Agraïments

Ara és quan de debò em queda la feina més feixuga, agrair a tots els que m'han acompanyat i ajudat durant aquests anys. I no vull dir que donar les gràcies sigui difícil, sino que tinc por que les paraules em traeixin i no expressin la veritable gratitut que sento.

Obligada estic a començar pels companys de laboratori, sense els quals em resulta inimaginable haver arribat al final d'aquesta tesis. I em crec més afortunada que d'altres. Sí, així és, ja que no puc ni vull separar polimèrics de sucreros i d'inorgànics. La llista és llarga, entre doctorants i professors, a tots, a tots plegats us dono les gràcies, als que hi sou ara i als que ja heu marxat. També agrair als companys de recursos científics la seva col.laboració i ajuda. Reunions de grup, esmorzars, cafès i xerrades, sopars de dijous i dinars a "instrumentació"..., tots aquests moments me'ls enduré amb mi i sé del cert que els enyoraré. No escolliría altres companys, us escolliría a vosaltres.

Disculpeu-me però si tinc unes paraules a banda per la Gemma, la Paca, l'Àlex, la Manuela i la Pi; i per la Marta, l'Amaia i la Carol. Crec que tots podeu entendre que ja no parlo només de companys sino d'amics. Amb vosaltres no he compartit tant sols química, sino també un bon grapat d'agradables estones: tertúlies literàries i cinematogràfiques, cervesetes al bar de la facu, podium en alguna que altra discoteca, classes alemany-espanyol, mojitos a la piscina, rialles i consells, trucades de telèfon a llarga distància... Per tots aquests moments i per la vostra amistat, gràcies de tot cor.

De les meves estades a Alemanya en tinc un molt bon record, mèrit que he d'atribuir al Benjamí, qui em va fer les coses molt fàcils i treballar amb ell va ser realment gratificant. Recordo el treball dur d'aquell parell de mesos i les ganes i entusiasme que hi varem posar. No vull oblidar a la comunitat espanyola, entre ells

l'Antón, el Jordi, l'Oriol i la Laia. Gràcies a tots per fer-me les coses més fàcils i agradables.

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Als meus pares, a la meva germana, al Josep Mª, a la Gemma i al petitó Jordi, gràcies per confiar cegament en mi i per respectar sempre les meves decisions. Us estimo molt.

Dani, T'im.

There are some hypotheses in science which are wrong. That's all right. It's the aperture to finding out what's right. Science is a self-correcting process. […] The most accepted and conventional ideas are often wrong and the fundamental insights can arise from the most unexpected sources.

Carl Sagan

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).

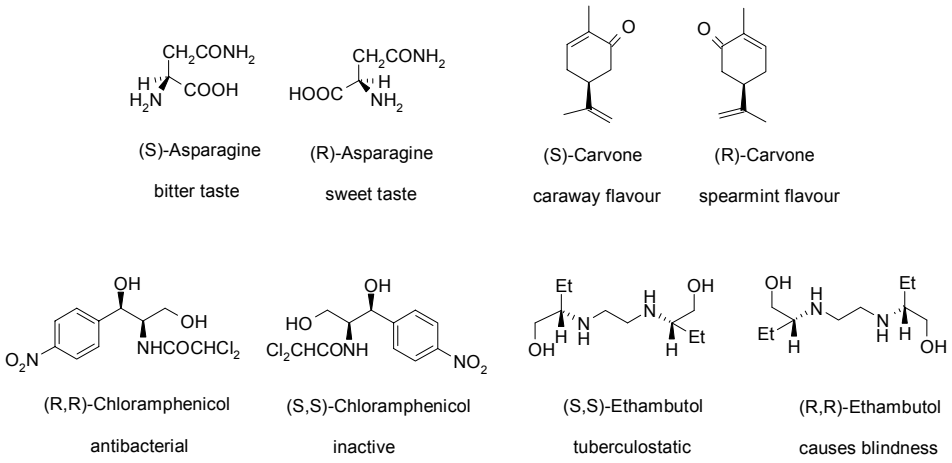


Figure 1

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.

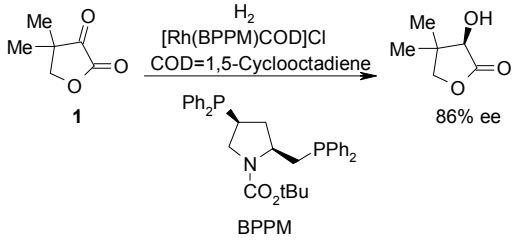
Classical resolution becomes particularly attractive when it can be combined with *in situ* racemization and crystallization-induced by diastereomeric adduct formation. When an enantiopure compound reacts with a mixture of enantiomers, a mixture of diastereomers is produced, separable by differences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

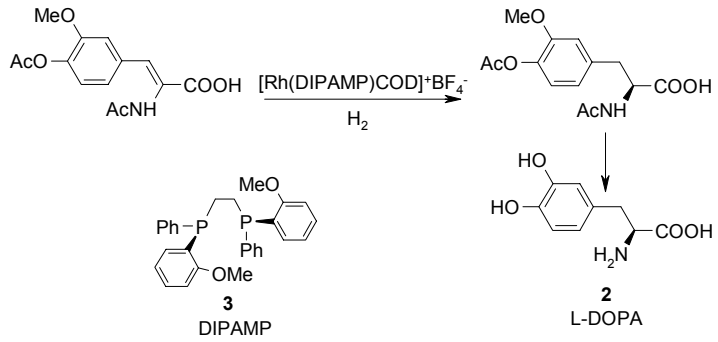
The chirality is introduced into the catalytic system by attaching ligands to the metal center, which make the environment asymmetric and are responsible for both the stereochemical control of the process and the increase in the reaction rate. Natural products are the most important source of chirality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

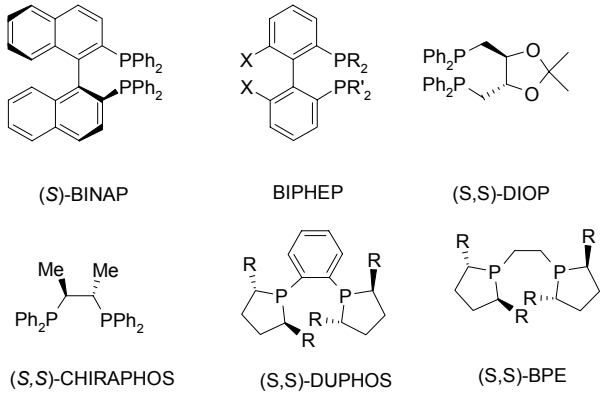
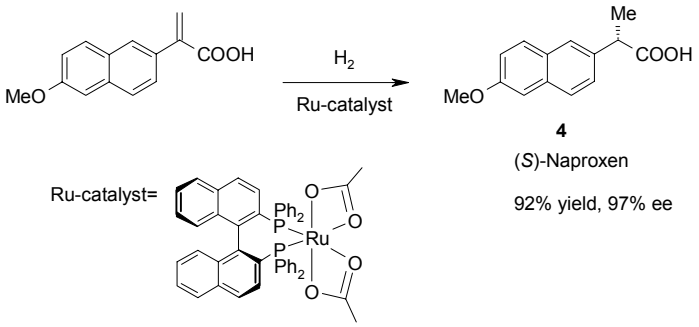


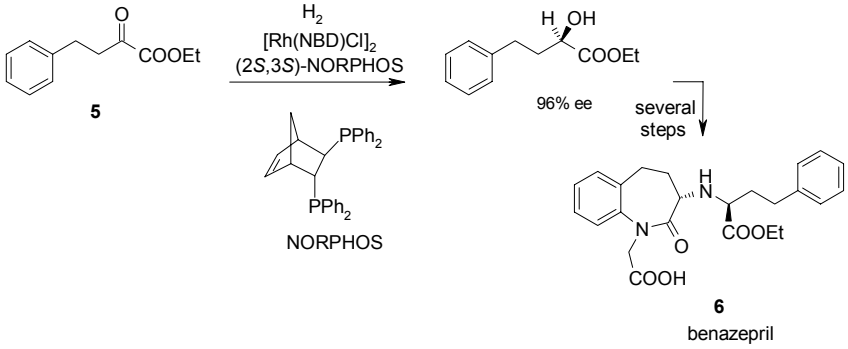
Figure 2

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).



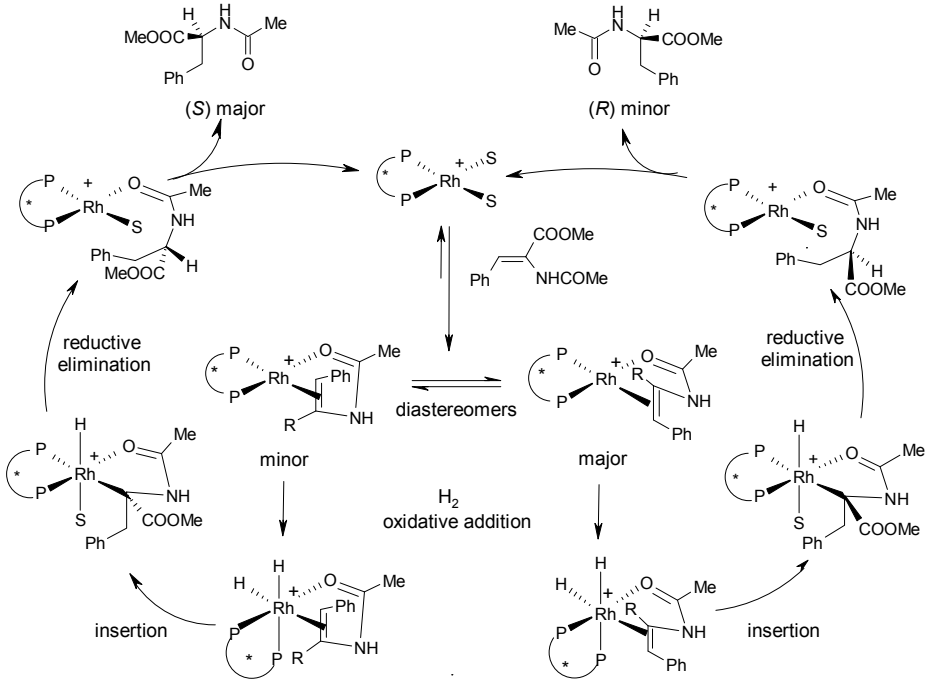
Scheme 3



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

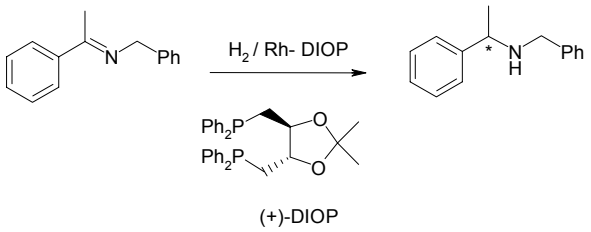
The rate and the mechanism of the interconversion of the diastereomers are very important, because if the oxidative addition of hydrogen is faster than the diastereomers interconversion, the optical yield should decrease.

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).



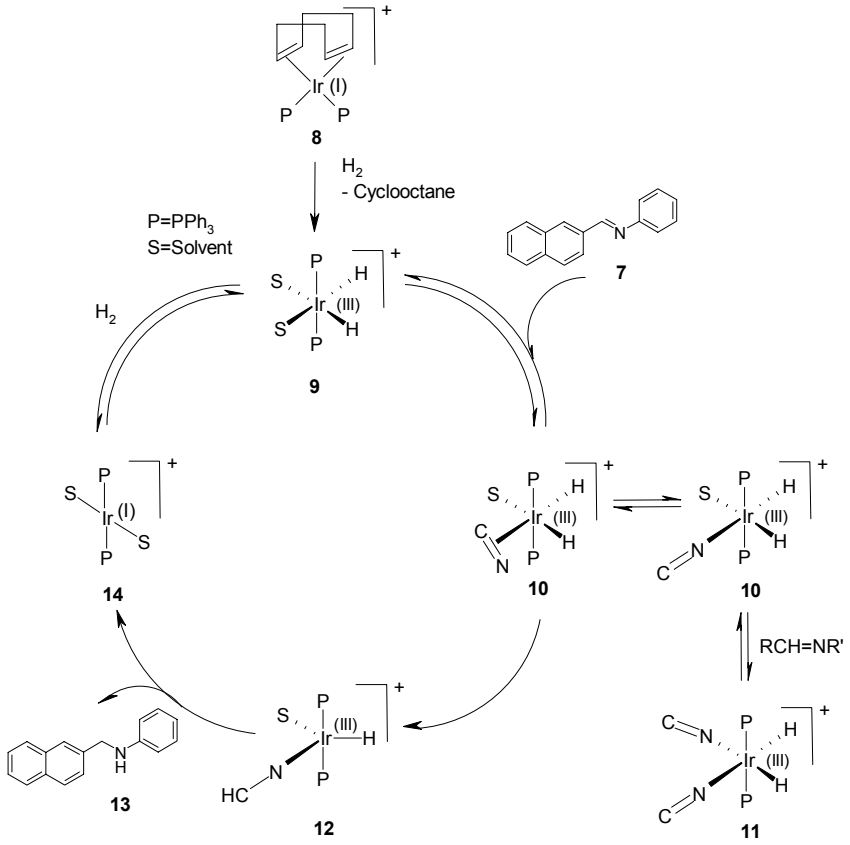
Scheme 6

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

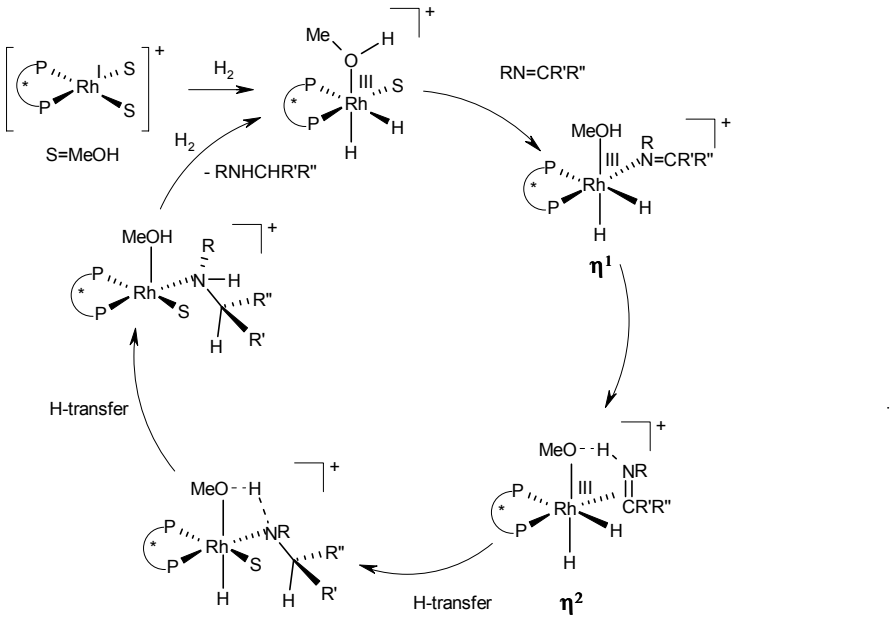
η^2-bonding mode is more likely to occur in the hydrogenation reaction. Although there is no experimental evidence for the existence of these species, it is assumed that while the η^1-N mode is out of the cycle, the η^2-bonding mode is the olefin-like intermediate that undergoes selective hydrogenation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



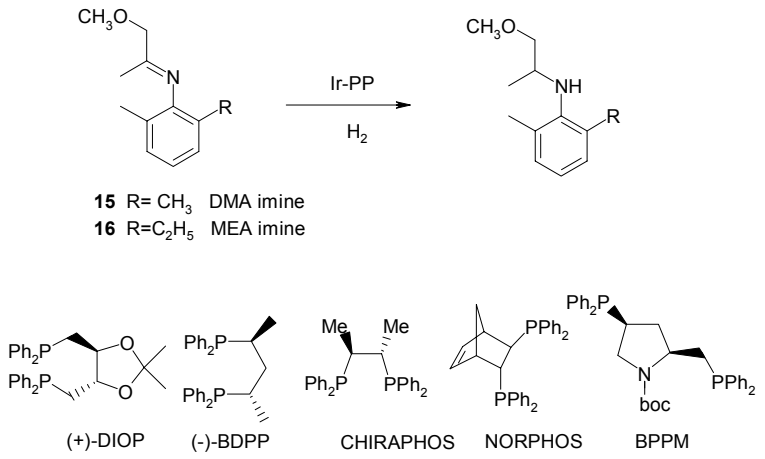
Scheme 8

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].

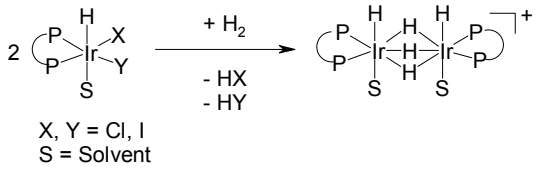


Scheme 9

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].

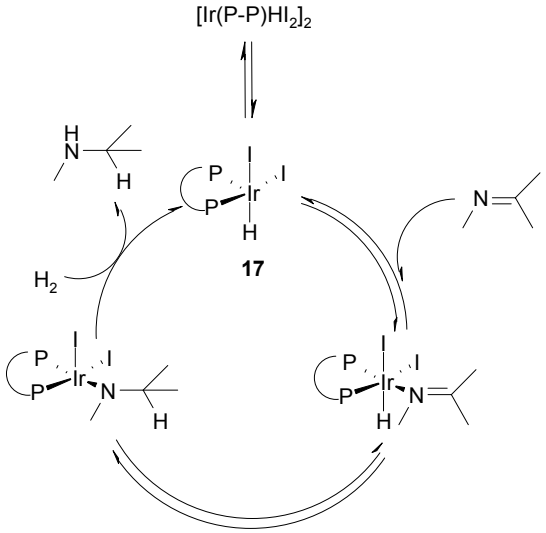
Blaser and co-workers [36] conclude that the mechanism of catalyst deactivation is the irreversible formation of inactive species, hydride-bridged structures analogues at those proposed by Crabtree for the hydrogenation of alkenes (Scheme 10) [38].



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).

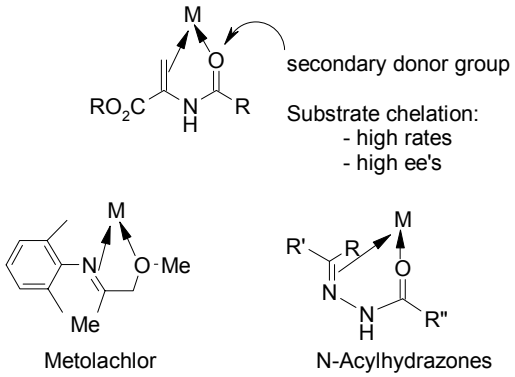
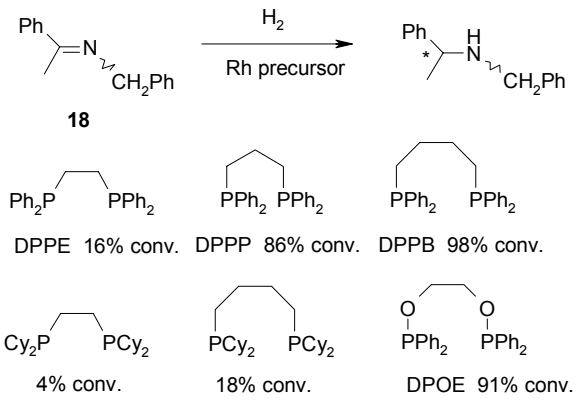


Figure 3

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).

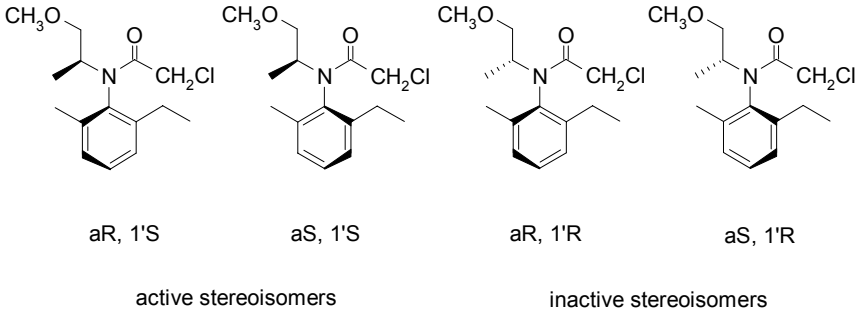
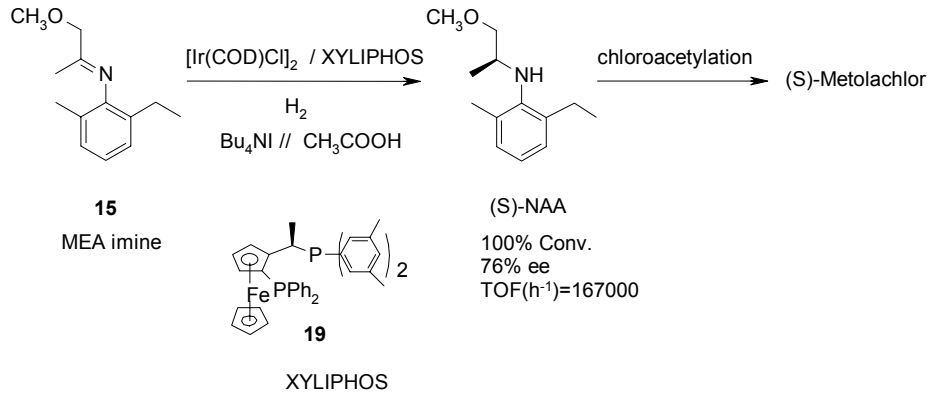


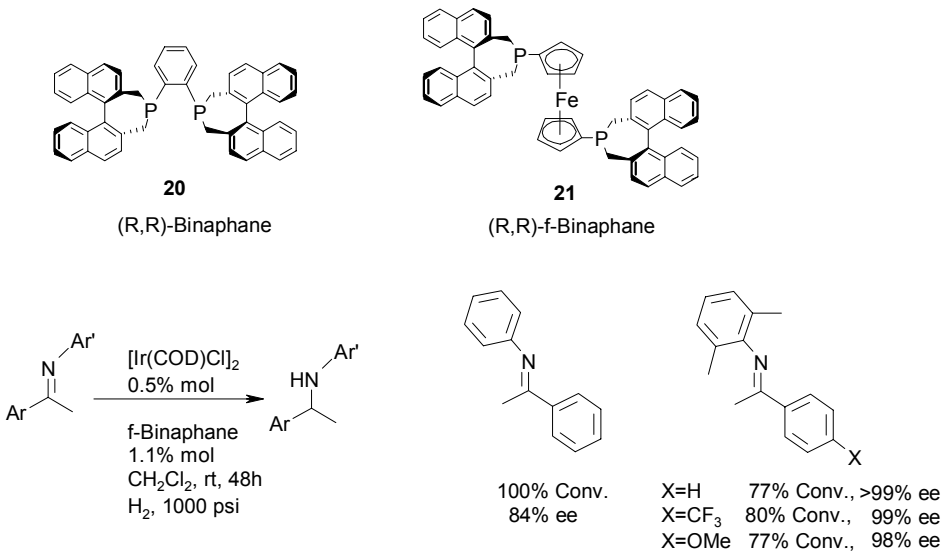
Figure 4

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].

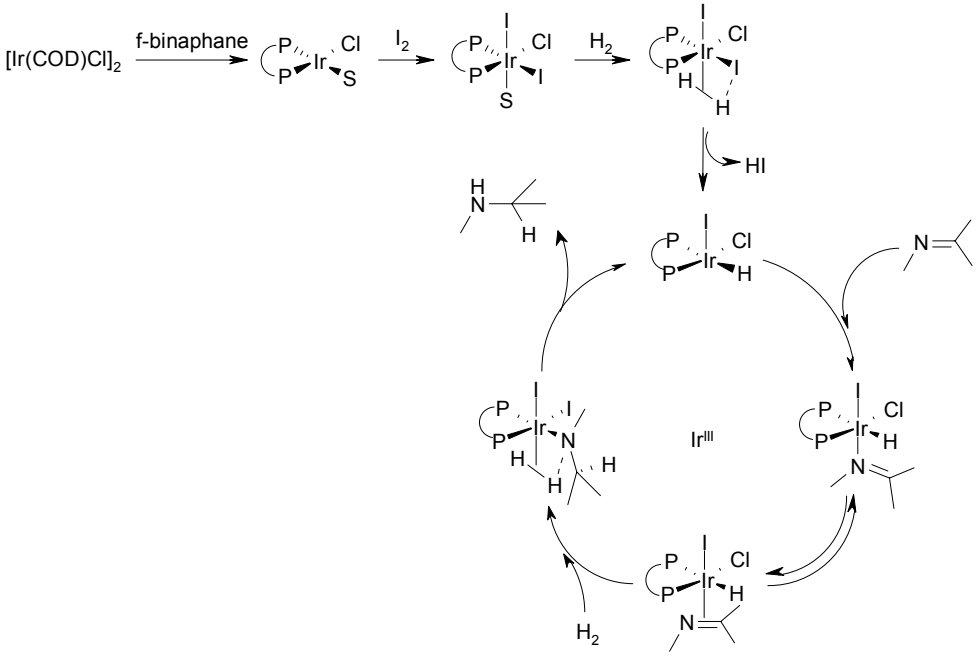


Scheme 14

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.

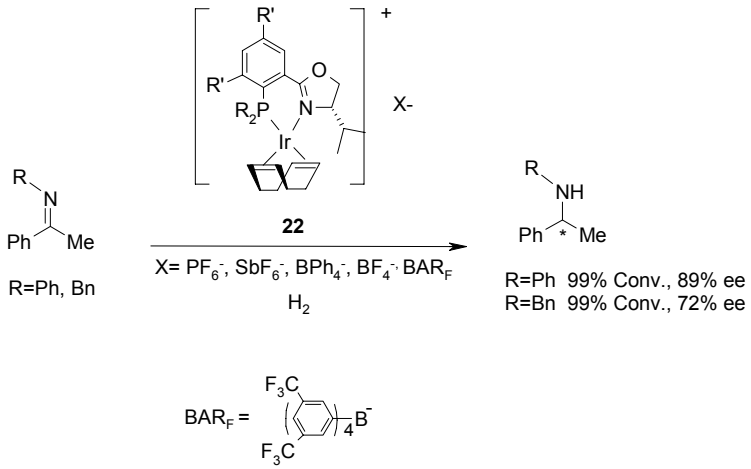
Zhang also observed an enhancement of the reactivity and enantioselectivity when I_2 was used as an additive and, on the basis of Osborn's studies, proposed a feasible catalytic cycle for the Ir-f-binaphane-I_2 system (Scheme 15).

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].

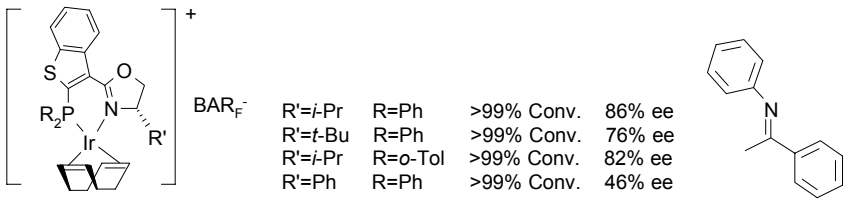
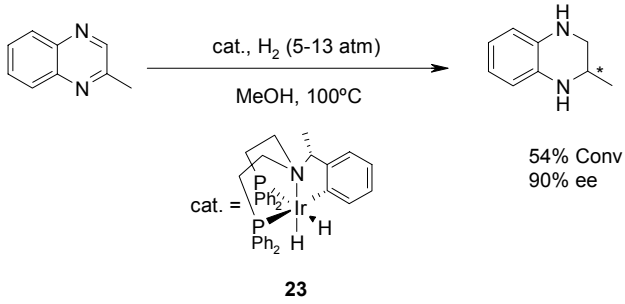


Figure 5

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).

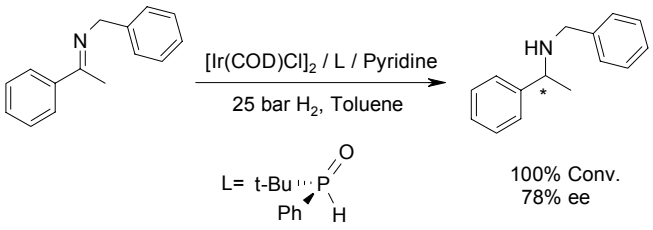


23

Scheme 17

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

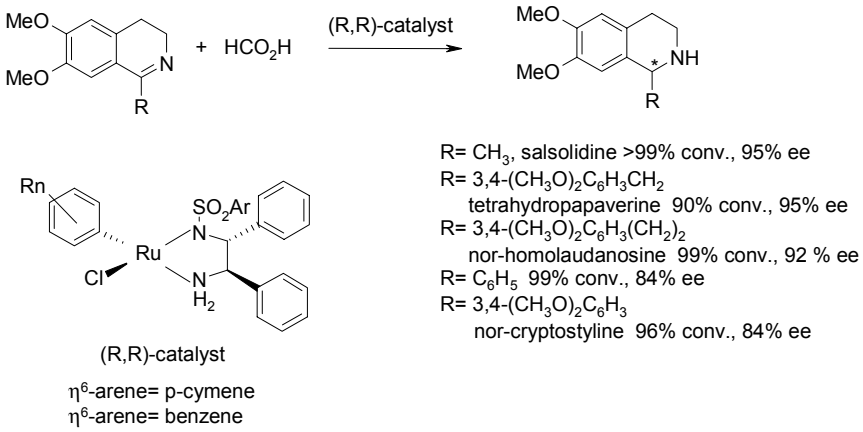
Most of the ligands that give a high degree of enantiocontrol are bidentate, and there are almost no examples of efficient chiral monodentate ligands for the asymmetric hydrogenation of imines. Feringa and co-workers [53] reported the application of monodentate secondary phosphine oxides as a new class 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).



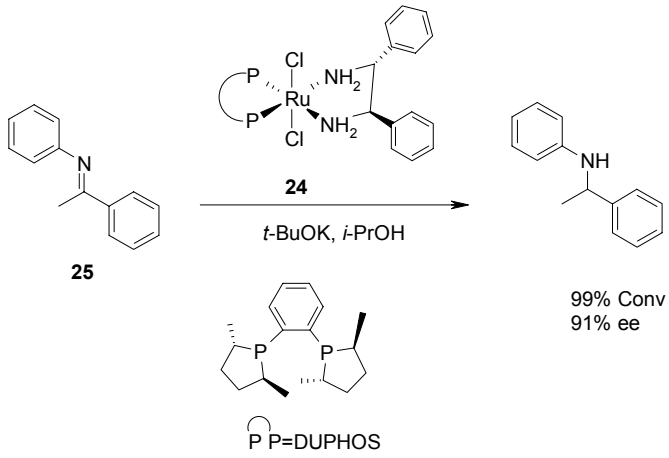
Scheme 18

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).

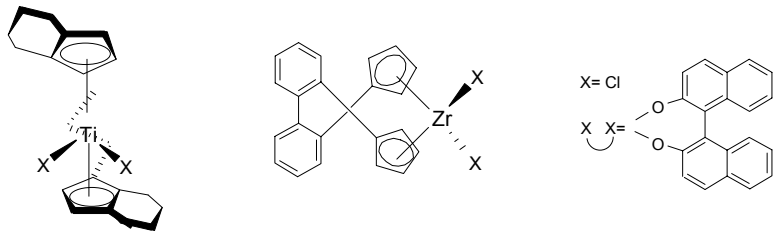


Figure 6

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].

