



Chapter 1

Introduction

1.1 Transition Metal-Catalyzed Asymmetric Hydrogenation: A Brief

Introduction^[1]

After the pioneering work by Wilkinson and Coffey, who discovered that a phosphine-based rhodium catalyst ($[\text{RhCl}(\text{PPh}_3)_3]$) was able to catalyze the reduction of unsaturated carbon-carbon bonds,^[2] metal-catalyzed hydrogenation has attracted increasing interest and has been developed into an extremely powerful method in the organic chemist's repertoire. In particular the preparation and deployment of chiral catalysts that enable the enantioselective hydrogenation of prochiral, unsaturated compounds to give highly enantioenriched molecules has been the object of numerous studies. The quest for chiral transition metal complexes to be used as homogeneous catalysts for hydrogenation started in the late 1960s. A milestone in this discovery process is the work of Knowles, who developed a chiral version of the Wilkinson catalyst by replacing the triphenylphosphine with a chiral phosphine (CAMP, Figure 1)^[3] and, later on, with a bisphosphine ligand (DIPAMP) inspired by Kagan (DIOP).^[4]

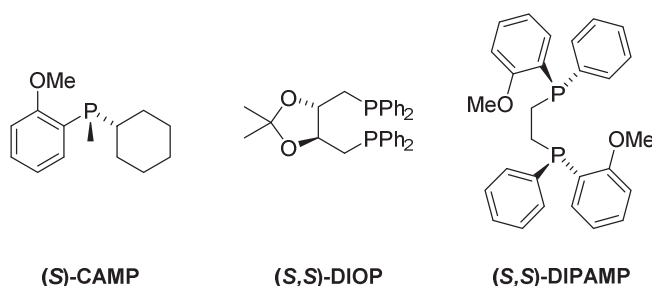


Figure 1: Structure of the first generation phosphine and bisphosphines used in rhodium-catalyzed asymmetric hydrogenation.

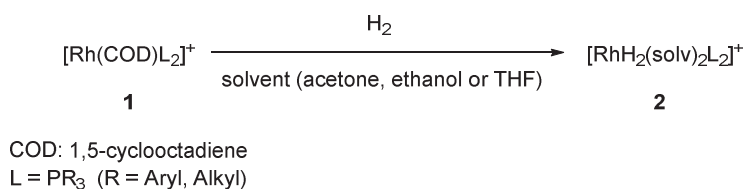
Following these seminal studies, a plethora of chiral phosphine-based ligands were developed in a short period of time for the rhodium-catalyzed asymmetric hydrogenation of C=C bonds.^[5] The substrate scope of this reaction though was limited to α -dehydroamino acids,^[4d] until the discovery that the BINAP-ruthenium system developed



by Noyori could be used to catalyze the asymmetric hydrogenation of a broader range of functionalized alkenes and, subsequently, ketones.^[6]

The fundamental work carried out by Knowles and Noyori in this field was awarded with the Nobel Prize for Chemistry in 2001.^[6d,7]

Besides the use of neutral rhodium complexes, like the Wilkinson's catalyst, in transition metal-catalyzed hydrogenation, Schrock and Osborn^[8] showed that also cationic species can catalyze this transformation. They found out that rhodium complex **1**, bearing two phosphines and a diene as ligands, reacted under hydrogenation conditions in the presence of a coordinating solvent like acetone, methanol or tetrahydrofuran to afford bis-solvated species **2** (Scheme 1). Such species could be isolated and turned out to be catalytically active.



Scheme 1: Study of the activity of cationic rhodium complexes by Schrock and Osborn.

