Asymmetric hydrogenation of imines, enamines and N-heterocycles using phosphoramidite ligands
Mrsic, Natasa

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter 1
Asymmetric hydrogenation using monodentate phosphoramidite ligands

In this chapter an overview of the asymmetric hydrogenation using monodentate phosphoramidite ligands is given. Recent developments are discussed.
Chapter 1

1.1 Rhodium catalyzed asymmetric hydrogenation - a historical overview

Asymmetric hydrogenation represents one of the most powerful catalytic methods for the preparation of enantiomerically pure compounds.\(^1,2\) High enantioselectivity, low catalyst loadings, essentially quantitative yields, perfect atom economy, and mild conditions are attractive features of this transformation. The first homogenous rhodium catalyzed hydrogenation was reported in 1939 by Iguchi.\(^3\) A range of organic and inorganic substrates were hydrogenated by aqueous solution of \(\text{RhCl}_3\), \([\text{Rh(NH}_3\text{)}_5(\text{H}_2\text{O})]\text{Cl}_3\) or \([\text{Rh(NH}_3\text{)}_4\text{Cl}_2]\text{Cl}\). The most important advances in homogenous hydrogenation in the next period were the successful use of rhodium-phosphine complexes. Wilkinson and co-workers studied intensively a complex of rhodium with triphenylphosphine \((\text{Rh(PPh}_3\text{)}_3\text{Cl})\), which has remarkable catalytic properties and is now known as Wilkinson’s catalyst. It was the first practical hydrogenation catalyst applicable under mild conditions, e.g. room temperature and atmospheric pressure of hydrogen. Wilkinson’s catalyst was employed in the selective hydrogenation of alkenes in the presence of other easily reduced groups such as \(\text{NO}_2\) or \(\text{CHO}\), and the hydrogenation of terminal alkenes in the presence of internal alkenes.\(^4,5\) The remarkable performance of this catalyst opened the field of catalytic enantioselective hydrogenation using chiral phosphines, pioneered by the groups of Knowles and Horner.\(^6-8\)

After Wilkinson’s discovery and the development of the synthesis of chiral phosphines by Mislow\(^9\) and Horner,\(^10\) both Knowles\(^6,7\) and Horner\(^8\) showed that it is possible to hydrogenate \(\text{C=C}\) double bonds using rhodium catalysts with chiral phosphine ligands in an asymmetric fashion. The ee values were initially modest (up to 15\%), the results however represented a proof of principle. An important breakthrough was accomplished by Kagan and Dang, with the use of a rhodium complex with the ligand DIOP. Using DIOP which has chirality in the backbone, in the reduction of unsaturated acids and amino acids, up to 72\% ee was obtained (Scheme 1.1).\(^11\)
Asymmetric hydrogenation using monodentate phosphoramidite ligands

\[
\text{COOH} \quad \text{R}^1 \quad \text{NHR}^2 \quad \xrightarrow{3.3 \text{ mol}\% [\text{RhCl}((-)-\text{DIOP})\text{S}]} \quad \text{COOH} \quad \text{R}^1 \quad \text{NHR}^2
\]

\[
\begin{align*}
\text{R}^1 &= \text{Ph, R}^2 = \text{Ac, 72\% ee} \\
\text{R}^1 &= \text{H, R}^2 = \text{COCH}_2\text{Ph, 68\% ee}
\end{align*}
\]

\[
\begin{align*}
\text{PPh}_2
\end{align*}
\]

Scheme 1.1 Kagan's asymmetric hydrogenation of dehydroamino acids

At the same time the group of Knowles focused on the use of phosphine ligands with chirality at the phosphorus atom in the asymmetric hydrogenation of \( N \)-acyl aminoacrylic acids. Enantioselectivities of up to 88\% were accomplished using P-chiral ligands (Figure 1.1).

\[
\begin{align*}
\text{Ph} & & \text{Ph} & & \text{Cy} \\
\text{R}^1\text{-Me} & & \text{P}^1\text{-Me} & & \text{P}^1\text{-Me} \\
\text{t}-\text{Pr} & & \text{O-Anisyl} & & \text{O-Anisyl} \\
28\% \text{ ee} & & 50-60\% \text{ ee} & & 80-88\% \text{ ee}
\end{align*}
\]

Figure 1.1 Ligands applied by Knowles et al. in the asymmetric hydrogenation of \( N \)-acyl aminoacrylic acids

A crucial achievement was accomplished by Knowles et al. in the process of the preparation of \( L \)-DOPA, a drug used for the treatment of Parkinson disease. The synthetic route included the key step of a prochiral enamide hydrogenation by an air stable rhodium complex with CAMP as ligand. This example represents the first application of homogenous hydrogenation on an industrial scale. The monodentate ligand CAMP was soon replaced by the bidentate bisphosphine ligand DIPAMP which led to an increase in \( ee \) of the hydrogenation products to 95\% (Scheme 1.2).
Rhodium complexes play an important role in the area of homogenous catalysis and especially homogenous hydrogenation, due to their remarkable reactivity and selectivity. Although the field expanded over the last 40 years, it is still continuously growing.\textsuperscript{15,16}