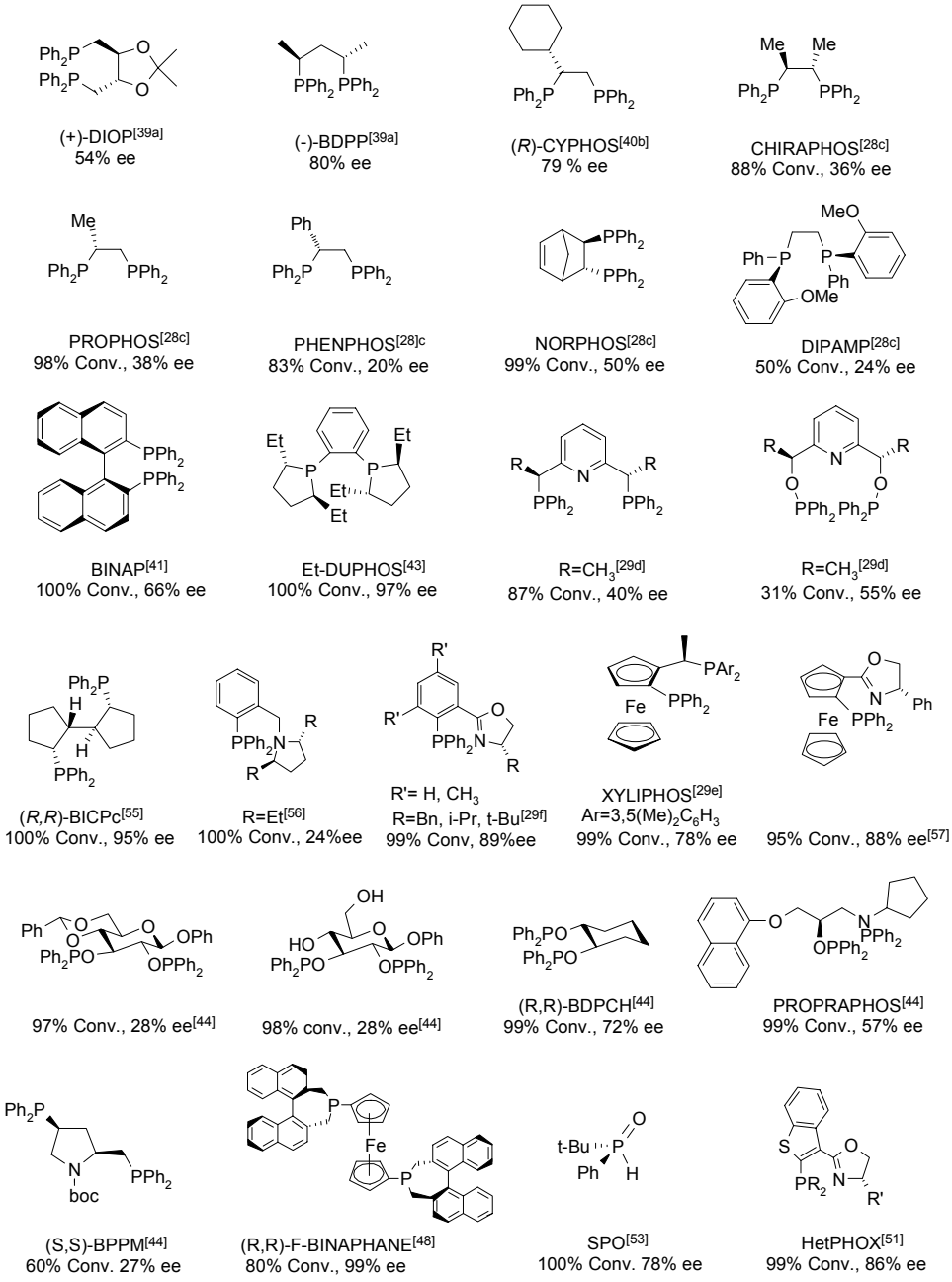
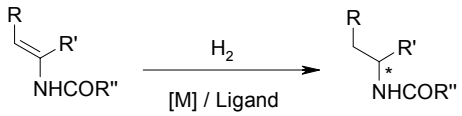

(+)-DIOP[39a]
54% ee
(-)-BDPP[39a]
80% ee
(R)-CYPHOS[40b]
79 % ee
CHIRAPHOS[28c]
88% Conv., 36% ee
PROPHOS[28c]
98% Conv., 38% ee
PHENPHOS[28]c
83% Conv., 20% ee
NORPHOS[28c]
99% Conv., 50% ee
DIPAMP[28c]
50% Conv., 24% ee
BINAP[41]
100% Conv., 66% ee
Et-DUPHOS[43]
100% Conv., 97% ee
R=CH3[29d]
87% Conv., 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).



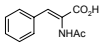
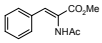
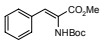
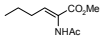
Scheme 21

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.

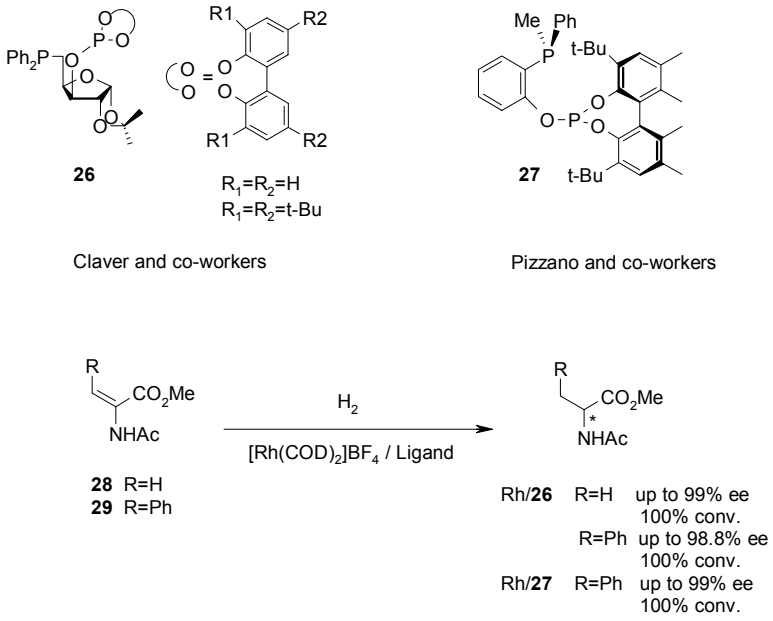
Table 1. Enantioselectivities in α-enamide hydrogenation using Rh/diphosphines [58][a]

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].

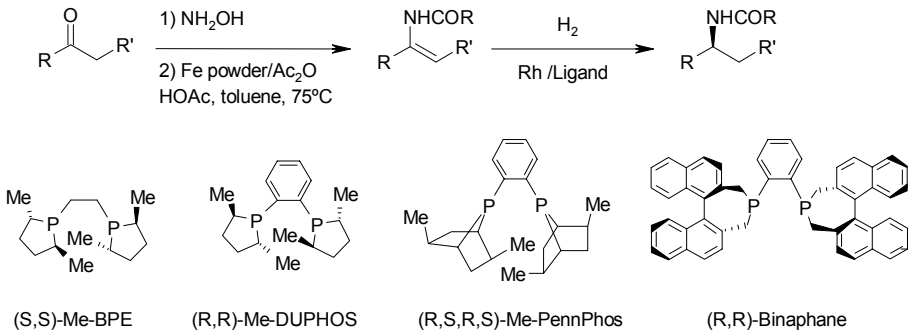
The most interesting feature of phosphine-phosphite ligands is the presence of two phosphorus functionalities with rather different electronic properties. When coordinated to a metal center, a good σ-donor ability can be expected for the phosphine groups, whereas a phosphite fragment should be a poorer 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).

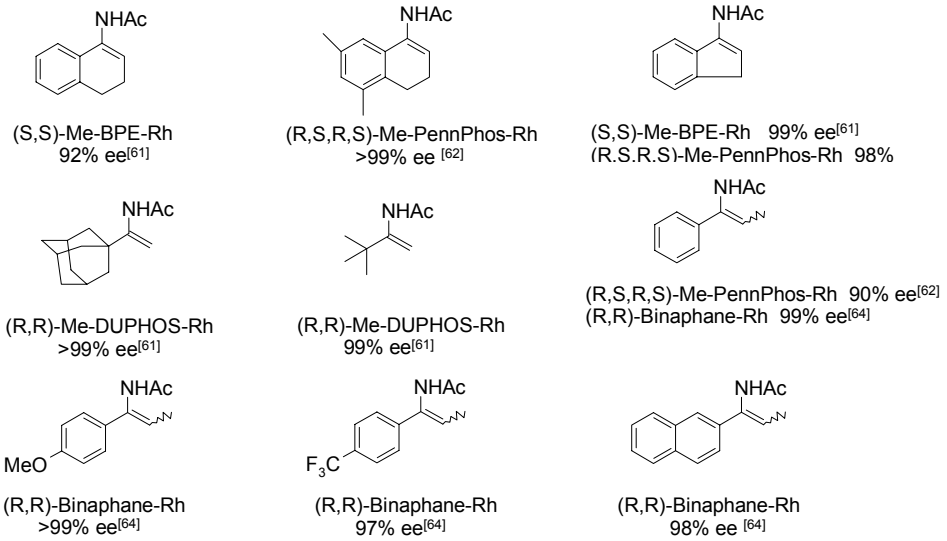


Figure 8

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].

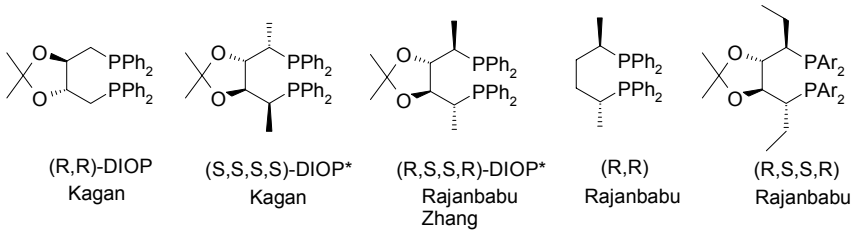


Figure 9

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).

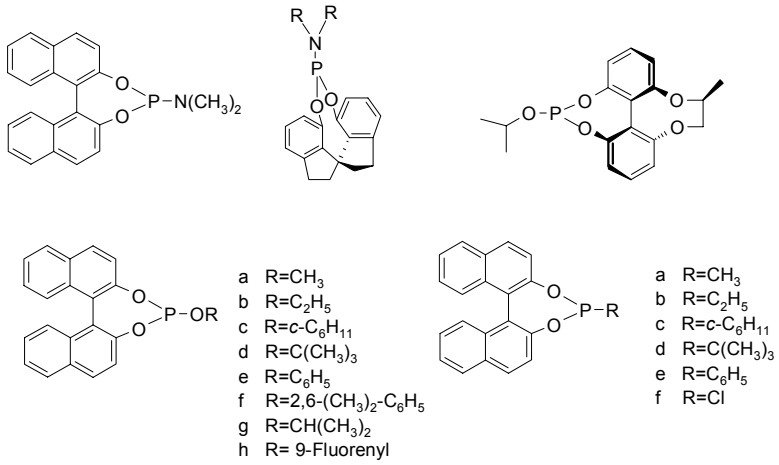
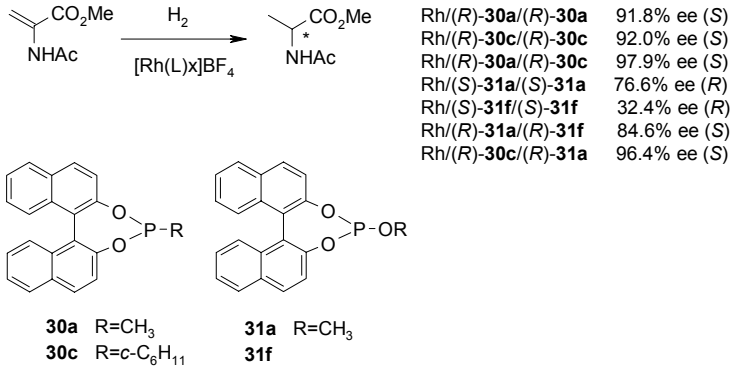


Figure 10

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.

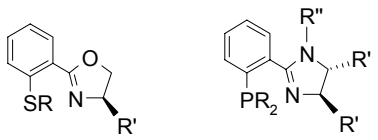


Figure 11

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.

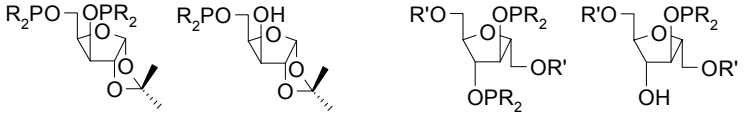


Figure 12

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2

N-donor Ligands: Oxazoline and Imidazoline Ligands

In recent years, the potential of N-donor ligands has been demonstrated in such metal-catalysed reactions as enantioselective cyclopropanation, hydrosilylation, Diels-Alder, hydrogenation and palladium catalysed allylic substitution, in which only P-donor ligands seemed to be effective. Oxazolines and imidazolines are two examples of N-donor ligands that are widely used in asymmetric catalysis and which are an attractive alternative to diphosphines for the hydrogenation of imines.

Chapter 2

2.1. Introduction

The development of new *N*-donor ligands with two different coordinative heteroatoms may be an attractive alternative to diphosphines. The bifunctional character of hybrid ligands has proven to be very useful in homogeneous catalysis and some important organic reactions catalysed by transition metal complexes with N⌒X ligands (X=coordinative atom, c.a. P, S, N…) are quite impressive in terms of selectivity and reactivity [1]. Thus, a transition metal complex with a bidentate ligand in which the two coordinating atoms are electronically different can impart stereoelectronic control in the formation of a specific product, resulting in enhanced selectivity [2]. Metal complexes with hybrid ligands containing N, S or P donor atoms are of increasing interest because of their ability to act as "hemilabile" ligands. For instance, nitrogen as a hard donor atom is capable of stabilizing metal ions in higher oxidation states whereas phosphorus or sulphur as soft donor atoms are best suited to stabilizing metals in lower to medium oxidation states.

Ligands containing the oxazoline moiety (**1a-f**) (Figure 1) have been widely explored in the last two decades and successfully used in such asymmetric reactions as enantioselective cooper and ruthenium cyclopropanation [3], iron, magnesium and copper catalysed Diels Alder [4], rhodium catalysed hydrosilylation [5], iridium catalysed hydrogenation [6] and palladium catalysed allylic substitution [7]. More recently, ligands carrying an imidazoline moiety (**1g-i**) (Figure 1) have been used in palladium catalysed copolymerisation [8], the ruthenium Diels Alder reaction [9], iridium catalysed enantioselective hydrogenation of prochiral olefins [10] and enantioselective diethyl zinc additions [11] affording promising results.

All these examples demonstrate the backbone variety and the ability of the hemilabile ligands to be coordinated to several metals. The coordination chemistry of these ligands and the structural characteristics of the resulting transition metal complexes have recently been reviewed [12].

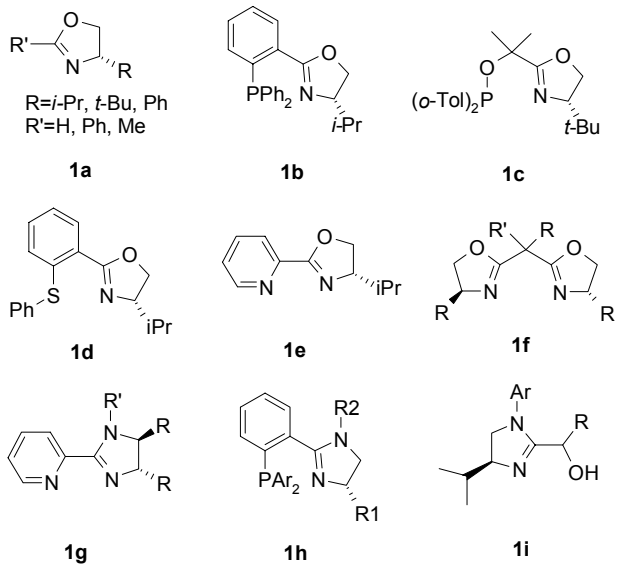


Figure 1

Oxazoline and imidazoline ligands are structurally similar and show attractive characteristics: versatility of the ligand design, the straightforward synthesis of ligands from readily available precursors, and the modulation of the chiral centers. The asymmetry induced by such heterobidentate systems is determined by a combination of steric and electronic interactions, so these ligands make it possible to control the enantioselectivity in catalytic reactions by creating an asymmetric environment provided by the oxazoline/imidazoline moiety and by combining soft and hard donor atoms (P, S, N) to modify the electronic properties on the metal center. Moreover, modifying the chelate ring size is another way of optimising the effectiveness of the catalytic system (Figure 2).

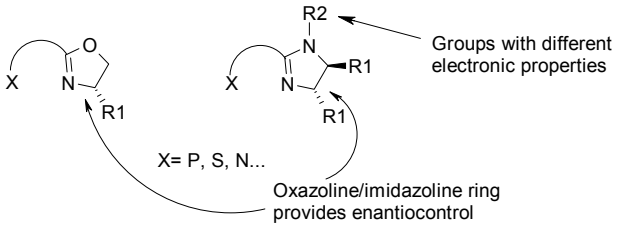
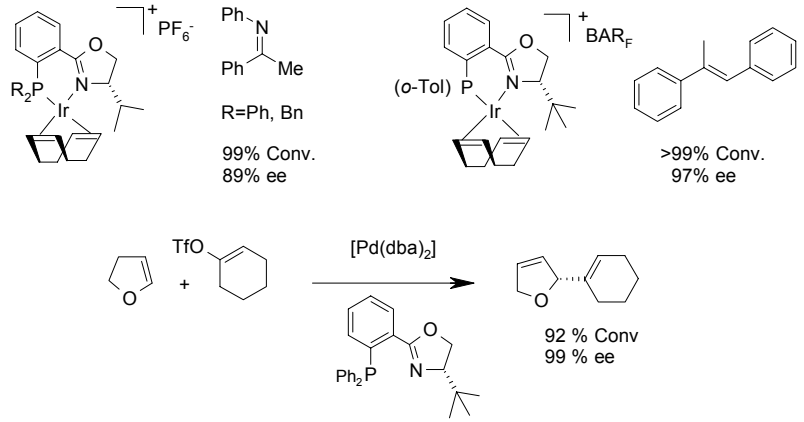


Figure 2

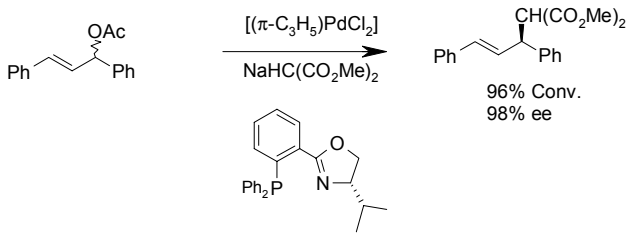
Nevertheless, oxazoline and imidazoline ligands have some important differences. For instance, the imidazoline ring is much more basic than the oxazoline ring [13]. Furthermore, the imidazoline unit makes it possible to introduce a variety of substituents into the aminic nitrogen, modifying its electronic properties. So these ligands are more tunable than the oxazoline analogues.

The phosphine-oxazoline ligands (P⌒N) were developed largely by Pfaltz [14] and proved to be versatile chiral ligands in a wide range of homogeneous catalytic reactions such as imine [15] and olefin [16] reductions with Ir(I) complexes as well as in Heck [17] reactions with Pd(0) (Scheme 1).



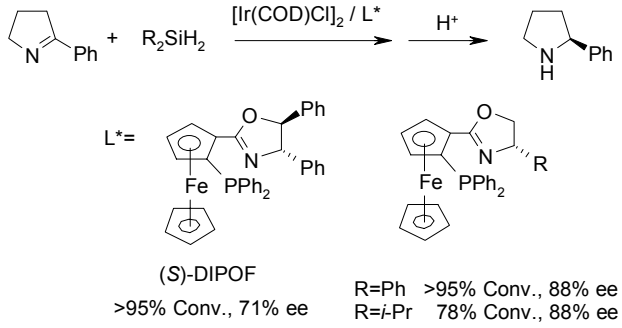
Scheme 1

At the same time, other groups worked independently on the synthesis of phosphinooxazoline ligands. Williams [18] and Helmchen [19], in particular, focused their attention on the palladium-catalysed allylic substitution (Scheme 2).



Scheme 2

Uemura and co-workers [20] proved that chiral ferrocenyl-phosphinooxazolines are effective ligands for the Ir(I)-catalysed asymmetric hydrosilylation of imines giving, after hydrolysis, the corresponding amines with high enantioselectivities (up to 88%) in almost quantitative yields (Scheme 3).



Scheme 3

In the field of N⌒S ligands, Pfaltz [21], Williams [18a] and Helmchen [19a] have reported the use of thioether-oxazoline ligands in palladium-catalysed allylic alkylation providing high enantiocontrol (Figure 3) [22,23].

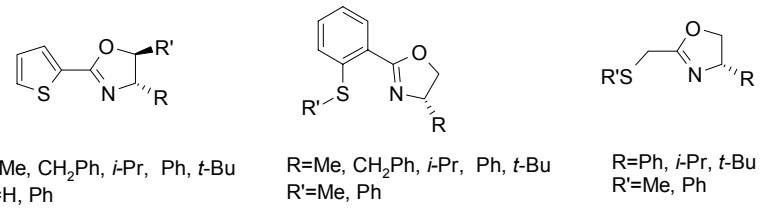


Figure 3

However, as far as we know, the use of N⌒S ligands in the hydrogenation of imines has not been reported.

Few examples of N⌒N ligands containing the oxazoline moiety are applied to the reduction of C=N [20], however, the results are disappointing. Oxazolinylpyridines are mainly used in palladium-catalysed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate (Figure 4) [7].

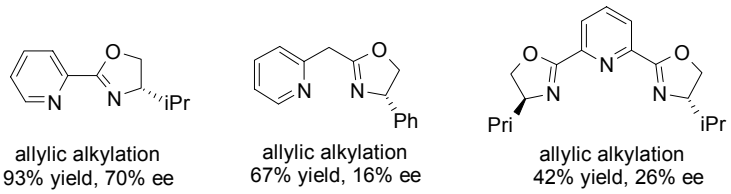


Figure 4

Ligands carrying an imidazoline unit have not received as much attention as

oxazoline ligands, although they are more electronically tunable by a proper choice of the group attached to the aminic atom. Pfaltz and co-workers [10] evaluated the use of phosphino-imidazoline ligands in the reduction of unfunctionalized olefins and, in several cases, ee's were higher than when phosphino-oxazoline ligands were used (Figure 5).

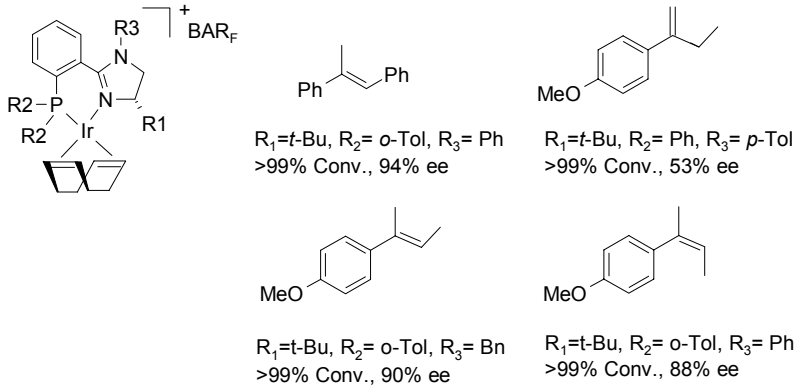


Figure 5

These results seem to indicate that *N*-donor ligands are gaining interest to replace the more widely used diphosphines in homogeneous catalysis. Moreover, the successful results of Pfaltz's cationic iridium catalysts based on diphenylphosphinooxazolines in imine reduction prompted us to check the aptitude of thioether-oxazoline (NS) and phosphino-imidazoline (NP) ligands towards the iridium-catalysed enantioselective reduction of prochiral imines, since they had not previously been used in this reaction.

2.2. Results and Discussion

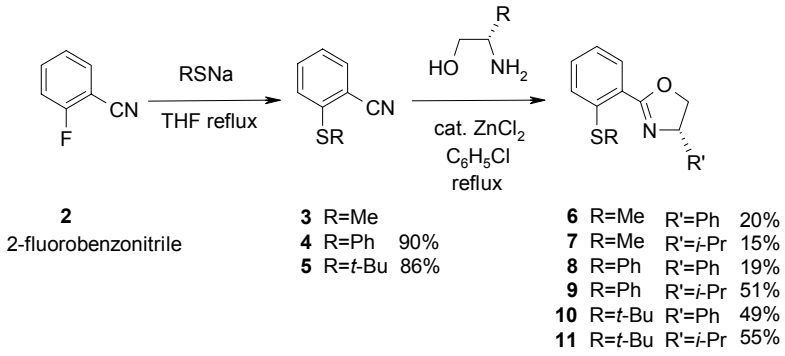
2.2.1. Thioether-oxazoline ligands

As mentioned above, although phosphino-oxazoline ligands have been successfully applied in the iridium-catalysed hydrogenation of imines, oxazoline-thioether ligands have never been used. These ligands can control the reactivities of metal sites owing to the different steric and electronic properties of the donor groups. It is worth noting that replacing the phosphorous moiety by sulphur creates a new stereogenic center, which can have a remarkable effect.

2.2.1.1. Synthesis of thioether-oxazoline ligands 6-11

We decided to prepare ligands **6-11,** which have methyl, phenyl or t-butyl groups attached to the sulphur atom, and phenyl or isopropyl on the stereogenic center of the ozaxoline ring. Compounds **6-9** have already been reported [22] and ligands **10** and **11** have been synthesized and characterized for the first time in this work. Oxazoline-thioether ligands **6-11** are readily accessible in a procedure of two steps; the reaction of 2-fluorobenzonitrile (**2**) with sodium thiolate salts affords compounds **3-5**. The reaction of **3-5** with homochiral amino alcohols (L-valinol and L- phenylglycinol) in the presence of a catalytic amount of zinc chloride using dry chlorobenzene as solvent allows to obtain the desired ligands **6-11** in poor to moderate yields (Scheme 4) [22].

Compound **3** was commercially available. The $ZnCl_2$ increases the electrophilicity of the ciano group, and favours condensation with the amino alcohol.



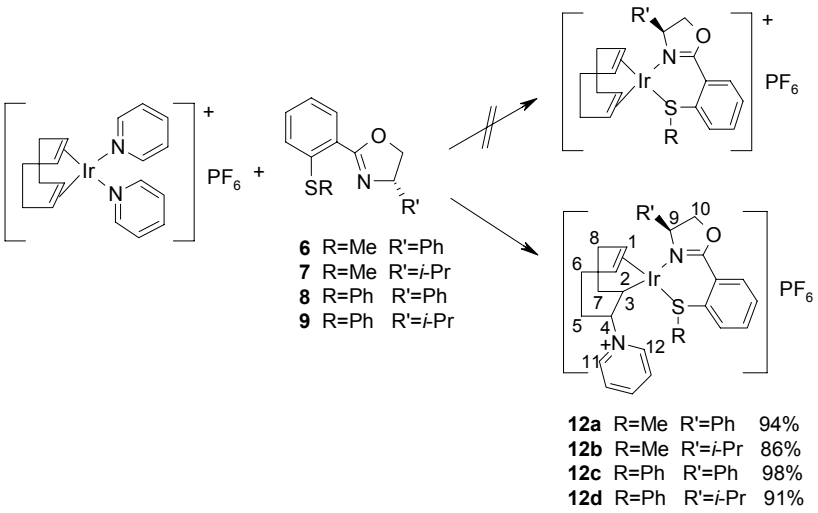
Scheme 4. Synthesis of thioether-oxazoline ligands **6-11**

Although this procedure is well established in the literature [22], the yields are only low or moderate. In an attempt to improve the yields, we used other catalysts like ytterbium triflate and solvents like *o*-dichlorobenzene (bp=178-180ºC), which makes it possible to increase the temperature of the reaction. The results, however, were not better. The use of an argon flow, which removes the ammonia formed, allows in some cases to obtain higher yields.

2.2.1.2. Synthesis and characterization of $[Ir(\sigma\text{-}\eta^2\text{-}PyC_8H_{12})L]PF_6$ (12a-d), $[Ir(\eta^4\text{-}COD)L]PF_6$ (13a) and $[Ir(\eta^4\text{-}COD)L]BF_4$ (13b)

With the aim of exploring the coordination chemistry of these ligands, we studied their reactivity towards different iridium (I) precursors. We initially selected $[Ir(\eta^4\text{-}COD)(Py)_2]PF_6$ (COD=C_8H_{12}=1,5-cyclooctadiene, Py=pyridine) which had been used as a precursor to prepare several Ir(I) complexes [24]. The reaction of the chiral oxazoline-thioether ligands **6-9** with $[Ir(\eta^4\text{-}COD)(Py)_2]PF_6$ in anhydrous CH_2Cl_2 at room temperature, was expected to occur with the displacement of the

two pyridine molecules affording the corresponding cationic Ir(I) complexes [Ir(η^4-COD)L]PF_6 (L=oxazoline-thioether ligands). However, this did not occur and the isolated complexes **12a-d** showed the structure depicted in Scheme 5.



Scheme 5. Synthesis of complexes**12a-d**

Isolated complexes **12a-d** were stable in air even in solution. Mass spectroscopy analysis and NMR experiments allowed us to elucidate the structure of compound **12a**.

The presence of pyridine was confirmed by ^1H and $^{13}C\{^1H\}$ NMR, and also by MS spectroscopy. The highest m/z 649.1 in the FAB spectrum corresponded to the M^+ $[C_{29}H_{32}SON_2Ir]^+$ and m/z 569 corresponded to M^+-Py.

The characteristic signals of the PF_6^- anion, which in this case is the counterion of the pyridinium salt, were also observed in the $^{31}P\{^1H\}$ spectrum at -144.1 ppm (septuplet, $J_{P\text{-}F}$= 712.8 Hz) and in $^{19}F\{^1H\}$ spectrum at -73.6 ppm (doublet, $J_{F\text{-}P=}$711.7 Hz).

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra showed signals corresponding to the COD ligand and to the coordinated thioether-oxazoline ligand. The eight signals corresponding to the aliphatic CH_2 protons of COD were unambiguously assigned by COSY and TOCSY experiments and by correlation with their respective carbons (Figure 6). The assignment of the olefinic COD revealed that whereas three of these signals appeared at the expected chemical shift (3-5 ppm), a signal corresponding to H3 appeared at 2.59 ppm. The HETCOR experiment demonstrated the correlation of H3 with a carbon appearing at 3.57 ppm (!!!) (Figure 6). This carbon must be directly bonded to the metal and since there are no additional protons in the COD structure, pyridine must be bonded in the neighbouring carbon. In fact, the chemical shift of H4 and C4 are in agreement with the values expected for a carbon bonded to a pyriridium salt.

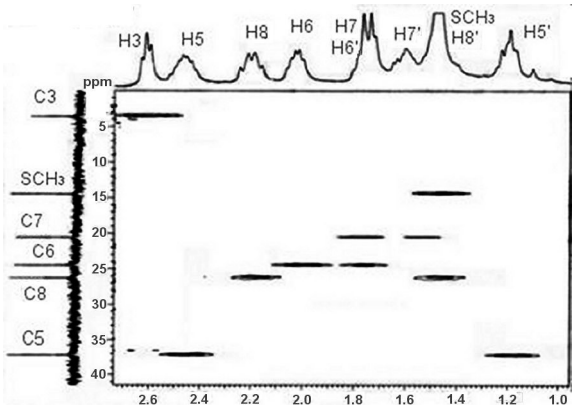


Figure 6 . A section of the HETCOR spectrum for **12a**

The stereochemistry of complex **12a** was proposed after a NOE experiment, which showed a signal enhancement of H11 and H12 of pyridine and H4 when the methyl group was irradiated (see Scheme 5).

Thus, the resulting structure, $[Ir(\sigma\text{-}\eta^2\text{-}PyC_8H_{12})L]PF_6$ (**12a**), consists of monomeric units with an Ir atom coordinated to a pyridinium-cyclooctaenyl via σ-C and π-C=C bonds and to the thioether-oxazoline ligand. The NMR data for **12a** are collected in Table 1.

Table 1. NMR Data of complex **12a**

	^{1}H NMR (ppm)		^{13}C{^{1}H} NMR (ppm)
H1	4.07	C1	87.1
H2	3.22	C2	67.3
H3	2.59	C3	3.6
H4	4.66	C4	70.9
H5, H5’	2.43, 1.21	C5	37.2
H6, H6’	2.03, 1.74	C6	24.5
H7, H7’	1.74, 1.54	C7	20.6
H8, H8’	2.20, 1.46	C8	26.3
H9	5.81	C9	66.6
H10, H10’	5.13 , 4.94	C10	77.9
H11	8.95	C11	154.8
H12	8.54	C12	152.6
Me	1.48	Me	14.5

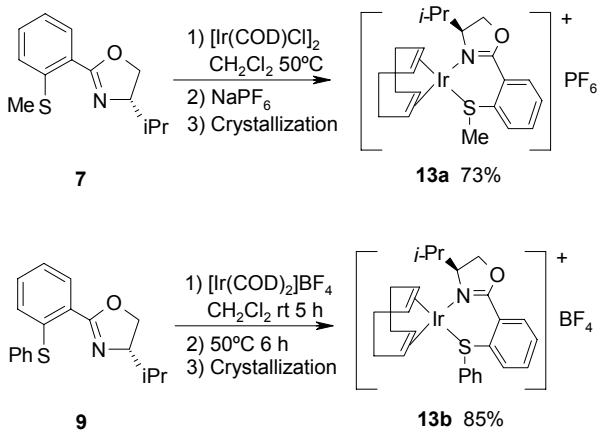
A reasonable explanation for these observations is that a nucleophilic attack of the removed pyridine to the C=C of the coordinated cyclooctadiene takes place, resulting in the formation of a piridinium salt and a C-Ir bond.

Olefins, which are usually unreactive to nucleophiles, do react with various nucleophiles such as malonates, acetates, hydroxides, etc, leading to new carbon-carbon bond formation when they are coordinated to metals [25]. Transition metals in high oxidation states such as palladium (II) or platinum (II) [26,27] are most suitable for this reaction, since they tend to withdraw electron density from the olefins. Likewise, several examples were reported with rhodium (I) [28] or iridium (I) [29] complexes, even with NR_nH_{3-n} as nucleophilic agents.