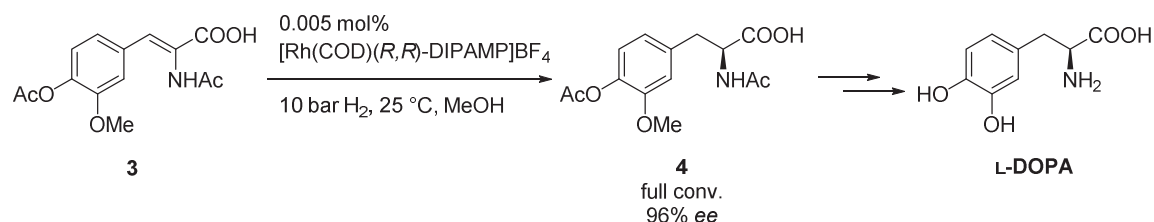
These experiments demonstrated that the dissociation of a solvent molecule from complex **2** is required to allow the coordination of the olefin substrate to the metal center and to start the catalytic cycle. This rate-determining step was found to be fast for these rhodium catalysts,^[9] but it was not for the corresponding iridium analogs, which were almost inactive.^[8a]

The pioneering work of Schrock and Osborn^[8] represents the first application of dienes, and in particular 1,5-cyclooctadiene (COD), as ligands for stabilizing the precatalyst. In the presence of hydrogen the COD ligand is reduced and leaves the coordination sphere of the complexes generating a cationic, coordinatively unsaturated catalyst precursor.

Nowadays, asymmetric hydrogenation is a powerful tool for the stereoselective synthesis of chiral molecules which find widespread application in both academia and industry. In fact, this reaction is characterized by numerous advantages, such as very high enantioselectivities, low catalyst loading, perfect atom economy and high conversions. All these features can be observed in the archetypal rhodium-catalyzed asymmetric

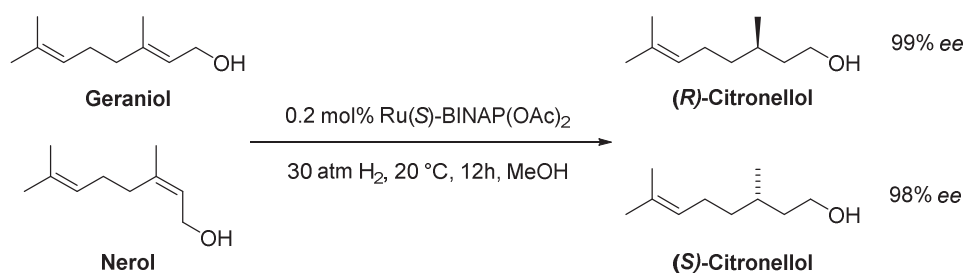


hydrogenation depicted in Scheme 2, where the stereogenic center of **4** is installed by hydrogenation of **3** affording a key intermediate in the synthesis of L-DOPA,^[10] a drug used in the treatment of Parkinson's disease.



Scheme 2: Key step in the synthesis of L-DOPA (Monsanto L-DOPA process).

Another classic example of asymmetric hydrogenation is the synthesis of (*R*)-citronellol, an intermediate in the preparation of vitamin E, or (*S*)-citronellol starting from geraniol or nerol respectively and using $\text{Ru}(\text{S})\text{-}(\text{BINAP})(\text{OAc})_2$ as the catalyst (Scheme 3).^[11]



Scheme 3: Ru catalyzed asymmetric hydrogenation of allylic alcohols.

The major drawback of Rh- and Ru- catalyzed asymmetric hydrogenation is the need for a coordinating group like an alcohol, a carboxylic acid, an amine or an ester, that directs the hydrogenation process, as shown in Scheme 2 and Scheme 3. This feature explains the chemoselectivity observed in Scheme 3, where the trisubstituted olefin adjacent to the alcohol is reduced, while the other double bond at C6 remains untouched. In fact, only a few Ru and Rh complexes bearing chiral bisphosphorous ligands gave successful results in the hydrogenation of unfunctionalized olefins.^[12] This limitation could be overcome by the use of chiral catalysts based on other transition metals, like platinum,^[13] zirconium or titanium. Indeed, after some pioneering work by Kagan,^[14] Vollhardt^[15] and Paquette,^[16] Buchwald described the use of chiral titanium^[17] and zirconium^[18] cyclopentadienyl derivatives for the asymmetric hydrogenation of unfunctionalized olefins. Despite the high enantioselectivities and conversions achieved using this methodology, the catalysts



developed by Buchwald were not broadly used in either academia or industry. Such metal complexes indeed present several disadvantages as they are moisture- and air-sensitive, require harsh reaction conditions and are effective only with a low substrate/catalyst ratio.^[17-18] Moreover, the catalyst precursors need activation by reaction with *n*-BuLi to generate the low-valent titanocene^[17] and zirconocene^[18] complexes.

