1

Introduction and Scope

The synthesis of enantiomerically pure compounds is one of the biggest challenges in organic synthesis and a major target in the industrial synthesis of physiologically active compounds. Even more important, however, are asymmetric transformations under catalytic conditions with high turn over rates and selectivity, avoiding by-products formation, which are in many cases a problem for the environment.

The present chapter introduces the concepts of chirality and stereoselective synthesis, discusses the importance of using homogeneous catalysis as a tool to obtain chiral products and explains the aim of this thesis.

Chapter *1*

1.1. Chirality and Stereoselective Synthesis

The concept of "chirality" has been known in chemistry since the 1870s and, in extremely simple terms, it means "handedness": that is, the existence of left/right opposition. For example, the left hand and right hand are mirror images and therefore "chiral". The term *chiral* is derived from the Greek name *kheir* meaning "hand" and was apparently coined by Lord Kelvin in 1904, in his Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light in which he said: "*I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."*

The concept of "asymmetry" was developed by J. H. van't Hoff [1] and J. A. Le Bel [2] in 1874 following the resolution by Louis Pasteur of a mixture of tartaric acid salt isomers during the period 1848-1853, in which he picked out the different crystal types by hand on the basis of the different physical appearance of the salt crystals.[3] Pasteur recognized that each of the isomers polarized light differently (one to the left and the other to the right) and this had to be due to an asymmetric grouping of atoms in the optically active molecules. Following Kekule's recognition in 1858 that carbon had a valence of 4 [4], van't Hoff and Le Bel independently recognized that when four different groups are attached to a carbon atom, arrayed at the corners of a tetrahedron, there are two possible different arrangements that give two different molecules called enantiomers.

Because enantiomers have identical physical properties (boiling point, densities, and reaction rates), except for the direction of rotation of polarized light, they are often viewed as a single entity. But enantiomers can exhibit distinct chemical behavior when they are subjected to a chiral environment, that is, any environment consisting of a single enantiomer. They do generally have different

aroma and flavour characteristics; more importantly, they have differences in toxicity and biological activity (Figure 1).

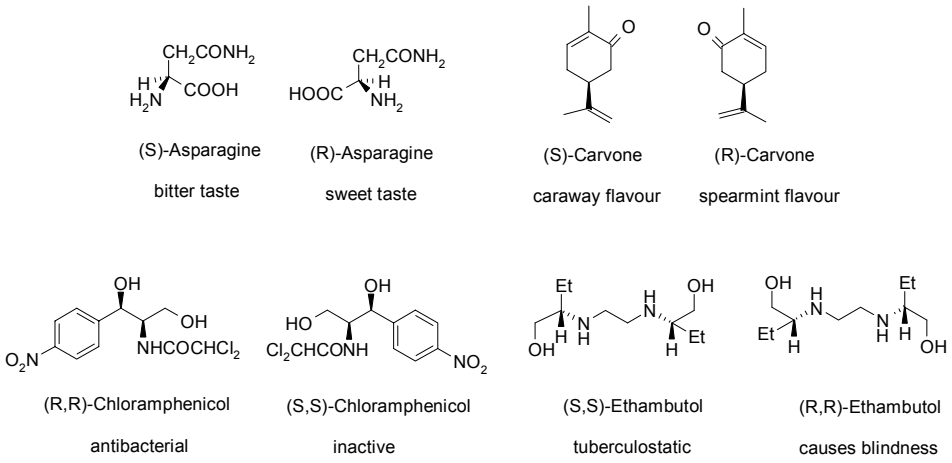


Figure 1

Considerable effort has been made in recent decades, from both the academic and industrial point of view, to contribute to the development of methods for the production of chiral substances in enantiomerically pure form.

If only one of the two enantiomers is responsible for the activity that justifies its production, the industrial tendency will be to produce only this single enantiomer at the lowest possible price, because it may lead to significantly greater savings than producing the racemic compound. To achieve this economically important goal, efficient stereoselective methods must be developed [5].

There are several approaches for preparing enantiomerically pure compounds: for example the utilization of "chiral pool" materials, separation of racemates (by crystallization, derivatization or kinetic resolution) and asymmetric synthesis.

Optically active natural products such as amino acids, carbohydrates, terpenes and alkaloids, which constitute the "chiral pool", are used as building blocks and they are incorporated into the target structure in order to achieve the desired chiral features.

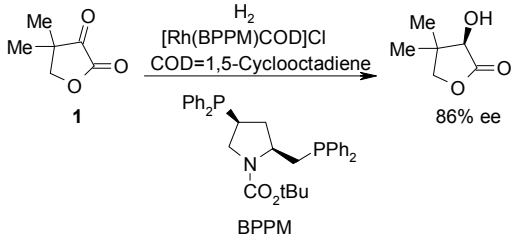
Classical resolution becomes particularly attractive when it can be combined with *in situ* racemization and crystallization-induced by diastereomeric adduct formation. When an enantiopure compound reacts with a mixture of enantiomers, a mixture of diastereomers is produced, separable by differences in the solubility properties or by chromatographic techniques.

Asymmetric synthesis makes it possible to obtain enantiomerically pure materials by transforming prochiral substrates with the intervention of an optically active agent, which expresses its chirality. Several strategies have been developed to achieve optimum stereocontrol. For example: 1) to use substrates that form highly ordered transition states; 2) to use chiral auxiliaries that can be incorporated and ultimately cleaved after one or more diastereoselective transformations; 3) to use chiral catalysts both enzymatic or non-enzymatic. Transition metals are applied to synthesise fine chemicals either catalytically or stoichiometrically, although as a general rule in industry, catalytic routes are preferred to stoichiometric ones whenever possible. This approach is environmentally friendly from the point of view that undesirable compounds are avoided.

1.2 Asymmetric Catalysis Applied to Hydrogenation Processes

Chiral catalysts based on transition metals constitutes one of the most used strategies and tries to mimic the role of enzymes in biological processes, where one molecule of catalyst can produce millions of new molecules in the most efficient and selective way [6]. Only rarely has the selectivity of an enzymatic process been

surpassed by a catalytic system based on transition metals. However, a good example of such an instance is the rhodium-catalysed asymmetric hydrogenation of **1** with [Rh(BPPM)COD]Cl (COD=1,5-cyclooctadiene) (Scheme 1) giving the reduced product in 86%ee, while the enzymatic reduction with baker's yeast gives only 72% ee [7].



Scheme 1

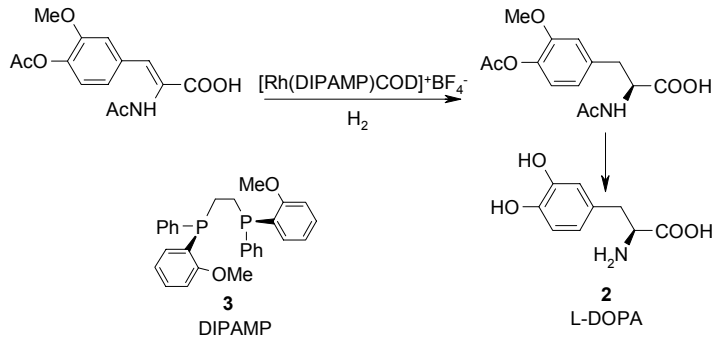
The chirality is introduced into the catalytic system by attaching ligands to the metal center, which make the environment asymmetric and are responsible for both the stereochemical control of the process and the increase in the reaction rate. Natural products are the most important source of chirality and for this reason are widely used as starting materials to synthesise chiral ligands.

In 1966 Wilkinson and his co-workers discovered that chlorotris(triphenylphosphine)rhodium, a complex soluble in apolar solvents (*e.g.* benzene), can be used as an efficient hydrogenation catalyst [8]. Not long before, Horner and Mislow had developed methods for preparing optically active phosphines with phosphorous as the chiral center [9]. The idea of replacing triphenylphosphine in the Wilkinson catalyst by a chiral phosphine was reported independently by Knowles and Sabacky at the Monsanto laboratories in the USA [10] and by Horner and his co-workers in Mainz, Germany [11], reasoning that if the triphenylphosphine were replaced by one of the enantiomers of a chiral

phosphine, it might be possible to produce a catalyst for the asymmetric hydrogenation of a pro-chiral substrate.

William. S. Knowles, Ryoji Noyori and K. Barry Sharpless received the Nobel Prize for Chemistry in 2001 for their achievements in the field of homogeneous catalysis, which contributed to the development of industrial syntheses of pharmaceutical products and other biologically active substances.

Knowles' aim was to develop an industrial synthesis of the amino acid L-DOPA (**2**), which had proved useful in the treatment of Parkinson's disease. The ligand used in Monsanto's industrial synthesis of L-DOPA in the early 1970s was the diphosphine ligand DIPAMP (**3**) (Scheme 2) [12].



Scheme 2

A rhodium complex with the ligand DIPAMP gave a mixture of the enantiomers of DOPA in 100% yield. The product contained 97.5% of L-DOPA. This was the first industrial catalytic asymmetric synthesis.