1.1.1 Mechanism of the rhodium catalyzed enantioselective hydrogenation

The mechanism of the asymmetric rhodium catalyzed hydrogenation has been examined extensively.\textsuperscript{17-20} Studies have mostly focused on cationic rhodium complexes with bisphosphine ligands, and enamides as substrates. Early mechanistic studies were done on the asymmetric hydrogenation of alkenes using Wilkinson’s catalyst.\textsuperscript{5,21} The most often encountered mechanism in asymmetric Rh-catalyzed hydrogenation was proposed by Halpern.\textsuperscript{20,22} Halpern studied Rh-CHIRAPHOS-catalyzed hydrogenation of enamides (Scheme 1.3).\textsuperscript{20,23}
Asymmetric hydrogenation using monodentate phosphoramidite ligands

CHIRAPHOS

Scheme 1.3 Halpern’s mechanism for the rhodium catalyzed hydrogenation of enamides

The mono-hydrido-alkyl intermediate is formed by addition of dihydrogen to the enamide complex, followed by transfer of a single hydride. Reductive elimination of the product regenerates the active catalysts and restarts the cycle. The rate determining step is the oxidative addition of hydrogen to the rhodium-substrate complex.

The two diastereoisomers of the catalyst-substrate complex interconvert inter- and intramolecularly. The reactivity of the minor diastereoisomer toward H₂ is higher than that of the major diastereoisomer. As a consequence, the stereochemical outcome of the reaction is determined by this reactivity, instead of the thermodynamic stability of the diastereomeric substrate complexes (Scheme 1.4).
Halpern and Landis were studying the influence of temperature and pressure on the interconversion of the substrate-catalyst complexes in the hydrogenation of methyl-(Z)-α-acetamidocinnamate. The oxidative addition is the step that determines absolute configuration and turnover-limiting step, and it was concluded that the increase of the ee with increase of the temperature is because the concentration of the minor diastereoisomer increased, whereas the ee decreased with increasing the pressure because the hydrogenation of the major diastereoisomer became significant.

Another relevant mechanism of rhodium catalyzed hydrogenation is the dihydride mechanism, proposed by Imamoto and Gridnev (Scheme 1.5). Mechanistic studies were performed on the hydrogenation of α-dehydroamino acids and other unsaturated substrates such as enamides, (E)-β-dehydroamino acids and dimethyl-1-benzoyloxyethenephosphonate using the rhodium complexes [Rh(diene)(t-Bu-BisP*)]+ (the diene is COD or NBD) as catalyst precursors.
Asymmetric hydrogenation using monodentate phosphoramidite ligands

Scheme 1.5 Dihydride mechanism by Imamoto and Gridnev

The catalytic cycle of the dihydride mechanism starts with the diastereoselective oxidative addition of hydrogen to the rhodium solvate complex. The major diastereomeric complex provides the major product. The following step is the addition of the substrate, followed by irreversible migratory insertion (rate determining step). The last step is the reductive elimination of the product to give the rhodium solvent complex, which can continue the catalytic cycle.

1.2 Iridium catalyzed asymmetric hydrogenation - a historical overview

Iridium made its major entrance into the field of organometallic chemistry in 1965 with the discovery of the weakly catalytically active Vaska’s complex ([IrCl(CO)(PPh₃)₂]). At the present time, iridium is a widely applied metal in modern homogenous catalysis. It tends to form stronger metal-ligand bonds, and consequently the compounds that represent reactive intermediates for rhodium, sometimes can be isolated in the case of iridium. Since [Ir(PPh₃)₂]⁺ in non-coordinating solvents was
found to be much more reactive than the rhodium analogue, it becomes clear that the dissociation of solvent or ligand molecules is much slower for iridium than for rhodium and this can lead to lower reaction rates with [IrCl\((PPh_3)_3]\)/MeOH. The other steps in the catalytic cycle with iridium are usually very fast, so if the dissociation step can be avoided, a highly active catalyst can be formed.

![Figure 1.2 Crabtree’s and Pfaltz’s iridium catalysts](image)

Compared to rhodium- and ruthenium-based counterparts, iridium catalysts are rather new in the field of asymmetric hydrogenation of olefins. Using an achiral catalyst, Crabtree and co-workers established the ability of iridium compounds to rapidly hydrogenate olefins\(^{27,28}\). Crabtree’s catalyst (Figure 1.2), catalyzes the hydrogenation of 1-hexene 100 times faster than Wilkinson’s catalyst. It also hydrogenates tri- and even tetrasubstituted olefins while Wilkinson’s catalyst is inactive towards the latter\(^{27}\). Crabtree’s catalyst also stands out in the diastereoselective, functional-group-directed hydrogenation of cyclic alkenes, consistently controlling the stereochemistry of the new stereocenter relative to the directing group better than the related rhodium catalysts\(^{29}\).

