-2''), 157.6 (C-2), 160.6 (C-6);

MS (EI) *m/z* (%) 340 ($M^{\bullet+}$, 18), 325 (22, $M^{\bullet+}$-CH_3), 82.9 (100); **HRMS** (EI) 340.1935 ($C_{24}H_{24}N_2$ requires 340.1939).

(7*R*,8*S*,10*S*)-(–)-2-[3'-(2''-Pyridinyl)phenyl]-7-isopropyl-11,11-dimethyl-1-azatricyclo[7.1.1.$0^{5,6}$]undeca-2,4,6-triene (–)-169b



$C_{26}H_{28}N_2$
Mol. Wt.: 368.51

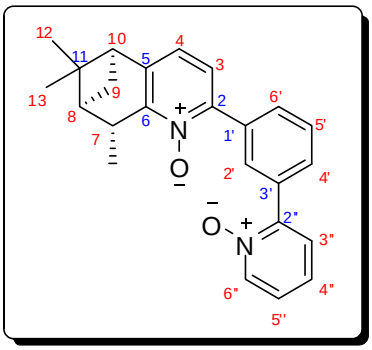
(–)-169b (84 mg, 37%): **$[\alpha]_D^{22}$** –1.9 (*c* 1.0, CH_2Cl_2); **IR** (NaCl) ν 2957 (m, C-H), 1585 (m, C=Car), 1565 (m, C=Car), 1434 (m, C=Car), 777 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.58 (s, 3H, 12-H), 0.81 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$), 1.18 (d, *J* = 7.0 Hz, 3H, CHC*H*'$_3$), 1.35 (d, *J* = 9.8 Hz, 1H, 9-H), 1.36 (s, 3H, 13-H), 2.32 (td, *J* = 5.9, 1.8 Hz, 1H, 8-H), 2.52 (dt, *J* = 9.8, 5.8 Hz, 1H, 9-H'), 2.68 (t, *J* = 5.8 Hz, 1H, 10-H), 2.80-2.90 (m, 1H, C*H*(CH$_3$)$_2$), 2.93 (dd, *J* = 4.2, 1.8 Hz, 1H, 7-H), 7.16 (ddd, *J* = 7.5, 4.1, 1.1 Hz, 1H, 5''-H), 7.19 (d, *J* = 7.8 Hz, 1H, 3-H), 7.48 (d, *J* = 7.8 Hz, 1H, 4-H), 7.50 (t, *J* = 7.7 Hz, 1H, 5'-H), 7.69 (td, *J* = 7.5 ,1.7 Hz, 1H, 4''-H), 7.75 (dt, *J* = 7.5, 1.1 Hz, 1H, 3''-H), 7.94 (d, *J* = 7.8 Hz, 1H, 6'-H), 8.06 (d, *J* = 7.8 Hz, 1H, 4'-H), 8.55 (s, 1H, 2'-H), 8.65 (ddd, *J* = 4.1, 1.7, 1.1 Hz, 1H, 6''-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.1 (*C*H$_3$CH), 21.0 (CH$_3$-12), 22.3 (*C*'H$_3$CH), 26.3 (CH$_3$-13), 29.4 (CH$_2$-9), 30.2 (*C*H(CH$_3$)$_2$), 41.2 (CH-8), 41.8 (C-11), 46.5 (CH-10), 49.1 (CH-7), 117.0 (CH-4), 120.6 (CH-3''), 122.0 (CH-5''), 125.0 (CH-2'), 126.7 (CH-6'), 127.2 (CH-4'), 129.0 (CH-5'), 133.3 (CH-3), 136.7 (CH-4''), 139.6 (C-5), 140.5 (C-1'), 140.9 (C-3'), 149.5 (CH-6''), 153.6 (C-2''), 157.5 (C-2), 159.1 (C-6); **MS** (EI) *m/z* (%) 368 ($M^{\bullet+}$, 22), 325 ($M^{\bullet+}$-*i*-Pr, 100), 283 (71); **HRMS** (EI) 368.2249 ($C_{26}H_{28}N_2$ requires 368.2252).

General Procedure for the *N*-Oxidation of Pyridine Derivatives 169a-b

m-Chloroperoxybenzoic acid (70%, 106 mg, 0.60 mmol, 4.0 equiv) was added portion-wise to a respective cool (0 °C) solution of (+)-**169a** (50 mg, 0.15 mmol, 1.0 equiv) and (–)-**169b**

(55 mg, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL). The mixture was then allowed to warm up to room temperature and stirred overnight. The mixture was washed with an aqueous solution of $NaHCO_3$ (10%; 5 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (10 g) using ethyl acetate to remove the unreacted starting material and some by-products, followed by methanol to afford pure (–)-**170a** and (–)-**170b** respectively.