In 1980 Noyori and co-workers published the synthesis of both enantiomers of the diphosphine ligand BINAP [13], which has been successfully used in asymmetric hydrogenations (Figure 2). Other ligands, which have also provided excellent results in hydrogenation processes, are depicted in the figure below,

featuring BIPHEP [14], DIOP [15], CHIRAPHOS [16], DUPHOS [17] and BPE [18] as the best-known examples.

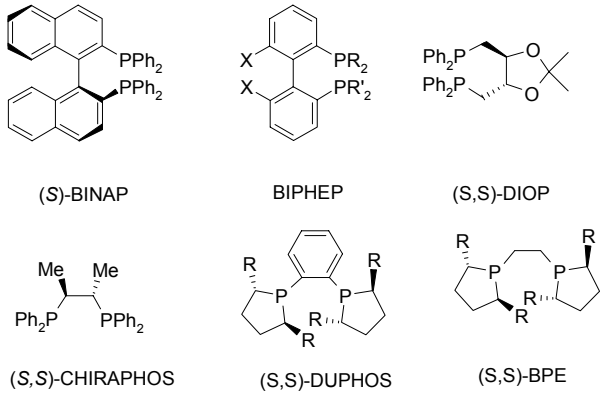
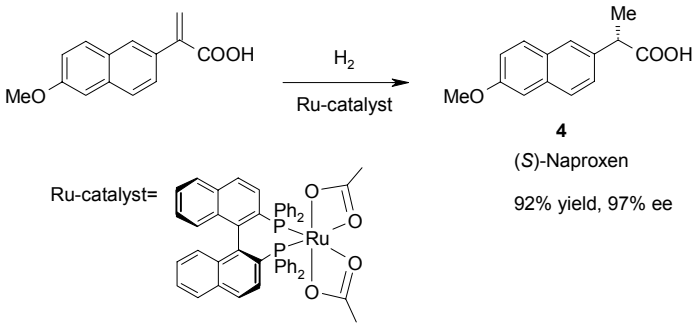


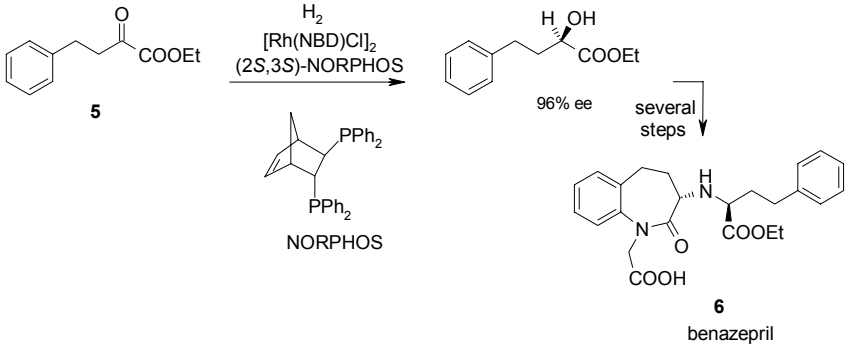
Figure 2

Since the early 1980s, the company Takasago International has used BINAP in the industrial synthesis of the chiral aroma substance menthol [19]. Later, Noyori exchanged rhodium, Rh(I), for another transition metal, ruthenium, Ru(II) [20], in an attempt to find more general catalysts with broader applications. The ruthenium(II)-BINAP complex hydrogenates many types of molecules with other functional groups. These reactions give high enantiomeric excess and high yields and can be scaled up for industrial use. Noyori's Ru-BINAP is used as a catalyst in the industrial production of an anti-inflammatory, naproxen (**4**) (Scheme 3) [20].

Enantioselective hydrogenation has been investigated by Blaser and co-workers [21] of Ciba-Geigy for the production of ethyl-(*R*)-2-hydroxy-4-phenylbutyrate (**5**), an intermediate in the synthesis of benazepril (**6**) (Scheme 4).



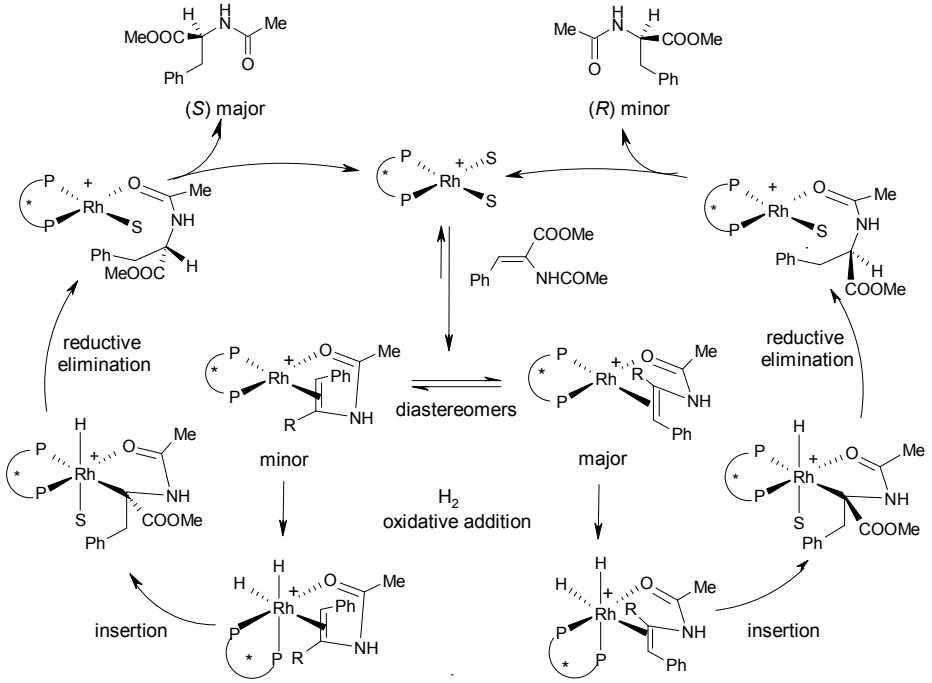
Scheme 3



Scheme 4

Mechanistic studies in the field of asymmetric hydrogenation of prochiral olefins already have a history of three decades. The transition metal, which binds the chiral ligand, has the ability to simultaneously bind both H_2 and the substrate. Then the H_2 is added to the double bond in the substrate. This is the vital hydrogenation stage, when a new chiral complex is formed from which the chiral product is released. Thus from a substrate that is not chiral, chirality is transferred from the chiral catalyst to the product.

Halpern [22] and Brown [23] provided experimental evidences for certain stages of the catalytic cycle and investigated the reason for the enantiomeric excess. In the case of the hydrogenation of the (Z)-α-benzamidocinnamic acid methyl ester by [Rh(*R,R*)-DIPAMP]$^{+}$, two diastereoisomeric adducts were identified in a ratio 10:1 (Scheme 5). Since the diastereomers have different energies, hydrogenation must take place more rapidly via the complex with the lowest energy, thus producing an excess of one of the enantiomers. Nevertheless, detailed kinetics and ^{31}P NMR studies showed that the major (*S*)-product arose from the minor diastereomer due to its much higher reactivity towards H_2.



Scheme 5

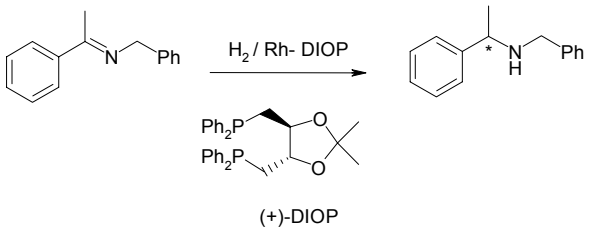
The rate and the mechanism of the interconversion of the diastereomers are very important, because if the oxidative addition of hydrogen is faster than the diastereomers interconversion, the optical yield should decrease.

1.3. Synthesis of Chiral Amines

1.3.1. Asymmetric Hydrogenation of Imines

The synthesis of enantiomerically enriched amines from prochiral compounds is of considerable industrial interest. Developing efficient catalysts for the enantioselective conversion of prochiral imines to the corresponding chiral amines is a major research target [24]. Although the enantioselective hydrogenation of olefins and ketones has been successfully achieved with several catalytic systems using phosphorous ligands, in the hydrogenation of imines enantioselectivities have only been high in a few cases [25].

In 1975, Scorrano [26] and Kagan [27] independently reported that rhodium-DIOP catalyst was able to produce chiral amines. Enantiomeric excess values reached 20% and 50% in the hydrogenation and hydrosilylation of acyclic imines, respectively (Scheme 6).