The ^{1}H NMR spectrum of complex **12b** showed only one species and the presence of pyridine, COD and oxazoline-thioether ligands, as in **12a**, although in this case the signals were broad even at -50ºC and could not be assigned unambiguously. ^{1}H NMR of complexes **12c-d** showed the presence of several species in equilibrium, where pyridine signals were also present. Lowering the temperature did not result in the resolution of one species. The presence of several species may be due to the formation of several regioisomers as a consequence of the nucleophilic attack of the pyridine on either C3 or C4. The formation of these regioisomeric complexes may be favored when a phenyl substituent is attached to the sulphur atom. Moreover, there is also the additional complexity that a new stereogenic center is created when the sulphur is coordinated to the metal center, which gives diastereoisomeric complexes. This behavior has previously been described for Rh [30] and Pd [31] complexes with thioether ligands.

Further investigation of the reaction of $[Ir(\eta^4\text{-COD})Cl]_2$ with ligand **7** in anhydrous CH_2Cl_2 at 50ºC for 1-2 hours under an inert atmosphere afforded the complex $[Ir(\eta^4\text{-COD})\mathbf{7}]PF_6$ (**13a**) after anion exchange by washing with an aqueous solution of $NaPF_6$ and crystallization from CH_2Cl_2/Et_2O (Scheme 4). Complex **13b** was synthesized by reacting $[Ir(\eta^4\text{-COD})_2]BF_4$ with ligand **9** in anhydrous CH_2Cl_2. These compounds were characterized by elemental analysis and NMR spectroscopy. The elemental analysis results showed that the compositions of the air-stable complexes **13a-b** correspond to a 1:1 metal complex of the M(COD) fragment and NS ligand. Although the ^{1}H NMR spectra of **13a-b** showed the signals corresponding to the coordinated oxazoline-thioether ligand and the η^4-cyclooctadiene appearing at the expected chemical shift, the signals were broad and a complete and unambiguous structural assignment on the basis of these data was not possible.

The catalytic behaviour of the systems formed by Ir/oxazoline-thioether ligands will be discussed later in section **2.2.3**.



7 **13a** 73%

9 **13b** 85%

Scheme 4. Synthesis of [Ir(η^4-COD)**7**]PF_6 (**13a**) and [Ir(η^4-COD)**9**]BF_4 (**13b**)

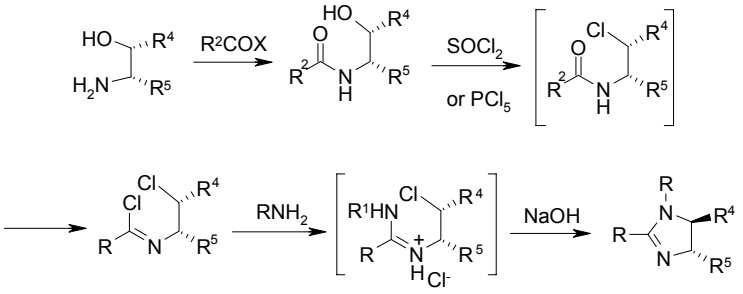
2.2.2. Phosphine-imidazoline ligands

Phosphine-imidazoline ligands are closely related to the phosphino-oxazoline reported by Pfaltz for the high effective asymmetric reduction of imines [15]. The imidazoline ring also makes it possible to modify the electronic properties by introducing electron-donor or withdrawing groups at the aminic nitrogen.

2.2.2.1. Synthesis and characterization of ligands 18a-c

The synthesis of imidazole derivatives has been reported using a variety of methods [32] but more specifically, the synthesis of imidazole derivatives bearing a 2-substituted aromatic group has been described in some recent papers by condensation of a diamine with aryl imidoesters [33]. This strategy involves the formation of the corresponding imidoesters, which were studied many years ago by Pinner [34]. However, following the imidoester procedure, the imidazoline ring is

normally constructed in only moderate yields [8,9,35]. An improved method for preparing imidazoline rings has recently been published by Casey and co-workers [36], while the present study was being made (Scheme 6).



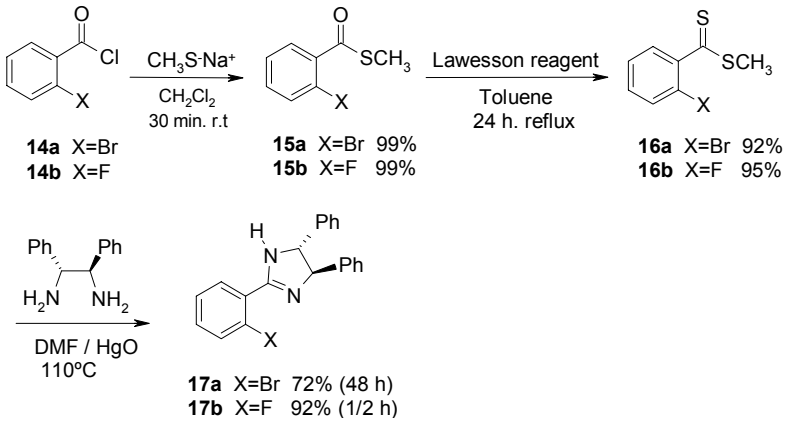
Scheme 6. Synthesis of 2-aryl-imidazolines

Enantiopure amino alcohols are converted into *N*-hydroxyethylamides, which are reacted with an excess of thionyl chloride to yield *N*-chloroethylimidoyl chlorides. These intermediates are treated with amines and anilines to produce *N*-chloroethylamidines, which are converted into imidazolines upon workup with aqueous hydroxide. This is a versatile method which allow to obtain the imidazolines from the corresponding amides in a 40-80% overall yield. Recently, Pfaltz published the synthesis of phosphine-imidazoline ligands on the basis of Casey's work and its application to the reduction of olefins [10].

Here, we report that dithioesters are useful precursors for the synthesis of *2*-arylimidazolines. After constructing the heterocycle moiety, we must then introduce the phosphino moiety to obtain the phosphine-imidazoline ligands.

As starting material, we selected the benzoyl chlorides **14a** and **14b**, which have a fluorine or bromine atom in the ortho position. These compounds should make it possible to introduce the phosphine moiety by different synthetic procedures.

Thus, 2-bromo-benzoylchloride and 2-fluoro-benzoylchloride (**14a-b**) reacted with methanethiolate sodium salt to afford 2-halo-thiobenzoic acid *S*-methyl esters (**15a-b**) in almost quantitative yield (Scheme 7). These compounds were subsequently treated with Lawesson's reagent to give dithioesters **16a-b** in excellent yield [37].



Scheme 7. Synthesis of 2-aryl-imidazolines **17a-b**

The imidazoline ring formation is due to the condensation of the dithioesters **16a-b** with a chiral diamine giving compounds **17a-b**. The driving force of the reaction is the precipitation of HgS by using a desulfurizing agent such as mercury (II) oxide [38]. Therefore, the reaction of **16a** with (1*R*,2*R*)-diphenylethylene diamine gave compound **17a** in a 66% overall yield. The condensation of compound **16b** with the chiral diamine worked considerably better, and the ring closure took place in only half an hour, isolating the compound **17b** in 92% yield. The overall yield was 86% in this case.

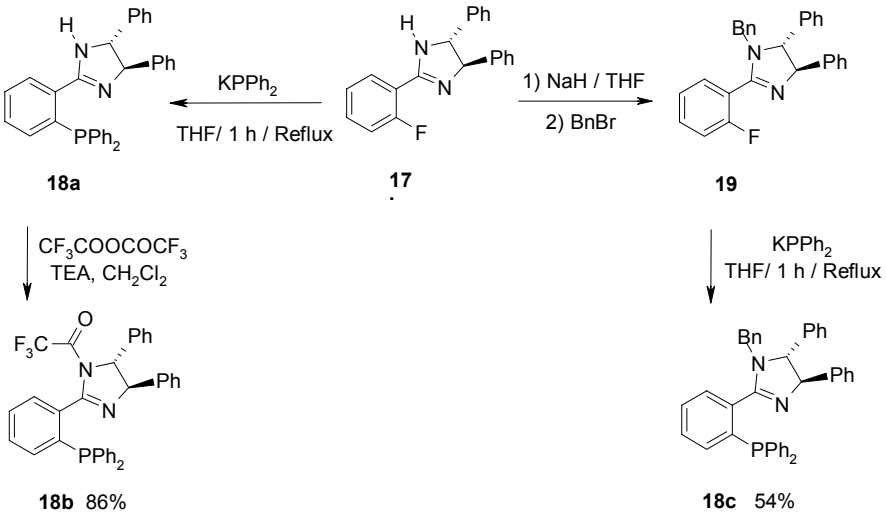
Having achieved our first goal, the next step was to introduce the phosphino moiety by lithium-halogen exchange prior to reaction with the electrophile, chlorodiphenylphosphine. However, despite numerous attempts, the

reaction of **17a** did not proceed with either n-BuLi or t-BuLi, even when the excess of lithium reagent was large. In almost all the cases the starting material was recovered. This suggests that the aryl-lithium intermediate was not formed. The only product that was isolated and charaterised was n-BuPPh_2, obtained by reaction of n-BuLi with Ph_2PCl.

Hence a different approach was required to introduce the phosphino group. Compound **17b** reacted with Ph_2PK in refluxing THF for an hour affording the phosphino-imidazoline ligand **18a** in 99% yield. The key step was now the reaction with Ph_2PK through an aromatic nucleophilic substitution reaction (Scheme 8) [35d,18a].

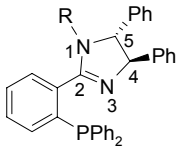
Tuning the electronic properties of ligands can have dramatic effects on the enantioselectivity in metal-catalysed reactions [39]. Accordingly, we decided to prepare the (*4R*,*5R*)-1-substituted-2-[(2-diphenylphosphine)phenyl]-4,5-diphenyl-4,5-dihydro-imidazoles (**18b, 18c**). Further reaction of **18a** with trifluoroacetate anhydride provided **18b** (Scheme 8). On the other hand, **17b** reacted with benzyl bromide to give compound **19** before the phosphine moiety was introduced to give **18c** (Scheme 8).

Ligands **18a-c** were characterized by ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$, HSQC NMR spectroscopy, mass spectrometry (MS) and elemental analysis. Table 2 collects some NMR selected data for ligands **18a-c**.



Scheme 8. Synthesis of phosphine-imidazoline ligands **18a-c**

Table 2. Selected ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR data for ligands **18a-c** recorded in $CDCl_3$

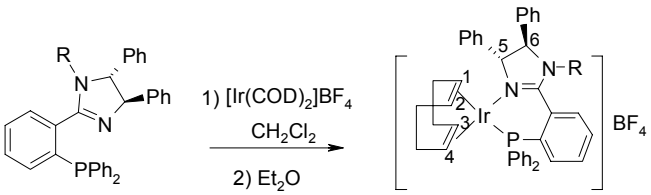


18a R=H
18b R=$COCF_3$
18c R=Bn

^{1}H (ppm)	**18a**	**18b**	**18c**
H4	4.48	5.16	4.36
H5	4.73	5.28	5.00
$^{13}C\{^{1}H\}$ (ppm)			
C=N	164.2	165.8	164.9
C4	71.3	70.0	72.2
C5	80.3	81.4	78.4
$^{31}P\{^{1}H\}$ (ppm)			
P	-10.3	-11.8	-12.3

2.2.2.2. Synthesis and characterization of $[Ir(\eta^4\text{-COD})L]BF_4$ (19a-c)

Cationic iridium(I) complexes **19a-c** (Scheme 9) were prepared by reaction between the cationic complex $[Ir(\eta^4\text{-COD})_2]BF_4$ (COD=cyclooctadiene) and a slight excess of the corresponding ligands in dichloromethane. The organometallic complexes $[Ir(\eta^4\text{-COD})L]BF_4$ (COD=1,5-cyclooctadiene, L=ligands **18a-c**) were precipitate by adding Et_2O.



18a R=H
18b R=$COCF_3$
18c R=Bn

19a R=H 97%
19b R=$COCF_3$ 61%
19c R=Bn 86%

Scheme 9. Synthesis of $[Ir(\eta^4\text{-COD})L]BF_4$ (**19a-c**)

The elemental analysis results showed that the compositions of the air-stable complexes **19a-b** correspond to a 1:1 metal complex of the M(COD) fragment and NP ligand. The FAB MS analysis of **19a** and **19b** showed the highest peaks at m/z 783.1 and 879.1, respectively, corresponding to M^+. The loss of cyclooctadiene is also observable at m/z 675.0 (**19a**, M^+-COD) and 771.0 (**19b**, M^+-COD).

The ^1H NMR spectra of **19a-c** showed signals for the cyclooctadiene ligand at the expected chemical shift (1.25-2.38 ppm, methylene protons) [15,40]. The olefinic protons of COD displayed two set of signals. Whereas H1 and H2 appeared as broad peaks at 4.14-5.12 ppm, H3 and H4 appeared at higher fields (2.77-3.41 ppm). In the $^{13}C\{^1H\}$ NMR spectra of **19a-b**, the C5 and C=N were shifted to lower

fields than the corresponding resonance in the free ligand (Tables 2 and 3). This observation is strong evidence of M-N coordination [41].

The $^{31}P\{^{1}H\}$ NMR spectra of **19a-c** displayed a singlet shifted to lower fields than the free ligand, which confirmed that the phosphorus atom was coordinated to the metal center [15].

Table 3. Selected ^{1}H and $^{31}P\{^{1}H\}$ NMR data for complexes **19a-c** recorded in $CDCl_3$

^{1}H (ppm)	**19a**	**19b**	**19c**
H1	4.85	4.91	5.12
H2	4.85	4.64	4.14
H3	2.90	3.41	2.80
H4	2.77	3.41	3.13
H5	4.93	5.20	5.59
H6	4.66	5.03	4.97
^{31}P (ppm)	15.5	15.3	15.5

Suitable single crystals were obtained for complex **19a**, which contains the phosphine-imidazoline ligand **18a**. The organometallic complex **19a** crystallized from 2-butanone and under inert conditions, in a monoclinic cell with the chiral space group $P2_1$. The molecular structure refined from the X-ray agrees with the proposed structure. The elementary cell of **19a** contains two independent molecules (*molecule A and molecule B*), which have the same chirality and are related by pseudosymmetry. Indeed, they are conformational isomers (Figure 7).

The two molecules of the unit cell adopt a three-dimensional configuration to minimize the electrostatic repulsions, and they also show an intermolecular π-stacking interaction between the two chelate phenyl rings that favours this arrangement, correlated by a local center of inversion (pseudosymmetry). The distance between the center of the benzene rings is about 3.84 Å.

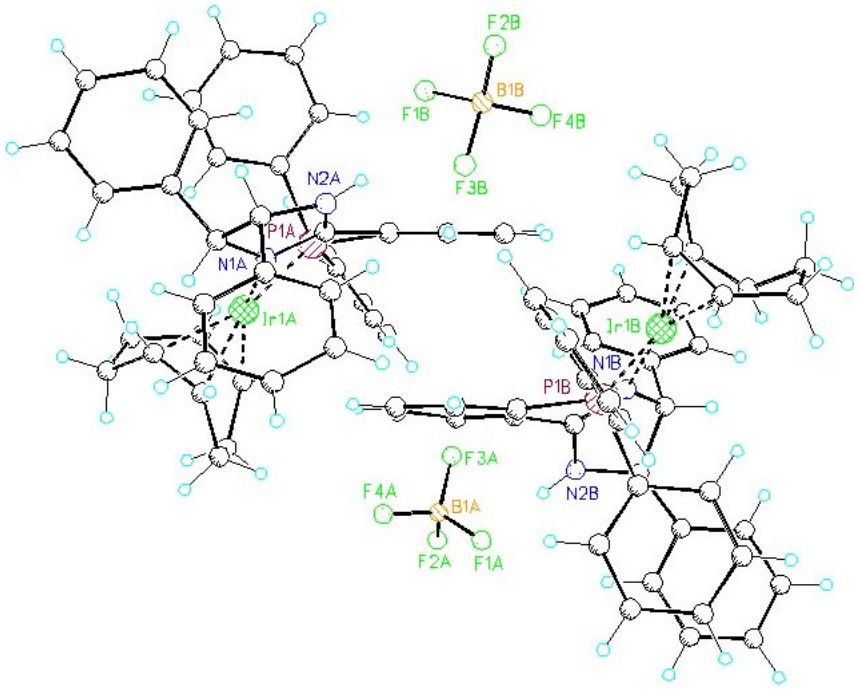


Figure 7. Crystal structure of **19a**

Moreover, an intramolecular π-stacking interaction is also observable in both *molecule A* and *molecule B*, between one of the phenyl groups of the phosphino moiety (C(30)-C(35)) and the phenyl group of the imidazoline moiety (C(12A)-C(17A), 4.336 Å in *molecule A* and C(18B)-C(23B), 3.90 Å in *molecule B*) (Figures 8 and 9).

Curiously the benzene ring (C(12A)-C(17A)) *at molecule A* is disordered in two positions with a ratio of 80:20, but there is no change in the chirality of *molecule A*.

The coordination geometry of the iridium atom in both molecules is square planar, since the midpoints of the double bonds of the COD ligands, the metal, P and N atoms all lie on a plane (main deviation from plane *molecule A*: 0.0264 Å

and *molecule B*: 0.0035 Å) [42]. The phenyl substituents on the phosphorous adopt a pseudoequatorial and a pseudoaxial position as was expected by comparison with the Ir-phosphine-oxazoline [6,15] and Ir-phosphine-imidazoline complexes [10].

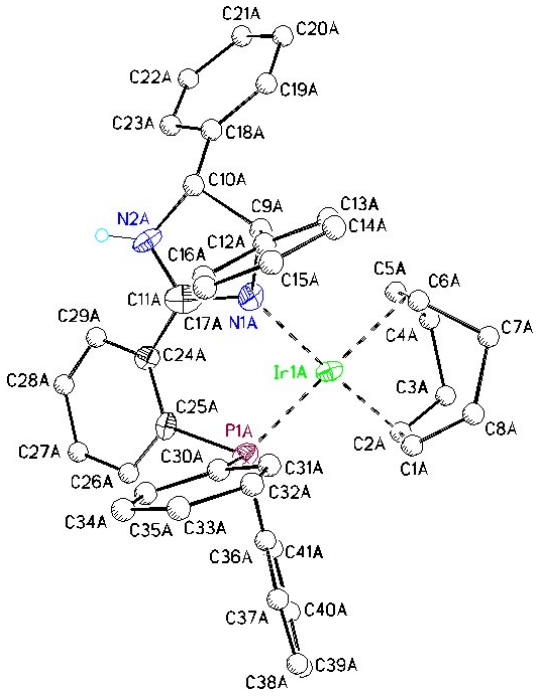


Figure 8. Crystal structure and atom numbering scheme of *molecule A* (**19a**)

The Ir-N distance (*molecule A:* 2.084(11) Å*; molecule B:* 2.095(11) Å) is shorter than the Ir-P distance (*molecule A*: 2.267(4) Å; *molecule B*: 2.279(4) Å) [42,43]. The distance from the metal to the midpoint of the C(5)=C(6) double bond *trans* to P (*molecule A*: 2.083(15) Å; *molecule B*: 2.102(12) Å) is significantly longer than the distance from the metal to the midpoint of the C(1)=C(2) double bond *trans* to N (*molecule A*: 2.010(13) Å; *molecule B*: 1.992(13) Å) indicating a clear *trans*-influence. This *trans*-influence is also observable for similar Ir/NP [42]

and Pd/NP[43] complexes. There are also differences between the C=C distances of COD.

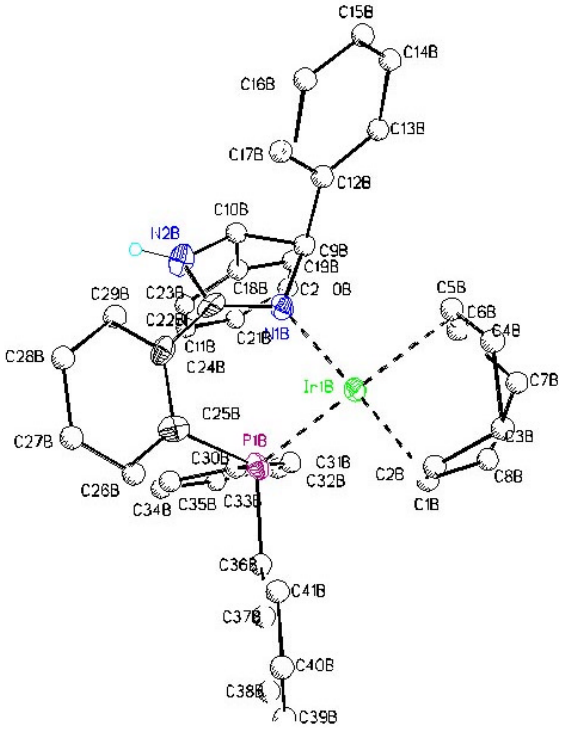
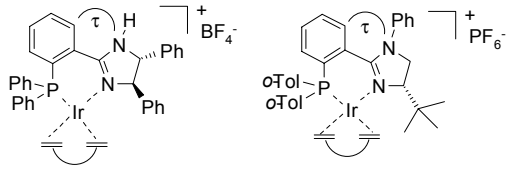


Figure 9. Crystal structure and atom numbering scheme of *molecule B* (**19a**)

In *molecule A*, the longer double bond is closer to the metal, *trans* to N (C(1)=C(2):1.368(17) Å vs C(5)=C(6): 1.34(2) Å), so backbonding from the metal appears to be greater *trans* to N [42]. In molecule B, these differences are smaller (C(1)=C(2):1.378(17) Å vs C(5)=C(6): 1.373(19) Å). Moreover, in *molecule A* the N(1)-C(11) and N(2)-C(11) bond distances, 1.337(17) and 1.323(15) Å, are consistent with a delocalization inside the N(1)-C(11)-N(2) fragment, as already

observed in the molecular structures of Ir/phosphine-imidazoline [10], Ru/pyridine-imidazoline [9] and Pd/pyridine-imidazoline complexes [8].

In both molecules, the rings of the chelating ligand (phenyl and imidazoline rings) are not coplanar, but slightly titled, as indicated by the C(29)-C(24)-C(11)-N torsion angle of -27.0º (in *molecule A*) and 45.2º (in *molecule B*). Although these values are similar to those reported by Pfaltz for a similar iridium complex (**20**) [10], the difference of 4º may be attributed to the different substitution of aminic nitrogen (Figure 10).



19a Molecule A τ=-27.0º **20** τ=-31º

Figure 10. Torsion angles in complexes **19a** and **20**

The absolute configuration for both molecules was determined with *R*(C(9)); *R*(C(10)) having a Flack Parameter of –0.003 with a standard deviation of 0.010 [44]. Expected values are 0 for correct and +1 for inverted absolute structure.

Table 4 shows a selection of bond lengths and angles of the molecular structures for *molecules A* and *B* of complex **19a**.

Table 4. Selected bond distances (Å) and angles (°) and geometrical parameters for complex **19a**

Empirical formula	$(C_{41}\ H_{39}\ B\ F_4\ Ir\ N_2\ P) \times 2$	
Formula weight	869.72	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 13.8464(7) Å	α= 90°.
	b = 13.5639(6) Å	β=98.779(2)°.
	c = 19.0698(8) Å	γ = 90°.
Ir(1A)···[C(1A)-C(2A)]	2.010(13)	
Ir(1A)···[C(5A)-C(6A)]	2.083(15)	
Ir(1A)-N(1A)	2.084(11)	
Ir(1A)-P(1A)	2.267(4)	
C(1A)-C(2A)	1.368(17)	
C(5A)-C(6A)	1.34(2)	
N(1A)-C(11A)	1.337(17)	
N(2A)-C(11A)	1.323(15)	
Ir(1B)···[C(1B)-C(2B)]	1.992(13)	
Ir(1B)···[C(5B)-C(6B)]	2.102(12)	
C(1B)-C(2B)	1.378(17)	
C(5B)-C(6B)	1.373(19)	
Ir(1B)-N(1B)	2.095(11)	
Ir(1A)-P(1B)	2.279(4)	
N(1B)-C(11B)	1.291(16)	
N(2B)-C(11B)	1.340(14)	
N(1A)-Ir(1A)-P(1A)	87.0(3)	
N(1B)-Ir(1B)-P(1B)	84.8(3)	
C(29A)-C(24A)-C(11A)-N(1A)	-27.0(15)	
C(29B)-C(24B)-C(11B)-N(1B)	45.2(15)	

2.2.3. Asymmetric Hydrogenation of Imines

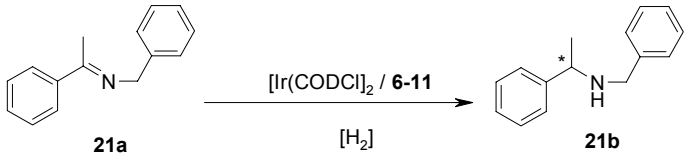
The Ir/thioether-oxazoline ligands **6-11**, the Ir/phosphine-imidazoline ligands **18a-c** and complex **12a** were tested as catalysts for the asymmetric hydrogenation of imines. Firstly, we focused on reducing the imine *N*-(phenylethylidene)benzylamine (**21a**) by systems generated *in situ* from $[Ir(COD)Cl]_2$/**6-11** and under 50 bar of H_2 pressure. The results are collected in Table 5.

When the catalytic precursor was formed by $[Ir(COD)Cl]_2$ in the presence of ligands **6**, **7**, **8** (Table 5, entries 2, 3, 4), conversions were lower than 50%. These results were similar to or lower than the conversion obtained with the iridium precursor when no ligand was added (entry 1). However, the iridium systems with ligands **9**, **10**, **11** (Table 5, entries 5, 6, 7) provided conversions between 80-100% in the same conditions. These results indicate that new catalytic systems are formed when the oxazoline-thioether ligands **9-11** are added to the iridium precursor. Conversions were higher when the electronic density on the sulphur atom of the thioether-oxazoline ligands was enhanced with the donor *t*-butyl group (Table 5, entries 6, 7).

It has been shown that in several Rh(I) [45] and Ir(I) [46] systems the presence of an additive improves the catalytic activity and the enantioselectivity. Among the most widely used additives are iodides and amines [47]. The experiments with ligands **6** and **7** (Table 5, entries 8, 9) provided higher conversion when Bu_4NI was used as additive. The results obtained in the experiments carried out with ligands **9** and **10** in the presence of Bu_4NI were maintained or were slightly lower than in the absence of additive.

No enantioselectivity was observed with these catalytic systems in the asymmetric hydrogenation of imine **21a**. Only the catalyst $[Ir(COD)Cl]_2$/**6** provided 15 % of enantiomeric excess.

Table 5. Hydrogenation of *N*-(phenylethylidene)benzylamine (**21a**)[a]



Entry	Precursor/Ligand	Solvent	Additive	Conv [%]
1	$[Ir(COD)Cl]_2$ / -	MeOH / DCE (1:1)	-	48
2	$[Ir(COD)Cl]_2$ / **6**	MeOH / DCE (1:1)	-	50
3	$[Ir(COD)Cl]_2$ / **7**	MeOH / DCE (1:1)	-	32
4	$[Ir(COD)Cl]_2$ / **8**	MeOH / DCE (1:1)	-	34
5	$[Ir(COD)Cl]_2$ / **9**	MeOH / DCE (1:1)	-	80
6	$[Ir(COD)Cl]_2$ / **10**	MeOH / DCE (1:1)	-	99
7	$[Ir(COD)Cl]_2$ / **11**	MeOH / DCE (1:1)	-	100
8	$[Ir(COD)Cl]_2$ / **6**	MeOH / DCE (1:1)	Bu_4NI	73
9	$[Ir(COD)Cl]_2$ / **7**	MeOH / DCE (1:1)	Bu_4NI	44
10	$[Ir(COD)Cl]_2$ / **8**	MeOH / DCE (1:1)	Bu_4NI	28
11	$[Ir(COD)Cl]_2$ / **9**	MeOH / DCE (1:1)	Bu_4NI	64
12	$[Ir(COD)Cl]_2$ / **10**	MeOH / DCE (1:1)	Bu_4NI	99
13	$[Ir(COD)Cl]_2$ / **10**	MeOH	-	95
14	$[Ir(COD)Cl]_2$ / **10**	C_6H_6	-	100
15	$[Ir(COD)Cl]_2$ / **10**	MeOH / C_6H_6 (1:1)	-	100
16[b]	**12a**	MeOH / DCE (1:1)	-	13
17	**12a**	MeOH / DCE (1:1)	-	39
18	**12a**	CH_2Cl_2	-	23

[a] 1% mol [Ir], 1.25% mol **6-11**, 1% mol Bu_4NI, 50 bar H_2, 25ºC, 24 h, DCE=dichloroethane [b] 30 bar

Such solvents as MeOH/$C_2H_4Cl_2$, MeOH, C_6H_6 and MeOH/C_6H_6 (Table 5, entries 12-15) have been tested, and they all gave total conversion.

The complex $[Ir(\sigma\text{-}\eta^2\text{-}PyC_8H_{12})L]PF_6$ **12a** was active in reducing imine **21a** into the corresponding amine (Table 5, entries 16, 17). Conversions were similar to those obtained with systems prepared *in situ* from $[Ir(COD)Cl]_2$/**7** and **8** (entries 3, 4 and 17).

After the results achieved with the Ir(I)/thioether-oxazoline catalysts, it can be concluded that replacing the phosphorus atom in the phosphine-oxazoline ligands by a sulphur atom has a dramatic effect. The Ir(I)/thioether-oxazoline catalysts do not provide stereocontrol in the hydrogenation of imine **21a**.

We then went on to explore the catalytic behavior of Ir(I)/phosphine-imidazoline catalysts with systems generated *in situ* from $[Ir(COD)Cl]_2$ or $[Ir(COD)_2]BF_4$ and **18a-c**, in order to evaluate the influence of the catalytic precursor. Precursors based on neutral complexes of Rh(I) and Ir(I) with diphosphines normally show higher enantioselectivities in the hydrogenation of some prochiral ketimines than the cationic ones, usually in a presence of an additive [46b-c,48]. We planned to investigate if this rule is also valid for cationic Ir(I)/phosphine-imidazoline systems.

Three different imines were chosen as models: the acyclic imines *N*-(phenylethylidene)benzylamine (**21a**) and *N*-(phenylethylidene)aniline (**22a**), and the cyclic imine 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**23a**), in which the geometry of the C=N double bond is fixed to *E*-configuration.

The catalytic systems based on $[Ir(COD)_2]BF_4$/**18a-c** were more active than the catalyst precursors $[Ir(COD)Cl]_2$/**18a-b** in the reduction of acyclic imines **21a** and **22a**, and in some cases conversion was complete within 16 hours (Table 6, entries 1-8). However, only for the most constrained imine **22a**, moderate enantiomeric excess (up to 51%) was achieved (Table 6, entry 8) when the catalytic system $[Ir(COD)_2]BF_4$/**18b** was used.

Hydrogenolysis products were also detected together with the desired secondary amine **21b**, because of the cleavage of the nitrogen-benzylic bond, which decreased selectivity [49] (Table 6, entries 1-4).

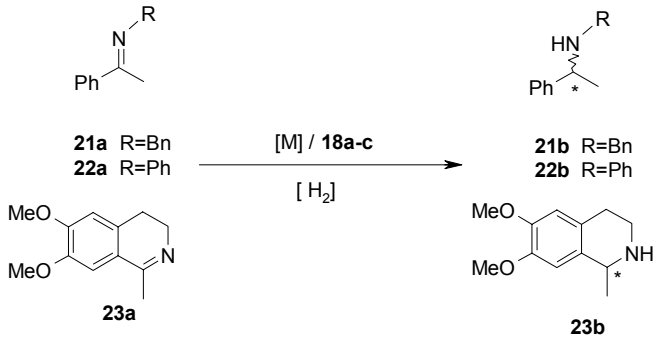
It should be noted that in the reduction of **22a**, the cationic system $[Ir(COD)_2]BF_4$/**18b** was more enantioselective than the neutral system $[Ir(COD)Cl]_2$/**18b** (Table 6, entries 6 and 8).

In general, the Ir(I) catalyst based on the withdrawing ligand **18b** was more effective than the catalysts Ir/**18a** under the conditions described (Table 6, entries 3, 4, 7, 8), which confirmed that the electronic properties of the ligands do not only influence the reaction rate but also the enantiocontrol of the process.

Four different metal precursors were tested, $[M(COD)Cl]_2$ and $[M(COD)_2]BF_4$ (M=Ir and Rh) in the reduction of cyclic imine **23a** and all conversions were very low (values of conversion <10%). Only with the cationic iridium precursor $[Ir(COD)_2]BF_4$ and ligands **18a-c** values of conversion between 20-40% were achieved in 18 h (Table 6, entries 9-11). It is reported that for the total hydrogenation of this imine, reaction times need to be longer (24-90h) [46b,c]. $[Ir(COD)_2]BF_4$/**18a** gave an enantiomeric excess up to 34%; the system $[Ir(COD)_2]BF_4$/**18b** based on the electro-withdrawing ligand **18b** afforded 26% ee, whereas the more electron-rich catalyst $[Ir(COD)_2]BF_4$/**18c** gave the worst value, nearly racemic.