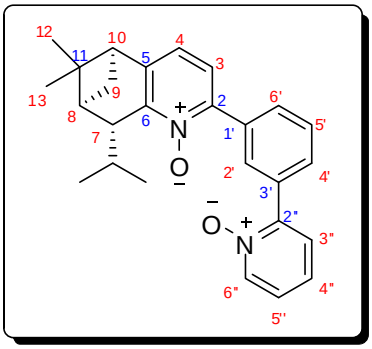
(7*R*,8*S*,10*S*)-(–)-2-[3'-(1''-oxido-2''-pyridinyl)phenyl]-7-11,11-trimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene-1-oxide (–)-170a



$C_{24}H_{24}N_2O_2$
Mol. Wt.: 372.46

(–)-170a (23 mg, 42%): **[α]$_D^{14}$** –31.0 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2933 (m, C-H), 1585 (m, C=Car), 1462 (m, C=Car), 1431 (m, C=Car), 1216 (m, N^+-O^-), 761 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.57 (s, 3H, 12-H), 1.33 (s, 3H, 13-H), 1.36 (d, *J* = 9.9 Hz, 1H, 9-H), 1.41 (d, *J* = 6.6 Hz, 3H, CH_3C(7)), 2.08 (td, *J* = 6.0, 2.8 Hz, 1H, 8-H), 2.48 (dt, *J* = 9.9, 6.0 Hz, 1H, 9-H'), 2.71 (t, *J* = 6.0 Hz, 1H, 10-H), 3.33 (qd, *J* = 6.6, 2.8 Hz, 1H, 7-H), 6.82 (d, *J* = 7.8 Hz, 1H, 3-H), 7.12-7.18 (m, 2H, 4-H, 5''-H), 7.22 (td, *J* = 7.7, 1.1 Hz, 1H, 4''-H), 7.42 (dd, *J* = 7.7, 2.0 Hz, 1H, 3''-H), 7.48 (t, *J* = 7.8 Hz, 1H, 5'-H), 7.77 (dd, *J* = 7.8, 1.7 Hz, 2H, 6'-H, 4'-H), 8.13 (t, *J* = 1.7 Hz, 1H, 2'-H), 8.24 (dd, *J* = 6.4, 1.1 Hz, 1H, 6''-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.7 (CH_3C(7)), 20.5 (CH_3-12), 25.8 (CH_3-13), 28.2 (CH_2-9), 35.0 (CH-7), 41.5 (C-11), 46.8 (CH-10), 47.3 (CH-8), 123.1 (CH-3), 124.3 (CH-3), 124.6 (CH-5''), 125.9 (CH-4''), 127.7 (CH-3''), 128.0 (CH-5'), 129.7 (CH-6'), 130.6 (CH-4'), 130.8 (CH-2'), 132.3 (C-5), 133.5 (C-1'), 140.3 (CH-6''), 144.6 (C-3'), 147.0 (C-2''), 149.0 (C-2), 150.1 (C-6); **MS** (FAB) *m/z* (%) 373 ($(M+H)^+$, 31), 338 (100), 215 (10), 75 (96); **HRMS** (FAB) 373.1919 ($C_{24}H_{25}N_2O_2$ $(M+H)^+$ requires 373.1916).

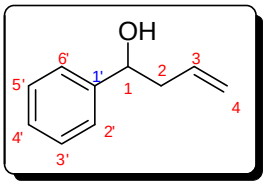
(7*R*,8*S*,10*S*)-(–)-2-[3'-(1''-oxido-2''-pyridinyl)phenyl]-7-isopropyl-11,11-dimethyl-1-azatricyclo[7.1.1.0^{5,6}]undeca-2,4,6-triene-1-oxide (–)-170b