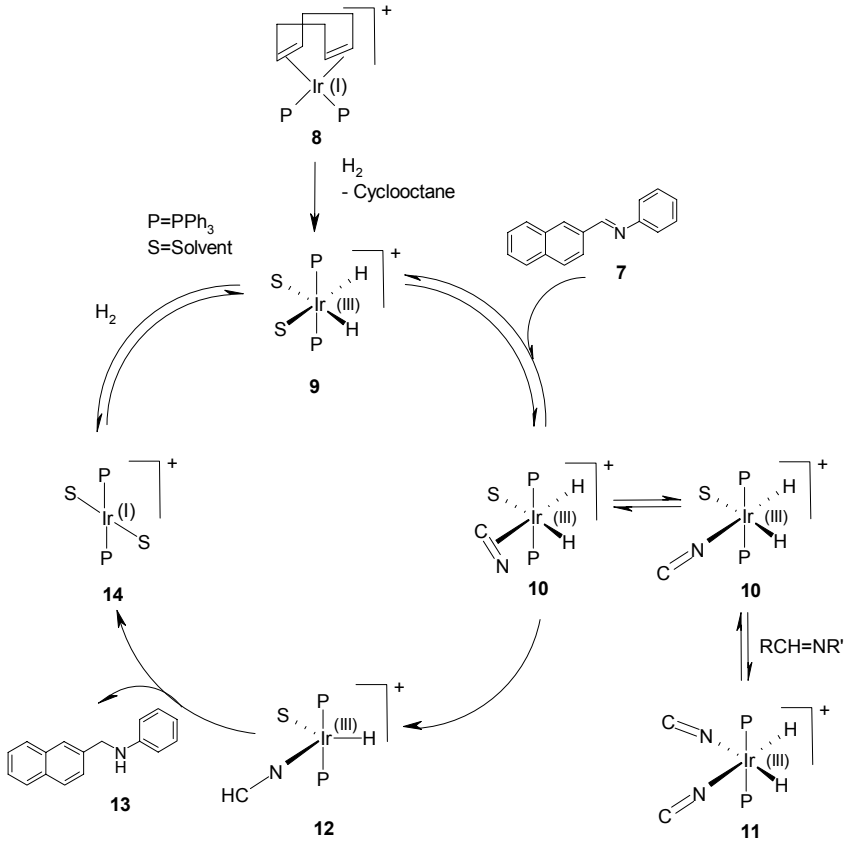
Scheme 6

In the late 80s, however, several publications reported enantiomeric excesses in the reduction of these substrates as high as 60-70% and, from this moment on, the asymmetric hydrogenation of prochiral imines received greater attention. In the last ten years, more than 30 papers have been published reporting enantiomeric excesses up to 90% using mainly rhodium [28] and iridium [29] with diphosphines, and more recently ruthenium [30], titanium [31] and zirconium [32]. Iridium-diphosphines are considered to be the most effective systems for the hydrogenation of imines and are in fact the most widely used. Nevertheless, all these systems generally have a very limited substrate scope.

Despite the fact that the number of efficient catalytic systems is growing very fast, there are very few studies on the mechanistic details of this reaction, and the catalytic cycle is not yet well established. This is an important limitation that affects the design of new efficient catalytic systems and the choice of the best reaction conditions. One of the few mechanistic and kinetic studies that has been made determines the experimental rate equation and the corresponding activation parameters of enthalpy and entropy for the non-asymmetric hydrogenation of *N*-(β-naphthylmethylene)aniline (**7**) using $[IrCOD(PPh_3)_2]PF_6$ (**8**) as catalyst precursor [33]. A catalytic cycle is proposed on the basis of the kinetic experiments and some NMR data (Scheme 7).

Under the conditions of the catalytic reaction and in the presence of a solvent, complex **8** reacts with hydrogen to give **9**, which is proposed as the initial species entering the catalytic cycle. Then, **9** coordinates one imine molecule (**7**) to form **10**. The next step is the first transfer of the hydride to the imine to yield the iridium-alkylaminium intermediate **12**, which evolves to release the product amine **13** by reductive elimination, the rate determining step, and produce the species $[Ir(S)_2(PPh_3)_2]PF_6$ (**14**). This species makes it possible for the cycle to begin again. It is important to note that imines can coordinate in two different modes to the metal center, by the nitrogen atom (η^1-N) or by the double C=N bond (η^2-N,C), where the

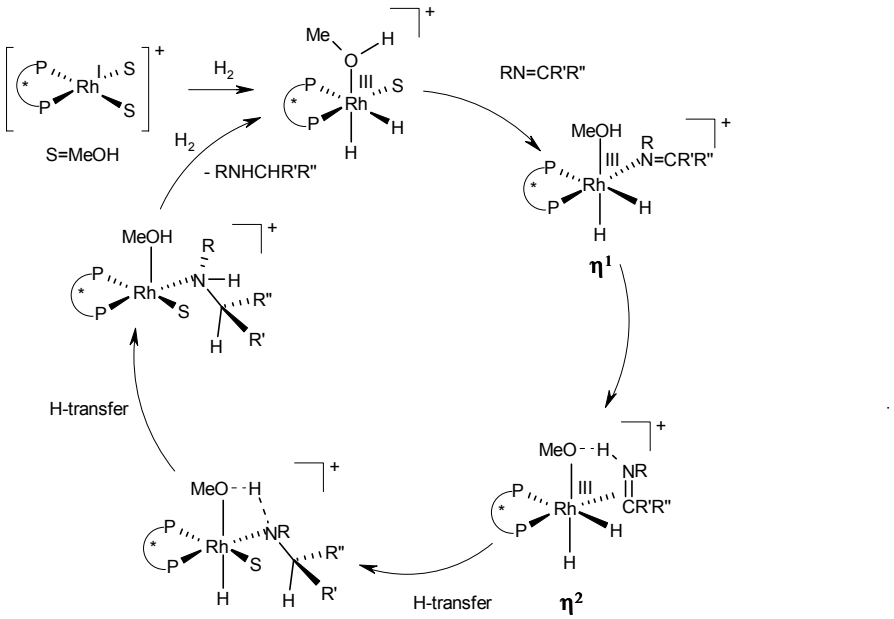
η^2-bonding mode is more likely to occur in the hydrogenation reaction. Although there is no experimental evidence for the existence of these species, it is assumed that while the η^1-N mode is out of the cycle, the η^2-bonding mode is the olefin-like intermediate that undergoes selective hydrogenation of the C=N bond.



Scheme 7

Brian James [34] realized that the use of methanol as solvent or co-solvent was essential to achieve high conversions with some Rh/diphosphine systems. He

suggested that methanol facilitates the change from η^1 to η^2-binding of the imine. A first assumption of a probably catalytic cycle was based on hydride route, where the imine must change to η^2-binding before the hydrogen transfer occurs (Scheme 8).



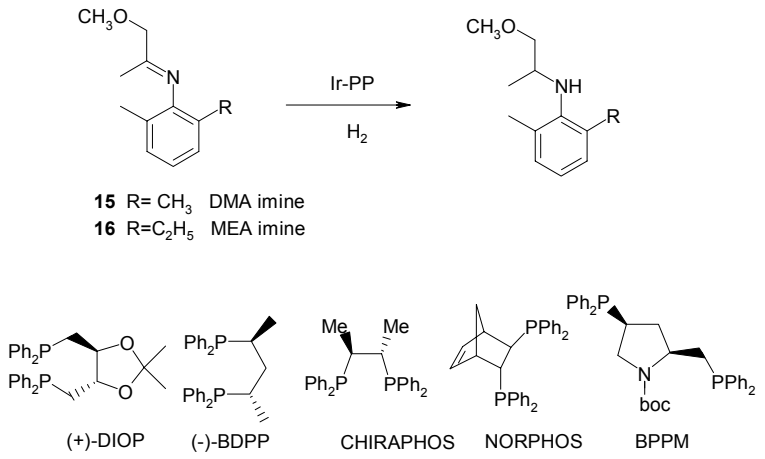
Scheme 8

However, further NMR mechanistic studies with [Rh(NBD)Cl]/chiral diphosphine/imine (chiral diphosphine=DIOP, CHIRAPHOS) [34] indicated that the imine binding to rhodium is a more facile process than hydride formation when chelating diphosphines are used as ligands. Thus, imine binding must be probably the first step in the catalytic cycle.

Other useful considerations can be extracted from literature. For instance, it is generally accepted that the systems based on iridium are more active than those based on rhodium and that the neutral systems formed *in situ* from

$[M(COD)Cl_2]$/Ligand are much more enantioselective than the systems formed from a cationic precursor $[M(COD)Ligand]^+X^-$ [29b,c,d].

Although high conversions and enantioselectivities can be achieved, the presence of an additive such as iodine or amines is often necessary to prevent the catalyst from deactivating, one of the main problems of this reaction. Catalyst deactivation mechanisms for homogenous catalysis have not been studied in as much depth as in heterogeneous catalysis. Even so, several types of homogeneous catalyst deactivation have been described [35]: "catalyst poisoning" consists of the coordination of impurities or other strong coordinating compounds that block the free coordination sites, while "product inhibition" inhibits the catalyst because the resulting product of the reaction coordinates to the metal center. The catalyst can also lose its activity through cluster formation, ligand degradation, the formation of stable inactive species or the loss of the proper oxidation state. Blaser and co-workers studied the deactivation mechanism in the hydrogenation of MEA (**15**) and DMA (**16**) imine with in situ $[IrCODCl]_2$-diphosphine systems (Scheme 9) [36].