1.2 Iridium-Catalyzed Asymmetric Hydrogenation^[1b,19]

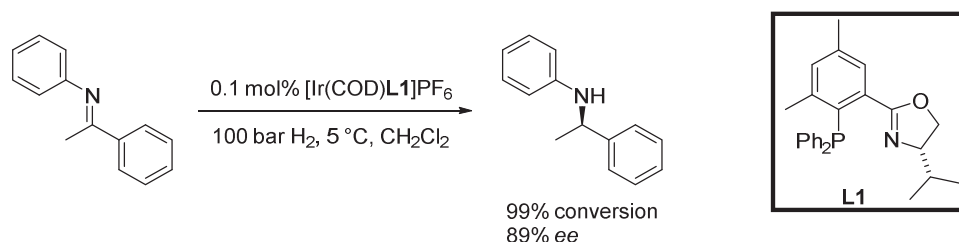
The first report of the use of iridium in hydrogenation reactions has been published by Crabtree,^[20] roughly ten years after the discovery of the Wilkinson catalyst. At that time, the research community was not interested in applying iridium for such transformation, since the iridium analogs of the Wilkinson catalyst, $[\text{IrCl}(\text{PPh}_3)_3]$ was known to react irreversibly with dihydrogen to form the stable $[\text{IrClH}_2(\text{PPh}_3)_3]$ complex. This species, unlike the Wilkinson catalyst, fails to undergo dissociation of a phosphine ligand to allow the binding of the olefin to the metal and thus starting the catalytic cycle.^[9] Similarly, the cationic iridium complexes $[\text{Ir}(\text{COD})\text{PR}_3]^+$ synthesized by Schrock and Osborn^[8], showed weak activity toward hydrogenation of olefins in coordinating solvents (see Scheme 1). Crabtree and coworkers recognized that this low activity was related to the binding strength of the solvent molecules bound to the metal center. They postulated that the strong coordinating solvents used in these experiments inhibit the dissociation of the latter from the active catalyst species, avoiding the coordination of the olefin and thus impeding the catalytic cycle. In order to circumvent catalysts deactivation, Crabtree decided to investigate the activity of $[\text{Ir}(\text{COD})(\text{PR}_3)_2]\text{PF}_6$ complexes in a non-coordinating solvent. After discouraging results in benzene, toluene and hexane, the use of dichloromethane and chloroform resulted in high activities. It was somewhat surprising that chlorinated media were the solvent of choice, since it was known that they might oxidize and deactivate low-valent complexes used in hydrogenation and were therefore avoided in Rh- and Ru-catalyzed hydrogenation.^[2a]

Among many related complexes, $[\text{Ir}(\text{COD})\text{PCy}_3(\text{Py})]\text{PF}_6$, the so-called Crabtree catalyst, turned out to be the most active catalyst for the hydrogenation of di-, tri- and tetra-substituted unfunctionalized olefins in non-coordinating solvents.^[8b,21] The disadvantage



of such complex is the competitive degradation to inactive dimers or trimers during the course of the reaction, which explains the low levels of conversion observed in spite of the high initial turnover frequency (TOF) observed.^[22]

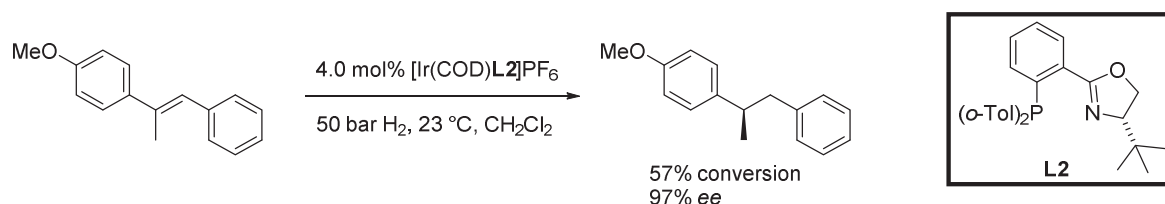
While the first chiral version of the Wilkinson catalyst was developed in a relatively short time,^[3] it took almost 20 years before the first chiral version of the Crabtree catalyst was disclosed. In 1997, our group published the first iridium-catalyzed asymmetric hydrogenation using bidentate N,P-ligands as chirality source (Scheme 4).^[23]



Scheme 4: First example of iridium-catalyzed asymmetric hydrogenation.