In summary, Ir(I)/phosphine-imidazoline catalysts gave moderate to low enantioselectivities in the hydrogenation of the imines **21a**, **22a** and **23a.**

Table 6. Hydrogenation of *N*-(phenylethylidene)benzylamine (**21a**), *N*-(phenylethylidene)aniline (**22a**) and 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline imine (**23a**)[a]



Entry	Imine	Ligand	Precursor	Conv [%]	Selec [%]	Ee [%][b]
1	**21a**	**18a**	$[IrCODCl]_2$	27	28	9 (+)
2	**21a**	**18b**	$[IrCODCl]_2$	44	38	11 (+)
3	**21a**	**18a**	$[Ir(COD)_2]BF_4$	48	64	3 (+)
4	**21a**	**18b**	$[Ir(COD)_2]BF_4$	75	83	5 (+)
5	**22a**	**18a**	$[IrCODCl]_2$	2	100	22 (-)
6	**22a**	**18b**	$[IrCODCl]_2$	14	100	14 (-)
7	**22a**	**18a**	$[Ir(COD)_2]BF_4$	100	100	15 (-)
8	**22a**	**18b**	$[Ir(COD)_2]BF_4$	100	100	51 (-)
9[c]	**23a**	**18a**	$[Ir(COD)_2]BF_4$	32	100	34 (-)
10[c]	**23a**	**18b**	$[Ir(COD)_2]BF_4$	42	100	26 (-)
11[c]	**23a**	**18c**	$[Ir(COD)_2]BF_4$	23	100	9 (-)

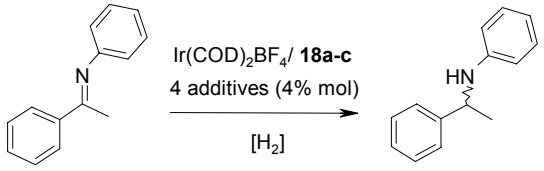
[a] 1% mol [Ir], 1.25% mol **18a-c**, 70 bar H_2, CH_2Cl_2, 25ºC, 16 h [b] no absolute configuration was determined [c] 60 bar H_2, 18 h

Since the best result was achieved by the more electron-poor catalyst formed by $[Ir(COD)_2]BF_4$/**18b** in the hydrogenation of **22a** with total conversion and 51% ee, we decided to investigate the role of additives in the hydrogenation of this imine. The selection of suitable halides or other additives, which can coordinate to the vacant site of the iridium complex, is important to improve the

enantioselectivity in the hydrogenation of imines [45a,46b,50] So two iodine derivatives and two amine derivatives were used as additives in the hydrogenation of **22a**.

The results obtained are summarized in the Table 7.

Table 7. Study of the effect of the additive on the hydrogenation of **22a**[a]



22a **22b**

Entry	Ligand	Additive	Conv [%]	Selec [%]	ee [%][b]
1	**18a**	--	100	100	15 (-)
2	**18a**	Bu_4NI	6	100	24 (+)
3	**18a**	I_2	100	100	0
4	**18a**	Phthalimide	99	100	12 (-)
5	**18a**	$BnNH_2$	92	99	13 (-)
6	**18b**	--	100	100	51 (-)
7	**18b**	Bu_4NI	81	100	27 (+)
8	**18b**	I_2	100	100	4 (+)
9	**18b**	Phthalimide	100	100	48 (-)
10	**18b**	$BnNH_2$	>99	99	24 (-)

[a] 1% mol [Ir], 1.25% mol **18a-c**, 4% mol additive, 70 bar H_2, CH_2Cl_2, 25ºC, 16 h [b] no absolute configuration was determined

Whereas the addition of Bu_4NI promoted the formation of the opposite enantiomer (Table 7, entries 1, 2, 6, 7), adding I_2 to the catalytic system gave racemic products (Table 7, entries 1, 3, 6, 8). Hence the cationic Ir(I)/phosphine-imidazoline/I^- systems did not lead to any improvement in the enantiocontrol of the process. This behavior has already been reported by Pfaltz [15] in the reduction of C=N with cationic Ir(I)/diphenylphosphinooxazolines catalysts, in which the

addition of Bu_4NI also decreased the ee and reversed the configuration of the final product. Besides, the catalytic system $[Ir(COD)_2BF_4]$/**18a**/Bu_4NI (Table 7, entry 2) induced a sharp decrease in the conversion.

The amine derivative additives generally did not have a strong influence on either conversion or enantioselectivity (Table 7, entries 1, 4, 5, 6, 9 and 10). The catalytic systems Ir(I)/**18a-b**/amine afforded complete conversions, demonstrating that in this particular case the strong coordinative amines do not poison the catalyst. A considerable decrease in the ee was only observed when benzylamine was added to $[Ir(COD)_2BF_4]$/**18b** (Table 7, entries 6 and 10).

2.3. Conclusions

In the preparation of iridium complexes containing oxazoline-thioether ligands starting from the iridium precursor $[Ir(\eta^4\text{-COD})Py_2]PF_6$, an unexpected nucleophilic attack of the pyridine on the coordinated cyclooctadiene with concomitant σ-Ir-C bond formation takes place, leading to the $[Ir(\sigma\text{-}\eta^2\text{-}PyC_8H_{12})L]PF_6$ (**12a-d**). When $[Ir(\eta^4\text{-COD})_2]BF_4$ was used as precursor the expected $[Ir(\eta^4\text{-COD})L]\ BF_4$ complexes were obtained.

Hydrogenation of imine **21a** with the catalytic systems formed *in situ* from $[Ir(\eta^4\text{-COD})Cl]_2$/**6-11** provided conversions of 30-100% in 24 hours, although no enantioselectivity was achieved. The new stereogenic center formed by the coordination of sulphur to the metal center may be responsible for the existence of different diastereomers during the catalytic cycle, which does not favour the stereoselectivity.

Complex **12a** was also active in the hydrogenation of imine **21a** although showed low conversions and no enantioselectivity.

A new improved synthetic procedure has been established to prepare 2-arylimidazolines starting from dithioesters.

The cationic Ir(I)-phosphine-imidazoline system is an efficient catalyst for the reduction of acyclic and cyclic imines, although the ee are only moderate.

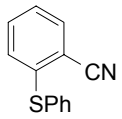
In general, the additives have a negative effect on the cationic iridium catalyst based on hemilabile ligands NX (X=S or P) and favour a change in the configuration of the final product, although the catalyst does not lose its activity when strong coordinative compounds such as amines are added.

2.4. Experimental Section

General Comments. All reactions were carried out in an argon atmosphere using standard Schlenk techniques. Solvents were distilled and degassed prior to use.
^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini spectrometer at 300 and 400 MHz. Chemical shifts were reported relative to tetramethylsilane for ^{1}H and $^{13}C\{^{1}H\}$ as internal reference, H_3PO_4 85% for $^{31}P\{^{1}H\}$ and trichlorofluoromethane for $^{19}F\{^{1}H\}$ as external references. Elemental analyses were carried out on a Carlo Erba Microanalyser EA 1108. VG-Autospect equipment was used for FAB mass spectral analyses with 3-nitrobenzylalcohol as matrix. EI mass spectra were obtained on an HP 5989 A spectrometer at an ionizing voltage of 70 eV. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Melting points were determinated in an open capillary tube with a Tottoli-Büchi 510 melting point apparatus and are uncorrected. IR spectra were recorded with the KBr disc for solid samples or the NaCl window for liquid samples on a MIDAC PROSPECT-IR spectrometer.

Single hydrogenation reactions were carried out in a Berghof or Parr 100 ml stainless steel autoclave and multi-screening hydrogenations were performed in a home-made 96-micro-titer plate in Bayer AG (Leverkusen-Germany). The catalytic reactions were monitored by GC on a Hewlett-Packard 5890A. Conversion was measured in an Ultra-2 (5 % diphenylsilicone/95% dimethylsilicone) column (25 m x 0.2 mm Ø). The enantiomeric excess of *N*-(phenylethylidene)benzylamine (**21a**) was determined by ^{1}H NMR (with mandelic acid as the resolution agent) or by chiral chromatography after derivation into the trifluoroacetamide compound.. The enantiomeric excess of *N*-(phenylethylidene)aniline (**22a**) was determined by chiral chromatography after derivation into the acetamide compound. The enantiomeric excess of the 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline imine (**23a**) was determined by chiral chromatography.

2-phenylthio-benzonitrile (4) [22c]

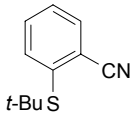


A solution of benzenethiol (18 mmols) in THF (4 ml) was added to a stirred mixture of sodium hydride (18 mmols) in THF (10 ml). To the resulting white precipitate, a solution of 2-fluorobenzonitrile (16 mmols) in THF (4 ml) was added.

The mixture was stirred under reflux for 48 h. The reaction mixture was poured into dichloromethane (40 ml) and washed with 15% aqueous NaOH (40 ml) and then with water (40 ml). The aqueous layers were extracted with dichloromethane (2x50 ml) and the combined extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by flash chromatography (Hexane/AcOEt 3:1) to afford a solid. The solid was recrystallized in THF/Hexane to afford 3g (90%) of compound **4** as a colourless crystalline solid. **NMR ^{1}H** (300 MHz, $CDCl_3$, ppm) 7.60-7.11 (m, 9H, arom.). **NMR ^{13}C** (74.5 MHz, $CDCl_3$, ppm) 141.3 (arom. C), 133.4, 133.2, 133.1, 132.9 (CH, arom.), 131.3 (C, arom.), 129.6,

128.7, 126.4 (CH, arom.), 116.5 (C≡N), 112.3 (C, arom.). **IR** (KBr, cm^{-1}): 3049 (=CH), 2217 (C≡N)

Synthesis of 2-terc-butylthio-benzonitrile (5)

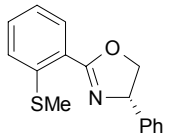


A solution of 2-methyl-2-propanethiol (9 mmols) in THF (2 ml) was added to a stirred mixture of sodium hydride (9 mmols) in THF (5 ml). To the resulting white precipitate a solution of 2-fluorobenzonitrile (8 mmols) in THF (2 ml) was added. The mixture was stirred under reflux for 48 h. The reaction mixture was poured into dichloromethane (20 ml) and washed with 15% aqueous NaOH (20 ml) and then with water (20 ml). The aqueous layers were extracted with dichloromethane (2x30 ml) and the combined extracts were dried (MgSO4), concentrated under reduced pressure and purified by column chromatography to give 1.3g (86%) of compound **5**. **NMR ^{1}H** (300 MHz, $CDCl_3$, ppm) 7.70-7.51 (m, 4H, arom.), 1.35 (s, 9H, $C(CH_3)_3$). **NMR ^{13}C** (74.5 MHz, $CDCl_3$, ppm) 138.8 (CH, arom.), 136.3 (C, arom.), 133.6- 132.3 (CH, arom.), 129.3 (CH, arom.), 121.0 (CH, arom.), 118.1 (C≡N), 48.8 ($\underline{C}(CH_3)_3$), 30.9 ($C(\underline{C}H_3)_3$).

General procedure for the synthesis of thioether-oxazoline ligands 6-11

In a 50-ml Schlenk flask, zinc chloride (44 mg, 0.32 mmols) was melted under high vacuum and cooled under nitrogen to room temperature. Chlorobenzene (20 ml) was then added followed by the corresponding thiobenzonitrile (6.4 mmol) and the aminoalcohol (9.6 mmol L-valinol or L-phenylglycinol). The mixture was heated under reflux for 48 h. The solvent was removed under reduced pressure to give an oily residue, which was dissolved in dichloromethane (30 ml). The solution was extracted with aqueous solution of NaCl (3x20 ml) and the aqueous phase with dichloromethane (30 ml). The combined organic extracts were dried ($MgSO_4$), and evaporated under reduced pressure.

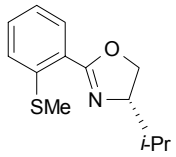
(*4S*)-4-phenyl-4,5-dihydro-2-[2-(methylthio)phenyl]-1,3-oxazoline (6) [22a]



Ligand **6** was obtained by following the general procedure described above. The reaction crude was purified by MPLC (CH_2Cl_2) to afford 344 mg (20% yield) of compound **6** as a solid product.

$[\alpha]_D^{25}$= + 78.3° (c=0.22, $CHCl_3$). **NMR ^{1}H** (300 MHz, $CDCl_3$, ppm) 7.8-7.1 (m, 9H, arom.), 5.45 (t, *J*=9Hz, 1H, CH), 4.66, (t, 1H, CH_2), 4.10 (t, *J*=7.7 Hz, 1H, CH_2), 2.4 (s, 3H, CH_3-S). **NMR ^{13}C** (74.5 MHz, $CDCl_3$, ppm) 163.9 (C=N), 142.6, 141.5 (arom. C), 131.2, 130.5, 128.8, 127.6, 126.8 (arom. CH), 124.8 (arom. C), 124.4, 123.7 (arom. CH), 74.2 (CH_2-O), 71.0 (CH-N), 16.0 (CH_3-S). **IR** (KBr, cm^{-1}): 3028 (=CH), 2980 (CH_3-S), 1636 (C=N).

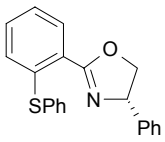
(*4S*)-4-isopropyl-4,5-dihydro-2-[2-(methylthio)phenyl]-1,3-oxazoline (7) [22a]



Ligand **7** was obtained by following the general procedure described above. The reaction crude was purified by MPLC (CH_2Cl_2) to afford 225 mg (15% yield) of compound **7** as a solid product.

$[\alpha]_D^{25}$= -81.4° (c= 0.24, $CHCl_3$). **NMR ^{1}H** (300 MHz, $CDCl_3$, ppm) 7.70-7.00 (m, 4H, arom.), 4.28 (dd, ^2J=9.3Hz, ^3J=7.8Hz 1H, CH), 4.12, (m, 1H, CH_2), 4.02 (t, *J*=7.8 Hz, 1H, CH_2), 2.36 (s, 3H, CH_3-S), 1.80 (m, ^3J=6.6 Hz, 1H, CH), 0.99 (d, ^3J=6.6 Hz, 3H, CH_3), 0.89 (d, ^3J=6.6 Hz, 3H, CH_3). **NMR ^{13}C** (74.5 MHz, $CDCl_3$, ppm) 162.3 (C=N), 141.1 (C, arom.), 130.9, 130.2 (CH, arom.), 125.2 (C, arom.), 124.3 (CH, arom.), 123.6 (CH, arom.), 73.6 (CH_2-O), 69.5 (CH-N), 33.1 (CH), 19.1 (CH_3), 18.4 (CH_3), 16.0 (CH_3-S). **IR** (KBr, cm^{-1}): 2958 (CH_3-S), 1649 (C=N).

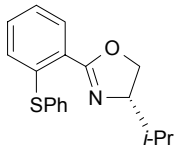
(*4S*)-4-phenyl-4,5-dihydro-2-[2-(phenylhylthio)phenyl]-1,3-oxazoline (8)



A total of 0.20 mmols (27.5 mg) of $ZnCl_2$ reacted with 4 mmols (845 mg) of 2-phenylthio-benzonitrile (**4**) and 6 mmols (825 mg) of L-phenylglycinol following the general procedure described above. The reaction crude was purified by MPLC (CH_2Cl_2) to afford 260 mg (19% yield) of compound **8** as a solid product.

$[\alpha]_D^{25}$= +58.5° (c= 0.22, $CHCl_3$). **NMR ^{1}H** (300 MHz, $CDCl_3$, ppm) 7.90-6.80 (m, 14H, arom.), 5.53 (dd, ^2J=10.4 Hz, ^3J=8.6 Hz, 1H, CH), 4.77, (dd, ^2J=10.4 Hz, ^3J=8.6 Hz, 1H, CH_2), 4.20 (t, ^3J=8.6 Hz, 1H, CH_2). **NMR ^{13}C** (74.5 MHz, $CDCl_3$, ppm) 163.9 (C=N), 142.5, 141.1 (C, arom.), 135.1 (CH, arom.), 133.4 (C, arom.), 131.1-126.8 (arom.), 125.1 (C, arom.), 124.7 (CH, arom.), 74.4 (CH_2-O), 70.9 (CH-N). **IR** (KBr, cm^{-1}) 3054 (=CH), 1629 (C=N).

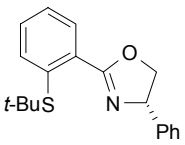
(*4S*)-4-isopropyl-4,5-dihydro-2-[2-(phenylthio) phenyl]-1,3-oxazoline (9) [22c]



A total of 0.25 mmols (34 mg) of $ZnCl_2$ reacted with 5 mmols (1 g) of 2-phenylthio-benzonitrile (**4**) and 7.5 mmols (775 mg) of L-valinol by following the general procedure described above. The reaction crude was purified by MPLC (CH_2Cl_2) to afford 756 mg (51% yield) of compound **9** as a solid product.

$[\alpha]_D^{20}$= – 49.3° (c=1.32, CH_3COCH_3). **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.81-6.80 (m, 9H, arom.), 4.33 (t, ^3J=8 Hz, 1H, CH), 4.19 (m, 1H, CH_2), 4.07 (t, ^3J=8 Hz, 1H, CH_2), 1.85 (m, ^3J=6.6 Hz, 1H, CH), 1.07 (d, ^3J=6.6 Hz, 3H, CH_3), 0.96 (d, ^3J=6.6 Hz, 3H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 161.8 (C=N), 140.7 (C, arom.), 134.9 (CH, arom.), 133.2 (CH, arom.), 130.4 (C, arom.), 129.7- 127.2 (arom.), 124.9 (C, arom.), 124.1 (CH, arom.), 73.3 (CH_2-O), 69.5 (CH-N), 32.8 (CH), 18.7 (CH_3), 18.3 (CH_3). **IR** (NaCl, cm^{-1}) 3062, 2960 (=CH), 1650 (C=N).

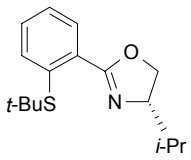
(*4S*)-4-phenyl-4,5-dihydro-2-[2-(terc-butylthio)phenyl]-1,3-oxazoline (10)



A total of 0.5 mmols (68 mg) of $ZnCl_2$ reacted with 10 mmols (1.91 g) of 2-terc-butylthio-benzonitrile (**5**) and 15 mmols (1.37 g) of L-phenylglycinol by following the general procedure described above. The residue was purified by column chromatography using CH_2Cl_2/Et_3N as solvent to give 1.5g (49% yield) of compound **10** as a yellow oil was obtained. Compound **10** decomposed slightly during the purification.

NMR ^{1}H (300 MHz, $CDCl_3$, ppm) 7.71-7.10 (m, 9H, arom.), 5.40 (dd, ^3J=8.4Hz, J=1.8Hz 1H, CH), 4.81, (dd, ^3J=8.4Hz, J=1.8Hz, 1H, CH_2), 4.30 (t, J=8.4 Hz, 1H, CH_2), 1.25 (s, 9H, $C(CH_3)_3$). **NMR ^{13}C** (74.5 MHz, $CDCl_3$, ppm) 166.1 (C=N), 142.5 (C, arom.), 138.6 (CH, arom.), 135.6 (C, arom.), 130.4 (C, arom.), 130.2-126.8 (arom.), 75.2 (CH_2-O), 70.5 (CH-N), 47.6 ($\underline{C}(CH_3)_3$), 31.4 ($C(\underline{C}H_3)_3$).

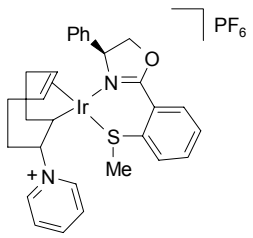
(*4S*)-4-isopropyl-4,5-dihydro-2-[2-(terc-butylthio)phenyl]-1,3-oxazoline (11)



A total of 0.25 mmols (68 mg) of $ZnCl_2$ reacted with 5 mmols (950 g) of 2-terc-butylthio-benzonitrile (**5**) and 7.5 mmols (685 mg) of L-valinol following the general procedure described above. The residue was purified by column chromatography using CH_2Cl_2/Et_3N as eluent to obtain 85.5 mg (55% yield) of compound **11** as a yellow oil.

$[\alpha]_D^{20}$= – 28.0° (c=0.33, CH_3COCH_3). **NMR ^{1}H** (300 MHz, $CDCl_3$, ppm) 7.71-6.80 (m, 4H, arom.), 4.37 (dd, ^3J=6.8 Hz, J=1.5Hz 1H, CH), 4.18 (t, ^3J=6.8 Hz, CH_2), 4.13 (m, 1H, CH_2), 1.84 (d, ^3J=6.6 Hz, 1H, CH), 1.35 (s, 9H, $C(CH_3)_3$), 1.04 (d, ^3J=6.6 Hz, 3H, CH_3), 0.96 (d, ^3J=6.6 Hz, 3H, CH_3). **NMR ^{13}C** (74.5 MHz, $CDCl_3$, ppm) 161.6 (C=N), 137.6-125.0 (arom.), 73.3 (CH_2-O), 69.7 (CH-N), 48.85 ($\underline{C}(CH_3)_3$), 32.7 (CH), 30.68 ($C(\underline{C}H_3)_3$), 18.6 (CH_3), 18.2 (CH_3). **IR** (NaCl, cm^{-1}) 3059, 2957 (=CH), 1648 (C=N).

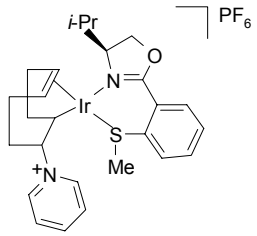
[Ir(σ-η^2-PyC$_8$H$_{12}$)6]PF$_6$ (12a)



A solution of ligand **6** (0.40 mmol) and [Ir(η^4-COD)(Py)$_2$]PF$_6$ (0.30 mmols) in 1 ml of anhydrous dichloromethane was stirred for two hours. Then cold degassed diethylether was added and a precipitate appeared. The solid was filtered and washed with cold and degassed diethylether to afford 223 mg (94%) of complex **12a**.

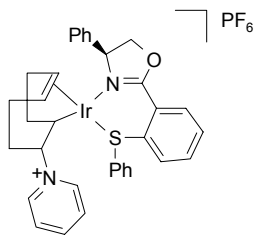
Elemental analysis calculated for C$_{29}$H$_{32}$F$_6$IrN$_2$OPS (%): C 43.88; H 4.06; N 3.53, S 4.04. **Found** (%): C 43.97; H 4.19; N 3.40, S 3.49. **MS FAB**: m/z (%): 649.1 (8.5, M$^+$), 572.1 (19.8, M$^+$-C$_6$H$_5$), 570.1 (63.5, M$^+$-Py), 462 (2.20, M$^+$-C$_{13}$H$_{17}$N), 136 (100, C$_8$H$_{10}$NO). **HRMS L-SIMS**: m/z [C$_{24}$H$_{27}$NOSIr]$^+$ **Calculated:** 570.14425 **Found**: 570.14537. **NMR ^{1}H** (400 MHz, CDCl$_3$, ppm) 8.95 (m, 1H, arom), 8.54 (m, 1H, arom), 7.79 (m, 4H, arom), 7.52 (m, 2H, arom), 7.41 (m, 2H, arom), 7.30 (m, 3H, arom), 7.05 (m 1H, arom), 5.81 (m, 1H, CH), 5.13 (m, 1H, CH$_2$), 4.96 (m, 1H, CH$_2$), 4.66 (m, 1H, CH), 4.07 (m, 1H, CH), 3.22 (m, 1H, CH), 2.59 (m, 1H, CH), 2.43 (m, 1H, CH$_2$), 2.22 (m, 1H, CH$_2$), 2.03 (m, 1H, CH$_2$), 1.74 (m, 1H, CH$_2$), 1.51 (s, 3H, CH$_3$-S), 1.21 (m, 1H, CH$_2$). **NMR ^{13}C** (100.6 MHz, CDCl$_3$, ppm) 176.5 (C=N), 154.7 (CH, arom.), 152.6 (CH, arom.), 147.8-123.4 (arom.), 87.1 (CH), 77.9 (CH$_2$-O), 70.9 (CH), 67.3 (CH), 66.6 (CH-N), 37.2 (CH$_2$), 26.3 (CH$_2$), 24.5 (CH$_2$), 20.6 (CH$_2$), 14.5 (CH$_3$-S), 3.6 (CH). **NMR ^{31}P** (161.9 MHz, CDCl$_3$, ppm) –144.1 (sept, $J_{P\text{-}F}$= 712.8 Hz). **NMR ^{19}F** (376 MHz, CDCl$_3$, ppm) –73.6 (d, $J_{F\text{-}P=}$711.7 Hz).

[Ir(σ-η^2-PyC$_8$H$_{12}$)7]PF$_6$ (12b)



Prepared following the same procedure described for **12a** in 86% yield. **NMR ^{1}H** (300 MHz, $CDCl_3$, ppm) 8.68 (m, 1H, arom), 8.48 (m, 1H, arom), 7.70 (m, 3H, arom), 7.19 (m, 3H, arom), 6,94 (m, 1H, arom), 4.68 (m, 2H, CH), 4.54 (m, 3H, CH), 4.33 (m, 1H, CH), 2.65 (m, 1H, CH), 2.51-0.82 (m, 8H, CH_2), 1.43 (s, 3H, CH_3-S), 1.07 (d, ^3J=6.9 Hz, 3H, CH_3), 0.64 (d, ^3J=6.9 Hz, 3H, CH_3)**. NMR ^{13}C** (74.5 MHz, $CDCl_3$, ppm) 197.5 (C=N), 154.7 (arom., CH), 152.7 (arom., CH), 138.9-123.7 (arom.), 87.5 (CH), 71.6 (CH_2-O), 70.8 (CH), 68.5 (CH), 65.9 (CH-N), 37.5 (CH_2), 30.3 (CH), 29.9 (CH_2), 26.8 (CH_2), 24.9 (CH_2), 20.9 (CH_3), 19.4 (CH_3), 14.9 (CH_3-S), 3.7 (CH).

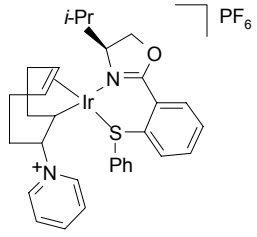
[Ir(σ-η^2-PyC$_8$H$_{12}$)8]PF$_6$ (12c)



Prepared following the same procedure described by **12a** in 98% yield. **Elemental analysis calculated for C$_{34}$H$_{34}$F$_6$IrN$_2$OPS** (%): C 47.71; H 4.00; N 3.27, S 3.75**. Found** (%): C 47.44 H 4.08; N 2.92, S 3.75.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 8.33-6.81 (m, arom.), 5.89-4.22 (m, CH_2-O, CH-N, COD), 2.97-1.37 (m, COD).

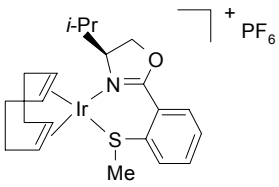
[Ir(σ-η^2-PyC$_8$H$_{12}$)9]PF$_6$ (12d)



Prepared following the same procedure described by **12a** in 91% yield. **Elemental analysis calculated for C$_{31}$H$_{36}$F$_6$IrN$_2$OPS** (%): C 45.30; H 4.41; N 3.41, S 3.9. **Found** (%): C 45.12; H 4.42; N 3.59, S 3.61. **MS FAB**: m/z (%) 598.1 (7.01, M^+-Py), 147 (100, C_9H_9NO).

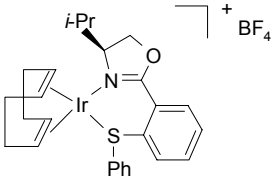
HRMS L-SIMS m/z $[C_{26}H_{31}NOSIr]^+$ **Calculated:** 598.1755 **Found:** 598.1752 **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 10.59-6.84 (m, arom.), 5.51-3.81 (m, CH_2-O, CH-N, COD), 2.50-0.45 (m, COD, CH, CH_3). **NMR ^{31}P** (161.9 MHz, CDCl3, ppm) –143.9 (sept, $J_{P\text{-}F}$= 712.7 Hz). **NMR ^{19}F** (376 MHz, CDCl3, ppm) –73.26 (d, $J_{F\text{-}P=}$713.3 Hz).

[Ir(η^4-COD)(7)]PF_6 (13a)



A solution of ligand **7** (0.150 mmol) and [Ir(η^4-COD)Cl]$_2$ (0.132 mmol) in dichloromethane (5 ml) was heated for 2 h at 50ºC in a sealed tube under argon. After cooling to room temperature, the solution was washed twice with an aqueous solution of NH_4PF_6 (0.4 M, two 10 ml portions). The red dichloromethane solution was washed with water and dried over Na_2SO_4. Crystallization from CH_2Cl_2/Et_2O and drying afforded 65.6 mg (73%) of compound **13a**. **Elemental analysis calculated for $C_{21}H_{29}F_6IrNOPS$** (%): C 37.05; H 4.26; N 2.06, S 4.70. **Found** (%): C 38.30; H 4.13; N 1.96, S 4.46.

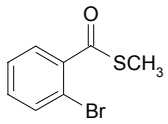
[Ir(η^4-COD)(9)]BF_4 (13b)



A solution of **9** (0.204 mmol) with dry and degassed dichloromethane (5 ml) was added dropwise to a chilled (-80ºC) solution of [Ir(η^4-COD)$_2$]BF_4 (0.204 mmol) with dry and degassed dichloromethane (4 ml). The solution was allowed to warm to 0ºC and stirred for 15 min. Then ethyl ether (30 ml) was added to precipitate 118.5 mg (85%) of complex **13b** as a yellow solid.

Elemental analysis calculated for $C_{26}H_{31}F_4IrNOBS$ (%): C 45.61; H 4.56; N 2.05, S 4.68. **Found** (%): C 45.92; H 4.31; N 1.92, S 4.81.

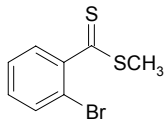
2-Bromo-thiobenzoic acid *S*-methyl ester (15a)



2-bromobenzoylchloride (1.96 ml, 15 mmol) was added dropwise at 0ºC to a suspension of 1.20 g (17 mmol) of methanethiolate sodium salt with 17 ml of dichloromethane. After 1 hour at room temperature, the reaction mixture was quenched with water (20 ml). After several extractions with dichloromethane, the combined organic layers were dried and concentrated to afford 3.5g (99 % yield) of compound **15a** as a yellow liquid, which was used without purification in the next reaction.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.64-7.59 (m, 2H, arom.), 7.38-7.29 (m, 2H, arom.), 2.5 (s, 3H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 193.5 (C=O), 139.6 (C, arom.), 134.1 (CH, arom.), 132.4 (CH, arom.), 129.3 (CH, arom.), 127.4 (CH, arom.), 118.9 (C, arom.), 12.8 (CH_3).

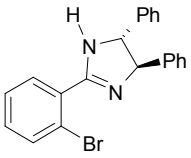
2-Bromo-dithiobenzoic acid *S*-methyl ester (16a)



Lawesson's reagent (2 g, 5.4 mmol) was added under argon to a solution of **15a** (325 mg, 1.4 mmol) in dry toluene (17 ml) and the mixture was heated to reflux. The reaction was monitored by TLC. When no starting material could be detected (ca. 24 hours), the reaction mixture was allowed to cool, and filtered. The solid was washed with toluene and the combined toluene solutions were evaporated and purified by flash column chromatography to afford 318 mg (92 % yield) of compound **16a** as a red liquid.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.57 (m, 1H, arom.), 7.35-7.20 (m, 3H, arom.), 2.78 (s, 3H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 230.4 (C=S), 147.7 (C, arom.), 133.6 (CH, arom.), 130.4 (CH, arom.), 128.2 (CH, arom.), 127.4 (CH, arom.), 118.6 (C, arom.), 20.9 (CH_3).

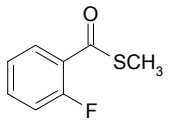
(*4R,5R*)-2-(2-bromophenyl)-4,5-diphenyl-4,5-dihydroimidazole (17a)



A solution of 2-bromo-dithiobenzoic acid *S*-methyl ester (**16a**) (914 mg, 3.7 mmol) in dimethylformamide (4ml) was added to a suspension of (*1R,2R*)-diphenylethylene diamine (786 mg, 3.7 mmol) and red mercury (II) oxide (814 mg, 3.7 mmol) in dimethylformamide (9 ml) at room temperature and vigorously stirred. The solution was heated at 110ºC for 48 hours. Then, the reaction mixture was filtered, concentrated under reduced pressure and purified by flash column chromatography (hexane/ethyl acetate 1:7) to afford 1 g (72% yield) of compound **17a** as a white powder.

m.p.= 148-150 ºC. $\mathbf{[\alpha]_D^{20}}$**=** + 0.601º (c=1.07, CH_2Cl_2). **Elemental analysis calculated for $C_{21}H_{17}BrN_2$.** (%): C, 67.34; H, 4.58; N, 7.44. **Found** (%): C, 67.22; H, 4.60; N, 7.46. **NMR ^{1}H** (300 MHz, $CDCl_3$, ppm) 7.72 (m, 1H, arom.), 7.59-7.57 (m, 1H, arom.), 7.35-7.24 (m, 12H, arom.), 4.83 (s, 2H, CH). **NMR ^{13}C** (75.4 MHz, $CDCl_3$, ppm) 163.1 (C=N), 143.2 (CH, arom.), 133.4 (CH, arom.), 132.6 (C, arom.), 131.5 (CH, arom.), 131.4 (CH, arom.), 129.2 (C, arom.), 128.7 (CH, arom.), 128.4 (CH, arom.), 127.6 (CH, arom.), 127.1 (CH, arom.), 126.8 (CH, arom.), 121.1 (C, arom.), 75.3 (CH).