In the late 1990s, Lightfoot, Pfaltz and co-workers recognized that a chiral analogue of Crabtree’s catalyst would have significant potential for asymmetric hydrogenation. They replaced the phosphine and pyridine ligands of Crabtree’s catalyst with phosphinoxazoline (PHOX) ligands\(^{30}\) to form a series of chiral, cationic iridium complexes (2, Figure 1.2) that

\(\text{Crabtree’s catalyst} \quad \text{Pfaltz’s catalyst} \)

1. \(\text{PF}_6^-\)
2. \(\text{PF}_6^-\)
3. \(\text{PF}_6^-\)
4. \(\text{PF}_6^-\)
5. \(\text{PF}_6^-\)
6. \(\text{PF}_6^-\)
7. \(\text{PF}_6^-\)
8. \(\text{PF}_6^-\)
9. \(\text{PF}_6^-\)
10. \(\text{PF}_6^-\)
11. \(\text{PF}_6^-\)
12. \(\text{PF}_6^-\)
13. \(\text{PF}_6^-\)
14. \(\text{PF}_6^-\)
15. \(\text{PF}_6^-\)
16. \(\text{PF}_6^-\)
17. \(\text{PF}_6^-\)
18. \(\text{PF}_6^-\)
19. \(\text{PF}_6^-\)
20. \(\text{PF}_6^-\)
21. \(\text{PF}_6^-\)
22. \(\text{PF}_6^-\)
23. \(\text{PF}_6^-\)
24. \(\text{PF}_6^-\)
25. \(\text{PF}_6^-\)
26. \(\text{PF}_6^-\)
27. \(\text{PF}_6^-\)
28. \(\text{PF}_6^-\)
29. \(\text{PF}_6^-\)
30. \(\text{PF}_6^-\)
Asymmetric hydrogenation using monodentate phosphoramidite ligands

hydrogenated prochiral imines to amines in a broad range of ee values (up to 89% ee).\(^{31}\)

Although the Ir/PHOX complexes 2 also catalyzed the hydrogenation of olefins with impressive ee values (75 - 97%), they formed inactive tri-iridium species over the course of the reaction.\(^{32}\) This tendency to trimerize, a reaction also observed with Crabtree’s catalyst 1\(^{,27}\) meant that high catalyst loadings of catalysts 2 (4 mol\%) were necessary for complete conversion of the olefin.\(^{33}\) To increase catalyst stability, Pfaltz and co-workers screened a range of reaction conditions, but found little improvement.

Figure 1.3 Pfaltz’s and Lightfoot’s chiral catalysts for the asymmetric hydrogenation of olefins

However, upon changing the counterion to the weakly coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ([BARF]\(^{-}\)), they obtained a highly active and selective olefin hydrogenation catalyst 3 (Figure 1.3) that was stable under the reaction conditions, and even to air and moisture.\(^{33}\)

Using kinetic\(^{34}\) and pulsed gradient spin echo NMR spectroscopic diffusion data,\(^{35}\) Pfaltz, Pregosin and co-workers have examined the effect of the anion in (PHOX)Ir-catalyzed hydrogenation, and found that large, weakly coordinating anions are crucial for activity. Furthermore, Pfaltz showed that the anion in the catalytic complex does not impact the stereoselectivity of hydrogenation.\(^{34}\) Almost all of the numerous iridium catalysts of the form [L\(^{*}\)Ir(COD)]\(^{+}\)[X\(^{-}\] for asymmetric olefin hydrogenation
that appeared after 3 featured modifications of the cation; [BArF]− is the anion of choice.36

Though Pfaltz and co-workers showed that catalysts 3 were active toward some functionalized olefins, several unfunctionalized olefins were as well hydrogenated with excellent stereoselectivity (≥94% ee) using low catalyst loadings (0.1 - 4 mol%). Prior to the development of 3, there had been few reports of highly enantioselective (≥94% ee) hydrogenations of unfunctionalized olefins,37 and these either had low turnover frequencies or required very low temperature (≤−75 °C) to be selective. The success of 3 in the stereoselective hydrogenation of unfunctionalized olefins triggered therefore intense efforts to design other chiral iridium complexes for this purpose. Developments in this field have been the subject of several reviews.36,38,39 Highly stereoselective hydrogenation of functionalized olefins by rhodium and ruthenium catalysts is well-developed, while most of the research on chiral iridium hydrogenation catalysts is based on the reduction of unfunctionalized olefins. Rhodium- and ruthenium-based catalysts are extremely selective for substrates with coordinating functionality; substrates with functional groups that do not coordinate well to the metal remain challenging for these catalysts. Iridium catalysts, on the contrary, achieve very high selectivity for unfunctionalized substrates. Therefore, they have potential for the asymmetric hydrogenation of olefins with poorly coordinating functional substituents, such as electrophilic groups.