$C_{26}H_{28}N_2O_2$
Mol. Wt.: 400.51

(–)-170b (27 mg, 45%): **[α]$_D^{14}$** –64.0 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2935 (m, C-H), 1587 (m, C=Car), 1465 (m, C=Car), 1436 (m, C=Car), 1216 (m, N^+-O^-), 762 (s, C-Har) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.53 (s, 3H, 12-H), 0.88 (d, *J* = 7.0 Hz, 3H, $CHCH_3$), 0.95 (d, *J* = 7.0 Hz, 3H, $CHCH'_3$), 1.33 (s, 3H, 13-H), 1.54 (d, *J* = 9.9 Hz, 1H, 9-H), 2.31 (td, *J* = 5.8, 2.4 Hz, 1H, 8-H), 2.46 (dt, *J* = 9.9, 5.8 Hz, 1H, 9-H'), 2.67 (t, *J* = 5.8 Hz, 1H, 10-H), 3.10-3.20 (m, 2H, 7-H, $CH(CH_3)_2$), 6.81 (d, *J* = 7.8 Hz, 1H, 4-H), 7.11-7.17 (m, 2H, 3-H, 5''-H), 7.21 (td, *J* = 7.7, 1.2 Hz, 1H, 4''-H), 7.42 (dd, *J* = 7.7, 2.0 Hz, 1H, 3''-H), 7.48 (t, *J* = 7.8 Hz, 1H, 5'-H), 7.74-7.78 (m, 2H, 6'-H, 4'-H), 8.09 (t, *J* = 1.5 Hz, 1H, 2'-H), 8.24 (dd, *J* = 6.4, 1.2 Hz, 1H, 6''-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.6 (CH_3-12), 20.9 (CH_3CH), 21.5 ($C'H_3CH$), 25.8 (CH_3-13), 27.8 ($CH(CH_3)_2$), 28.2 (CH_2-9), 42.3 (CH-8), 42.9 (C-11), 45.5 (CH-7), 46.6 (CH-10), 123.0 (CH-4), 124.3 (CH-3), 124.6 (CH-5''), 125.8 (CH-4''), 127.7 (CH-3''), 128.1 (CH-5'), 129.6 (CH-6'), 130.5 (CH-4'), 130.8 (CH-2'), 132.4 (C-5), 133.8 (C-1'), 140.3 (CH-6''), 145.2 (C-3'), 147.2 (C-2''), 149.0 (C-2), 149.2 (C-6); **MS** (FAB) *m/z* (%) 401 ($(M+H)^+$, 100), 385 ($(M+H)^+$-O, 26), 338 (23), 71 (20); **HRMS** (FAB) 401.2232 ($C_{26}H_{29}N_2O_2$ $(M+H)^+$ requires 401.2229).

1-Phenyl-3-buten-1-ol 141



$C_{10}H_{12}O$
Mol. Wt.: 148.20

Allyl trichlorosilane (80 µL, 0.47 mmol, 1.1 equiv) was added dropwise to a solution of the appropriate *N*-oxide (0.04 mmol, 10 mol%), ethyldiisopropylamine (0.35 mL, 2 mmol, 4.0 equiv) and benzaldehyde (41 µL, 0.4 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at -20 °C and the resulting mixture was stirred at that temperature overnight. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction, the aqueous layer was then extracted with CH_2Cl_2 (3×10 mL), and the combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was then purified by flash column chromatography on silica gel (15 g) using a mixture of petroleum ether and ethyl acetate (6:1) to afford pure **141** (for yields, see **Table 23** and **24**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.06 (brs, 1H, OH), 2.38-2.48 (m, 2H, 2-H), 4.65 (t, J = 6.2 Hz, 1H, 1-H), 5.04-5.11 (m, 2H, 4-H), 5.67-5.78 (m, 1H, 3-H), 7.16-7.22 (m, 1H, 4'-H), 7.25-7.29 (m, 4H, 2'-H, 3'-H, 5'-H, 6'-H) in agreement with literature data;[166] **Chiral HPLC** (IB, 0.75 mL.min^{-1}, hexane/2-propanol, 97.5:2.5) t_R = 13.5 min, t_S = 15.5 min.

7 References

[1] (a) Rouhi, A. M. *Chem. Eng. News* **2004**, June 14, p. 47. (b) Rouhi, A. M. *Chem. Eng. News* **2004**, Sept. 6, p. 41.

[2] Stinson, S. C. *Chem. Eng. News* **2001**, Oct. 1, p. 79.

[3] Seyden-Penne, J. *Chial auxiliaries and ligands in asymmetric synthesis*, Wiley: New-York **1995**.

[4] (a) Ojima, I. *Catalytic Asymmetric Synthesis*, Wiley-VCH: Weinheim, **1993**. (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*, Springer: Heidelberg, **1999**.

[5] Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*, Wiley-VCH: Weinheim, **2002**.

[6] For an excellent account of this area, see: (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; VCH: Weinheim, **2004**. (b) Dalko, P. I. *Enantioselective Organocatalysis*; Willey-VCH: Weinheim, **2007**.

[7] For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed. 2001*, *40*, 3726. (b) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (c) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.

[8] Ager, D. J. *Handbook of Chiral Chemicals*, Marcel Dekker, inc., New York **1999**.

[9] Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486.

[10] Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **1995**, *500*, 1 and references therein.

[11] Paterson, I; Lister, M. A.; McClure, C. K. Tetrahedron Lett. **1986**, *26*, 4787.

[12] Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.*, **1983**, *105*, 2077.