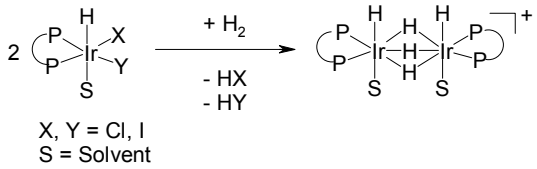


Scheme 9

This study reveals that the degree of deactivation is strongly dependent on ligand structure, solvent and temperature. The purity of the imine also seems to play a major role, and it is particularly important to avoid hydrolysis products such as the corresponding amines, which are extremely detrimental (catalyst poisoning).

What is more, because of the strong donor character of the NH group of the resulting reduced product, it is also possible to observe deactivation of the catalyst by "product inhibition", since the amine competes with the free imine for coordination at the catalytic site [37].

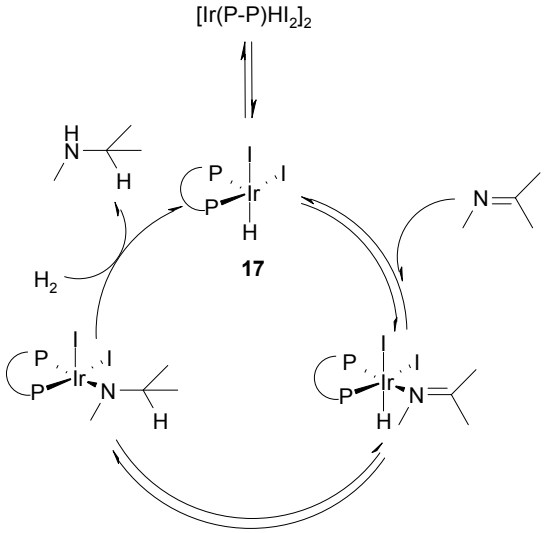
Blaser and co-workers [36] conclude that the mechanism of catalyst deactivation is the irreversible formation of inactive species, hydride-bridged structures analogues at those proposed by Crabtree for the hydrogenation of alkenes (Scheme 10) [38].



Scheme 10

These results showed the need for designing better catalysts with less deactivating tendency, and various strategies have been explored, such as the synthesis of new catalyst precursors. In this field, Osborn developed Ir(III) complexes $[Ir(P\text{-}P)I_4]^-$, $[Ir(P\text{-}P)HI_2]_2$, $[Ir(P\text{-}P)I_3]_2$ [39]. All these systems show good activities, high chemoselectivity and significantly improved resistance to deactivation. While the imine is efficiently hydrogenated, many other functional groups such as alkenes, ketones, esters, nitriles and nitro remain unchanged. Such high chemoselectivity has not previously been observed and is even better than in

stoichiometric conditions. Nevertheless, the enantioselectivities achieved with *N*-aryl, benzyl and alkyl imines are generally moderate. A reasonable catalytic cycle based on Ir(III) complexes is proposed and involves the dissociation of a dimer to yield an unsaturated complex $[Ir(P\text{-}P)HI_2]$ (**17**) (Scheme 11).



Scheme 11

There is evidence that this monohydrido-Ir(III) complex **17** is the active species. The imine is then coordinated and a hydride is transferred from the metal to the sp^2 carbon. The next step is the addition of hydrogen to give the desired amine and recover the monohydrido-Ir(III) complex. This catalytic cycle suggests that the hydrogenation of imines is not always governed by the same rules of the reduction of ketones and alkenes, at least with these Ir(III) systems.

As mentioned before, the use of additives seems to be essential to prevent deactivation of the catalyst, although their role is still not fully understood. This recently acquired knowledge about the most probable deactivation mechanism

suggests that the addition of iodine derivatives prevents the formation of the hydride-bridged inactive species described by Crabtree, that cause the premature end of the reaction, favouring perhaps the formation of Ir(III)–iodine complexes like the ones shown above and characterised by Osborn [39], following an Ir(III)-catalysed pathway.

Many other authors have reported the advantageous use of additives [40], mainly iodine, although there are also examples of the use of amines or alcohols with both rhodium- and iridium-phosphine systems [29c,40b]. Nevertheless, additives do not always have a beneficial role: the Ir-BINAP catalyst developed by Tani and co-workers, for instance, is not affected by the addition of iodide [41].

The coordination of substrate as chelate has been shown to be critical in the reduction of imines for the attainment of high enantioselectivities and high rates as well as occur in enamide and enol acetate hydrogenations [42]. The presence of an additional functional group that can be attached to the metal center facilitates the reduction of the C=C or C=N bond (Figure 3).

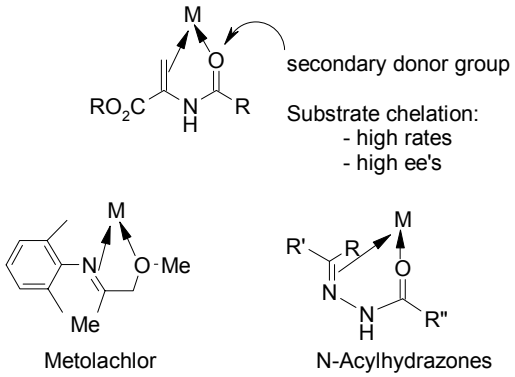
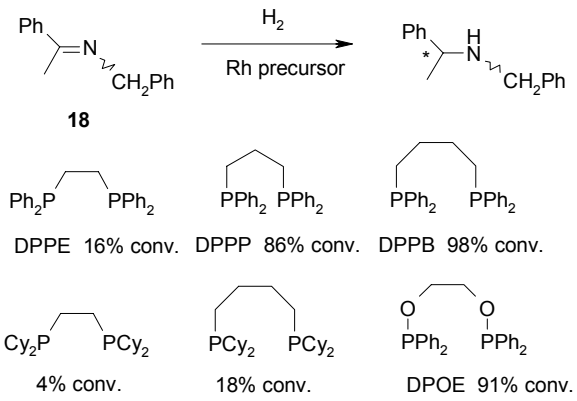


Figure 3

The imine metolachlor has a metoxy group, which can be coordinated to the metal. If the substrate does not have this secondary donor group, an strategy is to introduce an auxiliary group, which can easily be removed from the final product without loss of enantioselectivity, as N-acylhydrazones [42b,43] (Figure 3). These substrates can be converted after hydrogenation either to the desired free hydrazines or free amines without changing the stereochemical purity.

Börner and co-workers studied how the size of the chelating ring and the ligand structure affect the hydrogenation of *N*-(1-phenylethylidene)benzylamine (**18**) with achiral rhodium catalysts. The results showed that the chelates that form the smallest rings (five- and six-members) afford poor or modest yields (Scheme 12) [44]. On the other hand, the more flexible, seven-membered chelate based on DPPB converts the imine into the desired product within 2 hours.



Scheme 12

Moreover, the more electron-rich catalysts based on the dialkylphosphines give worse results than the electron-poorer diphosphinite in contrast with the widely accepted idea that more donor ligands favour the oxidative addition of the hydrogen

and subsequently the activity of the system. It can be concluded from Borner's work that this reaction is very sensitive to chelate size and to the substituents on the phosphorous atoms.

The most notable achievement in this field was made by the Ciba-Geigy scientists [29e,45] who developed a catalytic process for the industrial production of (*S*)-metolachlor.

Metolachlor is the active ingredient of *Dual*®, one of the most important grass herbicides used in maize and a number of other crops. Metolachlor has two chiral elements: a chiral axis (atropisomerism, due to hindered rotation around the C_{Ar}-N axis) and a stereogenic center, leading to four possible steroisomers (Figure 4).

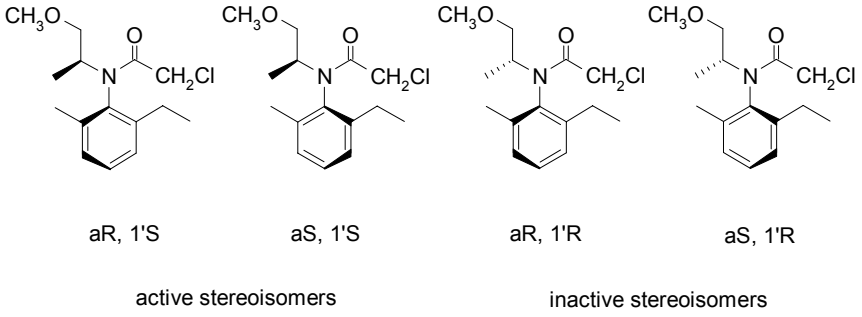
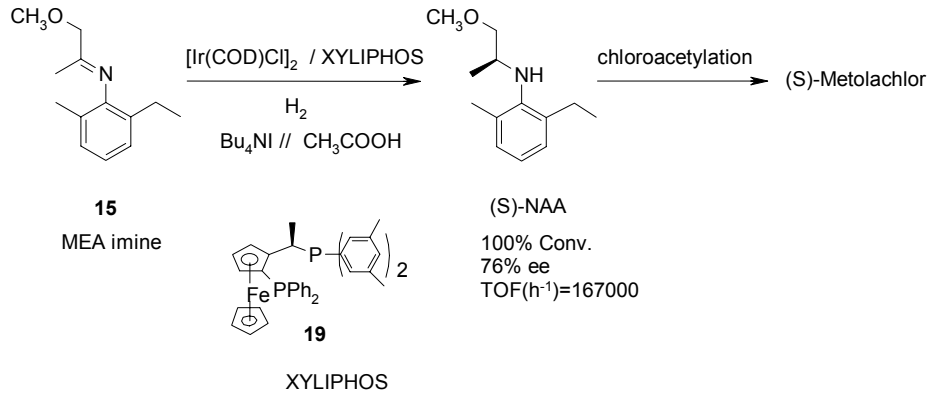