Promising results have been obtained in the asymmetric iridium-catalyzed hydrogenation of unfunctionalized olefins as well as imines,38,40 therefore continued development of this field could provide useful methods for the asymmetric hydrogenation of a range of compounds while broadening the substrate scope of iridium catalysts for the asymmetric hydrogenation.

1.2.1 Mechanism of the iridium catalyzed enantioselective hydrogenation

In a combined experimental and theoretical study by Brandt and co-workers, an IrIII-IrV catalytic cycle has been proposed (Scheme 1.6).41 The catalytic cycle starts with solvated iridium - dihydride complex; then the
two solvent molecules are replaced by an olefin and molecular hydrogen. The rate-determining step is the migratory insertion of the olefin into an Ir-hydride bond, a step that is energetically favored by the simultaneously oxidative addition of the coordinated hydrogen molecule. Subsequently, the reductive elimination of the saturated hydrocarbon completes the catalytic cycle.

Scheme 1.6 Two possible catalytic cycles for olefin hydrogenation by chiral iridium complexes

Alternatively, the groups of Buriak and Chen have published data in support of catalytic cycles with Ir and Ir intermediates. Buriak and co-workers used para-hydrogen induced polarization (PHIP) NMR spectroscopy to study the hydrogenation of [D8]-styrene by an achiral N-heterocyclic carbene-phosphine iridium complex in CDCl. Dietiker and Chen used gas-phase MS to study the hydrogenation of styrene by the Pfaltz's catalyst (R1 = Ph, R2 = i-Pr). The proposed catalytic cycle starts with solvated iridium-dihydride complex, followed by a solvent molecule being replaced by the olefin. The olefin dihydride complex is the resting state of the catalyst. The next step is insertion of the olefin into the iridium.
hydride bond together with coordination of a molecule of solvent, and the reductive elimination of the alkane. The cycle is completed with the addition of the dihydrogen molecule to the solvated iridium complex.

1.3 Monodentate phosphoramidite ligands in asymmetric hydrogenation

Bidentate chiral ligands were considered superior over monodentate ones in metal-catalyzed asymmetric hydrogenation for more than 30 years, as chelation was believed to be necessary to impart the rigidity to the metal complex for an efficient transfer of chirality.\textsuperscript{1,13,19,44}

Over the last decade chiral monodentate phosphines, phosphonites, phosphoramidites and phosphites were reported to lead to excellent results.
Asymmetric hydrogenation using monodentate phosphoramidite ligands

in the asymmetric hydrogenation of α- and β-dehydroamino acids, itaconic acid derivatives, and enamides.\textsuperscript{16,45}

Monodentate phosphoramidite ligands have the advantage of being readily accessible, structurally highly diverse, air stable and inexpensive compared to most bidentate ligands. In addition, they are amenable to parallel synthesis allowing rapid access to libraries of chiral phosphoramidite ligands.\textsuperscript{46} An overview of frequently used monodentate phosphoramidite ligands is shown in Figures 1.4 and 1.5.

![Diagram of reported successful monodentate phosphoramidite ligands]

\textbf{Figure 1.5} Reported successful monodentate phosphoramidite ligands
Chapter 1

1.3.1 Rhodium catalysts

1.3.1.1 Asymmetric hydrogenation of α-dehydroamino acids, enamides and itaconic acid derivatives

Since in our group monodentate phosphoramidite ligands have already successfully been applied in the copper-catalyzed 1,4-addition of dialkylzincs to olefins, it was decided to test the suitability of phosphoramidites in Rh-catalyzed asymmetric olefin hydrogenation. Disappointingly, a range of bidentate phosphoramidite ligands based on BINOL or TADDOL and bridged by C1 - C3 diamines led to slow hydrogenations and low enantioselectivities. Surprisingly, the use of the monodentate ligand MonoPhos L1a in the Rh-catalyzed asymmetric hydrogenation of methyl 2-acetamido-cinnamate led to an enantiomeric excess of 97% in aprotic dichloromethane and ethyl acetate (Scheme 1.7).

\[
\text{NHAc} \quad \text{COOMe} \quad 5 \text{ mol\% } [\text{Rh(COD)}_2]\text{BF}_4, 11 \text{ mol\% L1a} \quad \text{rt, 1bar H}_2, \text{ solvent} \quad \text{NHAc} \quad \text{COOMe}
\]

up to 97% ee

Scheme 1.7 Rh-catalyzed asymmetric hydrogenation of methyl 2-acetamido-cinnamate

In that same year, Pringle and co-workers and Reetz and co-workers reported the use of BINOL-based monodentate phosphonites and phosphites, respectively, in Rh-catalyzed asymmetric hydrogenation. The best results with the catalysts based on these ligands were also obtained in aprotic solvents.
Asymmetric hydrogenation using monodentate phosphoramidite ligands