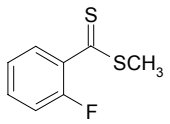
2-Fluoro-thiobenzoic acid *S*-methyl ester (15b)



Prepared following the procedure described for **15a** in 99% yield, and was used without purification in the next reaction.

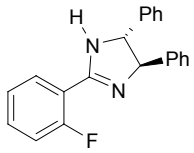
NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.82 (m, 1H, arom.), 7.45 (m, 1H, arom.), 7.18-7.08 (m, 2H, arom), 2.45 (s, 3H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 188.6 (C=O), 159.9 (d, $^1J_{C\text{-}F}$=257.1 Hz, C, arom.,), 134.2 (d, $^3J_{C\text{-}F}$=8.8 Hz, CH, arom.), 129.5 (CH, arom.), 125.2 (d, $^2J_{C\text{-}F}$=11.3 Hz, C, arom.), 124.1 (d, $^3J_{C\text{-}F}$=3.4 Hz, CH, arom.), 116.6 (d, $^2J_{C\text{-}F}$=22.2 Hz, CH, arom.), 12.0 (CH_3).

2-Fluoro-dithiobenzoic acid *S*-methyl ester (16b)



Prepared following the procedure described for **16a** in 95% yield. .**NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.56 (m, 1H, arom.), 7.34 (m, 1H, arom.), 7.13-7.03 (m, 2H, arom), 2.71 (s, 3H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 224.2 (C=S), 157.3 (d, $^{1}J_{C\text{-}F}$=253.1 Hz, C, arom.), 134.5 (d, $^{2}J_{C\text{-}F}$=12.4Hz, C, arom.), 132 (d, $^{3}J_{C\text{-}F}$=8.5 Hz, CH, arom.), 129.5 (CH, arom), 123.9 (d, $^{3}J_{C\text{-}F}$=3.7 Hz, C, arom.), 116.3 (d, $^{2}J_{C\text{-}F}$=22.2 Hz, CH, arom.), 20.9 (CH_3).

(4*R*,5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-4,5-dihydroimidazole (17b)

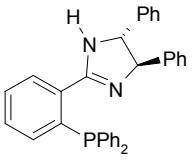


A solution of 2-fluoro-dithiobenzoic acid *S*-methyl ester (**16b**) (326 mg, 1.75 mmol) in dimethylformamide (3ml) was added to a suspension of (1*R*,2*R*)-diphenylethylene diamine (407 mg, 1.92 mmol) and red mercury (II) oxide (414 mg, 1.9 mmol) in dimethylformamide (2 ml) at room temperature and vigorously stirred. The solution was heated at 110ºC for 30 minutes. Then, the reaction mixture was filtered, concentrated under reduced pressure and purified by flash column chromatography to afford 509 mg (92% yield) of compound **17b** as a white powder.

$[\alpha]_D^{20}$= + 0.485º (c=0.811, CH_2Cl_2). **Elemental analysis calculated for $C_{21}H_{17}FN_2$** (%): C, 79.72, H, 5.42; N, 8.85. **Found** (%): C, 80.10, H, 5.32; N, 8.95. **HRMS:** m/z, $C_{21}H_{17}N_2F$ **Calculated**: 316.1376, **Found:** 316.1365. **MS (EI) m/z (%)**: 316 (11.3, M^+), 239 (1.28, M^+-Ph), 211 (100, $C_{14}H_{10}NF$) **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 8.28 (dt, 1H, *J*=7.6 Hz, *J*=1.6 Hz, arom.), 7.49-7.12 (m, 13H, arom.), 5.99 (s, 1H, NH), 4.89 (s, 2H, CH). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 162.1 (C=N), 159.4 (d, ^{1}J=32.9 Hz, C, arom.), 143.3 (C, arom.), 132.6 (d, ^{3}J=9.15 Hz, CH, arom.), 131.3 (d, ^{4}J=2.3 Hz, CH, arom.), 128 (CH, arom.), 127.5 (CH, arom.), 126.6 (CH, arom.), 124.6 (d, ^{3}J=3.1 Hz, CH, arom.), 117.6 (d, ^{2}J=10.6 Hz, C,

arom.), 116.1 (d, ^{2}J=23.6 Hz, CH, arom.). **NMR ^{19}F** (376.5 MHz, $CDCl_3$), -114.2 (m).

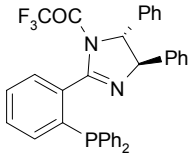
(4*R*,5*R*)-2-[(2-diphenylphosphine)phenyl]-4,5-diphenyl-4,5-dihydroimidazole (18a)



A mixture of 150 mg (0.475 mmols) of (4*R,*5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-4,5-dihydroimidazole (**17b**) in 40 µl of anhydrous tetrahydrofuran and 1.04 ml (0.522 mmols) of potassium diphenylphosphide (0.5 M in tetrahydrofuran) was heated at 60ºC for 1 hour. The reaction crude was then poured into water and extracted twice with dichloromethane. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography under argon to give 226 mg (99% yield) of compound **18a** as a white solid.

$[\alpha]_D^{20}$= -0.192º (c=0.57, CH_2Cl_2). **Elemental analysis calculated for $C_{33}H_{27}N_2P$** (%): C, 82.14, H, 5.64; N, 5.81 **Found** (%): C, 82.17, H, 5.48; N, 5.29. **HRMS (EI):** m/z, $C_{33}H_{27}N_2P$ **Calculated** 482.1912, **Found** 482.1911. **MS (EI) m/z (%)**: 482 (3.78, M^+), 405 (9.61, M^+-Ph), 301 (100, $C_{19}H_{14}N_2P$), 222 (3.59, $C_{15}H_{14}N_2$) **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.80 (m, 1H, arom.), 7.32-7.11 (m, 22H, arom.), 6.80 (m, 1H, arom), 5.86 (s broad, 1H, NH), 4.73 (m, 1H, CH), 4.48 (m, 1H, CH). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 164.2 (C=N), 143.3-126.7 (arom), 80.3 (CH), 71.3 (CH). **NMR ^{31}P** (161.9 MHz, $CDCl_3$), -10.3.

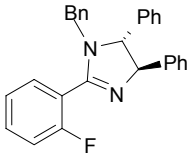
(4*R*,5*R*)-1-trifluoroacetate-2-[(2-diphenylphosphine)phenyl]-4,5-diphenyl-4,5-dihydroimidazole (18b)



A total of 45 µl (0.31 mmol) of trifluoroacetate anhydride was added to a solution of 100 mg (0.207 mmol) of (4*R*,5*R*)-2-(2-diphenylphosphine)-*trans*-diphenyl-4,5-dihydroimidazole **18a** and 60 µl of triethylamine in 1 ml of anhydrous dichloromethane. The solvent was

removed after 1 hour and the residue was purified by column chromatography with silica under argon to give 102.8 mg (86% yield) of compound **18b** as a white solid. **Elemental analysis calculated for $C_{35}H_{26}F_3N_2OP$** (%): C, 72.66, H, 4.53; N, 4.84, **Found** (%): C, 72.63, H, 4.34; N, 4.41. **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.60 (ddd, *J*=8 Hz, *J*=4.4 Hz, *J*=3 Hz, 1H, arom.), 7.47 (dt, *J*=7.6 Hz, *J*=0.8 Hz, 1H, arom.), 7.41-7.20 (m, 19H, arom), 7.11 (ddd, *J*=7.6 Hz, *J*=4 Hz, *J*=0.8 Hz, 1H, arom), 7.15 (t, *J*=1.2 Hz, 1H, arom), 7.00 (d, *J*=2.4 Hz, 1H, arom), 5.28 (d, ^{3}J=4.6 Hz, 1H, CH), 5.16 (d, ^{3}J=4.6 Hz, 1H, CH). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 165.8 (C=N), 155.1 (d, $^{2}J_{C\text{-}F}$=39.8 Hz, C=O), 141-125 (arom), 115.4 (d, $^{1}J_{C\text{-}F}$=289.1 Hz, CF_3), 81.4 (CH), 70.0 (CH). **NMR ^{31}P** (161.9 MHz, $CDCl_3$), -11.8. **NMR ^{19}F** (376.5 MHz, $CDCl_3$) –71.7.

(4*R*,5*R*)-1-benzyl-2-[(2-fluorophenyl)phenyl]-4,5-diphenyl-4,5-dihydroimidazole (19)

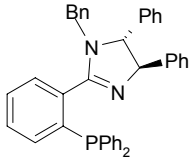


A total of 125 mg (0.395 mmol) of (4*R*,5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-4,5-dihydroimidazole (**17b**) in 1 ml of anhydrous tetrahydrofuran was added to a cooled solution (0ºC) of 17.4 mg (0.43 mmol) of NaH (60% in oil suspension) and 0.5 ml of anhydrous tetrahydrofuran. The mixture was stirred for 30 min and then benzyl bromide (47 µl, 0.395 mmol) was added dropwise. After 3 hours, the reaction was stopped by adding a few drops of methanol and further purification gave 88.5 mg (55% yield) of compound **19** as a pale yellow solid. Several attempts of purification were unsuccessful, and final product contained a 5% of starting material.

MS (EI) m/z (%): 406 (4.04, M^+), 315 (6.08, M^+-Bn), 211 (81.78, $C_{14}H_{10}NF$), 91 (100, C_7H_7). **HRMS (EI):** m/z, $C_{28}H_{23}FN_2$ **Calculated** 406.1845, **Found** 406.1853. **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.70 (m, 1H, arom.), 7.48 (m, 1H, arom), 7.47-7.19 (m, 15H, arom.), 6.90 (m, 2H, arom), 5.00 (d, ^{3}J=8.2 Hz, CH), 4.44 (d, ^{2}J=15.6 Hz, CH_2), 4.36 (d, ^{3}J=8.2 Hz, CH), 3.90 (d, ^{2}J=15.6 Hz, CH_2). **NMR ^{13}C**

(100.6 MHz, $CDCl_3$, ppm) 161.9 (C=N), 159.4 -116.1 (arom.), 78.4 (CH), 72.2 (CH), 49.0 (CH_2). **NMR ^{19}F** (376.5 MHz, $CDCl_3$), -112.9.

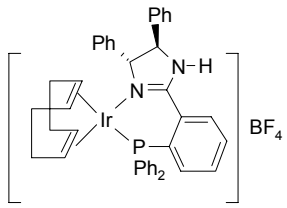
(4*R*,5*R*)-1-benzyl-2-[(2-diphenylphosphine)phenyl]-4,5-diphenyl-4,5-dihydroimidazole (18c)



A mixture of 88.5 mg (0.218 mmols) of (4*R*,5*R*)-1-benzyl-2-(2-fluorophenyl)-4,5-diphenyl-4,5-dihydroimidazole **19** and 0.5 ml (0.239 mmols) of potassium diphenylphosphide (0.5 M in tetrahydrofuran) was heated at 60ºC for 1 hour. The reaction crude was then poured into water and extracted twice with dichloromethane. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography under argon to give 68 mg (54% yield) of compound **18c** as a white solid. Several attempts of purification were unsuccessful, and final product contained a 5% of starting material.

MS (EI) m/z (%): 481 (100, M+-Bn), 91 (26.11, C_7H_7). **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.70 (m, 1H, arom.), 7.44 (m, 1H, arom), 7.38-7.10 (m, 25H, arom.), 6.90 (m, 2H, arom), 4.93 (d, ^{3}J=9.8 Hz, CH), 4.44 (d, ^{3}J=9.8 Hz, CH), 4.28 (d, ^{2}J=17 Hz, CH_2), 3.70 (d, ^{2}J=17 Hz, CH_2). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 164.9 (C=N), 143.9-126.8 (arom), 78.8 (CH), 72.8 (CH), 49.3 (CH_2). **NMR ^{31}P** (161.9 MHz, $CDCl_3$), -12.3.

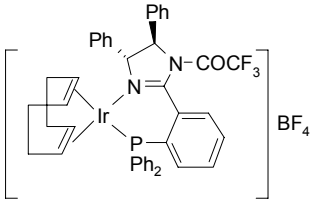
Synthesis of [Ir(η^4-COD)(18a)]BF_4 (19a)



A solution of **18a** (81.7 mg, 0.17 mmol) in dry and degassed dichloromethane (2.5 ml) was added dropwise to a chilled (-80ºC) solution of $[Ir(COD)_2]BF_4$ (70 mg, 0.141 mmol) in dry and degassed dichloromethane (3.5 ml) The solution was allowed to warm to 0ºC and stirred for 30 min. Then, ethyl ether (30 ml) was added to precipitate119 mg (97% yield) of compound **19a** as a pale red orange solid.

MS FAB m/z (%): 783.1 (100, M^+). **HRMS L-SIMS:** m/z, $[C_{41}H_{39}N_2PIr]^+$ **Calculated** 783.2480, **Found** 783.2467. **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 8.50-6.70 (m, 24H, CH arom), 4.93 (m, 1H, CH), 4.85 (m, 2H, CH, COD), 4.66 (m, 1H, CH), 2.90 (m, 1H, CH, COD), 2.77 (m, 1H, CH, COD), 2.37 (m, 1H, CH_2, COD), 2.14 (m, 1H, CH_2, COD), 2.03 (m, 3H, CH_2, COD), 1.67 (m, 1H, CH_2, COD), 1.48 (m, 2H, CH_2, COD). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 162.2 (C=N), 141.9-125.4 (arom), 95.6 (CH, COD), 93.2 (CH, COD), 78.8 (CH), 67.5 (CH), 59.8 (CH, COD), 59.5 (CH, COD), 34.4 (CH_2, COD), 31.5 (CH_2, COD), 29,8 (CH_2, COD), 27.5 (CH_2, COD). **NMR ^{31}P** (161.9 MHz, $CDCl_3$), 15.5.

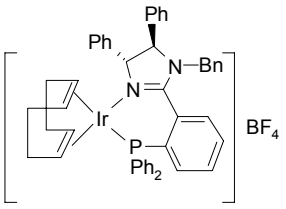
Synthesis of [Ir(η^4-COD)(18b)]BF_4 (19b)



A solution of **18b** (76.5 mg, 0.132 mmol) in dry and degassed dichloromethane (2 ml) was added dropwise to a chilled (-80ºC) solution of $[Ir(COD)_2]BF_4$ (55 mg, 0.11 mmol) in dry and degassed dichloromethane (2.8 ml). The solution was allowed to warm to 0ºC and stirred for 30 min. Then, ethyl ether (30 ml) was added to precipitate 64.9 mg (61% yield) of compound **19b** as a pale black-green solid.

MS FAB m/z (%): 879.1 (22.2, M^+). **HRMS L-SIMS:** m/z, $[C_{43}H_{38}F_3N_2OPIr]^+$ **Calculated** 879.2303, **Found** 879.3130. **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 8.00-6.51 (m, 24H, arom), 5.20 (m, 1H, CH), 5.03 (m, 1H, CH), 4.91 (m, 1H, CH, COD), 4.64 (m, 1H, CH, COD), 3.41 (m, 2H, CH, COD), 2.48 (m, 1H, CH_2, COD), 2.35 (m, 2H, CH_2, COD), 2.16 (m, 2H, CH_2, COD), 1.79 (m, 1H, CH_2, COD), 1.53 (m, 1H, CH_2, COD), 1.39 (m, 1H, CH_2, COD). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 163.3 (C=N), 157.4 (d, $^2J_{C\text{-}F}$=41.3Hz, C=O), 137.0-121.5 (arom, CF_3), 96.3 (CH, COD), 95.1 (CH, COD), 80.4 (CH), 69.7 (CH), 68.1 (CH, COD), 66.3 (CH, COD), 35.8 (CH_2, COD), 32.4 (CH_2, COD), 28,8 (CH_2, COD), 26.7 (CH_2, COD). **NMR ^{31}P** (161.9 MHz, $CDCl_3$), 15.3. **NMR ^{19}F** (376.5 MHz, $CDCl_3$), -71.1 (CF_3), -154.3 (BF_4).

Synthesis of [Ir(η^4-COD)(18c)]BF_4 (19c)



A solution of **18c** (63.5 mg, 0.11 mmol) in dry and degassed dichloromethane (2.5 ml). was added dropwise to a chilled (-80ºC) solution of $[Ir(COD)_2]BF_4$ (50 mg, 0.10 mmol) in dry and degassed dichloromethane (2.5 ml). The solution was allowed to warm to 0ºC and stirred for 30 min. Then, ethyl ether (30 ml) was added to precipitate 82.4 mg (86% yield) of compound **19c** as a pale red solid.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 8.14-6.59 (m, 29H, arom), 5.59 (m, 1H, CH), 5.12 (m, 1H, CH, COD), 4.97 (m, 1H, CH), 4.65 (br, 1H, CH_2), 4.14 (br, 1H, CH, COD), 4.02 (d, ^2J=15.2 Hz, 1H, CH_2), 3.13 (m, 1H, CH, COD), 2.80 (m, 1H, CH, COD), 2.10-1.42 (m, 8H, CH_2, COD). **NMR ^{31}P** (161.9 MHz, $CDCl_3$), 15.5

Crystal Structure Determinations

Crystal structure determination for 19a was carried out using a Siemens P4 diffractometer equipped with a SMART-CCD-1000 area detector, a MACScience

Co rotating anode with MoK radiation, a graphite monochromator and a Siemens low temperature device LT2 (T = -120 °C). The measurements were made in the range 1.70 to 31.55° for theta. Fullsphere data collection omega and phi scans. Programs used: Data collection Smart V. 5.060 (BrukerAXS 1999), data reduction Saint + Version 6.02 (Bruker AXS 1999) and absorption correction SADABS (Bruker AXS 1999). Crystal structure solution for 19a was achieved using direct methods as implemented in SHELXTL Version 5.10 (Sheldrick, Universtität Göttingen (Germany), 1998) and visualized using XP program. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL Version 6.10 (Sheldrick, Universtität Göttingen (Germany),2000). All non hydrogen atoms were refined including anisotropic displacement parameters. Hydrogen atoms were invariably placed in geometrically optimized positions and forced to ride on the atom to which they are attached.

General procedure for the Ir-catalysed hydrogenation of imines

$[Ir(COD)Cl]_2$ (0.022 mmol) or $[Ir(COD)_2]BF_4$ (0.045 mmol) was dissolved in 10 ml of dry, degassed solvent (usually MeOH/CH_2Cl_2 1:1 or CH_2Cl_2) in a Schlenk tube. The thioether-oxazoline or phosphine-imidazoline ligand (0.055 mmol) was then added, followed by the corresponding imine (4.4 mmol for a 100:1 imine:Ir ratio). The solution was transferred under argon to the autoclave via a syringe.

The reaction mixture was stirred overnight at room temperature under 70 bar of H_2 pressure.

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3

P-Donor Ligands: Xylose- and Mannitol-based Ligands

Carbohydrates, with their rich array of stereochemical and functional groups, are a popular source of starting materials for organic synthesis, and particularly for the synthesis of new ligands to be used in homogeneous catalysis. This chapter describes the synthesis of two families of phosphorous derivative ligands based on carbohydrate skeletons and their catalytic response towards the metal-catalysed hydrogenation of imines and enamides.

Chapter 3

3.1. Introduction

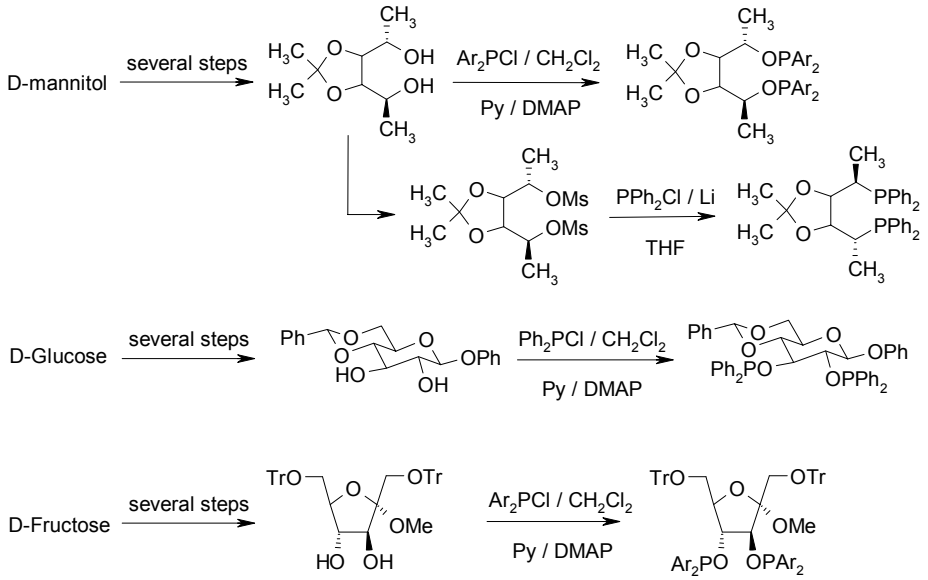
Chiral auxiliaries, reagents and ligands derived from natural products like amino acids and carbohydrates are often used to direct the steric course of asymmetric transformations [1]. In asymmetric catalysis, chirality is transferred from a chiral ligand attached to the metal center to a prochiral substrate. The synthesis of chiral ligands that can effectively transfer chirality, then, is of great importance. One of the most commonly used strategies for obtaining chiral ligands is to transform readily available natural homochiral compounds. Carbohydrates are part of the "chiral pool", carry several stereogenic centres and can be easily obtained enantiopure at a reasonable price. They are highly functionalised, however, in most cases, many or all of the hydroxy groups have to be protected or even removed if the ligand is to be effective for metal-catalysed reactions. This means that it is essentially the backbone and the bulky shape of the whole molecule that transfers the chirality from the ligand to the final product [2].

Scheme 1 shows how versatile carbohydrates can be in synthesizing ligands containing phosphorus functions by a highly flexible route in which the key step is to introduce the phosphorous moiety by reacting the corresponding alcohol with diarylchlorophosphines or lithium diphenylphosphides [3].

A review of the literature shows that carbohydrates were first used to prepare chiral phosphorus ligands in 1978, when Sinou [4], Cullen [5] and Thompson [6] independently reported the synthesis and application of new tertiary phosphorus compounds related to monosaccharides with pyranose or furanose structures in some catalytic hydrogenation processes (Figure 1).

Not much later, in the early 80s Bruner [7] described the synthesis of new phosphorus ligands traced back to mannitol, xylose and glucose. The monophosphinite **6**, phosphinite-phosphite **7** and diphosphite **8** were prepared starting from 1,2:5,6-di-*O*-isopropyldidene-mannitol in a one step procedure by

reaction with chlorophosphorus compounds (Figure 2). The phosphine-phosphinite **9** and the monophosphine **10** were synthesised from D-xylose derivatives and monophosphine **11** from D-glucose (Figure 2).



Scheme 1

Jackson [8] reported the synthesis and application of diphosphinite **12** in metal-catalysed hydroformylation and hydrocyanation reactions (Figure 2). This ligand was prepared from tartaric acid. Although tartaric acid is not a carbohydrate, it is one of most important starting materials for a variety of highly selective chiral ligands with C_2-symmetry [2,9].

It is noteworthy that, in the last decade, the synthesis and development of new ligands based on carbohydrate skeletons has undergone a huge increase and many reports discuss the impressive results obtained in several metal-catalysed processes [2,10].

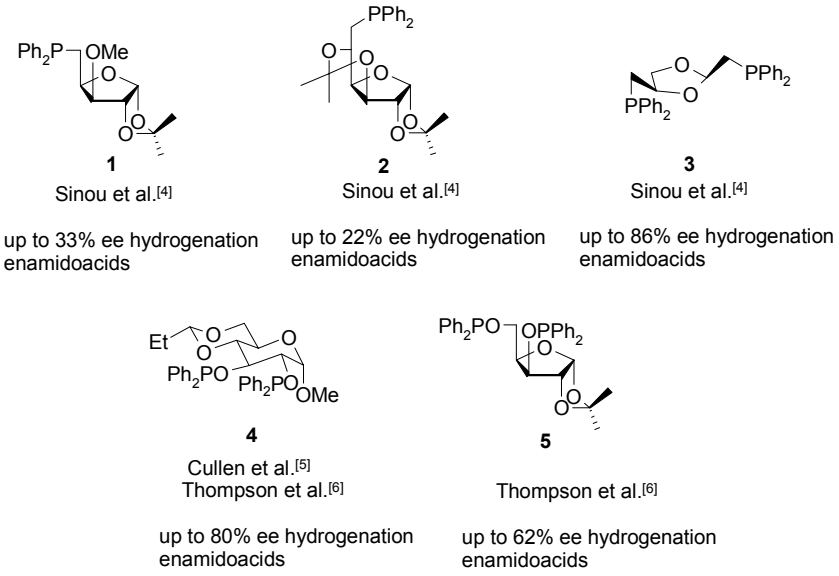


Figure 1

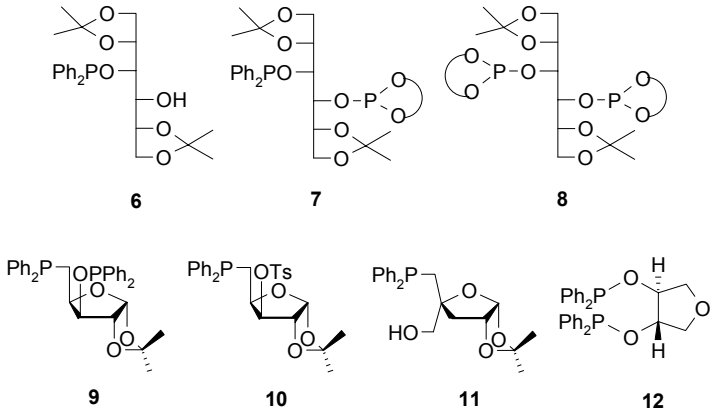


Figure 2

Based on carbohydrates, ligands with C_1- and C_2-symmetry have been synthesised and successfully used in asymmetric catalysis. C_1-symmetric ligands may be traced back mainly to pyranoses (Figure 3).

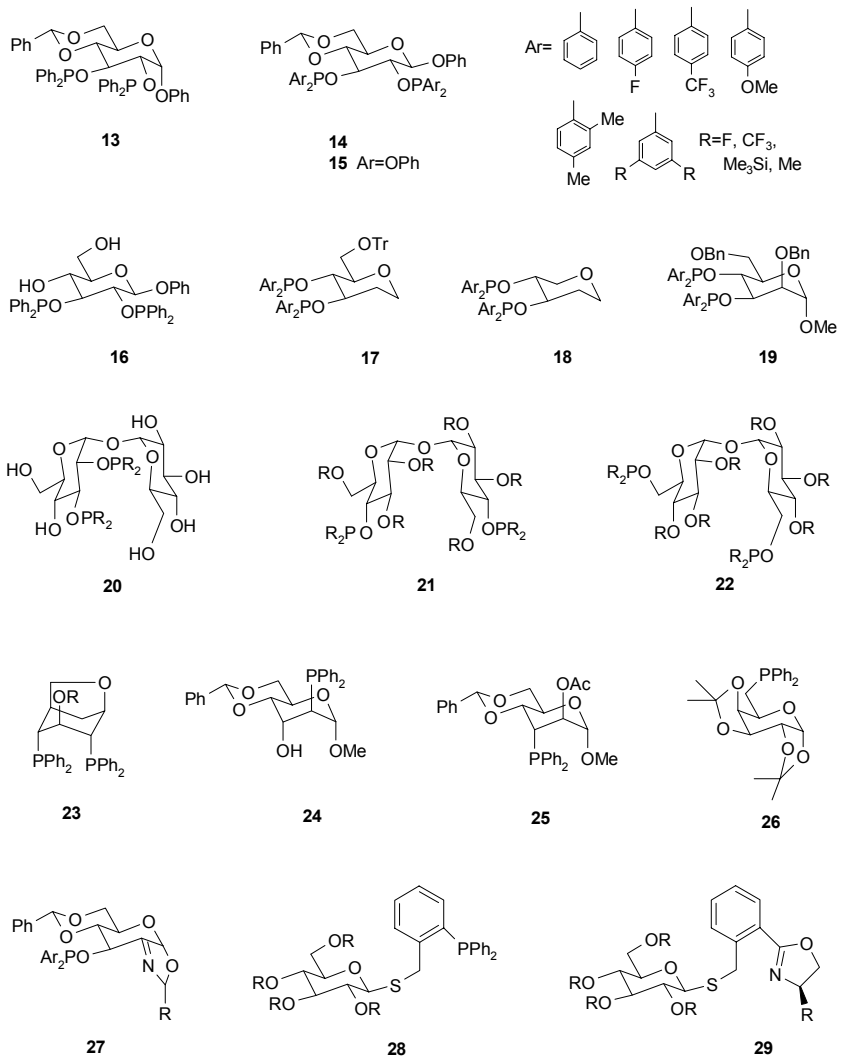


Figure 3. C_1-symmetric pyranoside ligands derived from carbohydrates

The pyranoside ligands **13** and **14** (Figure 3) differ in the configuration of the anomeric carbon. While diphosphinite **13** (α-OPh) provided enantioselectivities in the hydrogenation of enamidoacids up to 80%, the diphosphinite **14** (β-OPh)

provided values as high as 96% [11]. Besides, diphosphinite **14** (Ar=Ph) was also successfully used in Rh-catalysed hydroformylation of styrene. However, the analogous phosphite **15** showed disappointing enantioselectivities in the hydroformylation of vinyl acetate [12].

In addition, Rajanbabu realized that the diphosphinites **16** and **17-19** (Figure 3) promoted the formation of opposite enantiomers in the Rh-catalysed hydrogenation of dehydroamidoacids with no significant variation in the enantiomeric excess [3a,13]. These pyranoside ligands, whose phosphorus functionalities are located at C2 and C3 or at C3 and C4, were indeed pseudo-enantiomers. Rajanbabu also performed an in-depth study with this family of ligands on how the electronic properties of the ligands affected the selectivity and rates of processes such as Ni-catalysed hydrocyanation of vinylarenes [3b,10g] or Rh-catalysed asymmetric hydrogenations of dehydroamidoacids [3a,10g]. The tuning of the electronic properties of the chelating atoms is related to a variation in the enantiomeric excess, although the reason why enantioselectivity depends on the electronic properties of ligands has still to be explained. However, some studies by Koenig [14] and Achiwa [15] show that more electron-rich phosphines enhance not only the activity of the catalyst by strengthening the d-σ^* interaction but also the enantioselectivitity. One possible explanation is that the more electron-rich phosphines increase the d-π^* back-donation between the metal and the coordinated unsaturated substrate and, therefore, the η^2 chelation between the metal and C=X becomes more rigid and leads to high enantioselectivity.

As mentioned in Chapter 1, it is assumed that diphosphines give the best rates of imine hydrogenation, therefore, other phosphorous ligands have scarcely been used in the reduction of C=N. So there are few examples in the literature in which diphosphinites **14** (Ar=Ph), **16**, **18** and diphosphite **15** promote the transformation of imines into chiral amines with rhodium systems giving conversions higher than 97% [16] (Figure 3). However, only the system

[Rh(COD)**18**]BF_4 gave 72% ee when $BnNH_2$ was used as additive. With [Rh(COD)**14**]BF_4 and [Rh(COD)**16**]BF_4, the same enantiomeric excess (28%) was obtained, which demonstrated that the free hydroxyl groups at positions C-4 and C-6 do not have any influence on the catalytic results. Disappointingly, only 1% ee is reported for the system [Rh(COD)**15**]BF_4.

How to recover and reuse the catalyst after the catalytic reaction is still an unsolved problem in homogeneous catalysis [17], and in many cases, if the catalyst shows enough activity it is not later reused. Carbohydrates have a polyhydroxylic nature, which could favour their solubility in water and make it possible to work with a recyclable and environmentally friendly two-phase system using water-soluble catalysts. In an attempt to use ligands based on carbohydrates in biphasic systems, Uemura [18] and Rajanbabu [19] reported the diphosphinites **20**-**22** (Figure 3).

While the preparation of phosphinites or phosphites derived from monosaccarides is synthetically ease because it takes advantage of the many hydroxyl functionalities of carbohydrate skeletons, synthesizing phosphines is more difficult. However, some examples of monophosphines have been introduced in Figure 2, where the phosphine functionality is attached to a primary carbon. The introduction of a phosphorus atom into the secondary carbon of carbohydrates by nucleophilic replacement competes with undesired elimination reactions. Nevertheless, Vasella [20] reported the synthesis of diphosphine **23** and its application in the Ru-catalysed hydrogenation of β-ketoesters and Rh-catalysed hydrogenation of enamidoacids with moderate results (Figure 3).

Ligands with only one donor function have been dealt with less in the literature, because it has been generally accepted that chelating ligands give higher enantioselectivities. However, Sinou [4] and Bruner [7] reported the successful application of monodentate ligands **1**, **2**, **10** and **11** in asymmetric catalysis (Figures

1 and 2). In addition, monophosphines **24**, **25** and **26** [21] have recently been synthesized (Figure 3).

With the "hemi-labile ligands" phosphinoaminosugar **27** [18], phosphinothiosugar **28** [22] and oxazolinethiosugar **29** [18] enantioselectivities up to 96% were achieved in the Pd-catalysed allylic substitution (Figure 3).

Just a few examples of C_1-furanoside ligands for enantioselective catalytic transformations are known in the literature (Figure 4).