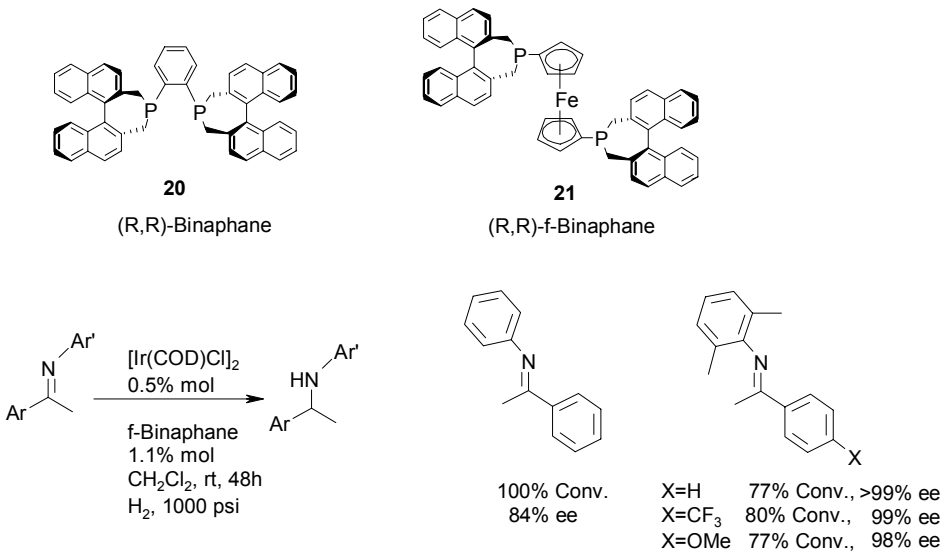
Figure 4

About 95% of the herbicidal activity of metolachlor resides in the two (1'*S*)-diastereoisomers; therefore, it was necessary to develop an enantioselective synthesis for its industrial production. After years of fruitless research, Ciba-Geigy [46] patented an iridium catalyst prepared *in situ* from $[Ir(COD)Cl]_2$ with a ferrocene ligand (Xyliphos (**19**)) [47] and applied it to the hydrogenation of the MEA imine (**15**) (Scheme 13).



Scheme 13

The highest enantioselectivity (>99% ee) achieved in the asymmetric hydrogenation of imines up to date was obtained using the Ir-ferrocene binaphane complex reported by Zhang in the hydrogenation of a hindered imine (Scheme 14) [48].

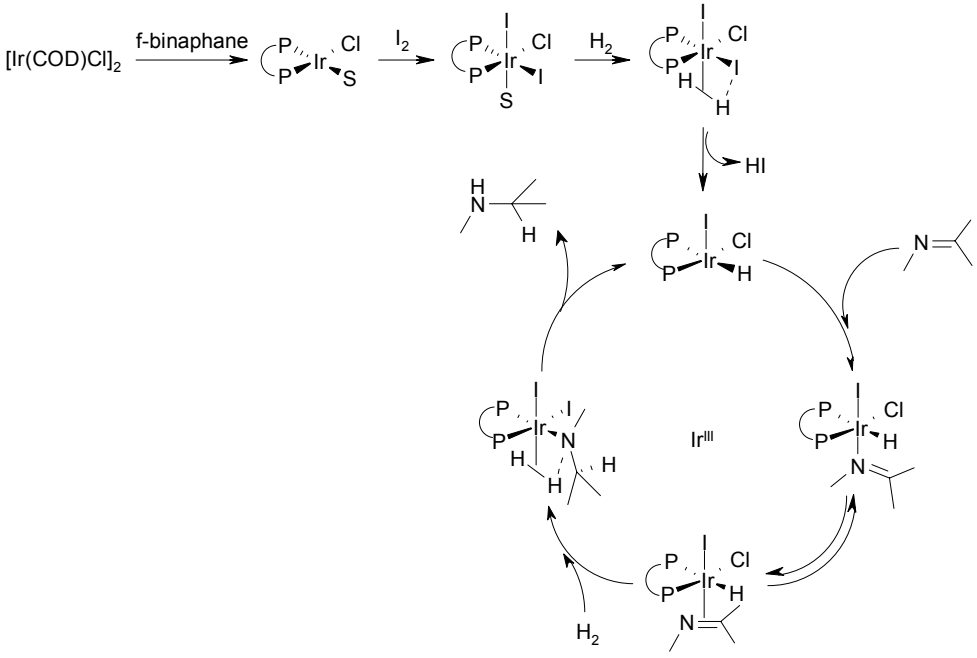


Scheme 14

Curiously, the chiral analogous phosphane ligand, binaphane (**20**), was not effective for the rhodium- or iridium-catalysed hydrogenation of imines. Its steric and electronic properties had to be altered by introducing a ferrocene backbone leading the Ir(I)-1,1'-bisphosphanoferrocene (**21**, f-binaphane) ligand.

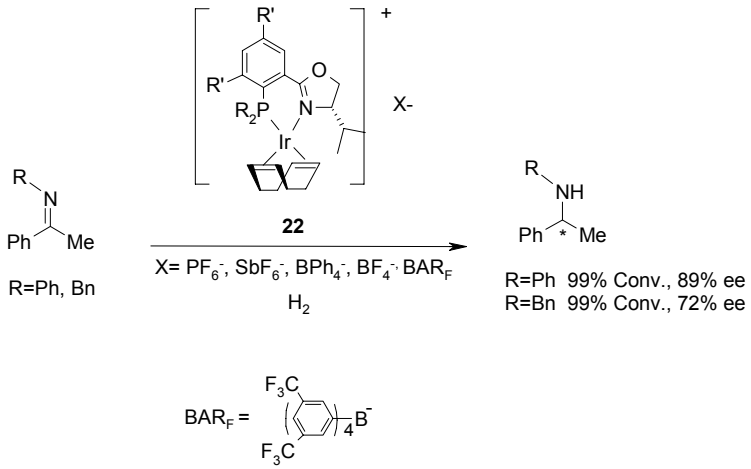
Zhang also observed an enhancement of the reactivity and enantioselectivity when I_2 was used as an additive and, on the basis of Osborn's studies, proposed a feasible catalytic cycle for the Ir-f-binaphane-I_2 system (Scheme 15).

The oxidative addition of iodine leads to an Ir(III)-catalysed pathway with a heterolytic cleavage of H_2, giving Ir(III)-H species that are analogous to those proposed by Osborn.



Scheme 15

Phosphines are used mainly as the preferred ligands in hydrogenation reactions. There are, however, a few examples of the successful application of heteroatomic ligands in the reduction of C=N. These ligands replace one phosphorous by nitrogen or another coordinating atom. In this context, Pfaltz [29f,49] investigated the application of cationic Ir(I) complexes with diphenylphosphinooxazolines (**22**) in imines reduction. This catalyst, which provides enantioselectivities up to 89% in acyclic substrates, represents one of the most successful examples of cationic precursors used in the asymmetric hydrogenation of imines (Scheme 16).



Scheme 16

The addition of iodide to Pfaltz's catalyst has a dramatic effect, in contrast to earlier findings with Ir-diphosphano complexes where enantioselectivities are much higher when additives are used. Non-coordinating counterions such as PF_6^-, SbF_6^-, BPh_4^-, or BF_4^- have similar behaviour, and no remarkable changes are observed in either activity or enantioselectivity. However, when the supercritical

carbon dioxide ($scCO_2$) was used as the reaction medium, the choice of the anion had a dramatic effect on the enantioselectivity [50]. The counterion tetrakis-3,5-bis(trifluoromethyl)-phenylborate (BAR_F) led to the highest enantioselectivities. As a result of these findings, a new class of heterocyclic phosphino-oxazoline cationic iridium complexes has recently been developed to enlarge the scope of the asymmetric reduction of imines (Figure 5) [51].