[13] For a recent review on camphor-based ligands, see: Chelucci, G. *Chem. Soc. Rev.* **2006**, *35*, 1230.

[14] Knühl, G.; Sennhenn, P.; Helmchen, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1845.

[15] Gavryushin, A.; Polborn, K.; Knochel, P. *Tetrahedron: Asymmetry* **2004**, *15*, 2279.

[16] (a) Gladiali, S.; Chelucci, G.; Soccolini, F.; Delogu, G.; Chessa, G. *J. Organomet. Chem.* **1989**, *370*, 285. (b) Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1992**, *48*, 3653. (c) Chelucci, G.; Cabras, M. A.; Saba, A. *J. Mol. Catal. A: Chemical* **1995**, *95*, L7. (d) Chelucci, G.; Caria, V.; Saba, A. *J. Mol. Catal. A: Chemical* **1998**, *130*, 51.

[17] Hayoz, P.; von Zelewsky, A. *Tetrahedron Lett.* **1992**, *33*, 5165.

[18] For reviews concerning the CHIRAGEN ligands and their applications, see: (a) Knof, U.; von Zelewsky, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 302. (b) von Zelewsky, A. *Coord. Chem. Rev.* **1999**, *190-192*, 811. (c) Mamula, O.; von Zelewsky, A. *Coord. Chem. Rev.* **2003**, *242*, 87.

[19] For some selected publications, see: (a) Hayoz, P.; von Zelewsky, A.; Stoeckli-Evans, H. *J. Am. Chem. Soc.* **1993**, *115*, 5111. (b) Fletcher, N. C.; Keene, F. R.; Ziegler, M.; Stoeckli-Evans, H.; Viebrock, H.; von Zelewsky, A. *Helv. Chim. Acta* **1996**, *79*, 1192. (c) Gianini, M.; von Zelewsky, A.; Stoeckli-Evans, H. *Inorg. Chem.* **1997**, *36*, 6094. (d) Ziegler, M.; Monney, V.; Stoeckli-Evans, H.; von Zelewsky, A.; Sasaki, I.; Dupic, G.; Daran, J-C.; Balavoine, G. G. A. *J. Chem. Soc. Dalton Trans.* **1999**, 667. (e) Mamula, O.; von Zelewsky, A.; Bark, T.; Stoeckli-Evans, H.; Neels, A.; Bernardinelli, G. *Chem. Eur. J.* **2000**, *6*, 3575. (f) Lötscher, D.; Rupprecht, S.; Collomb, P.; Belser, P.; Viebrock, H.; von Zelewsky, A.; Burger, P. *Inorg. Chem.* **2001**, *40*, 5675. (g) Kolp, B.; Abeln, D.; Stoeckli-Evans, H.; von Zelewsky, A. *Eur. J. Inorg. Chem.* **2001**, 1207. (h) Suhr, D.; Lötscher, D.;

Stoeckli-Evans, H.; von Zelewsky, A. *Inorg. Chimi. Acta* **2002**, *341*, 17. (i) Loï, M.; Gilby, L. M.; von Zelewsky, A. *Synth. Comm.* **2002**, *32*, 119. (j) Quinodoz, B.; Labat, G.; Stoeckli-Evans, H.; von Zelewsky, A. *Inorg. Chem.* **2004**, *43*, 7994.

[20] For some selected publications, see: (a) Malkov, A. V.; Bella, M.; Langer, V.; Kočovský, P. *Org. Lett.* **2000**, *2*, 3047. (b) Chelucci, G.; Saba, A. *Synth. Comm.* **2001**, *31*, 3161. (c) Chelucci, G.; Chessa, S.; Orrù, G. *J. Mol. Catal. A: Chemical* **2004**, *220*, 145. (d) Chelucci, G.; Muroni, D.; Manca, I. *J. Mol. Catal. A: Chemical* **2005**, *225*, 11.

[21] For reviews concerning 2,2'-bipyridines, see: (a) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129. (b) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831.

[22] Collomb, P.; von Zelewsky, A. *Tetrahedron: Asymmetry* **1998**, *9*, 3911.

[23] Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry* **1998**, *9*, 531.

[24] Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 4727.

[25] Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659.

[26] Chelucci, G.; Craba, S.; Saba, A.; Soccolini, F.; Sotgiu, G. *J. Mol. Catal. A: Chemical* **2000**, *164*, 173.

[27] (a) Chelucci, G.; Cabras, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 965. (b) Chelucci, G.; Muroni, D.; Pinna, G. A.; Saba, A.; Vignola, D. *J. Mol. Catal. A: Chemical* **2003**, *191*, 1. (c) Chelucci, G.; Muroni, D.; Saba, A.; Soccolini, F. *J. Mol. Catal. A: Chemical* **2003**, *197*, 27.