Using L1a as a ligand, a large range of olefins, such as substituted 2-acetamido-cinnamic acids and esters (up to 99% ee), 2-acetamido acrylic acid and methyl ester (up to 99% ee), itaconic acid (97% ee) and its methyl ester (94% ee) were hydrogenated with excellent ee’s. Catalytic hydrogenation of N-acetyl-α-arylenamides using [Rh(COD)2]BF4 and MonoPhos L1a results in full conversions and high ee’s (Scheme 1.8). Slightly better results were obtained by Chan using the rather similar ligand L1b. In the same period Chan reported the use of Monophos and H8-BINOL-derived phosphoramidite L2a in the hydrogenation of enamides with excellent ee.

In collaboration with the Reetz group, we developed the use of the ligands PipPhos L1d and MorfPhos L1e, which led to even better results in most applications than L1a. Excellent and in some cases unprecedented enantioselectivities were obtained in the hydrogenation of N-acyldehydroamino acid esters, dimethyl itaconate, acyclic and cyclic N-
acylenamides.\textsuperscript{56} PipPhos \textbf{L1d} was also the ligand of choice in the asymmetric hydrogenation of $\beta$-alkyl itaconates (up to 99\% \textit{ee}).\textsuperscript{57}

In 2003, Jiang and Chan and co-workers reported the use of H$_8$-Monophos \textbf{L2a} in the hydrogenation of $\alpha$-dehydroamino acids with up to 99.9\% \textit{ee}.\textsuperscript{58} Zhou published the use of spiro phosphoramidite ligand \textbf{L3} (SIPHOS), which also leads to excellent results in asymmetric hydrogenation\textsuperscript{59} but takes seven steps plus a resolution to prepare.\textsuperscript{60} Zhang reported synthesis of monodentate spiro phosphoramidite ligand \textbf{L4} and its application in rhodium catalyzed asymmetric hydrogenation of $\alpha$-dehydroamino acid derivatives and itaconic acid with up to 99\% \textit{ee}.\textsuperscript{61}

Reetz recently reported the use of nonsymmetrical BINOL-based phosphoramidites containing only a single substituent in the 3 (and not the 3') position in the hydrogenation of itaconates and enamides with excellent \textit{ee}.\textsuperscript{62}

The first Rh-catalyzed enantioselective hydrogenation of dimethyl 2-methylene glutarate and its derivatives has been reported by Zheng and Hu.\textsuperscript{63} Chiral ferrocene based monodentate phosphoramidite ligand \textbf{L5} (FAPhos) was employed, high enantioselectivity (92\% \textit{ee}) with full conversion was achieved.

A new class of dendritic monodentate phosphoramidite ligands was reported by the group of Fan in the asymmetric hydrogenation of $\alpha$-dehydroamino acid esters and dimethyl itaconate.\textsuperscript{64} High enantioselectivities (up to 98\% \textit{ee}) and catalytic activities (up to 4850 h$^{-1}$ TOF) were achieved, which are better or comparable to those obtained from MonoPhos. Recently, the groups of Zhou and Fan demonstrated the importance of the dendritic wedges on enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins, such as $\alpha$-dehydroamino acid derivatives and enamides. Higher enantioselectivities were achieved as the dendritic wedges on the \textit{N}-atom of the phosphoramidite ligand became bigger.\textsuperscript{65}

With respect to the development of the hydrogenation methodologies in "green solvents" Lyubimov reported Rh-catalyzed asymmetric hydrogenation of itaconates and 2-acetamidoacrylate using monodentate phosphoramidite and phosphite ligands in supercritical carbon dioxide. Using phosphoramidites \textbf{L1d} and \textbf{L1e} enantioselectivities of up to 99\%
Asymmetric hydrogenation using monodentate phosphoramidite ligands

were obtained. The high reaction rates are attributed to the higher miscibility and higher diffusivity of gaseous hydrogen in the supercritical medium when compared to that in dichloromethane. The advantage of this method is low price of both phosphoramidite ligands and carbon dioxide.

It is not strictly necessary to have BINOL-based ligands for good results. Using ligand L6 based on catechol and a chiral amine also resulted in ee’s up to 99% in the rhodium catalyzed asymmetric hydrogenation of dehydroamino acids and enamides.

Ding reported in 2005 preliminary results on the design, synthesis, and application of a new class of monodentate phosphoramidite ligands (DpenPhos L7a and L7b). Excellent ee’s (up to 99.9%) and conversions were obtained in the hydrogenation of dehydroamino acid methyl esters and acetyl enamides.

Ding also found that monodentate phosphoramidite ligands having a primary amine moiety (L7c) lead to excellent results in the hydrogenation of (Z)-methyl α-(acetoxy)acrylates and (E)-β-aryl itaconate derivatives. This high reactivity may be attributed to the existence of intermolecular hydrogen bonding between adjacent monophosphoramidite ligands around the Rh metal center.