Rajanbabu reported the diphosphinite **30** [21b] derived from fructose, which was very efficient in the Ni-catalysed hydrocyanation of olefins, as well as the monophosphinite **44** [21b] and its use in hydrovinylation (Figure 4).

Bruner et al. [7a] reported moderate enantioselectivities (up to 35%) with phosphine-phosphinite **31** in the rhodium-catalysed hydrogenation of (Z)-α-acetamidocinnamic acid (Figure 4).

Kagan and Börner synthesized hydroxyphosphines **33** and **34** [23], which have a tetrahydrofuran backbone, from L-ascorbic acid (Figure 4).

Van Leeuwen et al. [24] reported the synthesis and use of a family of diphosphites related with structure **35** in the rhodium-catalysed hydroformylation of styrene. In the last few years, our group at the Rovira i Virgili University has made an important contribution to developing many different types of phosphorous ligands such as diphosphites **36-38** [25], phosphoroamidite-phosphites **39-40** [26], phosphine-phosphite **41** [27] and diphosphines **42-43** [10h,28] with a furanose structure and xylo-, gluco- or ribo- configuration (Figure 4).

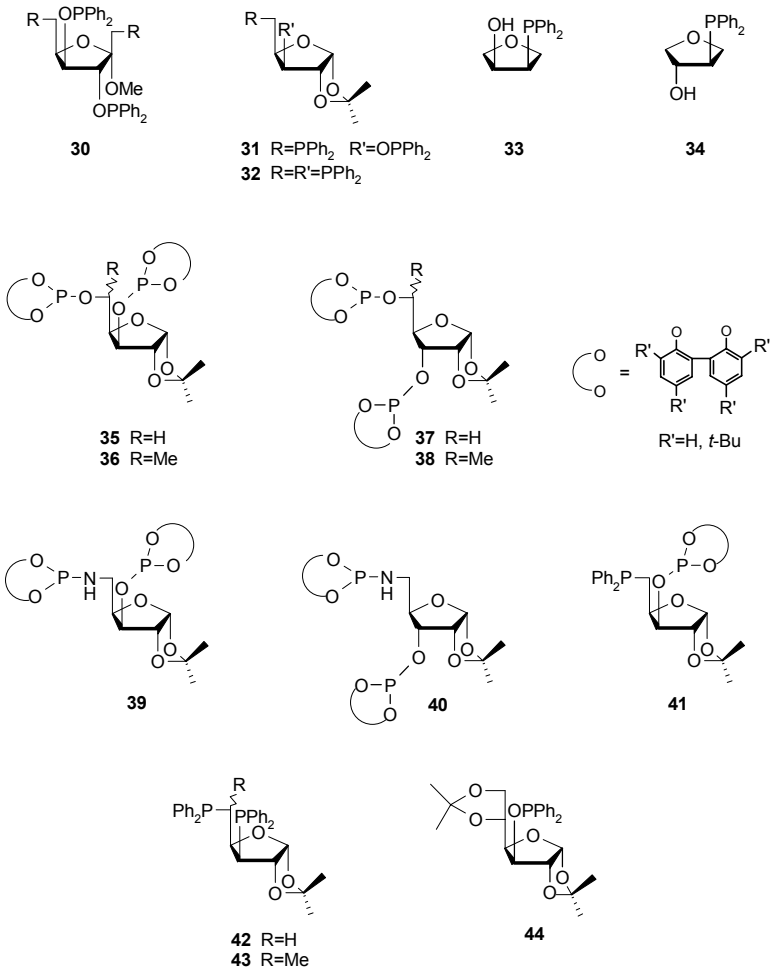


Figure 4. C_1-symmetric furanoside ligands **30-44** derived from carbohydrates

Ligands derived from glucose introduce a new stereogenic center at the C-5 position close to one of the coordinating phosphorous atoms. This new stereocenter enhances the enantioselectivity; for instance, in the Rh-asymmetric hydroformylation of styrene the ee rose from 61% to 90% when ligand **36** [25a] was used instead of ligand **35** [24].

The chiral diphosphite **35** [25b], based on a xylose backbone, and the diphosphite **37** [25c], based on a ribose backbone, were tested in the asymmetric hydrogenation and hydroformylation of prochiral olefins. It was concluded that the configuration of the product is controlled by the configuration of the stereogenic carbon atom C-3.

The phosphoroamidite-phosphites **39-40** [26] gave enantioselectivities up to 65% in the Rh-catalysed hydroformylation of styrene.

The phosphine-phosphite **41** proved to be an excellent ligand in the asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives. Systems generated *in situ* from $[Rh(COD)_2]BF_4$/**41** [27a], showed better activities and enantioselectivities (>99% ee) than the Rh/diphosphine **42** [28a] and diphosphite **35** [24] counterparts (under mild conditions: 1 bar of H_2 pressure, room temperature).

The phosphines **42-43** were tested in the rhodium-catalysed asymmetric hydroformylation of styrene and other vinyl arenes, and provided regioselectivites on the branched hydroformylated product up to 97% with ee's up to 58% [10h].

All these examples illustrate that chiral C_1-diphosphinite, diphosphite and phosphoroamidite ligands based on carbohydrate skeletons with furanose structures are potentially very useful in catalytic processes.

C_2-symmetric chiral ligands are particularly useful as mediators of stereochemical information. The introduction of this symmetry element means that: (1) both faces of the ligand become equivalent; (2) the number of the competing diastereomeric transition states is reduced significantly; (3) the C_2 symmetry element often also simplifies the synthesis of ligands.

C_2-symmetric ligands are mainly derived from mannitol. Phospholanes **45** [29] and **46** [30], examples of monodentate ligands, have been reported by Zhang and Rajanbabu, respectively (Figure 5).

The well-known diphosphines (R,R)-DIOP (**47**) [31], and DUPHOS (**48a**) [32], which are among the most efficient ligands used in catalysis, also present C_2-symmetry.

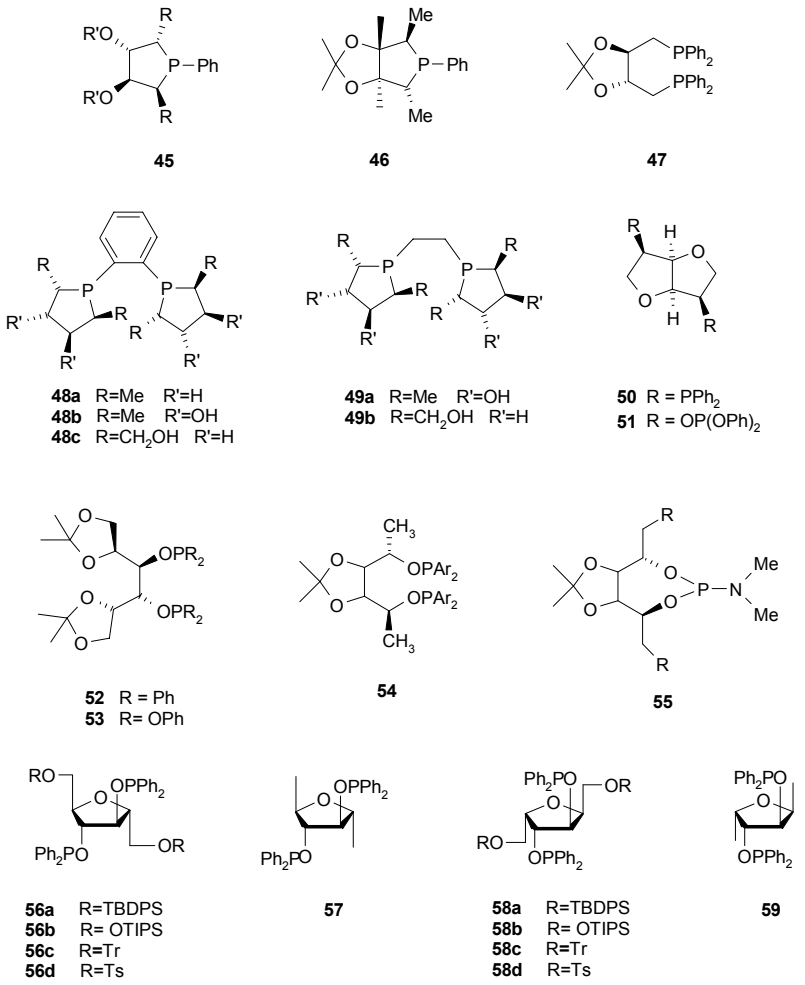


Figure 5. C_2-symmetric ligands **45-59** derived from carbohydrates

Several groups have synthesized a wide variety of DuPHOS-analogues (**48b-c**) [33] and BPE-analogues (**49b**) [34], in which the characteristic 2,5-dimethylphospholano ring is substituted by other phospholano rings prepared from mannitol and free hydroxyl groups are incorporated to solubilize the ligands in water (Figure 5).

The diphosphine **50** [35] and diphosphite **51** [36] are responsible for the high enantioselectivities achieved in some asymmetric hydrogenation processes.

Other ligands also prepared from D-mannitol are diphosphite **53** [33], diphosphinites **52** and **54** [37], and phosphoroamidite **55** [38] (Figure 5).

Recently, our group [39] designed two new families of diphosphinites derived from D-mannitol (**56-57**) and L-iditol (**58-59**) with a tetrahydrofuran backbone and C_2-symmetry (Figure 5). These ligands have been used in rhodium-catalysed hydrogenation of prochiral olefins to obtain useful chiral precursors of amino acids and have proved to be very active as well as enantioselective. These two families have the same configuration at C3 and C4, but opposite configurations at C2 and C5. The enantioselectivity of the process is closely influenced by these secondary stereocenters, which shows that the D-mannitol derivatives **56-57** were more enantioselective than the L-iditol derivatives **58-59**. However, the absolute configuration of the resulting product is the same for all the D-mannitol and L-iditol ligands, which shows that it is independent of the configuration of C2 and C5. It is difficult to establish a general pattern for the influence of the protecting groups of the primary alcohols, but it seems that the TBDPS is the most suitable protecting group to achieve high enantioselectivities.

As far as we know, no Ir(I) catalysts bearing diphosphinite or diphosphite ligands based on carbohydrates have been reported in the asymmetric hydrogenation of imines. We felt, therefore, that it would be interesting to investigate the catalytic behavior towards the iridium-catalysed reduction of C=N of some ligands, which provided good results in other hydrogenation processes. So,

the C_1-symmetric diphosphinite **5** [6] and diphosphites **35** [24] based on D-xylose (Figures 1 and 4) were tested in the catalytic reduction of ketimines. In addition, we planned to enlarge the family of C_2-phosphinites related to structure **56a** based on D-mannitol (Figure 5), by preparing new ligands with different electronic properties. We also prepared new C_1- ligands traced back to D-xylose and D-mannitol to check their ability to reduce imines and enamides.

3.2. Results and Discussion

3.2.1. Xylose-based ligands

As stated in Chapter 1, Börner and co-workers [16] found that electron-rich dialkylphosphines provided worse conversions than the more electron-poor diphosphinites in the rhodium-catalysed hydrogenation of acyclic imines, in contrast to what was expected. So, ligands with more π-accepting properties like diphosphinites and diphosphites may be able to satisfactorily reduce prochiral imines. In accordance with this, we proposed to check the catalytic capability of diphosphinite **5** [6] and diphosphites **35a** and **35b** [24] (Figure 6) in the reduction of acyclic and cyclic ketimines with iridium precursors.

In the course of our studies we also isolated the monodentate ligand **60** (Figure 6), and since interesting results have recently been reported in the reduction of enamides with monodentate ligands [40], we decided to test the monophosphinite **60** in the asymmetric rhodium-catalysed reduction of enamides.

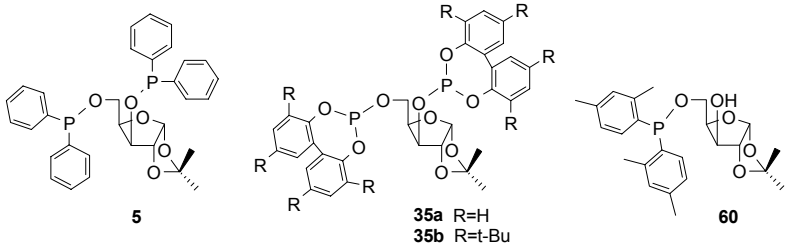
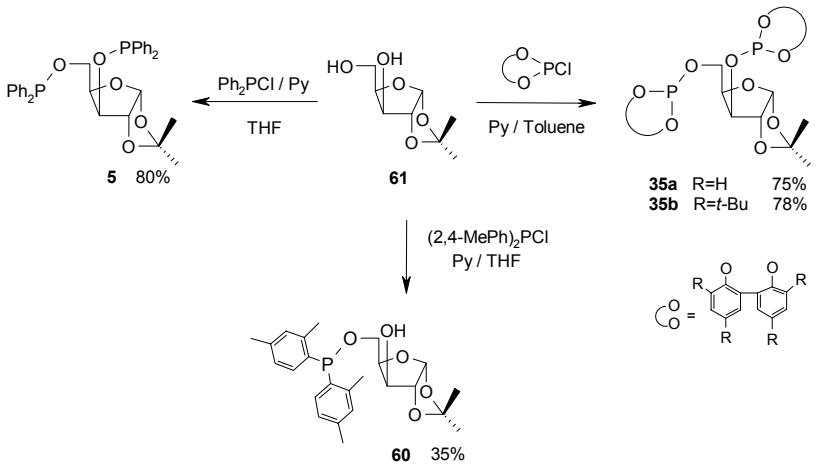


Figure 6

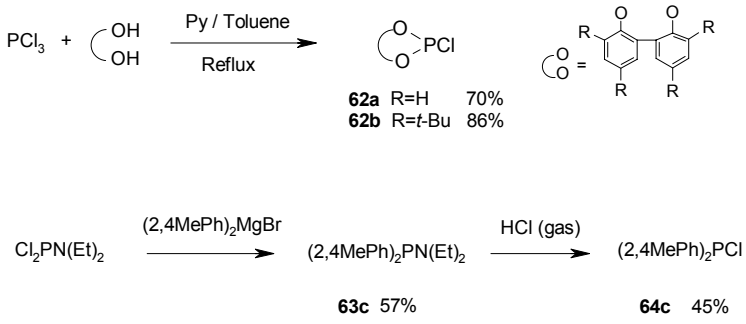
3.2.1.1. Synthesis and characterization of ligands 5, 35a-b and 60

Ligands **5** and **35a-b** were prepared satisfactorily by using the general procedures described in the literature [3,6,11,24]. The diol 1,2-*O*-isopropylidene-D-xylofuranose (**61**) was converted into the corresponding phosphinite or phosphite by treatment with R_2PCl/pyridine and purified by flash column chromatography under inert atmosphere with dry and degassed solvents (Scheme 2).



Scheme 2. Synthesis of ligands **9**, **35a-b** and **60**

PPh_2Cl was commercially available, but the phosphorochloridites **62a-b** ($(RO)_2PCl$) were prepared from the corresponding diol and PCl_3 in good yields (Scheme 3). The bis(2,4-dimethylphenyl)chlorophosphine (**63c**) was prepared from dichloro(diethylamino)phosphine and the Grignard reagent bis(2,4-dimethylphenyl)magnesiumbromide. The resulting diarylaminophosphine was then treated with anhydrous HCl.



Scheme 3. Synthesis of **62a-b**, **63c** and **64c**

When **61** was treated with an excess of bis(2,4-dimethylphenyl)chlorophosphine (**64c**), the phosphorylation of the primary alcohol took place selectively to give the compound **60** as the major product (Scheme 2).

Various assays increasing the phosphorus reagent excess or forcing the conditions did not make it possible to obtain the diphosphinite derivative. A considerable number of side products containing phosphorus were also detected in the reaction mixture. One of these side compounds in particular had a peculiar $^{31}P\{^1H\}$ NMR pattern of two sets of doublets with a large coupling constant (J=237 Hz), which indicated a possible P-P bond. Although this compound was not isolated in pure form and could not be completely and unambiguously characterised, the ^1H NMR spectrum showed a compound, which incorporated xylose backbone and

aromatic groups. Section **3.2.2** (pags. 120-123) will propose and discuss in depth a feasible structure for a similar compound with a mannitol backbone.

Thus, we reasoned that when the nucleophilic attack of the primary hydroxyl group is rate limiting and other side reactions compete, the phosphitylation reaction is completely selective for less hindered primary hydroxyl group.

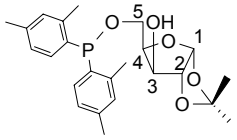
Ligands **5**, **35a-b** and **60** were unequivocally characterized by NMR and MS techniques. The spectroscopic data of **5** and **35a-b** were in agreement with the published bibliographic data [7,24].

The $^{31}P\{^{1}H\}$ NMR spectrum of ligand **60** showed only one signal instead of the two signals expected for a disubstituted compound (Table 1).

The $^{13}C\{^{1}H\}$ NMR spectrum revealed that C5 appeared as a doublet at 67.8 ppm with a coupling constant $^{2}J_{C5\text{-}P}$=20.5 Hz, but that C3 appeared as a singlet at a similar chemical shift to C3 in compound **61**. These findings indicated that the phosphorus moiety was introduced only at the primary alcohol. Besides, the ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra showed signals corresponding to aromatic rings and methyl groups. The methyl groups attached to the aromatic rings did not become equivalents, and appeared as four different signals. In the $^{13}C\{^{1}H\}$ NMR spectrum, the signals corresponding to the *ortho*-methyl groups appeared as doublets due to the coupling with the phosphorus atom, with a coupling constant $^{3}J_{\underline{C}H3\text{-}P}$=8.4 Hz.

The MS FAB shows a peak at m/z 430.2 corresponding to M^{+}. The elemental analysis of C and H fits the molecular composition $C_{24}H_{31}O_5P$.

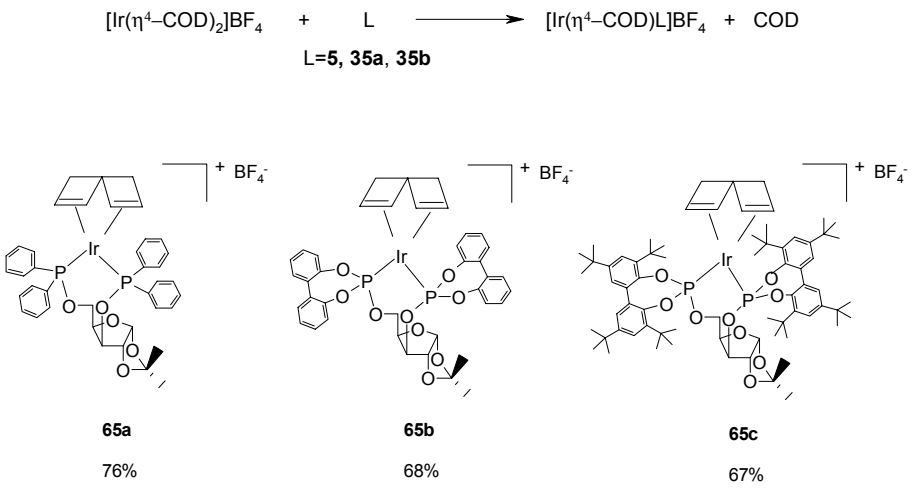
Table 1. Selected spectroscopic NMR data for ligand **60** recorded in $CDCl_3$



	^{1}H NMR (ppm)		^{31}C{^{1}H} NMR (ppm)
Arom	7.15-7.07	Arom	136.0-130.1
H1	5.82 (s)	C1	104.9
H2	4.47 (s)	C2	85.4
H3	4.31 (br)	C3	75.9
H4	4.24 (br)	C4	79.0 (d) $^3J_{C4,P}$=7.6 Hz
H5/H5’	4.19 (m)	C5	67.8 (d) $^2J_{C5,P}$=20.5 Hz
C(C$\underline{H}_3$)$_2$	1.49 (s), 1.32 (s)	$\underline{C}$(CH$_3$)$_2$	111.8
		C($\underline{C}$H$_3$)$_2$	27.1, 26.5
2,4-C$\underline{H}_3$	2.42 (s), 2.34 (s), 2.31 (s), 2.28 (s)	2,4-$\underline{C}$H$_3$	21.5 (s), 21.4 (s), 20.4 (d), 20.2 (d) $^3J_{\underline{C}H3,P}$=8.4 Hz
O$\underline{H}$	2.82		
^{31}P{^{1}H} NMR (ppm)	108.9		

3.2.1.2. Synthesis of [Ir(η^4-COD)L]BF_4 (65a-c)

The corresponding cationic Ir(I) complexes **65a-c** were prepared by reaction in dichloromethane of [Ir(η^4-COD)$_2$]BF_4 (COD=cyclooctadiene) with the ligands **5**, **35a** and **35b** (Scheme 4). Complexes **65a-c** were isolated as a moderately air-stable powder by adding ethyl ether [28a].



Scheme 4. Synthesis of iridium complexes **65a-c**

The elemental analysis of C and H matched the stoichiometry [Ir(η^4-COD)L]BF_4 (L= **5**, **35a-b**). The FAB mass spectra for complex **65c** showed the highest ion at a m/z value of 1367.3, which corresponds to the cationic mononuclear species. Moreover, the loss of cyclooctadiene is also observable. The $^{31}P\{^1H\}$ NMR spectra showed two doublets due to the ^{31}P-^{31}P coupling. These doublets are sharp in the case of complex **65a**, but broad for complexes **65b-c**. The ^1H and $^{13}C\{^1H\}$ NMR spectra of **65b-c** are in agreement with the published bibliographic data [25b].

3.2.2. Mannitol-based ligands

As mentioned in the Introduction, our group has recently developed a new family of C_2-symmetry ligands based on the monosaccharide D-mannitol with a

tetrahydrofuran structure (**56-59**) (Figure 5), which provided encouraging results in the rhodium-catalysed asymmetric hydrogenation of α,β-dehydroamino acids. These ligands have the following general structural characteristics (Figure 7): (1) they are "tailor-made" ligands, which make it possible to modify the carbohydrate skeleton and the phosphorus moiety easily and independently; (2) they have C_2-symmetry; (3) the presence of other stereocenters, in addition to those that anchor the phosphorous moiety, influences the conformational flexibility and, therefore, the asymmetric induction; (4) the phosphorus unit may be phosphinite, phosphite, phosphoroamidite or even phosphine, leading to a considerable number of ligands; (5) the size of the chelate can vary from 5 to 7 members depending on the phosphorus functions, and gives organometallic complexes with considerable conformational flexibility; (6) the primary alcohols can be functionalised with bulky protecting groups so that their influence on the enantiocontrol can be studied; (7) it may be possible to recover the catalyst after use by immobilising the ligand in a solid support (polymer, silicagel, etc.) or by introducing polyhydroxilate or perfluorate chains to solubilise the ligand in water or supercritical fluids.

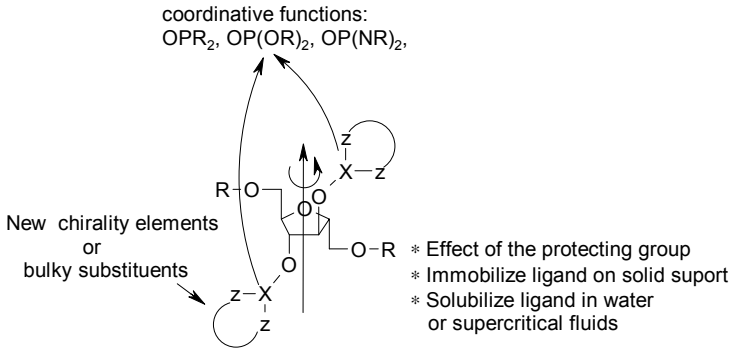
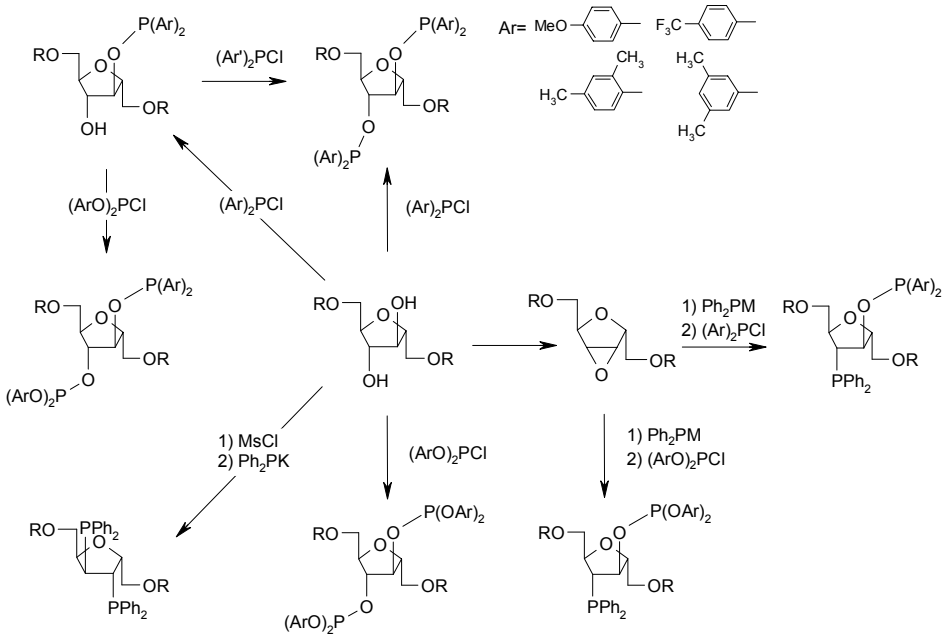


Figure 7

Scheme 5 illustrates some of the ligands that can be prepared from the protected 2,5-anhydro-D-mannitol.



Scheme 5

Strategies for controlling regio- or stereoselectivity in catalytic reactions have usually involved designing or manipulating the catalyst steric enviroment, even though the electronic properties of ligands can have profound effects on the selectivity and rates of fundamental catalytic processes [3].

So it is important to investigate both the electronic and the steric effects. Our aim was to enlarge this new family of C_2-diphosphinites by synthesising a set of diphosphinites (**66a-c**), related to ligand **56a,** with different modifications on the aryl groups attached to the phosphorus atoms (Figure 8).

The monodentate ligand **67** was also unexpectedly obtained, as occurred with the xylose derivative ligand **60**. So compound **67** enabled us to investigate the synthesis of new non-symmetrical ligands by introducing a second phosphorous moiety. Thus the C_1-symmetric ligands **68**, **69a-b** were also prepared (Figure 8).

Further, we investigated the catalytic behavior of the bidentate ligands **56a**, **66a-c**, **68** and **69a-b** towards the asymmetric iridium- and rhodium-catalysed C=N and C=C reductions, as well as the monodentate ligand **67** in the asymmetric rhodium-catalysed C=C reduction.

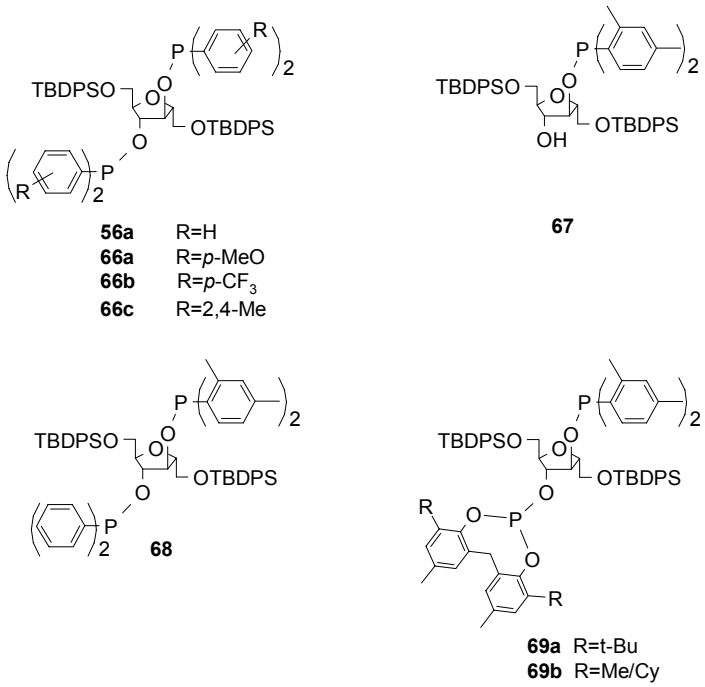
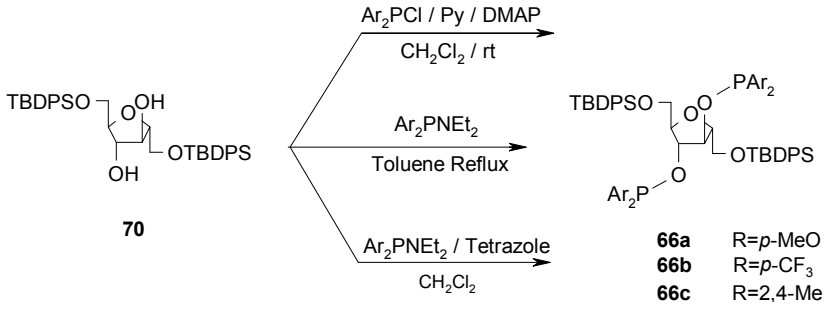


Figure 8

3.2.2.1. Synthesis and characterization of ligands 66a-c, 67, 68, 69a-b

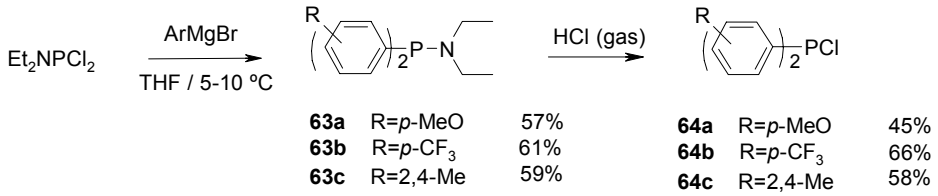
The chiral backbone of these ligands is the 2,5-anhydro-D-mannitol (**70**) in which the two primary alcohols were appropriately protected with tert-butyl-diphenylsilyl group by standard methods (Scheme 6). The resulting diol is then converted into the corresponding diarylphosphinite ligands by treatment with R_2PCl/base [3] or with R_2PNEt_2 [41] and purified by flash column chromatography under inert atmosphere using dry and degassed solvents. By these methods, the series of C_2-diphosphinites **66a-c** were synthesised in one step (Scheme 6).



Scheme 6

To synthesise these new ligands various diaryldiethylaminophosphines (**63a-c**) and diarylchlorophosphines (**64a-c**) had to be prepared first, in accordance with the Rajanbabu protocol (Scheme 7) [3].

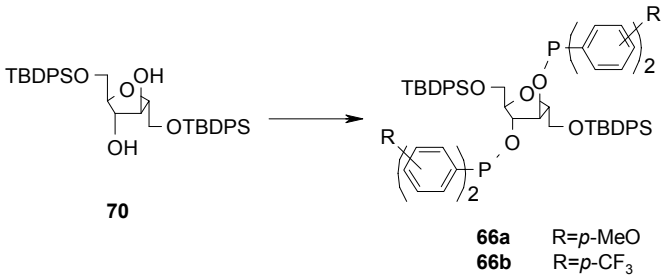
Grignard reagents (ArMgBr), formed by the reaction of magnesium with the correspoding aryl bromides, were treated with Et_2NPCl_2 to give the aminophosphine intermediates (**63a-c**), which were isolated and characterised. Finally, HCl bubbling replaced the amino moiety by a chlorine atom to give the diarylchlorophosphines (**64a-c**).



Scheme 7

It was more difficult than expected to synthesise the desired ligands. When the diol **70** was reacted with the chlorophosphine **64a** in the stardard conditions described by Rajanbabu, the starting material was totally converted but a complex and inseparable mixture of compounds was obtained. Many other unidentified side phosphorus compounds were obtained and the amount of ligand **66a** was less than 10% measured by RMN (Table 2, entry 1) [3].

Table 2. Synthesis of ligands **66a** and **66b**



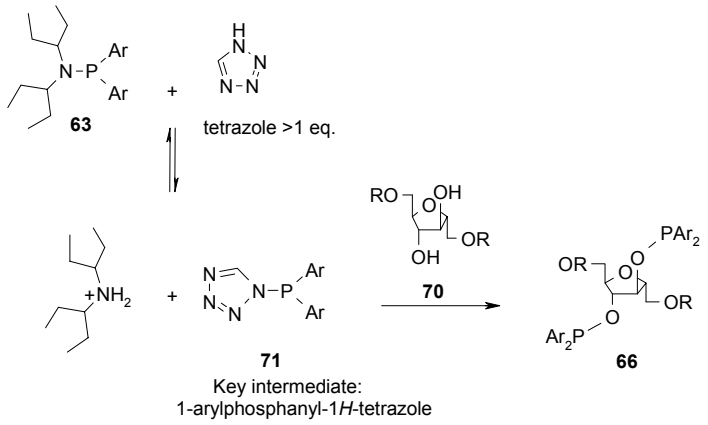
Entry	Reagents	Solvent	T [ºC]	Time [h]	Conv. [%]	Yield [%]
1[a]	**64a** / Py / DMAP	CH_2Cl_2	rt	16	100	Not isolated[b]
2	**63a**	Toluene	110	24	100	23
3	**63b**	Toluene	110	24	100	28
4	**63a** / Tetrazole	CH_3CN/CH_2Cl_2	rt	1/2	100	59

[a] Py=pyridine, DMAP=dimethylaminopyridine [b] Ligand **66a** could not be isolated in pure form from the reaction mixture by column chromatography

Ligands **66a** and **66b**, however, were isolated by an unoptimized direct reaction of the aminophosphine **63a** or **63b** (Table 2, entries 2 and 3) with diol **70** in refluxing toluene [41]. Although all the starting material disappeared, ligands **66a** and **66b** were obtained in low yields (23% and 28%, respectively) after purification by column chromatography under argon. Many other side compounds were formed under these reaction conditions. These phosphorous compounds seem not to be very stable under purification conditions (silica or even alumina).