[28] Chelucci, G.; Saba, A.; Soccolini, F. *Tetrahedron* **2001**, *57*, 9989.

[29] Malkov, A. V.; Bella, M.; Stará, I. G.; Kočovský, P. *Tetrahedron Lett.* **2001**, *42*, 3045.

[30] (a) Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kočovský, P. *J. Mol. Catal. A: Chemical* **2003**, *196*, 179. (b) Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219.

[31] Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, Vol. 2, 2nd Ed., Wiley-VCH, Weinheim **2004**.

[32] (a) Knowles, W. R. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998. (b) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008. (c) Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024.

[33] Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625.

[34] Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1848.

[35] Gusso, A.; Baccin, C.; Pinna, F.; Strukul, G. *Organometallics* **1994**, *13*, 3442.

[36] For a review: see, Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272.

[37] For reviews on phosphine-oxazoline iridium complexes for hydrogenation, see: (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (b) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33. (c) Roseblade, S. J.; Pfaltz, A. *C. R. Chimie* **2007**, *10*, 178. (d) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402.

[38] For reviews see: (a) Hassall, C. H. *Org. React.* **1957**, *9*, 73. (b) Krow, G. C. *Org. React.* **1993**, *43*, 251. (c) Strukul, G. *Angew. Chem. Int. Ed.* **1998**, *37*, 1198. (d) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737. (e) Le Paith, J.; Frison, J.-C.; Bolm, C. In *Modern Oxidation Methods* (J.-E. Bäckvall, Ed), Wiley-VCH, Weinheim **2004**, p. 267. (f) Bolm, C.; Palazzi, C.; Beckmann, O. In *Transition Metals for Organic Synthesis, Vol. 2, 2nd Ed.* (M. Beller, C. Bolm, Eds), Wiley-VCH, Weinheim **2004**, p. 267.

[39] Criegee, R. *Justus Liebigs Ann. Chem.* **1948**, *560*, 127.

[40] Doering, W. v. E.; Dorfman, E. *J. Am. Chem. Soc.* **1953**, *75*, 5595.

[41] Doering, W. v. E.; Speers, L. *J. Am. Chem. Soc.* **1950**, *72*, 5515.

[42] Murray, M. F.; Johnson, B. A.; Pederson, R. L.; Ott, A. C. *J. Am. Chem. Soc.* **1956**, *78*, 981.

[43] Turner, R. B.; *J. Am. Chem. Soc.* **1950**, *72*, 878.

[44] Mukaiyama, T.; Yamada, T. *Bull. Chem. Soc. Jpn*, **1995**, *68*, 17.

[45] (a) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533. (b) Allan, G.; Carnell, A. J.; Escudero Hermandez, M. L.; Pettman, A. *Tetrahedron* **2001,** *57*, 8193.

[46] For recent reviews on asymmetric metal-catalysed Baeyer-Villiger oxidation, see: (a) Bolm, C.; Beckmann, O. In *Comprehensive Asymmetric Catalysis* (E. N. Jacobsen; A. Pfaltz; H. Yamamoto, Eds), Springer, Heidelberg **1999**; Chapter 22. (b) Katsuki, T. *Russ. Chem. Bull. Int. Ed.* **2004**, *53*, 1859. (c) Bolm, C. In *Asymmetric Synthesis – The Essentials* (Christmann, M.; Bräse, S., Eds), Wiley-VCH, **2006**, p. 55.

[47] Suzuki, M.; Takada, H.; Noyori, R. *J. Org. Chem.* **1982**, *47*, 902.

[48] Matsubara, S.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2029.

[49] Hao, X.; Yamazaki, O.; Yoshida, A.; Nishikido, J. *Tetrahedron Lett.* **2003**, *44*, 4977.

[50] Jacobson, S. E.; Tang, R.; Mares, F. *J. Chem. Soc. Chem. Commun.* **1978**, 888.

[51] Campestrini, S.; Di Furia, F. *J. Mol. Cat.* **1993**, *79*, 13.

[52] (a) Hermann, W. A. *J. Organomet. Chem.* **1995**, *500*, 149. (b) Phillips, A. M. F.; Romão, C. *Eur. J. Org. Chem.* **1999**, 1767.

[53] (a) Del Todesco Frisone, M.; Pinna, F.; Strukul, G. *Organometallics* **1993**, *12*, 148. (b) Baccin, C.; Gusso, A.; Pinna, F.; Strukul, G. *Organometallics* **1995**, *14*, 1161.