1.3.1.2 Asymmetric hydrogenation of β-dehydroamino acid derivatives

Another class of substrates that required the development of new ligands was the β-dehydroamino acid derivatives. From published results with bidentate phosphines, it was clear that hydrogenation of the E isomers is rather easy, and in fact, in our group we were able to develop the rhodium-catalyzed asymmetric hydrogenation of (E)-4 using MonoPhos L1a as a ligand with 95% ee. Slight modification of the ligand structure led to the ligand L1f that induced up to 99% ee in the hydrogenation of the E isomers (Scheme 1.9). However, the commonly used synthesis of these substrates from the acetoacetates via amination and acetylation leads mainly to the Z precursors. Most probably, this is related to the strong internal hydrogen bond between the ester carbonyl and the NH of the amide.
Chapter 1

Scheme 1.9 Asymmetric hydrogenation of β-dehydroamino acid derivatives

Minor modification of the ligand structure led to an excellent ligand, L1i, that induced up to 95\% ee in the hydrogenation of (Z)-4 in i-propanol. This solvent is capable of breaking the hydrogen bond in the substrate, thus enabling its bidentate binding to the metal. The rate of this catalyst was compared with catalysts based on a number of well known bidentate ligands and the phosphite analogue of L1i (NH replaced by O), showing that the catalyst is only surpassed by DUPHOS in rate but surpasses all tested ligands in terms of ee.\textsuperscript{72}

The acetyl protecting group is not a requirement for high enantioselectivity. Hydrogenations of N-formyl-dehydroamino esters also proceed with excellent enantioselectivities, with PipPhos L1d as the best ligand (Scheme 1.10).\textsuperscript{73} Excellent enantioselectivities (up to >99\% ee) were obtained for the Z isomers. Very high enantioselectivities can also be achieved (up to 97\% ee) for the E isomers of substrates with alkyl substituents. The formyl group can be removed or modified easily after the hydrogenation, under mild conditions.
Asymmetric hydrogenation of *N*-formyl-dehydroamino esters

**Scheme 1.10** Asymmetric hydrogenation of *N*-formyl-dehydroamino esters

1.3.1.3 *Asymmetric hydrogenation of enol acetates and carbamates*

Asymmetric hydrogenation of enol acetates, gives access to chiral alcohols after hydrolysis of the acetate ester. Since enol acetates are structurally very similar to enamides, the asymmetric hydrogenation of this class of substrates was also examined in our group. Surprisingly, using MonoPhos \textbf{L1a} as a ligand, the saturated acetate and carbamate was obtained with an ee of only 10% and 19%, respectively. However, replacing MonoPhos \textbf{L1a} by PipPhos \textbf{L1d} greatly improved the hydrogenation results with both aromatic enol acetates and enol carbamates (Scheme 1.11).74
Chapter 1

Asymmetric hydrogenation of enol acetates and enol carbamates

1.3.1.4  Asymmetric hydrogenation of α,β-unsaturated carboxylic acids using mixed ligand approach

Both the group of Reetz\textsuperscript{75} and our group\textsuperscript{76,77} have shown that the use of mixtures of chiral monodentate ligands can improve enantioselectivity and reactivity. It is also possible to use mixed complexes based on a monodentate chiral ligand and a non-chiral phosphorus ligand.\textsuperscript{78-81} In our group the \textit{mixed ligand approach} has been employed in rhodium catalyzed asymmetric hydrogenations\textsuperscript{76,78,80} and additions of boronic acids.\textsuperscript{77,81} The fact that the structure of monodentate ligands can be varied easily enables us to screen a very large number of different complexes in the asymmetric hydrogenation.
Asymmetric hydrogenation using monodentate phosphoramidite ligands

Scheme 1.12 The monodentate ligand combination approach

Since the catalytically active species most likely contains two monodentate ligands, two homo-complexes, $\text{Ir(L}^1\text{)}_2$ and $\text{Ir(L}^2\text{)}_2$, and the hetero-complex $\text{Ir(L}^1\text{L}^2\text{)}$ will be formed simultaneously (Scheme 1.12). The hetero-complex represents a new catalyst, and if it is endowed with higher activity and selectivity than the two homocomplexes, it will lead to better results.