In an atempt to find milder reaction conditions, aminophosphine **63a** was treated with the weak acid 1*H*-tetrazole before **70** was added [42]. The reaction to form ligand **66a** worked considerably better and the yield increased to 59% (Table 2, entry 4). By slightly modifying the general synthetic procedure used in the phosphitylation of nucleotides, we found a suitable method for attaching phosphorylate functions to carbohydrates to give phosphinites. The mechanism is probably similar to the one reported for the phosphitylation of nucleotides using phosphoroamidites ($(RO)_2PN(i\text{-}Pr)_2$) as a phosphorus reagent [43]. Protonation of the diarylaminophosphine **63** by the weak acid 1*H*-tetrazole, followed by nucleophilic attack by the tetrazolide ion, gives the 1-arylphosphanyl-1*H*-tetrazole (**71**) (Scheme 8). Subsequently nucleophilic attack of hydroxyl groups from **70** on **71** gives the desired protected phosphinite ligands **66**.

With regard to the synthesis of diphosphinite **66c**, Table 3 shows the reaction conditions tested to attach the bis(2,4-dimethylphenyl)chlorophosphine moiety to the mannitol backbone. Although not all the assays were successful at forming **66c**, we found reaction conditions that were suitable for preparing and isolating diphosphinite and monophosphinite ligands **66c** and **67**, but not selectively.

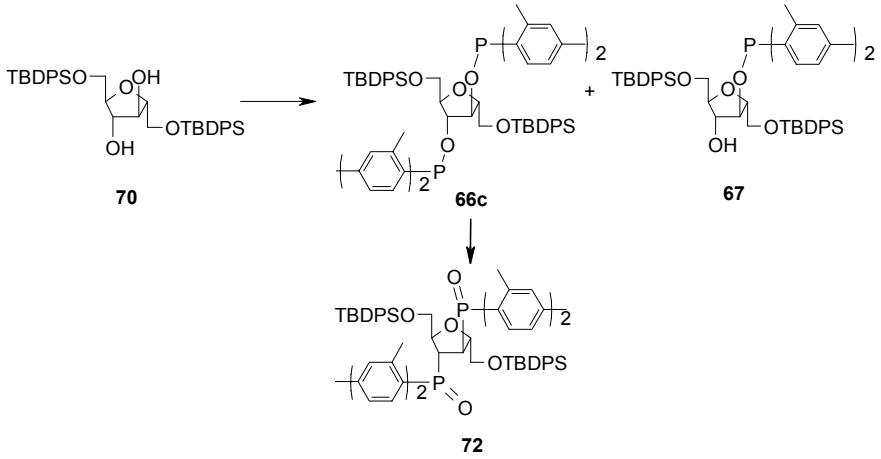


Scheme 8

When diol **70** reacted with diarylchlorophosphine **64c** and pyridine/DMAP in CH_2Cl_2 gave a mixture in which the major product did not correspond to either **66c** or **67** (Table 3, entry 1). The spectroscopic analysis revealed that the unidentified compound was the phosphine oxide **72** (Table 3, entry 1). The MS spectrum showed the highest m/z at 1120.4, which fits with the molecular composition $C_{70}H_{82}O_5P_2Si_2$. The loss of the *tert*-butylphenyl group was also observable at m/z 881.3 (M^+-TBDPS). $^{31}P\{^1H\}$ and ^1H NMR revealed a C_2-symmetric compound. However, the chemical shift of the phosphorus atom did not agree with the expected chemical shift for phosphinite compounds. The phosphorus signal appeared at 16.9 ppm in the $^{31}P\{^1H\}$ NMR spectrum in agreement with the chemical shift of some phosphine oxides ($((CH_3)_2CHCH_2P(O)Ph_2$ $\delta^{31}P$=20 ppm; $(CH_3CH_2)_2CHP(O)Ph_2$ $\delta^{31}P$=38 ppm; $(C_6H_{11}P(O)Ph_2$ $\delta^{31}P$=33 ppm) [44]. It has long been known that some phosphinite esters undergo "self-isomerization" to the corresponding phosphine oxide [45]. Normally isomerization can be effected by heating and is catalysed by impurities in the reaction mixture or by adding small quantities of iodine or R'X. Indeed, because of the ease of the isomerization

process, it has frequently been difficult to isolate phosphinite esters. Early attempts to prepare methyl- and benzyldiphenyl-phosphinite esters [46] led only to the corresponding phosphine oxides. An attempt to reduce the compound **72** with $HSiCl_3$ did not proceed.

Table 3. Synthesis of ligands **66c** and **67** and formation of **72**



Entry	Reagent	Solvent	T[a] [ºC]	Time [h]	Ratio **66c**/**67**
1[a]	**64c** / Py / DMAP	CH_2Cl_2	rt	16	--
2	**64c** / Et_3N	THF	rt	16	0/1
3	**63c**	Toluene	110	24	--
4	**63c** (4eq)/Tetrazole (5.6eq)	CH_2Cl_2/CH_3CN	rt	3	1/3
5	**63c** (4eq)/Tetrazole (5.6eq)	CH_2Cl_2/CH_3CN	60	7	--
6	**63c** (8eq)/Tetrazole (11.2eq)	CH_3CN	rt	24	1/1

[a] Py=piridine, DMAP=dimethylaminopyridine

When the reaction conditions were slightly modified using THF instead of CH_2Cl_2, and Et_3N instead of pyridine at room temperature (Table 3, entry 2), only one phosphine moiety was introduced to give the monodentate ligand **67** in a 48%

yield. A considerable amount of a side product was observed, whereas it was not in CH_2Cl_2.

This side product was isolated and characterised, and the $^{31}P\{^1H\}$ NMR spectrum showed a set of two doublets at +42.6 ppm and –44.2 ppm with a large coupling constant of 234 Hz. This indicated that there was probably a P-P bond of two unequal phosphorous atoms. Besides, the ^1H and $^{13}C\{^1H\}$ NMR spectra showed a C_2-symmetric compound, following the pattern observed in previous ligands with this symmetry element, two protons of the tetrahydrofuran ring and two protons of the exocyclic methylene group, as well as four singlets associated to four different methyl groups of the aromatic rings. The bidimensional HMQC spectrum ^{31}P-^1H showed the correlation between the two different phosphorus atoms and the aromatic and methyl groups (Figure 9).

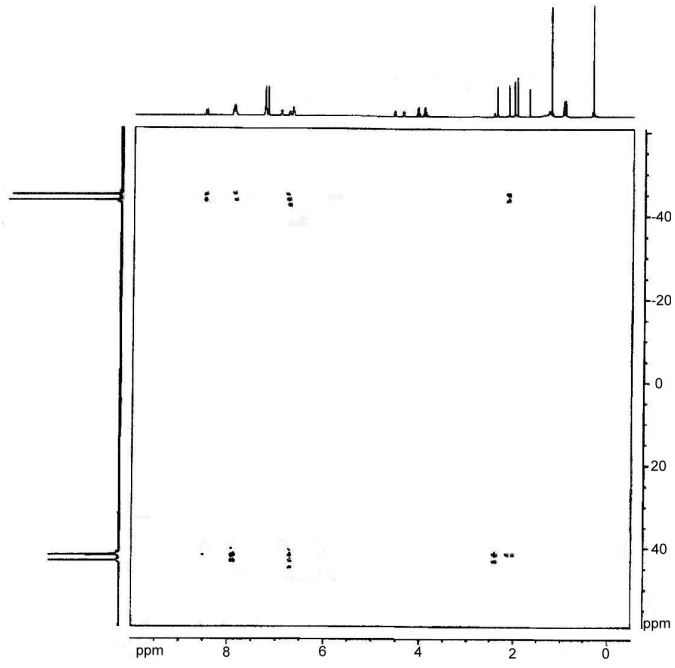
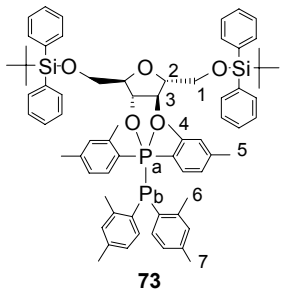


Figure 9. HMQC ^{31}P-^1H spectrum

The MS analysis showed that the highest peak, at m/z 1120.5, corresponded to a compound with a molecular composition of $C_{70}H_{82}P_2O_5Si_2$. A feasible structure, which fits all these experimental data, is proposed in Figure 10.



73

Figure 10

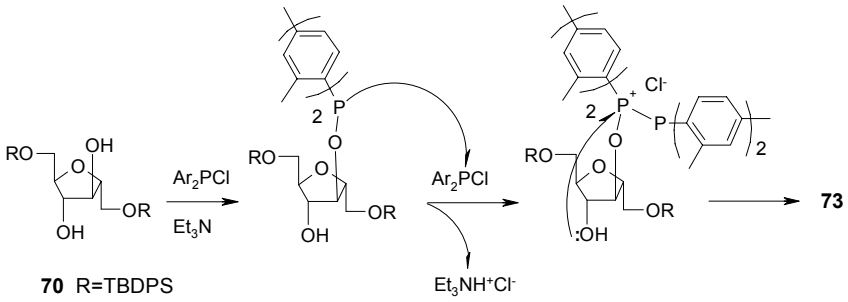
However, as can be observed in the ^{31}P-^{1}H spectrum (Figure 9), the couplings between Pa-H3 and Pa-C3 through the oxygen atom were not detectable. The ^{31}P-^{1}H and ^{31}P-^{13}C couplings depen on the molecular geometry and in particular of the dihedral angle, the hybridisation of phosphorus (P^{III}, P^{IV+}, P^{V}), the hybridisation of carbon, and the substituents attached to these atoms [47]. There are several experimental Karplus type curves for the geometrical dependence of ^{31}P-^{1}H couplings, mainly in derivatives of trivalent phosphorus [47]. Thus, it is possible that the geometrical arrangement of the molecule and its dihedral angles give values of $^{3}J(P\text{-O-C-}H3)$ and $^{2}J(P\text{-O-}C3)\approx 0$ Hz.

There are several examples in the literature of compounds of the type R_2P-$P(O)R_2$ [47] (R=Ph, $J_{P\text{-}P}$=224 Hz, δP^{III}=21.6 ppm and δP^{V}=-36.9 ppm) with P^{III} and P^{V} that have coupling constants and chemical shifts similar to those shown by **73**. Examples of P^{V} compounds of the type $P(OR)_2R_3$ or $P(OR)_5$ [47] show the following chemical shifts: $P(OEt)_2(Ph)_3$ δP^{V}=-55 ppm; $P(OMe)_5$ δP^{V}=-67 ppm;

$P(OPh)_5$ δP^V=-85 ppm, which are also in agreement with the chemical shift of P^V in compound **73**.

Scheme 9 shows a plausible mechanism for the formation of compound **73**. Firstly, the expected nucleophilic attack of one hydroxyl group on the diarylchlorophosphine takes place. Subsequently, however, it is the attached phosphorus atom that acts as a nucleophile toward a second molecule of the diarylchlorophosphine. Under specific reaction conditions it may be possible to favour the selective attack of the phosphorus atom, and not the remaining hydroxyl group, on a second electrophile reagent. The bulkiness of the bis(2,4-dimethylphenyl)chlorophosphine reagent may be responsible for the selectivity observed, increasing the difference in the reaction rate between the two hydroxyls.

Phosphorus atom, like all elements of the third period, is characterized by having rather diffuse frontier orbitals, which favour long-range interactions and the formation of P-P bonds [48]. They can also act as both nucleophiles or electrophiles. Finally, the nucleophilic attack of the oxygen atom on P^{IV+} gives compound **73** by removing HCl.



Scheme 9

In an attempt to prevent compound **73** from forming and to continue exploring new synthetic procedures of preparing **66c** and **67**, we also tried to build

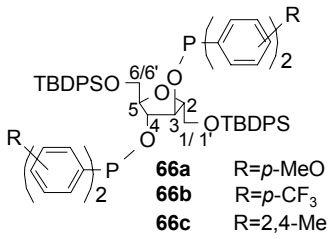
the bond P-O directly from the corresponding aminophosphine **63c** in toluene at 110°C [41]. However, a complicated mixture of compounds was obtained which could not be purified (Table 3, entry 3).

Treating diol **70** with the aminophosphine **63c** and 1*H*-tetrazol in the standard conditions [42] it was possible to obtain a mixture of di- and monosubstitute ligands. Ligands **66c** and **67** were isolated by column chromatography in a ratio 1/3 (Table 3, entry 4). Several attempts were made to force the reaction into the total conversion of the disubstituted compound **66c** (Table 3, entries 4-6). When the temperature and reaction time were increased, only the starting material was recovered. This seems to indicate that the reaction is reversible in this conditions (Table 3, entry 5). When we used a higher number of equivalents of aminophosphine **63c** and 1*H*-tetrazole the ratio was 1/1, but we could not exclusively obtain the disubstituted compound **66c**.

The diphosphinite ligands **66a-c** displayed the expected pattern for C_2-symmetric compounds. The $^{31}P\{^1H\}$ NMR spectra displayed only one signal between 110.5-115.1 ppm, which agreed with the expected chemical shift for phosphinite compounds. Simple ^1H and $^{13}C\{^1H\}$ NMR spectra showed three groups of signals in the region corresponding to the tetrahydrofuran backbone (H1/H1'=H6/H6'; H2=H5; H3=H4 and C1=C6; C2=C5; C3=C4) (Table 4). The most significant difference in the chemical shift was observed for H3 and C3, which appear at higher δ than in diol **70** (Δδ=0.6-0.8 in ^1H NMR spectra and Δδ=5-6 ppm in ^{13}C NMR spectra). The couplings between H3 and the phosphorus atom are observable through the oxygen ^3J(*P*-O-C*H*). Also some signals in the $^{13}C\{^1H\}$ NMR spectra show multiplicity due to the coupling with the phosphorus atom (^2J(P-O-C3) and ^3J(P-O-C-C2)). However, the value of the coupling constants could not always be determined because the NMR spectra were second-order spectra. The signals were unambiguously assigned by bidimensional experiments (HSQC and COSY) and the proposed structures were also confirmed by MS

spectrometry. Table 4 collects the ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR data for ligands **66a-c**.

Table 4. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR data for ligands **66a-c** recorded in $CDCl_3$



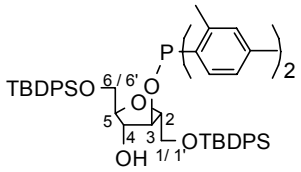
^{1}H NMR (ppm)	**66a**[a]	**66b**	**66c**
Arom	7.76-6.63	7.65-7.25	7.55-6.70
H1/H1'	3.89 (dd) / 3.19 (dd) $^{2}J_{H1H1'}$=11.2 Hz, $^{3}J_{H1H2}$=4 Hz	3.82 (dd) / 3.62 (dd) $^{2}J_{H1H1'}$=11.2 Hz, $^{3}J_{H1H2}$=4 Hz	3.65 (dd) /3.54 (dd) $^{2}J_{H1H1'}$=10.8 Hz, $^{3}J_{H1H2}$=5.2 Hz
H2	4.39 (m)	4.18 (m)	4.09 (m)
H3	5.18 (m)	5.01 (m)	4.66 (m)
$C(C\underline{H}_3)_3$	1.13 (s)	1.05 (s)	0.74 (s)
MeO	3.17 (s) / 3.16 (s)	--	--
CF_3	--	--	--
2,4-$C\underline{H}_3$	--	--	2.14 (s), 2.13 (s), 2.12 (s), 2.11 (s)
$^{13}C\{^{1}H\}$ NMR (ppm)			
Arom	160.7-113.9	134.3-125.3	141.0-126.7
C1	64.1	63.6	64.2
C2	84.5	83.4	84.5
C3	85.0 (m)	86.2 (m)	85.5 (m)
$C(\underline{C}H_3)_3$	27.0	27.0	27.0
$\underline{C}(CH_3)_3$	19.4	19.5	19.4
MeO	55.3 / 55.2	--	--
CF_3	--	122.7	--
2,4-$\underline{C}H_3$	--	--	21.4 (b), 20.7 (d, $^{3}J_{C\text{-}P}$=7.74Hz), 20.52 (d, $^{3}J_{C\text{-}P}$=6.84Hz)
$^{31}P\{^{1}H\}$ NMR (ppm)	115.1	110.5	102.6

[a] ^{1}H NMR spectrum of **54a** was recorded in C_6D_6.

It is important to note that the phenyl rings attached to the phosphorus atom did not become equivalent, showing two different signals for the CH_3O and four different signals for the 2,4-CH_3 groups. The FAB MS analysis of **66a** and **66c** showed that the highest values of m/z were at 1129.3 and 1121.6 respectively, which corresponded to the M^+.

The structural elucidation of monodentate ligand **67** is supported by ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra (Table 5) as well as by the bidimensional COSY, HSQC and HMBC experiments and MS spectroscopy.

Table 5. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR data for ligand **67** recorded in $CDCl_3$



67

	^1H NMR (ppm)		$^{13}C\{^1H\}$NMR (ppm)
Arom	7.59-6.87	Arom	138.1-127.6
H1/H1'; H6/H6'	3.73-3.52 (m)	C1 / C6	64.7 / 64.1
H2	3.99 (br)	C2	83.9 (d, $^3J_{C2P}$=6 Hz)
H3	4.47 (m)	C3	86.0 (d, $^2J_{C3P}$=18 Hz)
H4	4.31 (br)	C4	78.0 (d, $^3J_{C4P}$=4.5 Hz)
H5	3.99 (br)	C5	85.0 (s)
$C(C\underline{H}_3)_3$	0.96 (s), 0.94 (s)	$C(\underline{C}H_3)_3$	27.2, 27.0
		$\underline{C}(CH_3)_3$	21.4, 21.5
2,4-$C\underline{H}_3$	2.30 (s), 2.17 (s), 2.11 (s), 2.06 (s)	2,4-$\underline{C}H_3$	20.5 (d, $^3J_{C-P}$=12.2Hz), 20,3 (d, $^3J_{C-P}$=12.3Hz), 19.6 (s), 19.5 (s)
OH	2.79 (br)		
$^{31}P\{^1H\}$NMR (ppm)	102.7		

The most relevant difference with respect to bidentate ligand **66c** is that monodentate ligand **67**, obviously, did not present C_2-symmetry. Therefore, the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra showed 6 groups of signals corresponding to the tetrahydrofuran backbone. Moreover, while C3 in $^{13}C\{^{1}H\}$ NMR spectrum displayed an increase of 6.3 ppm with regard to the diol **70**, C4 only varied by 1.69 ppm. The $^{31}P\{^{1}H\}$ NMR spectrum showed one signal at 102.7 ppm in agreement with the expected chemical shift.

The two upfield-shifted resonances for two *t*-butyl groups in a ratio 9:9 in the ^{1}H NMR spectrum indicated that these groups were not equivalent. Neither were the two phenyl rings attached to the phosphorus atoms equivalent. They showed four signals in a ratio 3:3:3:3 attributed to the 2,4-CH_3 groups. A correlation between the proton of the hydroxyl group and H4 was observed in the COSY spectrum.

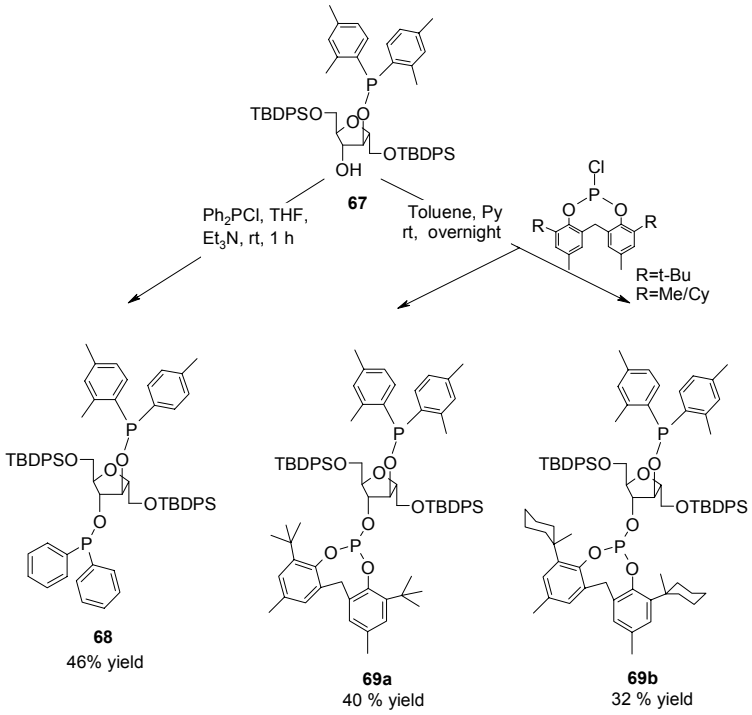
The FAB MS analysis showed the highest m/z value at 881.46 corresponding to the M^+.

Because of increasing interest in chiral non-C_2-symmetric bidentate ligands with electronically different phosphorus atoms [49], diphosphinites carrying two phosphorous atoms with quite different electron densities or phosphinite-phosphite are an attractive choice. Therefore, as well as testing the monodentate ligand **67** in catalysis, we decided to explore the synthesis of non-symmetrical ligands by introducing a second different phosphorous moiety (Scheme 10).

Three ligands with C_1 symmetry were prepared by standard methods [6,24]. The non-symmetrical diphosphinite **68** was obtained in moderate yield by reaction of **67** with diphenylchlorophosphine and triethylamine.

The phosphinite-phosphite ligands **69a** and **69b** were isolated after purification in 40% yield and 32% yield, respectively, after reaction of **67** with two different phosphorochlororidites ($(RO)_2PCl$) in a mixture of toluene and pyridine.

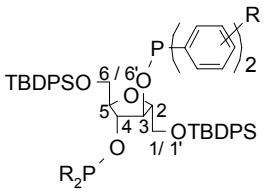
The phosphorochlororidites used had very bulky groups at the *ortho* position of the phenyl groups, but they incorporated a methylene group between the aromatic rings to give more flexible structures than those related to the bisphenol moieties [24] used in the synthesis of xylose ligands **35a-b** (Schemes 2 and 3).

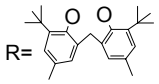
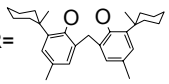


Scheme 10

The ligands **68** and **69a-b** were characterized by NMR techniques (^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H} and HSQC) showing C_1-symmetry pattern. Tables 7 and 8 summarize the NMR data for these ligands

Table 6. ^{1}H and $^{31}P\{^{1}H\}$ NMR data of **68**, **69a** and **69b** recorded in $CDCl_3$



68 R=Ph **69a** R=  **69b** R= 

^{1}H NMR (ppm)	**68**	**69a**	**69b**
Arom	7.67-6.91	7.69-6.73	7.71-6.74
H1/H1	3.75-3.57 (m)	3.98-3.72 (m)	4.01-3.74 (m)
H6/H6’	3.75-3.57 (m)	3.98-3.72 (m)	4.01-3.74 (m)
H2	4.17-4.11 (m)	4.30 (m)	4.30 (m)
H3	4.89-4.79 (m)	4.92 (m)	4.85 (m)
H4	4.89-4.79 (m)	5.79 (m)	5.67 (m)
H5	4.17-4.11 (m)	4.67 (m)	4.62 (m)
$SiC(C\underline{H}_3)_3$	1.10 (s), 1.00 (s)	1.04 (s), 0.98 (s)	1.05 (s), 0.97 (s)
2,4-$C\underline{H}_3$	2.25 (s), 2.23 (s), 2.19 (br), 2.14 (br)	2.31 (br, 2.28 (br), 2.26 (br), 2.26 (br)	2.36 (br), 2.28 (br), 2.24 (br), 2.29 (br)
CH_2	--	4.13 (d), 3.15 (d) ^{2}J=12.2 Hz	4.12 (d), 3.15 (d) ^{2}J=12.8 Hz
$C(C\underline{H}_3)_3$	--	1.29 (s), 1.22 (s)	--
p-$C\underline{H}_3$Ph	--	2.26 (s), 2.19 (s)	2.27 (s)
Cyclohexyl	--	--	1.54-1.12
$C\underline{H}_3$-Cy	--	--	1.16 (s), 1.09 (s)
$^{31}P\{^{1}H\}$NMR (ppm)	114.2, 102.7	127.9, 102.8	127.8, 103.2

The incorporation of a second different unit of phosphorus was corroborated by a second signal in the $^{31}P\{^{1}H\}$ NMR spectrum shifted in the region

for phosphite compounds and by the displacement of C4 in the $^{13}C\{^1H\}$ NMR spectrum ($\Delta\delta$=7.61 ppm in ligand **68** and 2.2 ppm in ligand **69a**) with regard to monodentate ligand **67**. Signals in the ^1H and $^{13}C\{^1H\}$ spectra corresponding to aromatic, *t*-butyl, cyclohexyl and methyl fragments confirmed that a new phosphorus fragment had been incorporated. In ligands **69a** and **69b**, the two protons of the bridged methylene group appeared as diastereotopics with $\Delta\delta\approx$1ppm in their chemical shift.

The FAB MS analysis of **69a** showed a peak at m/z 1249.12 corresponding to the M^+ ($C_{77}H_{94}O_7P_2Si_2$).

Table 7. $^{13}C\{^1H\}$ NMR data of **55** and **56a** recorded in $CDCl_3$

$^{13}C\{^1H\}$NMR (ppm)	**68**	**69a**
Arom	139.3-127.9	145.6-126.8
C1 / C6	64.1 (s), 63.9 (s)	64.3, 63.9
C2	84.3 (m)	85.2
C3	85.6 (m)	85.9 (m)
C4	85.6 (m)	80.3 (m)
C5	84.3 (m)	85.4
$SiC(\underline{C}H_3)_3$	26.8	27.0 (s), 26.9 (s)
$\underline{SiC}(CH_3)_3$	19.4	19.4
2,4-$\underline{C}H_3$	21.3, 20.7 (d), 20.6 (d) $^3J_{C\text{-}P}$=13.7Hz	21.3 (s), 20.8 (d), 20.6 (d) $^3J_{C\text{-}P}$=13.7Hz
$\underline{C}H_2$	--	34.8
$C(\underline{C}H_3)_3$	--	31.2 (s), 31.1 (s)
$\underline{C}(CH_3)_3$	--	19.5 (s)
p-$\underline{C}H_3Ph$	--	21.5 (s), 21.4 (s)

3.2.3. Asymmetric Hydrogenation of Imines

As has been discussed in Chapter 1, the asymmetric hydrogenation of imines is of interest for obtaining enantiomerically enriched amines. Rhodium and iridium cationic systems bearing diphosphines have proved to be highly effective at reducing ketimines. Therefore, only few rhodium/diphosphinite or rhodium/diphosphite systems have been used in the reduction of acyclic imines [16].

Xylose- and mannitol-diphosphinites (**5, 56a, 66a-c, 68**), xylose-diphosphites (**35a-b**) and mannitol-phosphinite-phosphites (**69a-b**) have been used in the iridium-catalysed asymmetric hydrogenation of acyclic and cyclic ketimines to evaluate their potential as ligands in the reduction of C=N (Figure 11).

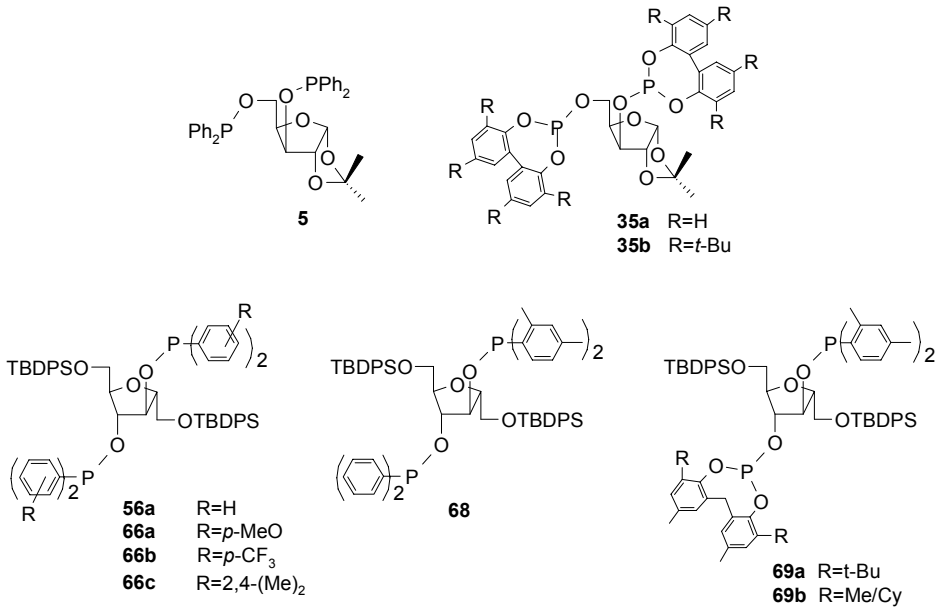
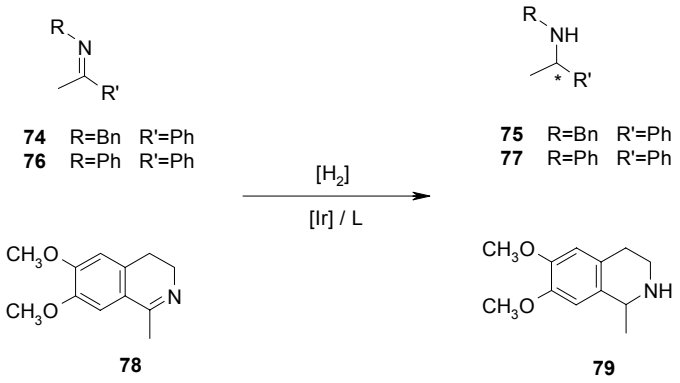


Figure 11

Two acyclic imines were chosen as model substrates to be reduced, *N*-(phenylethylidene)benzylamine (**74**) and *N*-(phenylethylidene)aniline (**76**). The reduction of cyclic imine 6,7-dimethoxyl-1-methyl-3,4-dihydroisoquinoline (**78**), in which the geometry of the C=N double bond is fixed to *E*-configuration was also studied (Scheme 11).



Scheme 11

First, we focused on the asymmetric hydrogenation of a representative non-cyclic ketimine, *N*-(phenylethylidene)benzylamine (**74**). Imine **74** has been reduced satisfactorily (ee higher than 78%) mainly with iridium systems based on diphosphines such as BINAP [50] or cationic iridium precursors containing NP ligands such as diphenylphosphinooxazolines [51] ligands and more recently with an iridium system formed by $[Ir(COD)Cl]_2$ and a phosphine oxide as ligand [52]. Besides, rhodium catalysts containing diphosphinites gave enantioselectivities up to 72% [16].

The hydrogenation of **74** was carried out using the cationic iridium complexes **65a-c** as catalytic precursors. The catalytic precursors $[Ir(COD)(L)]BF_4$ (**65a-c**; L= **5**, **35a**, **35b**) (Scheme 4, p. 112) were tested at several hydrogen

pressures and with various solvents. Catalysts **65a-c** were active at 25-100 bar of hydrogen and 25ºC and provided complete hydrogenation into amine **75** in 16 hours. The cationic iridium precursor **65b** did not provide enantioselectivity in any conditions, even when different solvents (MeOH, CH_2Cl_2) and pressures were tested. Only with catalyst precursors **65a** and **65c** were moderate ee obtained, 46 and 21%, respectively. However, we found that in the hydrogenation of **74** with these catalytic systems, the ee values were not reproducible, even when the conditions were strictly maintained. It has been previously reported that ee's obtained in the asymmetric hydrogenation of *N*-(phenylethylidene)benzylamine are poorly reproducible [16,53].

Having established in the above experiments the conditions in which imine **74** is most likely to be reduced, we performed a broad ligand screening. We were also interested in investigating the reproducibility of the results in the hydrogenation of imine **74** with other catalytic systems.

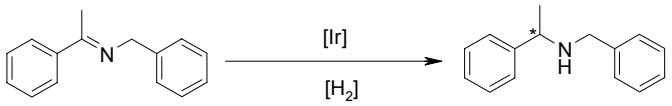
The criteria for choosing the most appropriate precatalyst were how it affected the activity and the enantioselectivity of the system. So we studied the influence of the catalyst precursor. Imine **74** was reduced by systems generated *in situ* from both $[Ir(COD)Cl]_2$ and $[Ir(COD)_2]BF_4$ by adding diphosphinites (**56a**, **66a-b**, **68**) and phosphinite-phosphite (**69a**) (Table 8).