[54] Yamada, T.; Takahashi, K.; Kato, K.; Takai, T.; Inoki, S.; Mukaiyama, T. *Chem. Lett.* **1991**, 641.

[55] Murahashi, S-I.; Oda, Y.; Naota, T. *Tetrahedron Lett.* **1992**, *33*, 7557.

[56] For reviews see: (a) Mihovilovic, M. D.; Müller, B.; Stanetty, P. *Eur. J. Org. Chem.* **2002**, 3711. (b) Alphand, V.; Furstoss, R. In *Enzymes Catalysis in Organic Synthesis* (K. Drauz; H. Waldmann, Eds), VCH, Weinheim **1995**, p. 754 and references therein.

[57] Murahashi, S-I.; Ono, S.; Imada, Y. *Angew. Chem. Int. Ed.* **2002**, *41*, 2366.

[58] (a) Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. *Tetrahedron Lett.* **1996**, *37*, 7583. (b) Kanger, T.; Kriis, K.; Paju, A.; Pehk, T.; Lopp, M. *Tetrahedron: Asymmetry* **1998**, *9*, 4475.

[59] (a) Bolm, C.; Schlingloff, G. *J. Chem. Soc. Chem. Commun.* **1995**, 1247. (b) Bolm, C.; Kim Khanh Luong, T.; Schlingloff, G. *Synlett* **1997**, 1151. (c) Bolm, C.; Schlingloff, G.; Bienewald, F. *J. Mol. Catal. A* **1997**, *117*, 347.

[60] Bolm, C.; Beckmann, O. *Chirality* **2000**, *12*, 523.

[61] Shinohara, T.; Fujioka, S.; Kotsuki, H. *Heterocycles* **2001**, *55*, 237.

[62] Bolm, C.; Beckmann, O.; Cosp, A.; Palazzi, C. *Synlett* **2001**, *9*, 1461.

[63] (a) Bolm. C.; Beckmann, O.; Palazzi, C. *Can. J. Chem.* **2001**, *79*, 1593. (b) Bolm, C.; Beckmann, O.; Kühn, T.; Palazzi, C.; Adam, W.; Rao, P. B.; Saha-Möller, C. R. *Tetrahedron: Asymmetry* **2001**, *12*, 2441. (c) Bolm, C.; Frison, J-C.; Zhang, Y.; Wulff, W. D. *Synlett* **2004**, *9*, 1619. (d) Frison, J-C.; Palazzi, C.; Bolm, C. *Tetrahedron* **2006**, *62*, 6700.

[64] (a) Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 6911. (b) Uchida, T.; Katsuki, T. *Helv. Chim. Acta* **2002**, *85*, 3078.

[65] Watanabe, A.; Uchida, T.; Ito, K.; Katsuki, T. *Tetrahedron Lett.* **2002**, *43*, 4481.

[66] Matsumoto, K.; Watanabe, A.; Uchida, T.; Ogi, K.; Katsuki, T. *Tetrahedron Lett.* **2004**, *45*, 2385.

[67] Ito, K.; Ishii, A.; Kuroda, T.; Katsuki, T. *Synlett* **2003**, *5*, 643.

[68] Sugimura, T.; Fujiwara, Y.; Tai, A. *Tetrahedron Lett.* **1997**, *38*, 6019.

[69] Aoki, M.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 187.

[70] Miyake, Y.; Nishibayashi, Y.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2233.

[71] Evans, D.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *Nature* **1965**, *208*, 1203.

[72] (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis, 2nd Ed.* (I. Ojima, Ed), Wiley-VCH, Weinheim **2000**, Chapter 1. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis* (E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds), Springer, Heidelberg **1999**, Chapter 5.1.

[73] Halterman, R. H. In *Comprehensive Asymmetric Catalysis* (E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds), Springer, Heidelberg **1999**, Chapter 5.2.

[74] (a) Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569. (b) Troutman, M. V.; Appella, D. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4916.

[75] (a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205. (b) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

[76] (a) Lightfoot, A.; Schnider, P.; Pflatz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2897. (b) Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Rosner, T.; Schnider, P.; Zimmermann, N. *Chirality* **2000**, *12*, 442.

[77] Smidt, S. P.; Zimmermann, N.; Studer, M.; Pfaltz, A. *Chem. Eur. J.* **2004**, *10*, 4685.

[78] Cozzi, P. G.; Zimmermann, N.; Hilgraf, R.; Schaffner, S.; Pfaltz, A. *Adv. Synth. Catal.* **2001**, *343*, 450.

[79] Li, X.; Li, Q.; Wu, X.; Gao, Y.; Xu, D.; Kong, L. *Tetrahedron : Asymmetry* **2007**, *18*, 629.