This catalyst class, named PHOX, is based on chiral oxazolines, which are derived from chiral amino acids and a tertiary phosphine.^[24] These ligands have found application also in palladium^[24a,24b,24d] and iridium^[24c] catalyzed allylic substitution reactions as well as other transition metals-catalyzed reactions.

In 1998 another reports by our group showed the power of this catalyst class in the hydrogenation of unfunctionalized olefins (Scheme 5).^[25]



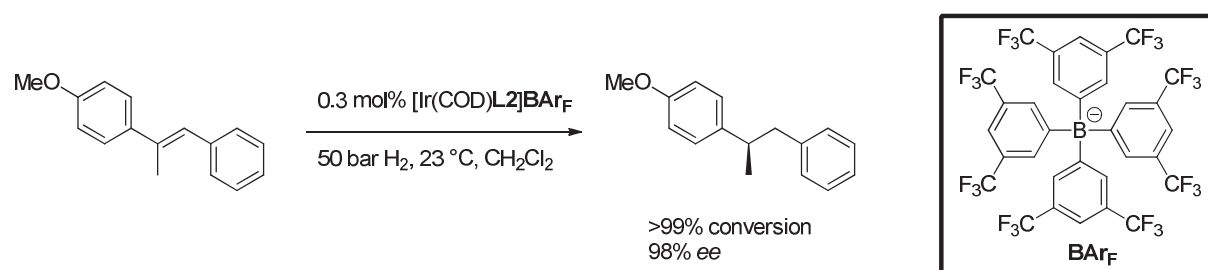
Scheme 5: Application of PHOX ligand **L2** in the asymmetric hydrogenation of unfunctionalized olefins.

A variety of unfunctionalized olefins could be reduced with very good enantioselectivities but, unfortunately, high catalyst loading was required to achieve good conversions.^[25] Despite the high initial TOF, the catalyst underwent deactivation in a short period of time. Addition of molecular sieves and the use of dry solvents resulted beneficial, although not

sufficient to reach full conversion. The cause of this deactivation, like in the case of Crabtree's catalyst, was found to be the irreversible formation of an inactive trinuclear complex.^[26]

1.2.1 Counterion Effect

When the hexa fluoro phosphate (PF_6^-) counteranion was replaced by the bulky tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F^-),^[27] only a very low catalyst loading (0.3 mol%) was necessary to achieve full conversion in the asymmetric hydrogenation of unfunctionalized olefins (compare Scheme 5 and Scheme 6).^[25]



Scheme 6: Counterion effect on the iridium-catalyzed asymmetric hydrogenation.

The BAr_F^- anion is considerably less coordinating than the previously used counteranions and therefore does not compete with the substrate in binding to the metal center.^[1b,19,28]

This stabilizes the key intermediate in the catalytic process, a bishydride olefin complex, thus promoting the hydrogenation pathway over the deactivation process.^[28a]

Nowadays the vast majority of the catalysts used for asymmetric hydrogenation have a cationic iridium metal center, a COD ligand, a BAr_F^- counterion and an N,P-ligand (in some cases a C,P-ligand with and N-heterocyclic carbene is used, see Section 1.2.3).

1.2.2 N,P-Ligands for Asymmetric Hydrogenation

After the report of the phosphine-oxazolines as good N,P-ligands in the iridium-catalyzed asymmetric hydrogenation, a plethora of other catalysts has been synthesized. In most cases, a six membered ring is formed between the N,P-ligand and the iridium center. The phosphorus moiety is normally a phosphine^[25,29] or a phosphinite^[30] but also some phosphites^[31] have been used.