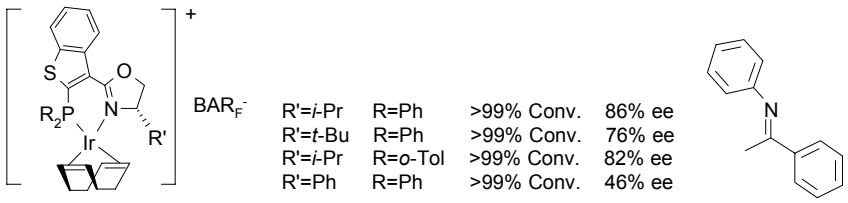
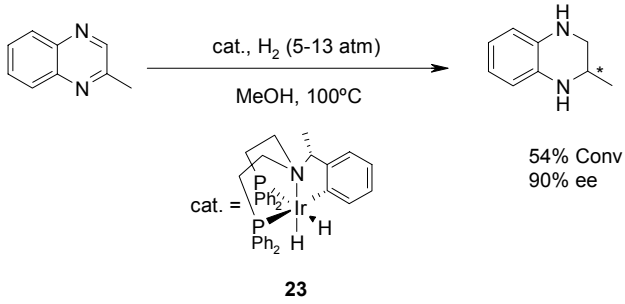


Figure 5

Bianchini [52] investigated the use of an orthometalated dihydride iridium complex *fac-exo*-(R)-[$IrH_2\{C_6H_4C^*H(Me)N(CH_2CH_2\text{-}PPh_2)_2\}$ (**23**) as catalyst precursor in the reduction of quinoxalines with ee up to 90% (Scheme 17).

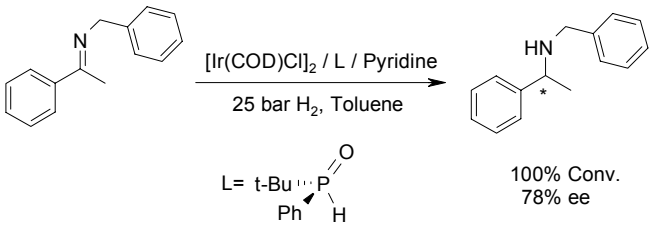


23

Scheme 17

This is the only example in which the catalyst is capable of reducing 2-substituted quinoxalines with attractive optical yields.

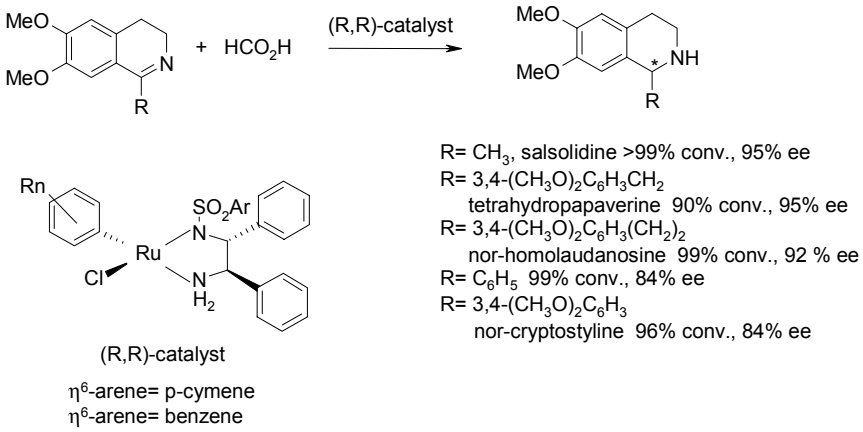
Most of the ligands that give a high degree of enantiocontrol are bidentate, and there are almost no examples of efficient chiral monodentate ligands for the asymmetric hydrogenation of imines. Feringa and co-workers [53] reported the application of monodentate secondary phosphine oxides as a new class of ligands in Ir(I)-catalyzed asymmetric imine hydrogenation. Conversions were good even at very low hydrogen pressures (1-25 bar). This catalytic system uses pyridine as an additive by analogy to the Crabtree's catalyst, $[Ir(COD)(PCy_3)Py]PF_6$, which showed high activity in alkene hydrogenation [38], and proved its effectiveness when 2 equivalents of pyridine were used with respect to iridium (Scheme 18).



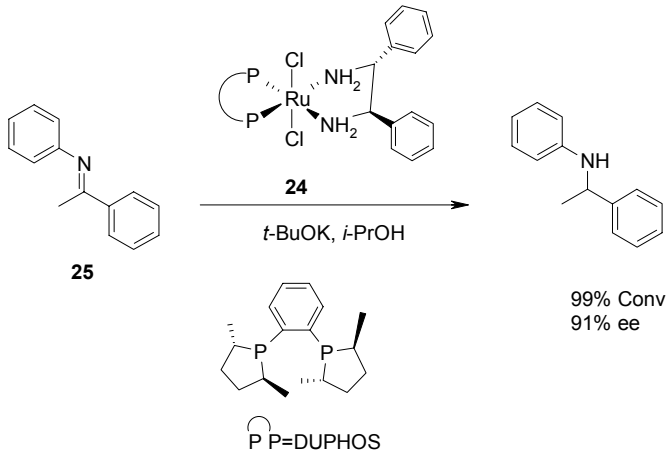
Scheme 18

Other metals have also been used in this reaction. Noyori applied arene-Ru(II) complexes, which had some suitable chiral 1,2-diamine ancillaries, to the asymmetric transfer hydrogenation of imines with a mixture of formic acid-triethylamine (Scheme 19) [30b].

More recently, Chiro-Tech [30i,54] patented a ruthenium catalyst [Ru(DUPHOS)(chiral diamine)Cl_2] (**24**) that achieves enantioselectivities up to 91% in the hydrogenation of *N*-(phenylethylidene)aniline (**25**) (Scheme 20).



Scheme 19



Scheme 20

Since the early 1990s, Buchwald et al. [31] and Brintzinger et al. [32] have been working with titatium and zirconium, respectively, to study the development

and application of new catalytic systems based on chiral ansa-metallocene compounds (Figure 6).

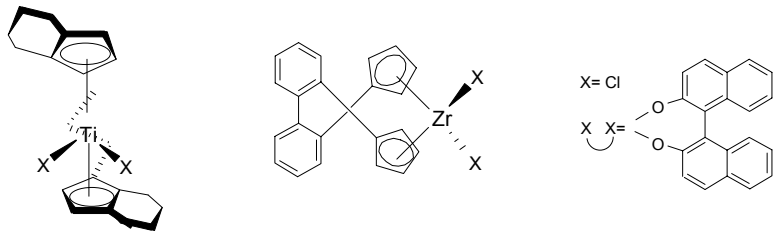


Figure 6

The asymmetric hydrogenation of cyclic ketimines with a chiral ansa-titanocene catalyst affords amines with excellent enantioselectivity under a variety of conditions. The reaction is general for cyclic imines with ring sizes of between 5 and 7 members and exhibits a high degree of functional group compatibility. In addition, the biphenyl-bridged zirconocene complex gives selectivities that are similar to those obtained with the titanocene complex.

Figure 7 shows a selection of ligands, mainly diphosphines, which have been successfully used in the asymmetric hydrogenation of different imines [55,56,57].

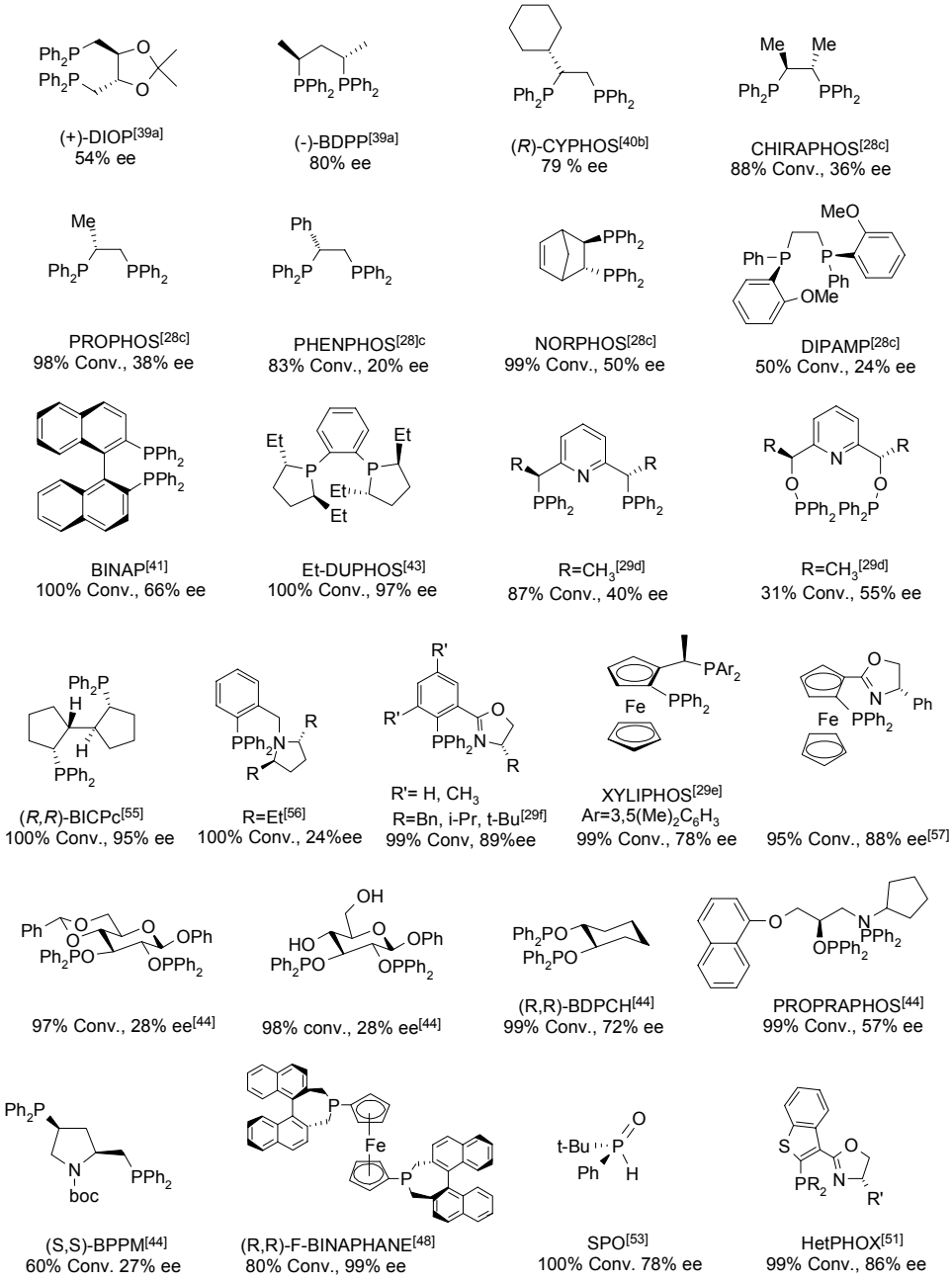
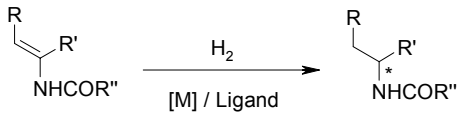