[80] Xu, G.; Gilbertson, S. *Tetrahedron Lett.* **2003**, *44*, 953.

[81] Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 2318.

[82] Tang, W.; Wang, W.; Zhang, X. *Angew. Chem. Int. Ed.* **2003**, *42*, 943.

[83] (a) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513. (b) Liu, D.; Dai, Q.; Zhang, X. *Tetrahedron* **2005**, *61*, 6460.

[84] Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713.

[85] (a) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3941. (b) Bunlaksananusorn, T.; Knochel, P. *J. Org. Chem.* **2004**, *69*, 4595.

[86] Drury III, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 70.

[87] Li, X.; Kong, L.; Gao, Y.; Wang, X. *Tetrahedron Lett.* **2007**, *48*, 3915.

[88] Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995.

[89] Bernardinelli, G. H.; Kündig, E. P.; Meier, P.; Pfaltz, A.; Radkowski, K.; Zimmermann, N.; Neuburger-Zehnder, M. *Helv. Chim. Acta* **2001**, *84*, 3233.

[90] Schenkel, L. B.; Ellman, J. A. J. Org. Chem. 2004, 69, 1800.

[91] Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023.

[92] Blankenstein, J.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4445.

[93] Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, *344*, 40.

[94] Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308.

[95] (a) Liu, Q-B.; Yu, C-B.; Zhou, Y-G. *Tetrahedron Lett.* **2006**, *47*, 4733. (b) Liu, Q-B.; Zhou, Y-G. *Tetrahedron Lett.* **2007**, *48*, 2101.

[96] Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5194.

[97] (a) Powell, M. T.; Hou, D-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878. (b) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113.

[98] Källström, K.; Andersson, P. G. *Tetrahedron Lett.* **2006**, *47*, 7477.

[99] (a) Bolm, C.; Focken, T.; Raabe, G. *Tetrahedron: Asymmetry* **2003**, *14*, 1733. (b) Focken, T.; Raabe, G.; Bolm, C. *Tetrahedron: Asymmetry* **2004**, *15*, 1693.

[100] Källström, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. *Adv. Synth. Catal.* **2006**, *348*, 2575.

[101] Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536.

[102] Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, *9*, 1659.

[103] Mazet, C.; Smidt, S. P.; Meuwly, M.; Pfaltz, A. *J. Am. Chem. Soc.* **2004**, *126*, 14176.

[104] Fan, Y.; Cui, X.; Burgess, K.; Hall, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 16688.

[105] Dietiker, R.; Chen, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 5513.

[106] Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

[107] Dang, T. P.; Kagan, H. B. *J. Chem. Soc. Chem. Commun.* **1971**, 481.

[108] For reviews concerning the asymmetric application of *P*,*N*-ligands, see: (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (b) Chelucci, G.; Orrù, G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471. (c) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.

[109] For the original publication, see: Zecher, W.; Kröhnke, F. *Chem. Ber.* **1961**, *69*, 690. For a review, see: Kröhnke, F. *Synthesis* **1976**, 1.

[110] Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135.

[111] (a) Horner, L.; Balzer, W. D. *Tetrahedron Lett.* **1965**, *6*, 1157. (b) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887. (c) Wu, H-C.; Yu, J-Q.; Spencer, J. B. *Org. Lett.* **2004**, *6*, 4675.

[112] For a review concerning borane-protected phosphines, see: Ohff, M.; Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1998**, 1391.

[113] Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244.

[114] Boekelheide, V. C.; Linn, W. J. *J. Am. Chem. Soc.* **1954**, *76*, 1286.

[115] Mitsunobu, O. *Synthesis* **1981**, 1.

[116] Dodge, J.; Nissen, J.; Presnell, M. *Organic Syntheses*, Coll. Vol. 9, 607; Vol 73, 110.

[117] Cappelli, A.; Anzini, M.; Vomero, S.; Canullo, L.; Mennuni, L.; Markovec, F.; Doucet, E.; Hamon, M.; Menziani, M. C.; De Benedetti, P. G.; Bruni, G.; Romeo, M. R.; Giorgi, G.; Donati, A. *J. Med. Chem.* **1999**, *42*, 1556.

[118] Ueno, H.; Maruyama, A.; Miyake, M.; Nakao, E.; Nakao, K.; Umezu, K.; Nitta, I. *J. Med. Chem.* **1991**, *34*, 2468.

[119] Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 2446.

[120] Rahaim, R.; Maleczka, R. *Tetrahedron Lett.* **2002**, *43*, 8823.

[121] (a) Williams, D. B. G; Lombard, H.; van Niekerk, M.; Coetzee, P. P. *Phosphorus, Sulfur and Silicon* **2002**, *177*, 2115. (b) Williams, B. S.; Dani, P.; Lutz, M.; Spek, A. L.; van Koten, G. *Helv. Chim. Acta* **2001**, *84*, 3519.