Contribution by the Pfaltz group

Since 1998 our group has developed a multitude of new N,P-ligands for the iridium-catalyzed asymmetric hydrogenation, of which the most efficient are depicted in Figure 2.

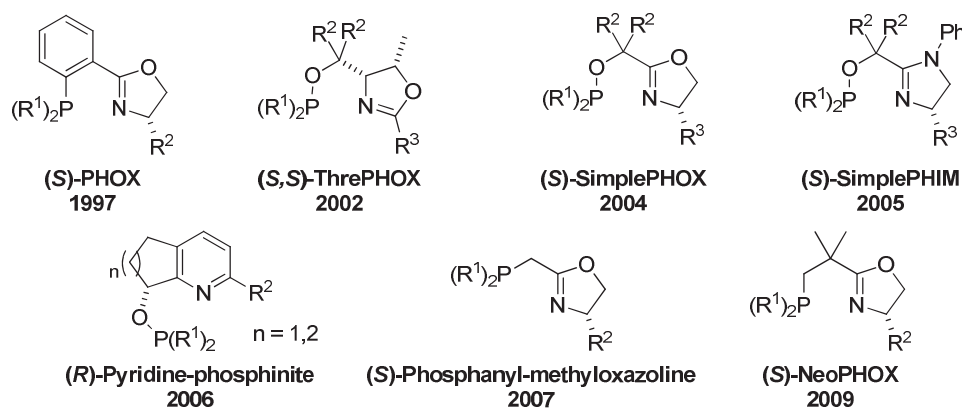
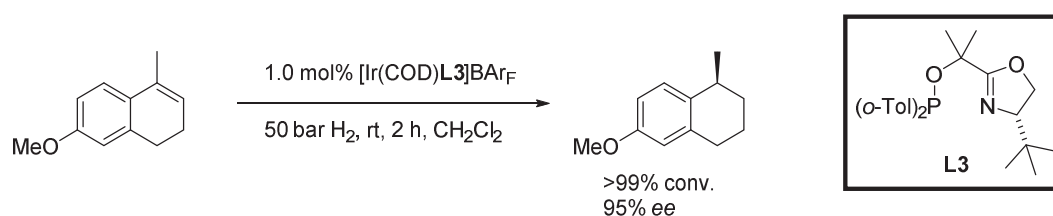


Figure 2: Selection of N,P-ligands developed in the Pfaltz laboratories.

In 2002 the ThrePHOX ligands class was developed.^[30b] This class is substantially different from the PHOX ligands. In fact, besides the use of a phosphinite as P-moiety, the stereogenic information was moved to the center of the backbone. A unique property of this ligand class is the presence of a second stereogenic center on the oxazoline moiety. The ThrePHOX ligands have been successfully applied to the reduction of terminal olefins,^[30b] and later on of 4*H*-chromenes.^[32]

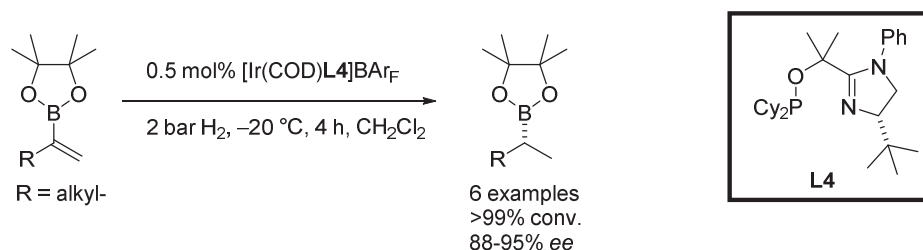
Some years later, the easily synthesized SimplePHOX family^[30c] was applied to the asymmetric hydrogenation of functionalized olefins like acrylic esters, allylic alcohols, and, most importantly, cyclic substrates like 1-methyl-3,4-dihydronaphthalene (Scheme 7).^[30c]



Scheme 7: Application of the SimplePHOX ligand **L3** to the asymmetric hydrogenation of cyclic substrates.