At DSM where, in the course of finding an active and enantioselective catalyst for the hydrogenation of an $\alpha$-alkyl-cinnamic acid, it was found that addition of a non-chiral phosphine ligand to the rhodium phosphoramidite catalyst led to greatly enhanced rate and enantioselectivity (up to 99% ee, Scheme 1.13). In this research, it was determined that triarylphosphines induce the highest increase in rate and enantioselectivity. Trialkylphosphines had much less effect than triarylphosphines. The asymmetric hydrogenation of 2-methyl-cinnamic acid was examined using eight different BINOL-based phosphoramidite ligands with and without added triphenylphosphine. In every single case, the added triphenylphosphine improved the rate and the enantioselectivity. A number of different $\alpha,\beta$-disubstituted unsaturated acids were hydrogenated using the same catalytic system. Good to excellent ee's were obtained in all cases.
Chapter 1

Scheme 1.13 Asymmetric hydrogenation of unsaturated carboxylic acids using a mixed ligand approach

1.3.1.5 Asymmetric hydrogenation of \(\beta\)-dehydroamino acids using mixed ligand approach

As mentioned earlier, the use of mixtures of ligands can also be applied to two different chiral monodentate ligands. In our group, this approach was tested in the asymmetric hydrogenation of acetylated \(\beta\)-3-dehydroamino acid esters (Scheme 1.14).\(^76\)

Scheme 1.14 Asymmetric hydrogenation of Z-\(\beta\)-3-dehydroamino acid esters

Mixtures of two phosphoramidite ligands were examined, using \(\text{L}1\text{a}, \text{L}1\text{f}, \text{L}1\text{i}, \text{L}1\text{j}, \text{L}1\text{k},\) and \(\text{L}2\text{a}\) in the Rh-catalyzed asymmetric hydrogenation of an aliphatic and aromatic Z-\(\beta\)-3-dehydroamino acid ester (Scheme 1.14).
Asymmetric hydrogenation using monodentate phosphoramidite ligands

Most combinations of two different ligands induced lower enantioselectivities. However, there was one exception: all combinations that included the NH ligand \( \text{L1i} \) led to better results. Particularly striking was the combination with ligand \( \text{L1j} \), which was the worst performer in the homo series in combination with \( \text{L1i} \).

After having established the asymmetric hydrogenation of \( \beta^3 \)-dehydroamino acids with excellent results, \( \beta^2 \)-dehydroamino acids were also examined (Scheme 1.15).\(^7\) Initial screening suggested that these substrates behaved very similarly to the \( \alpha \)-alkylated cinnamic acids.

\[
\begin{align*}
\text{R} & \quad \text{NH} \\
\text{O} & \quad \text{OH} \\
\& & \quad \text{O} \\
\text{R} & \quad \text{NH} \\
\text{O} & \quad \text{OH} \\
\end{align*}
\]

\(27a, R = \text{H}, \text{ up to } 91\% \text{ ee}\)

\(28a, R = \text{ o-Me}, \text{ up to } 90\% \text{ ee}\)

\(29a, \text{ m-Me}, \text{ up to } 91\% \text{ ee}\)

\(30a, \text{ p-Me}, \text{ up to } 91\% \text{ ee}\)

\(31a, \text{ p-Cl}, \text{ up to } 85\% \text{ ee}\)

**Scheme 1.15** \( \beta^2 \)-Amino acids via mixed ligand asymmetric hydrogenation

In order to screen a large number of ligands/catalysts in a short period of time, a parallel synthesis of ligands can be performed. This is possible with a high-throughput experimentation (HTE) approach. This methodology can be applied in the cases where ligands can be readily synthesized using a robot. Prepared ligand library can then be tested in a catalytic reaction which significantly speeds the ligand/catalyst optimization process.\(^4\)\(^6\)\(^8\)\(^2\)

Therefore, a ligand library containing 96 ligands was screened in the hydrogenation of \( \beta^2 \)-dehydroamino acids, in the presence of 1 equiv of PPh\(_3\). Since ligands based on 3,3'-dimethyl-BINOL gave the best results, a library of 16 phosphoramidites and 6 triarylphosphines was screened. Ligand \( \text{L1l} \) again emerged as the best ligand, but in this case, several triarylphosphines gave good results. Hydrogenation of \( 27 \) using Rh/\( \text{L1l} \) without added triarylphosphine resulted in very low ee.
Finally, Reek, van Leeuwen and co-workers have developed a strategy for the formation of supramolecular catalysts based on the self-assembly of monodentate P ligands. This approach has been successfully applied in rhodium catalyzed hydroformylation\(^8\) and asymmetric hydrogenation.\(^4\) Mixtures of monodentate BINOL-derived phosphoramidites or phosphites were used in combination with phosphines and were assembled together via hydrogen bonding or metal-ligand interactions.

### 1.3.2 Iridium catalysts

Apart from rhodium, iridium is reported as well to lead to excellent results in the asymmetric hydrogenation using monodentate phosphoramidite ligands. An important breakthrough was achieved by the DSM group, where an active but also highly enantioselective catalyst for the iridium-catalyzed asymmetric hydrogenation of \(\alpha\)-dehydroamino acids was developed.\(^5\) The catalyst was containing the bulky phosphoramidites \(\text{L8}\) based on a biphenol backbone with substituents in the 3,3’ position, derived from the neutral catalyst precursor \([\text{Ir(COD)(L)Cl}]\) containing only one phosphoramidite ligand per metal. The catalyst was relatively fast (TOF = 150 h\(^{-1}\)) and induced an enantioselectivity of up to 98%.