(+)-DIOP[39a]
54% ee
(-)-BDPP[39a]
80% ee
(R)-CYPHOS[40b]
79 % ee
CHIRAPHOS[28c]
88% Conv., 36% ee
PROPHOS[28c]
98% Conv., 38% ee
PHENPHOS[28]c
83% Conv., 20% ee
NORPHOS[28c]
99% Conv., 50% ee
DIPAMP[28c]
50% Conv., 24% ee
BINAP[41]
100% Conv., 66% ee
Et-DUPHOS[43]
100% Conv., 97% ee
R=CH3[29d]
87% Conv., 40% ee
R=CH3[29d]
31% Conv., 55% ee
(R,R)-BICPc[55]
100% Conv., 95% ee
R=Et[56]
100% Conv., 24%ee
R'= H, CH3
R=Bn, i-Pr, t-Bu[29f]
99% Conv, 89%ee
XYLIPHOS[29e]
Ar=3,5(Me)2C6H3
99% Conv., 78% ee
95% Conv., 88% ee[57]
97% Conv., 28% ee[44]
98% conv., 28% ee[44]
(R,R)-BDPCH[44]
99% Conv., 72% ee
PROPRAPHOS[44]
99% Conv., 57% ee
(S,S)-BPPM[44]
60% Conv. 27% ee
(R,R)-F-BINAPHANE[48]
80% Conv., 99% ee
SPO[53]
100% Conv. 78% ee
HetPHOX[51]
99% Conv., 86% ee

Figure 7

1.3.2. Asymmetric Hydrogenation of Enamides

The asymmetric hydrogenation of enamides is a convenient and economical route for preparing chiral α-amino acid derivatives (R'=CO_2R) or chiral amine derivatives (R'=alkyl) (Scheme 21).



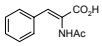
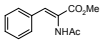
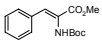
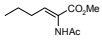
Scheme 21

Reducible substrates that contain both a carbonyl (amide) group and a carbon-carbon double bond, such as enamides, are very important. The ability to reduce only one group and leave the other unaffected is a challenging task in organic synthesis, particularly in the preparation of pharmaceutical and agrochemical products.

In general, the most efficient catalysts for α-enamide hydrogenations are those derived from rhodium complexes bearing chiral C_2-symmetric diphosphine ligands [58]. Table 1 summarizes the best enantioselectivities obtained with Rh/diphosphine catalysts in the reduction of α-enamides to produce α-amino acid derivatives.

The catalytic system Rh/Et-DUPHOS [59] is clearly more enantioselective than the others for the production of α-amino acid derivatives. It hydrogenates the substrates bearing β-phenyl and β-alkyl substituents reasonably well. Neither of the other ligands is capable of reducing tetrasubstituted olefins satisfactorily.

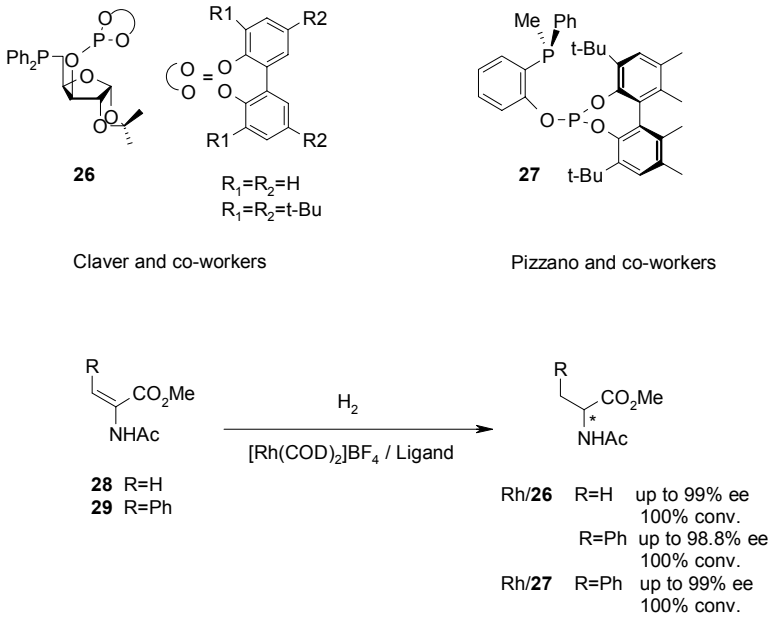
Table 1. Enantioselectivities in α-enamide hydrogenation using Rh/diphosphines [58][a]

Substrate	Et-DUPHOS	DIPAMP	PROPAPHOS	BPPM	CHIRAPHOS
	99	95	--	82	79
	99	94	88	91	89
	99	96	86	93	85
	99	95	93	82	--
	99	96	--	80	82
	99	65	--	57	71
	98[b]	55	--	0	--

[a] Table 1 was extracted from the literature, as indicated by the reference. Hydrogenations were performed using cationic catalyst precursors of type $[Rh(COD)(diphosphine)]^+X^-$ ($X=BF_4$, PF_6, SbF_6, OTf). [b] The ligand used was Me-BPE.

As examples of ligands with different phosphorus functionalities, new phosphine-phosphite ligands (**26, 27**) have been developed and applied in the rhodium-catalysed asymmetric hydrogenation of methyl-(*N*)-acetamidoacrylate (**28**) and methyl-(Z)-(*N*)-acetamidocinnamate (**29**) collecting values of ee up to 99% (Scheme 22) [42a,60].

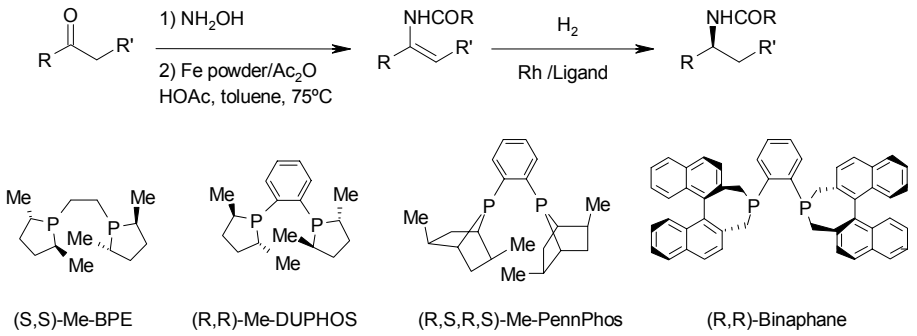
The most interesting feature of phosphine-phosphite ligands is the presence of two phosphorus functionalities with rather different electronic properties. When coordinated to a metal center, a good σ-donor ability can be expected for the phosphine groups, whereas a phosphite fragment should be a poorer σ-donor and a better π-acceptor. Besides, ligand **27** has a stereogenic phosphorus, which has a strong influence on the enantiocontrol of the process [60].



Scheme 22

In the last three decades, chiral amino acids and their derivatives have been synthesised very successfully through asymmetric hydrogenation with Rh/diphosphane catalysts. In comparison, there are very few successful examples of the asymmetric hydrogenation of enamides without the carboxyl functionality.

Burk and co-workers [61] and Zhang and co-workers [62] independently developed a three-step procedure for the asymmetric catalytic reductive amidation of ketones. This procedure makes it possible to prepare a wide range of new enamides that can subsequently be hydrogenated with Me-DUPHOS-Rh, Me-BPE-Rh, PennPhos-Rh and (*R,R*)-binaphane-Rh catalyst systems (Scheme 23).