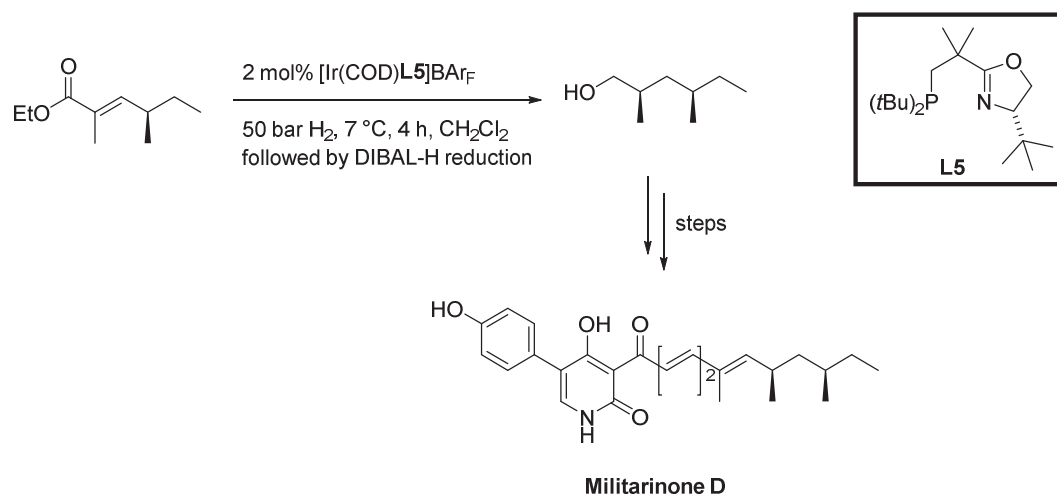
The success of this ligand structure paved the way to the synthesis of related ligand families, like the SimplePHIM^[30f] and the NeoPHOX.^[29d] The usefulness of the SimplePHIM ligands has been recently shown in the asymmetric hydrogenation of terminal vinyl

boronates^[33] to yield chiral boronates, highly versatile building blocks in organic synthesis (Scheme 8).



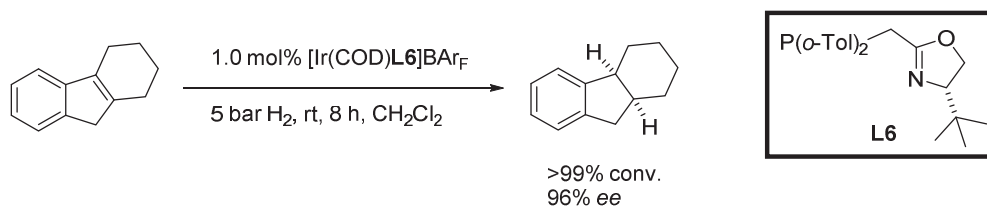
Scheme 8: Application of SimplePHIM ligand **L4** to the asymmetric hydrogenation of terminal vinyl boronates.

NeoPHOX ligands found application in the reduction of a broader range of substrates, among others in the synthesis of the precursors of some natural products. Noteworthy is the use of catalysts based on this ligand class in the synthesis of the key intermediate of Militarinone D,^[34] a pyridone alkaloid isolated from an entomopathogenic fungus that shows general neurotogenic activity (Scheme 9).



Scheme 9: Key step in the total synthesis of Militarinone D.

All the ligands described so far form a six-membered chelate ring with the metal center. However, this property is not a must and indeed also five-membered chelate structures like phosphanyl-methyloxazoline^[29b,35] have been shown to catalyze hydrogenation reactions in a very efficient way.^[36] Using such catalyst class the asymmetric hydrogenation of unfunctionalized tetrasubstituted double bonds became more accessible (Scheme 10).^[29b,36-37]



Scheme 10: Asymmetric hydrogenation of tetrasubstituted double bonds.