Beller reported recently a synthesis of a ligand library of monodentate H\(_8\)-BINOL-based phosphoramidites bearing aryl substituents in the 3,3’-position of the BINOL core. Synthesized ligands were applied in the Ir-catalyzed asymmetric hydrogenation of 2-amidocinnamates to obtain different \(\alpha\)-amino acid derivatives in up to 99 % ee\(^6\).

Same group reported Ir-catalyzed asymmetric hydrogenation of \(\beta\)-dehydroamino acid precursors\(^7\) in the presence of chiral monodentate H\(_8\)-BINOL-based phosphoramidites. Separate studies for the \(E\) and \(Z\) isomers showed crucial differences between the two hydrogenation reactions. After optimization of the reaction conditions, enantioselectivities of up to 94% ee were achieved for the \(E\) isomers. Importantly, to obtain high enantioselectivity, substitution at the 3,3’-position of the ligands was found to be necessary. Same catalyst was employed successfully in the hydrogenation of enamides.\(^8\) Using non-coordinating salts as additives (NaBF\(_4\), NaClO\(_4\)) enantioselectivity of up to 93% was obtained.
In 2006, Faller reported the use of combination of Monophos L1a and pyridines in the iridium-catalyzed asymmetric hydrogenation of cyclic imines. Enantioselectivities of only up to 58% were achieved.

## 1.4 Synthesis of phosphoramidite ligands

Phosphoramidites can be synthesized via three different routes (Scheme 1.16). In the first one, BINOL is heated at 80 °C in neat phosphorus trichloride in order to obtain the chlorophosphite, which is then reacted with the desired amine, in the presence of triethylamine (route A). In the case of sterically demanding phosphoramidites, the lithium amide, instead of the amine, is reacted with the chlorophosphite. The second method consists of the preparation of MonoPhos by stirring BINOL with hexamethylphosphoramide.

![Scheme 1.16 Synthesis of phosphoramidite ligands](image)

Different phosphoramidites are subsequently prepared by amine exchange with MonoPhos (Route B). The third method consists of stirring
the secondary amine with phosphorus trichloride. The resulting phosphoramidous dichloride thus prepared is reacted with BINOL in the presence of a base, giving the desired phosphoramidite ligand (Route C).91

1.5 Aim and outline of this thesis

As mentioned earlier, asymmetric hydrogenation represents a versatile, clean and atom economic method for the production of enantiopure compounds. Since in our group phosphoramidite ligands were successfully employed in the asymmetric hydrogenation of various benchmark substrates, we were interested in extending the scope of these reactions to more challenging classes of compounds. We were particularly interested in the asymmetric hydrogenation of heteroaromatic compounds such as quinolines, quinoxalines and indoles, due to the fact that chiral heterocyclic compounds are often found as part of the structures of pharmaceuticals and physiologically active natural products.

Imines and enamines in general represent challenging substrates for the asymmetric hydrogenation, since most of the reported hydrogenation catalysts are still not acceptable for industrial applications. Ligands employed are often expensive and demand tedious synthetic routes for their preparation. There are several reasons why imines are difficult substrates for the hydrogenation.92 One is a smaller thermodynamic gain from the reduction of C=N bond relative to the C=C bond of an olefin. There is also a less effective orbital overlap and lower affinity of the C=N for the metal center due to the \( \eta^1 \)-binding mode of the imine bond compared to the \( \eta^2 \)-bonding of the olefin. In addition, competitive coordination of the hydrogenated product may lead to “catalyst poisoning”. Finally, increased steric hindrance at the unsaturated moiety of imine may also retard the hydrogenation, which is well established with olefinic substrates. Since phosphoramidites are low-cost, easy to synthesize and highly modular, the aim of this thesis was the development of efficient catalysts for the hydrogenation of imines and enamines.

In Chapter 2 the asymmetric hydrogenation of 2,6-substituted quinolines is described, using mixtures of phosphoramidite and phosphine ligands. Different additives were examined and a rationale for their effect is given. Chapter 3 focuses on the hydrogenation of quinoxalines. The
Asymmetric hydrogenation using monodentate phosphoramidite ligands

preparation of primary chiral amines via asymmetric hydrogenation of N-aryl imines and their subsequent deprotection is described in Chapter 4, while Chapter 5 focuses on the hydrogenation of indoles. Finally in Chapter 6 a route to N-aryl β-amino acid derivatives via asymmetric hydrogenation is shown.

1.6 References

Chapter 1

Asymmetric hydrogenation using monodentate phosphoramidite ligands

Chapter 1


Asymmetric hydrogenation using monodentate phosphoramidite ligands


Chapter 1


Asymmetric hydrogenation using monodentate phosphoramidite ligands