Scheme 23

These catalysts were some of the few that were able to reduce mixtures of *E* and *Z* enamides with high enantioselectivities [63]. They also demonstrated their potential in the reduction of enamides derived from cyclic ketones α–tetralone and 1-indanone, giving very impressive results (Figure 8).

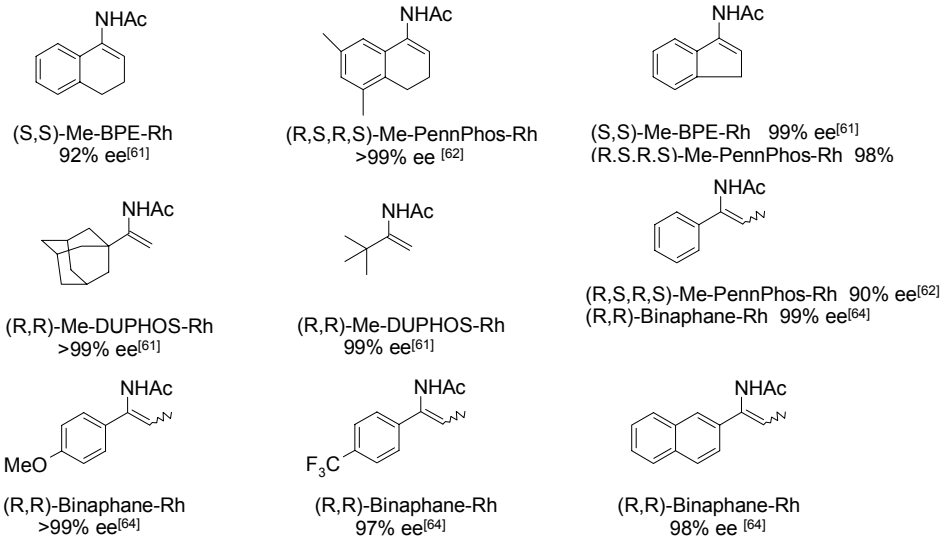


Figure 8

Besides, the (*R,R*)-Me-DUPHOS-Rh system gave ees up to 99% in the reduction of alkyl enamides, and the (*R,R*)-binaphane-Rh catalyst provided the highest enantioselectivities (95-99.6% ee) in the hydrogenation of an isomeric mixture of (*E*)- and (*Z*)-β-substituted-α-arylenamides [64].

The Rh/(*R,R*)-DIOP complex gave only moderate ee's in the hydrogenation of alkyl- and aryl-enamides [65] probably because of its conformational flexibility. Besides, the stereogenic centers are too far from the coordinating atoms and the transfer of backbone chirality to the phenyl groups on the phosphine goes through a methylene group. To overcome this drawback, Kagan synthesized ligand (*S,S,S,S*)-DIOP* in which stereogenic centers are closer to the phosphines (Figure 9) [66].

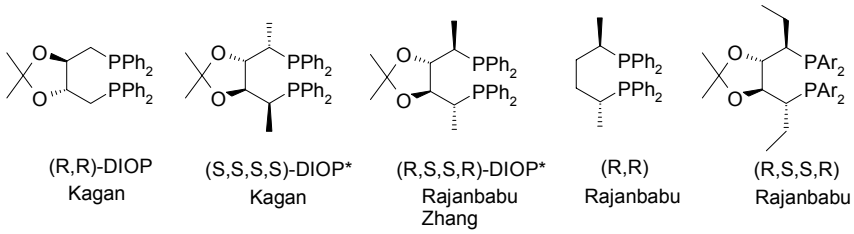


Figure 9

Disappointingly, this ligand induced very low enantioselectivity in the reduction of enamides, probably due to the two methyl groups in axial positions in the chelate ring, which resulted in an unfavourable conformation. Accordingly, Rajanbabu [65] and Zhang [67] independently modified the (*S,S,S,S*)-DIOP* backbone, and inverted the configuration of the methyl groups. The resulting ligand (*R,S,S,R*)-DIOP* led to extremely high enantioselectivities (up to 98%). Rajanbabu synthesized modified DIOP derivatives in order to study the ligand substituent effects on asymmetric induction, and concluded that changes in the ligand backbone and the chelating phosphorus atoms result in dramatic changes in the

enantioselectivity of $Rh^{+}L^{*}$-catalysed enamide hydrogenations (Figure 9).

All these ligands that give a high degree of enantiocontrol are bidentate. However, many groups have recently reported the use of monodentate ligands as highly efficient ligands for the rhodium-catalysed enantioselective reduction of enamides. These monodentate ligands are monophosphoramidites [68,69] monophosphites [70,71] and monophosphonites [71,72] (Figure 10).

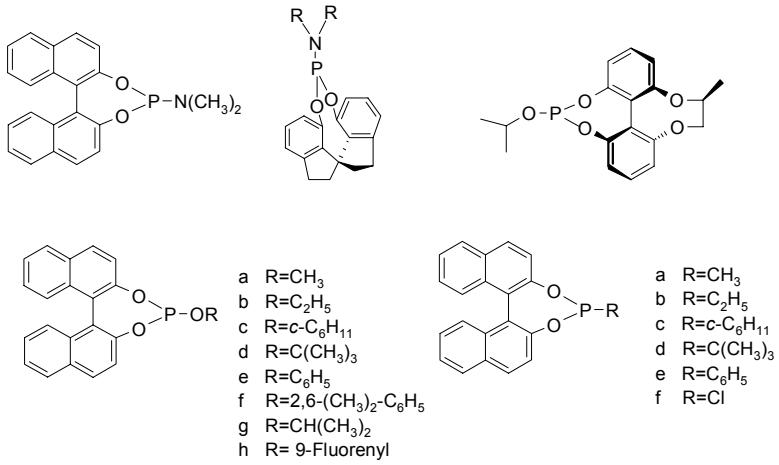
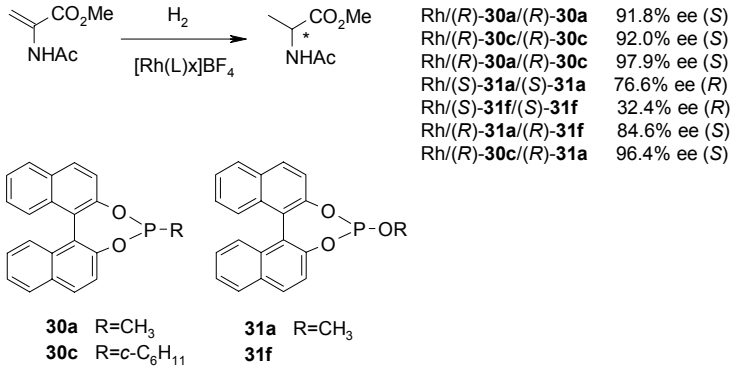


Figure 10

Reezt described a new concept in the area of combinatorial enantioselective transition-metal catalysis, mixing chiral monodentate ligands. The method is relevant whenever in the transition state of the reaction at least two monodentated ligands (L) are coordinated to the metal (M) of the active catalyst MLx. When there are two different ligands L^{a} and L^{b} in the reaction mixture, there are at least three different catalysts in equilibrium: two homocombinations $ML^{a}L^{a}$ and $ML^{b}L^{b}$ and one hetereocombination $ML^{a}L^{b}$. The results obtained showed that in some cases the mixture of all three catalysts made it possible to obtain higher enantioselectivities

than the pure homocombinations. Initial kinetic studies indicate that this mixture is a more active catalyst. However, the source of the increased enantioselectivity is still not known (Scheme 25) [71c].



Scheme 24

1.4. Scope of this thesis

The aim of the thesis is to develop new catalytic systems capable of producing enantiomerically enriched amines by reduction of imines and enamides in the most efficient and selective way. To achieve this important goal, new and versatile catalytic systems have been synthesised based on chiral modular ligands containing NS, NP and PP coordinating atoms.

Chapter 2 deals with the synthesis of *N*-donor ligands that contain oxazoline or imidazoline moieties and sulphur or phosphorus, respectively, as second coordinating atom (Figure 11). Furthermore, the organometallic iridium complexes of these ligands were prepared and studied in depth by NMR and X-Ray

analysis. Finally, their catalytic potential has been checked in the iridium-catalysed asymmetric reduction of ketimines.

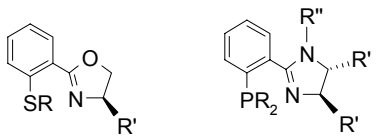


Figure 11

Chapter 3 describes the preparation of two families of phosphorous ligands based on carbohydrate structures: diphosphites, diphosphinites, phosphinite-phosphite and monophosphite ligands with C_1- and C_2- symmetry (Figure 12). These ligands were also applied in iridium and rhodium-catalysed asymmetric catalysis involving both imine and enamide reductions.

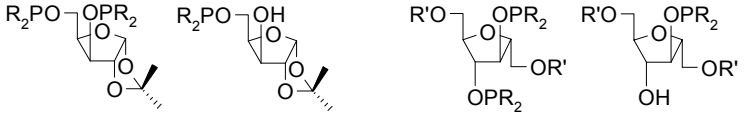


Figure 12

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