In addition to ligands that possess an oxazoline moiety as a source of chirality, another N,P-ligand structure proved to be very useful for the iridium-catalyzed asymmetric hydrogenation of several substrates: the pyridine-phosphinite ligand class.^[30g] Chiral molecules of this type were first synthesized in 2006 in our group and closely mimic the structure of the Crabtree catalyst. Moreover the rigid conformation given by the bicyclic core seems to be crucial for achieving high enantioselectivities.^[30d]

Nowadays this is one of the most powerful ligand classes in the field of iridium-catalyzed asymmetric hydrogenation, mainly due to their broad substrate scope. Indeed, not only unfunctionalized olefins, but also furan derivatives,^[30g] α,β -unsaturated esters^[38] and vinyl borates^[33] could be reduced with excellent results using iridium catalysts based on this ligand class (Figure 3).

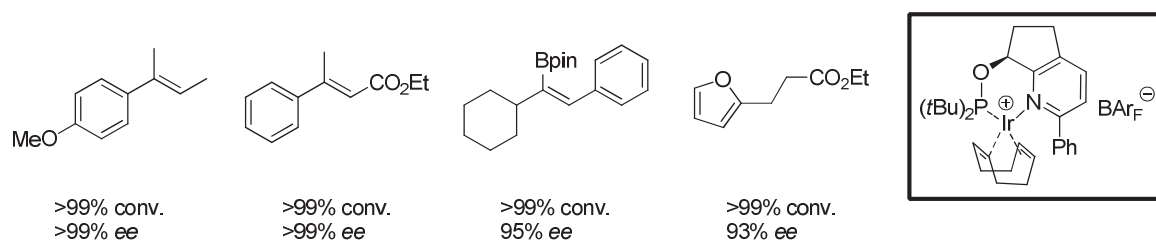


Figure 3: Selection of substrates that can be reduced by a bicyclic pyridine phosphinite-derived iridium catalyst.

In recent years these iridium complexes have found broad application in the asymmetric hydrogenation of key intermediates of many natural products.^[34,39]

Contribution by other laboratories

Besides our group, many other researchers have been interested in the synthesis of novel, powerful N,P-ligands for iridium-catalyzed asymmetric hydrogenation. The Andersson group focused its attention on the development of new PHOX-derived ligands, as well as bicyclic thiazole complexes for the asymmetric hydrogenation of functionalized^[40] and unfunctionalized olefins^[41] and imines.^[42]

The Ding and Zhou laboratories on the other hand showed that larger chelate rings with the metal center are also promising ligands for this transformation. More precisely, seven^[43] (SpinPHOX, Ding), or even nine^[44] (SiPHOX, Zhou) membered systems can act as catalysts in the reduction process of α,β -unsaturated carboxylic acids achieving excellent results.^[44-45] The main characteristic of these ligands is given by the spirocyclic core which keeps the structure rigid allowing for efficient enantiodiscrimination (Figure 4).

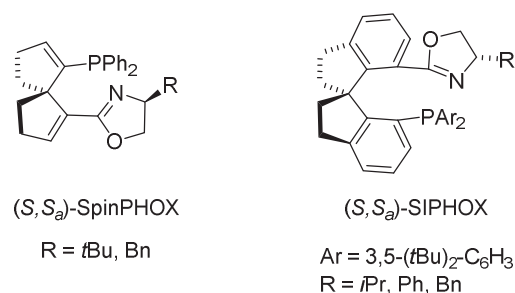


Figure 4: Structures of the spirocyclic ligands SpinPHOX and SiPHOX.

Interestingly, SpinPHOX-derived catalysts are able, besides the hydrogenation of C=C, also to catalyze the asymmetric hydrogenation of imines with remarkably high yield and selectivity.^[43]

In general the asymmetric hydrogenation of C=N bonds, among others quinolines, can also be carried out with N,P-^[46] and P,P-ferrocenyl-based^[47] complexes.

More rare is the enantioselective reduction of C=O bonds catalyzed by iridium complexes. Only in the last few years an efficient catalyst based on an N,P-ligand has been developed for this reaction by the Zhou group.^[48] This methodology is noteworthy as it can be applied to the chemoselective reduction of carbonyl groups leaving olefins situated in close proximity untouched (Scheme 11).^[49]