[122] For method, see, e.g.: Kündig, E. P.; Meier, P. *Helv. Chim. Acta* **1999**, *82*, 1360.

[123] For the method, see: Tsvetkov, E. N.; Bondarenko, N. A.; Malakhova, I. G.; Kabachnik, M. I. *Synthesis* **1986**, 198.

[124] (a) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879. (b) Hassner, A.; Dillon, J. L. *J. Org. Chem.* **1983**, *48*, 3382.

[125] Koul, S.; Singh, B.; Taneja, S. C.; Qazi, G. N. *Tetrahedron* **2003**, *59*, 3487.

[126] We would like to thank Dr. Andy Parkin for the X-ray analysis of iridium complex (+)-**133b**.

[127] Verendel, J. J.; Andersson, P. G. *Dalton trans.* **2007**, 5603.

[128] Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G.; Valoti, E. *J. Org. Chem.* **1991**, *56*, 183.

[129] (a) Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887. (b) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825. (c) Blanc, C.; Agbossou-Niedercorn, F.; Nowogrocki, G. *Tetrahedron: Asymmetry* **2004**, *15*, 2159. (d) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 2318. (e) Cheemala, M. N.; Knochel, P. *Org. Lett.* **2007**, *9*, 3089.

[130] Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kočovský, P. *Org. Lett.* **2004**, *6*, 2253.

[131] Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.

[132] For reviews, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373. (c) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29.

[133] Brook, M. A. Silicon in *Organic Organometallic and Polymer Chemistry*; John Wiley & Sons, Inc: Toronto, **2000**.

[134] Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; (J. Otera: Ed.); Wiley-VCH: Weinheim, **2000**, Chapter 11.

[135] Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807.

[136] Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.

[137] Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200.

[138] (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453. (b) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620.

[139] Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161.

[140] (a) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kobayashi, Y. *Tetrahedron Lett.* **1996**, *37*, 5149. (b) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513.

[141] Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021.

[142] Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488.

[143] Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419.

[144] (a) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 2767. (b) Iseki, K.; Mizuno, S.; Kobayashi, S.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977.

[145] Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799.

[146] Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4,* 1047.

[147] Malkov, A. V.; Dufkova, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3674.

[148] Wong, W-L.; Lee, C-S.; Leung, H-K.; Kwong, H-L. *Org. Biomol. Chem.* **2004**, *2*, 1967.

[149] Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005**, *7*, 3151.

[150] Uenishi, J.; Hamada, M. *Synthesis* **2002**, 625.

[151] Gomez-Vidal, J.; Silverman, R. *Org. Lett.* **2001**, *3*, 2481.

[152] Gribble, G. W.; Nutaitis, C. F. *Synthesis* **1987**, 709.

[153] Ding, C. L.; Lu, X.; Nishimura, K.; Silverman, R. B. *J. Med. Chem.* **1993**, *36*, 1711.

[154] Kourist, R.; Gonzalez-Sabin, J.; Liz, R.; Rebolledo, F. *Adv. Synth. Catal.* **2005**, *347*, 695.

[155] Kinnaird, J. W. A.; Yee Ng, P.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920.

[156] Cao, W.; Erden, I.; Grow, R. H.; Keeffe, J. R.; Song, J.; Trudell, M. B.; Wadsworth, T. L.; Xu, F-P.; Zheng, J-B. *Can. J. Chem.* **1999**, *77*, 1009.

[157] Coelho, F.; Azevedo, M. B. M.; Boschiero, R.; Resende, P. *Synth. Commun.* **1997**, *27*, 2455.

[158] Srivastava, R. R.; Singhaus, R. R.; Kabalka, G. W. *J. Org. Chem.* **1999**, *64*, 8495.

[159] Depres, J-P.; Navarro, B.; Greene, A. E. *Tetrahedron* **1989**, *45*, 2989.

[160] Bolm, C.; Beckmann, O.; Kühn, T.; Palazzi, C.; Adam, W.; Bheema Rao, P.; Saha-Möller, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2441.

[161] Resende, P.; Almeida, W. P.; Coelho, F. *Tetrahedron: Asymmetry* **1999**, *10*, 2113.

[162] Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047.

[163] Imada, Y.; Iida, H.; Murahashi, S-I.; Naota, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 1704.

[164] Lawston, I. W.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1983**, *11*, 2629.

[165] Oi, S.; Taira, A.; Honma, Y.; Sato, T.; Inoue, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 598.

[166] Loh, T-P.; Zhou, J-R.; Yin, Z. *Org. Lett.* **1999**, *1*, 1855.