These systems were active in reducing imine **74** and provided conversions between 70-100% within 16 hours at 70 bar of H_2 pressure in CH_2Cl_2. However, hydrogenolysis products were also detected together with the desired secondary amine **75**, because of the cleavage of the nitrogen-benzylic bond, which decreased selectivity [54]. The $[Ir(COD)_2]BF_4$/L systems provided worse selectivities than $[Ir(COD)Cl]_2$/L with values lower than 85% (Table 8, entries 6-10).

Most of these systems did not provide enantiocontrol in the hydrogenation of **74**. Only the system formed by $[Ir(COD)_2]BF_4$ and phosphinite-phosphite **69a** gave a noteworthy ee of 73% (Table 8, entry 10). Moreover, it is important to note

that whereas no enantioselectivity was achieved using $[Ir(COD)Cl]_2$/**69a**, the system formed by $[Ir(COD)_2]BF_4$/**69a** proved to be superior in terms of enantioselectivity, and produced the chiral amine **75** rather effectively (Table 8, entries 5 and 10). The findings show that the precatalysts are important if a high degree of enantioselectivity is desired [55].

Table 8. Hydrogenation of **74** with Ir/L catalytic systems. Effect of the precatalyst [a]



74 **75**

Entry	Precatalyst	Conv [%]	Selec [%]	Ee[b] [%]
1	$[Ir(COD)Cl]_2$/**56a**	100	95	0
2	$[Ir(COD)Cl]_2$/**66a**	74	85	0
3	$[Ir(COD)Cl]_2$/**66b**	93	92	5 (-)
4	$[Ir(COD)Cl]_2$/**68**	100	90	0
5	$[Ir(COD)Cl]_2$/**69a**	100	90	0
6	$[Ir(COD)_2]BF_4$/**56a**	82	76	9 (-)
7	$[Ir(COD)_2]BF_4$/**66a**	70	68	0
8	$[Ir(COD)_2]BF_4$/**66b**	85	76	11 (-)
9	$[Ir(COD)_2]BF_4$/**68**	82	68	6 (+)
10	$[Ir(COD)_2]BF_4$/**69a**	100	85	73 (-)

[a]Reaction conditions: 1% mol [Ir], 1.25 % mol ligand, 70 bar H_2, 16 h, 25ºC, CH_2Cl_2 [b] absolute configuration was not determined

The mannitol-based ligands **69a-b** have C_1-symmetry, bulky groups in the *ortho* positions of the aryl rings and combine the electronic properties of phosphinite and phosphite functionalities. The seven-membered Ir(I)-chelate based

on phosphinite-phosphite ligands **69a-b** provided better results than the more conformationally flexible eight-membered Ir(I) chelate based on diphosphinite **5** or diphosphite **35b**. So, the accurate tuning of structural and electronic parameters makes the Ir(I)/mannitol-based phosphinite-phosphite systems the most suitable of all the catalysts tested in this study to reduce imine **74** satisfactorily.

We also studied the effect of temperature and additives on both activity and enantioselectivity in the hydrogenation of **74** using the catalyst $[Ir(COD)_2]BF_4$/**69a-b** (Table 9). Several reports have shown that additives may improve catalytic activity and enantioselectivity [56]. Halides [57] and amines are the most widely used additives [50].

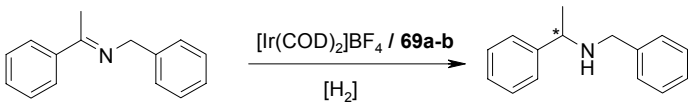
When **74** was hydrogenated with the catalyst $[Ir(COD)_2]BF_4$/**69a** at shorter reaction times or at lower temperatures (0ºC) (Table 9, entries 2 and 3), the activity of the catalytic system and the optical yield decreased. After half an hour, conversion was only 24% resulting in a TOF[h^{-1}]=48 (TOF= turnover frequency) (Table 9, entry 2). The lower enantiomeric excess obtained at shorter times or lower temperatures suggests that the catalytic species responsible for enantiocontrol needs longer times or higher temperatures to be formed.

The results obtained with catalysts $[Ir(COD)_2]BF_4$/**69a** and $[Ir(COD)_2]BF_4$/**69b** are depend heavily on the presence of iodide ions. Addition of Bu_4NI deactivates the catalyst and causes a sharp decrease in conversion and enantioselectivity (Table 9, entries 1, 4, 9, 10).

I_2 also had a dramatic effect on the selectivity and enantioselectivity of the catalytic system. The selectivity in the desired amine **75** decreased spectacularly and favoured the hydrogenolysis of amine **75** (Table 9, entries 5, 11). Besides, the ee dropped to almost zero when the experiments were carried out in the presence of 10% mol of I_2 at 25ºC (Table 9, entries 5 and 11). The combination of a lower temperature (0ºC) and the addition of I_2 resulted in a considerable variation in the

optical yield, favoring the formation of the opposite enantiomer in 76% ee (Table 9, entry 6).

Table 9. Hydrogenation of **74** with $[Ir(COD)_2]BF_4$ / **69a**, **69b**. Study of the effect of temperature and additive[a]



74 **75**

Entry	Ligand	Additive[b]	Temp. [ºC]	Time [h]	Conv [%]	Selec [%]	Ee[c] [%][c]
1	**69a**	--	25	16	100	85.5	73 (-)
2	**69a**	--	25	0.5	24	100	68 (-)
3	**69a**	--	0	2	4.3	100	40 (-)
4	**69a**	Bu_4NI	25	16	9.5	100	16 (-)
5	**69a**	I_2	25	16	100	17	1.4 (-)
6	**69a**	I_2	0	2	1.4	100	76 (+)
7	**69a**	Phthalimide	25	16	100	89	75 (-)
8	**69a**	$BnNH_2$	25	16	97	91	76 (-)
9[d]	**69b**	--	25	2	17	93	52 (-)
10	**69b**	Bu_4NI	25	16	9	100	11 (-)
11	**69b**	I_2	25	16	100	87	0
12	**69b**	Phthalimide	25	16	63	100	54 (-)
13	**69b**	$BnNH_2$	25	16	91	81	58 (-)

[a] Reaction conditions: 1% mol catalyst, 1.2% mol ligand, 70 bar H_2, 25ºC, 16h, CH_2Cl_2 [b] 10% mol additive [c] absolute configuration was not determined [d] 30 bar H_2

These findings allow us to speculate about the role of the iodide. Since the imine is coordinated to the metal by one of the two enantiotopic faces, the addition of iodide must influence the opposite coordinating mode of the imine [58], which is more selective at low temperatures when the conformational mobility of the system is reduced.

The addition of amine derivatives did not have a very strong influence, at least at 25ºC, and both conversion and enantioselectivity were maintained (Table 9, entries 7, 8, 12, 13). This indicates that amines, which are also the reaction products, do not deactivate the catalyst and conversion of the substrate is almost total.

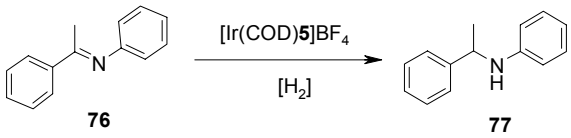
A rather broad ligand screening was also carried out with *N*-aryl imine **76**, which has a more constrained structure and is less basic than imine **74**. Imine **76** is very efficiently hydrogenated by iridium systems bearing the ferrocenyl-phosphine (*R,R*)-f-binaphane (ee up to 84%) and by the cationic iridium complexes with diphenylphosphinooxazolines (ee up to 89%) [51b,59].

The homogeneous catalysts were based on iridium and modified by adding different diphosphinite, diphosphite and phosphinite-phosphite ligands. The effect of pressure and temperature on the conversion to the amine, the optical yield and the effect of additives on these parameters were also investigated.

Initially we studied the hydrogenation of **76** at different pressures and temperatures using the complex [Ir(COD)**5**]BF_4 (**65a**) as catalyst precursor (Table 10). Enantioselectivities were best (57%) at low pressures (Table 10, entries 1-3). Curiously, a higher substrate/catalyst ratio and a lower temperature decrease the enantioselectivity (Table 10, entries 4 and 6). This dependence of the enantiomeric excess on the temperature has also been observed in the hydrogenation of **74**, which agrees with the hypothesis that the most enantioselective species needs higher temperatures if it is to be formed.

When Bu_4NI was used as additive at 0ºC, the enantioselectivity fell sharply and promoted the opposite enantiomer (Table 10, entry 7). Similar behaviour was also observed in the hydrogenation of **74** with [Ir(COD)$_2$]BF_4/**69a** at 0ºC, when I_2 was added (Table 9, entry 6).

Table 10. Hydrogenation of imine **76** using complex [Ir(COD)**5**]BF_4 (**65a**) as catalyst[a]



76 **77**

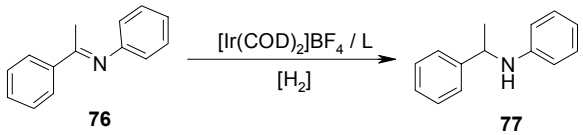
Entry	P [bar]	T [°C]	Additive	Conversion [%]	ee [%]
1	10	25	-	83	57 (*S*)
2	25	25	-	95	56 (*S*)
3	50	25	-	92	38 (*S*)
4[b]	50	25	-	20	22 (*S*)
5	85	25	-	98	30 (*S*)
6	25	0	-	85	20 (*S*)
7[c]	25	0	Bu_4NI	96	15 (*R*)

[a] Reaction conditions: 1% mol catalyst, 18 h, CH_2Cl_2 [b] 0.1% mol catalyst [c] 25% mol additive, 5 h

Imine **76** was also satisfactorily reduced to secondary amine **77** by systems generated *in situ* from $[IrCODCl]_2$/L and $[Ir(COD)_2]BF_4$/L (L=**35a-b**, **56a**, **66a-c**, **68**, **69a**) at 70 bar of H_2 pressure in CH_2Cl_2. Whereas the catalysts $[IrCODCl]_2$/L provided no noteworthy enantioselectivities (up to 10%), the $[Ir(COD)_2]BF_4$/L systems proved to be more enantioselective and gave ee values as high as 70% (Table 11, entry 5).

The catalytic system $[Ir(COD)_2]BF_4$/diphosphites **35a-b** were active in the hydrogenation of imine **76** (Table 11, entries 1 and 2), and selectively provided the amine **77.** They did not achieve enantioselectivity under these conditions, however.

Table 11. Hydrogenation of imine **76** using $[Ir(COD)_2]BF_4$ / L catalytic system. Effect of the additive [a]



76 **77**

Entry	Ligand	Time [h]	Additive[b]	Conv. [%]	Selec [%]	Ee[c] [%]
1	**35a**	16	--	40	100	0
2	**35b**	16	--	100	100	5 (-)
3	**56a**	16	--	100	100	65 (+)
4	**66a**	0.25	--	26	100	nd[d]
5	**66a**	1	--	98	100	70 (+)
6	**66a**	16	--	100	100	70 (+)
7	**66b**	16	--	100	100	31 (-)
8	**66c**	1	--	6	100	15 (-)
9	**68**	16	--	98	99	3 (+)
10	**69a**	16	--	99	100	0
11	**35a**	16	Bu_4NI	78	100	0
12	**35a**	16	I_2	100	100	0
13	**35b**	16	Bu_4NI	100	100	46 (-)
14	**35b**	16	I_2	100	100	31 (-)
15	**35b**	16	Phthalimide	49	96	9 (-)
16	**35b**	16	$BnNH_2$	10	71	7 (-)
17	**56a**	16	Bu_4NI	42	100	19 (-)
18	**56a**	16	I_2	100	100	10 (-)
19	**56a**	16	Phthalimide	98	100	66 (+)
20	**56a**	16	$BnNH_2$	52	97	42 (+)
21	**66a**	16	Bu_4NI	71.1	100	19 (+)
22	**66a**	16	I_2	100	100	5 (-)
23	**66a**	16	Phthalimide	99.3	100	70 (+)
24	**66a**	16	$BnNH_2$	43.6	94	52 (+)
25	**66b**	16	Bu_4NI	100	100	12 (+)
26	**66b**	16	I_2	100	100	4 (-)
27	**66b**	16	Phthalimide	99	100	9 (-)
28	**66b**	16	$BnNH_2$	25	90	10 (-)
29	**68**	16	Bu_4NI	58	100	15 (+)

[a] Reaction conditions: 1% mol $[Ir(COD)_2]BF_4$], Ratio 1% mol Ligand, 70 bar, 25ºC, 16 h, CH_2Cl_2 [b] 4% mol additive [c] absolute configuration was not determined. [d] not determined

The systems $[Ir(COD)_2]BF_4$/diphosphinite (**56a, 66a-b**) afforded enantioselectivities between 31-70% (Table 11, entries 3-7), whereas the Ir(I) systems carrying the diphosphinite ligand **66c**, which introduces methyl groups into the aromatic rings to increase either the electron density on phosphorus or the steric hindrance, only afforded 6% conversion and 15% ee in 1 hour (Table 11, entry 8).

The cationic iridium complex with C_1-diphosphinite **68** and phosphinite-phosphite **69a** provided racemic mixtures (Table 11, entries 9 and 10).

The most striking result in Table 11 is the value of ee obtained with $[Ir(COD)_2]BF_4$ and the more electron-donor ligand **66a** (up to 70%) (Table 10, entries 5 and 6). The substrate was almost completely reduced within 1 hour. The more electron-donor properties of ligand **66a,** which incorporates a methoxy group into the aromatic rings, may be the reason for this higher activity.

Whereas $[Ir(COD)_2]BF_4$/**56a** provided an ee of 65% under these conditions (Table 11, entry 3)**,** the catalyst based on $[Ir(COD)_2]BF_4$ and the less donor ligand **66b** gave low enantioselectivities and promoted the formation of the opposite enantiomer (Table 11, entry 7).

It should be pointed out that of all the ligands presented in this study, diphosphinite ligands provided the best results for the iridium-catalysed reduction of the *N*-aryl imine **76** affording moderate ee's (Table 10, entry 1: Ir(I)/diphosphinite **9** up to 57%; and Table 11 entries 3, 5, 7: Ir(I)/diphosphinite **66a** up to 70%)).

The seven-membered Ir(I)-chelate based on the mannitol derivative ligand **66a** provided better results than the eight-membered Ir(I)-chelate based on the xylose derivative ligand **9**. Of the mannitol derivative diphosphinites, the more electron donor diphosphinite **66a** provided more enantioselective Ir(I) catalysts (Table 11, entry 5).

These findings suggest that the electronic parameters of the ligands have a considerable effect on the enantiomeric excess. Imine **76**, which is less basic than

imine **74**, may require more electron donor catalytic systems able to increase the d-π* back-donation between the metal and the coordinated imine, resulting in a more rigid metal-imine η^2 chelation and enhancing the optical yield [14,15].

The effect of adding halide ions or amine derivative to these catalytic systems was also examined.

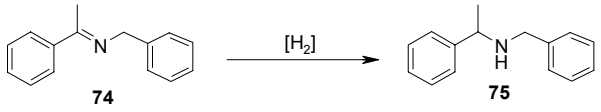
The addition of Bu_4NI or iodine to the catalyst $[Ir(COD)_2]BF_4$/**35a** improved conversion but did not modify the ee (Table 11, entries 1, 11 and 12). However, when Bu_4NI was used as additive together with $[Ir(COD)_2]BF_4$/**35b**, the optical yield increased to 46% ee (Table 11, entries 2 and 13). Iodine also improved the enantiomeric excess, but not as much as Bu_4NI (Table 11, entry 14). Phthalimide and benzylamine were also used as additives, but they promoted the deactivation of the catalytic system, probably by poisoning the catalyst (Table 11, entries 15 and 16). This confirms the importance of additives in the asymmetric hydrogenation of imines and shows for the first time that diphosphite ligands with iridium systems can also provide ee in this process.

When Bu_4NI or I_2 were added to $[Ir(COD)_2]BF_4$/**56a, 66a-b**, the enantioselectivity dropped sharply (Table 11, entries 17, 18, 21, 22, 25, 26), favouring the formation of the reduced product with the opposite configuration. This behaviour seems to be general for the hydrogenation of acyclic imines **74** and **76** with these catalytic systems when iodine derivatives are used as additives.

The $[Ir(COD)_2]BF_4$/**68** catalyst became enantioselective when Bu_4NI was added achieving 15% ee (Table 11, entries 9 and 29).

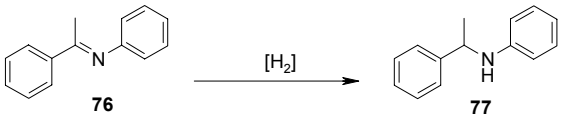
In general, when amines were used as additives there was no notable effect on the enantioselectivity. Nevertheless, the addition of benzylamine slowed the reaction down considerably and the activity of the catalytic system decreased, probably because of an irreversible coordination of the primary amine that occupied free sites and poisoned the catalyst.

To sum up, the combination of the electronic and structural characters of the ligands and Ir(I) complexes must be optimal for each *N*-aryl imine, which shows the limited substrate scope of this reaction. Nevertheless, in general when iodine derivatives are added to the Ir(I)/L catalysts in the reduction of both imines, the formation of the opposite enantiomer is promoted. Scheme 12 collects the best results obtained here in the asymmetric reduction of imines **74** and **76** with Ir(I) / *P*-donor ligands based on D-xylose and D-mannitol backbones.



74 **75**

[Ir(COD)$_2$]BF$_4$/**69a**	100% conv., 73% ee (-)
[Ir(COD)$_2$]BF$_4$/**69a**/I$_2$	76% ee (+)
[Ir(COD)$_2$]BF$_4$/**69b**	52% ee (-)
[Ir(COD)**5**]BF$_4$	97% conv., 46% ee
[Ir(COD)**35b**]BF$_4$	95% conv., 21% ee



76 **77**

[Ir(COD)$_2$]BF$_4$/**56a**	100% conv., 65% ee (+)
[Ir(COD)$_2$]BF$_4$/**66a**	98% conv., 76% ee (+)
[Ir(COD)**5**]BF$_4$	83% conv., 57% ee
[Ir(COD)**35b**]BF$_4$/Bu$_4$NI	100% conv. 46% ee

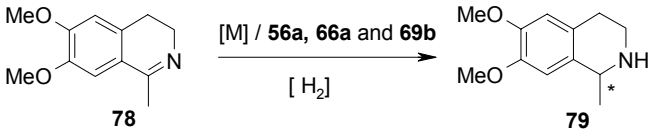
Scheme 12

We next turned our attention to the hydrogenation of imine **78**. This substrate is one of the most typical cyclic imines reported in the literature and is reduced principally by iridium and rhodium complexes with diphosphines at high H_2 pressure [60,49b,56a].

A preliminary screening of the reduction of **78** with both [M(COD)Cl]$_2$ and [M(COD)$_2$]BF$_4$ (M=Rh or Ir) using diphosphinites (**56a, 66a-c**) and diphosphinite-

phosphite ligands (**69a-b**) showed that, although all the systems were active, the enantiomeric excesses were lower than 10% in almost all cases. Table 12 collects some of the results obtained in the hydrogenation of **78** by $[M(COD)Cl]_2$ and $[M(COD)_2]BF_4$ (M=Rh or Ir) using diphosphinites (**56, 66a-c**) and diphosphinite-phosphite ligands (**69a-b**).

Table 12. Hydrogenation of **78** with $[M(COD)Cl]_2$ and $[M(COD)_2]BF_4$ (M=Rh or Ir)./ **56a**, **66a**, **69b**[a]



78 **79**

Entry	Ligand	Precursor	Conv. [%]	Ee[b] [%]
1	**56a**	$[Ir(COD)Cl]_2$	34	3 (+)
2	**66a**	$[Ir(COD)Cl]_2$	84	15 (+)
3	**69b**	$[Rh(COD)_2]BF_4$	2	30 (-)
4[c]	**69b**	$[Ir(COD)_2]BF_4$	43	4 (+)

[a] 1% catalyst, 1.2% mol Ligand, 70 bar, 25ºC, 16 h, CH_2Cl_2. [b] absolute configuration was not determined. [c] 20 h

The Ir(I) catalysts based on diphosphinite **56a** did not achieve enantioselectivity. However, the catalyst $[Ir(COD)_2]BF_4$, which bears the more donor diphosphinite ligand **66a**, gave an ee of 15%.

While the catalyst $[Ir(COD)_2]BF_4$/phosphinite-phosphite ligand **69b** provided 43% conversion and a racemic mixture, $[Rh(COD)_2]BF_4$/**69b** was less active but gave 30% ee (Table 12, entry 3, 4).

3.2.4. Asymmetric Hydrogenation of Enamides

The rhodium-catalysed asymmetric hydrogenation of α-arylenamides has recently attracted considerable attention [61]. Impressive results have been achieved with rhodium catalysts and diphosphines such as Me-DUPHOS [61b], Me-BPE [61], (R,R)-binaphane [62] and DIOP [61g], with enantioselectivities as high as 99%. Many groups have recently reported the use of monodentate ligands such as monophosphoramidites [40a,63], monophosphonites [64] and monophosphites [40g,d-f] as highly efficient ligands for the rhodium-catalysed enantioselective reduction of enamides.

Diphosphinites (**56a, 66a-b, 68**), diphosphites (**35a-b**), phosphinite-phosphite (**69a**) and monophosphinites (**60**, **67**) have been used in the rhodium-catalysed asymmetric hydrogenation of α-arylenamides (Figure 12).

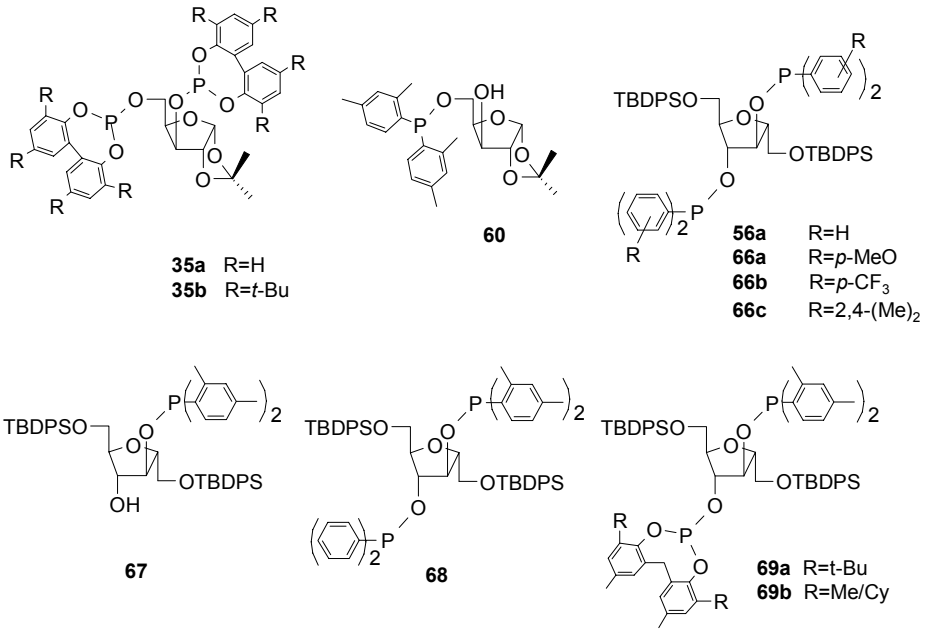
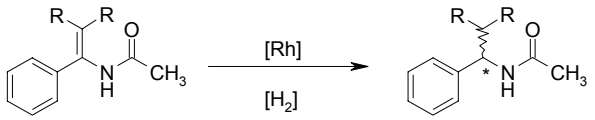


Figure 12

Initial experiments focused upon α-arylenamide **80**, and then went on to examine the tetrasubstituted α-arylenamide **82** (Scheme 13).

Firstly, several experiments were performed to screen the optimal conditions for hydrogenating *N*-acetylphenylethenamine **80.** Several rhodium catalyst precursors were checked: $[Rh(NBD)_2]PF_6$ (NBD=nobornadiene); $[Rh(COD)_2]X^-$ (COD=1,5-cyclooctadiene, X=BF_4 or OTf); $[Rh(COD)Cl]_2$; with bidentate ligands at 3.5 bar of H_2 pressure in CH_2Cl_2. Table 13 collects the most interesting results.



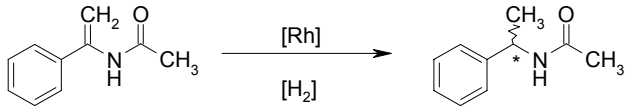
80 R=H
82 R=Me

81 R=H
83 R=Me

Scheme 13

$[Rh(NBD)_2]PF_6$ and $[Rh(COD)_2]X^-$ (X=BF_4 or OTf) were found to be more effective catalyst precursors than a neutral Rh species $[Rh(COD)Cl]_2$) [61a,d,e]. They provided the reduced product **81** in high conversions and selectivities, and moderate enantioselectivities (Table 13). In general, the differences in the ee values achieved with different cationic Rh(I) precursors are not considerable. In the literature, it is generally accepted that the well known hydrogenation with cationic rhodium(I) of the diolefin COD takes place more slowly than the hydrogenation of NBD [65] and the hydrogenation of this diolefinic ligands must takes place before the prochiral substrate [66]. In general, the differences between the rhodium(I) precursors containing COD or NBD ligands were not great. However, the catalysts $[Rh(NBD)_2]PF_6$/**35b**/**56a**/**68** were more active than the analogues precatalysts bearing COD instead of NBD (Table 13, entries 3, 4, 5, 7, 13, 14).

Table 13. Hydrogenation of **80** with Rh(I)/L. Effect of precursor[a]



80 **81**

Entry	Ligand	Precursor	Conv [%]	Selec [%]	ee[b] [%]
1	**35a**	$[Rh(NBD)_2]PF_6$	98	95	0
2	**35a**	$[Rh(COD)_2]BF_4$	>99	>99	3 (+)
3	**35b**	$[Rh(NBD)_2]PF_6$	95	83	32 (+)
4	**35b**	$[Rh(COD)_2]BF_4$	31	79	35 (+)
5	**56a**	$[Rh(NBD)_2]PF_6$	100	100	48 (-)
6	**56a**	$[Rh(COD)_2]BF_4$	99	99	44 (-)
7	**56a**	$[Rh(COD)_2]OTf$	59	96	40 (-)
8	**66a**	$[Rh(NBD)_2]PF_6$	>99	99	33 (-)
9	**66a**	$[Rh(COD)_2]BF_4$	95	99	35 (-)
10	**66a**	$[Rh(COD)_2]OTf$	90	99	28 (-)
11	**66b**	$[Rh(COD)_2]BF_4$	99	98	22 (+)
12	**66b**	$[Rh(COD)_2]OTf$	95	93	50 (+)
13	**68**	$[Rh(NBD)_2]PF_6$	>99	98	20 (-)
14	**68**	$[Rh(COD)_2]BF_4$	41	90	20 (-)
15	**69a**	$[Rh(NBD)_2]PF_6$	99	98	22(-)
16	**69a**	$[Rh(COD)_2]BF_4$	>99	99	31 (-)
17	**69a**	$[Rh(COD)_2]OTf$	>99	98	27 (-)
18	**69a**	$[Rh(COD)Cl]_2$	8	39	25 (-)

[a] Reaction conditions: 1% mol $[Rh(olefin)_2]X$, 0.5% mol $[Rh(COD)Cl]_2$, 1.2% mol ligand, 3.5 bar H_2, CH_2Cl_2, 25ºC, 16 h [b] absolute configuration was not determined.

The systems based on $[Rh(COD)Cl]_2$ bearing diphosphites **35a-b** or diphosphinites **56a, 66a-b** and **68** gave low conversions and selectivities and values of ee<5% in almost all cases.

While Rh(I)/**35a** catalysts provided racemic mixtures (Table 13, entries 1, 2), Rh(I)/**35b** produced the reduced product **81** with optical yields up to 35%. (Table 13, entries 3, 4). %. It seems that bulky *tert*-butyl groups must be present in the *ortho* positions of the biphenyl moiety of diphosphite **35b** if enantioselectivities are to be provided, as was previously found in the hydrogenation of dehydroaminoacid derivatives [27b] and in imine reductions (see section 3.2.3).

The electronical variation of the diphosphinite ligands **56a**, **66a-b** in the Rh-catalysed reduction of **80** did not cause dramatic changes in the enantioselectivity (Table 13, entries 5-12). Nevertheless, Rh(I)/**56a** generally gave slightly higher ees than the more electron donor catalyst Rh(I)/**66a** or the less electron donor catalyst Rh(I)/**66b** (Table 13, entries 6, 9 and 11).

The catalyst based on $[Rh(COD)_2]X$ (X=PF_6 or BF_4) bearing the C_1-diphosphinite **68** provided ee's up to 20%. However, the activity of the system was higher when the counterion PF_6 was used instead of BF_4 (Table 13, entries 13 and 14).

Although the **69a**-$[Rh(olefin)_2]X$ (olefin=NBD or COD; X=PF_6, BF_4 or OTf) catalysts satisfactorily reduced the α-arylenamide **80** with high conversions (>99%), the enantioselectivities were only between 22-31%. The catalyst $[Rh(COD)Cl]_2$/**69a** provided an ee of 25%. The conversion and selectivity, however, were low (Table 13, entry 18).

We next turn our attention to the asymmetric hydrogenation of **80** catalysed by rhodium-monodentate phosphinite complexes. Recently many papers have described highly enantioselective Rh catalysts containing chiral monodentate phosphonites [40d,64], phosphites [40d-g] or even phosphoroamidites [40a,67]. However, as far as we know there are no reports of the Rh(I)-catalysed asymmetric hydrogenation of α-arylenamides using monophosphinite ligands.

Initially, we performed a screening in order to establish the most suitable rhodium precursor. Surprisingly, whereas the catalysts $[Rh(olefin)_2]X$

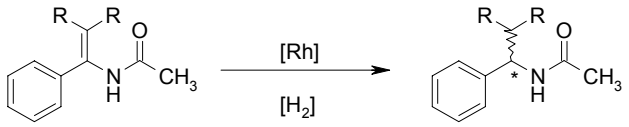
(olefin=NBD or COD; X=PF_6, BF_4 or OTf) bearing the monophosphinites **60** or **67** did not provide any noteworthy enantioselectivities, $[Rh(COD)Cl]_2$/**60** or **67** catalysts gave ee's up to 76 and 63%, respectively (Table 14, entries 1-4 and 9-12). However, the conversions and the selectivities achieved using the neutral rhodium precursor were very low (Table 14, entries 4 and 12).

As expected, when the hydrogen pressure was increased, the conversion was higher or even complete within 16 hours, and the selectivity of the desired compound **81** was total (Table 14, entries 5, 6 and 13). Moreover, at higher H_2 pressure the enantiomeric excess was maintained or improved.

A slight improvement was observed when the experiment was carried out at low temperature (0ºC), even though the reactivity of the catalytic system was decreased (Table 14, entry 8).

The fact that the selectivity of the process depends on the hydrogen pressure suggests that there is a possible isomerization process under the catalytic conditions. Rhodium catalysts should favor the isomerization of α-arylenamide **80** to imine **84**, which is also capable of being reduced to give secondary amine **81** (Scheme 13). Whereas at high H_2 pressure both compounds **80** and **84** were reduced satisfactorily, at low H_2 pressures only **80** is reduced to give a mixture of the desired amine **81** and imine **84**.

Table 14. Hydrogenation of **80** and **82** with Rh(I)/monophosphinites **60** and **67**

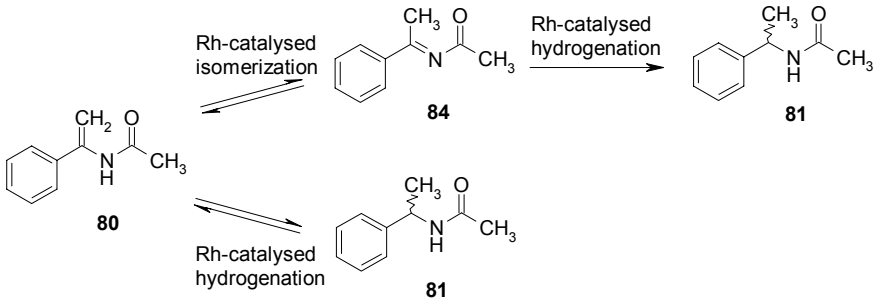


80 R=H
82 R=Me

81 R=H
83 R=Me

Entry	Enamide	Ligand	Precursor	H_2 [bar]	Conv [%]	Selec [%]	ee[b] [%]
1	**80**	**60**	$[Rh(NBD)_2]PF_6$	3.5	21	68	5 (+)
2	**80**	**60**	$[Rh(COD)_2]BF_4$	3.5	nd	nd	nd
3	**80**	**60**	$[Rh(COD)_2]OTf$	3.5	97	95	9 (+)
4	**80**	**60**	$[RhCODCl]_2$	3.5	6	52	76 (+)
5	**80**	**60**	$[RhCODCl]_2$	30	86	100	75 (+)
8[c]	**80**	**60**	$[RhCODCl]_2$	30	1	100	82 (+)
6	**80**	**60**	$[RhCODCl]_2$	70	100	100	79 (+)
7[d]	**80**	**60**	$[RhCODCl]_2$	70	100	100	75 (+)
9	**80**	**67**	$[Rh(NBD)_2]PF_6$	3.5	99	97	18 (-)
10	**80**	**67**	$[Rh(COD)_2]BF_4$	3.5	15	73	19 (-)
11	**80**	**67**	$[Rh(COD)_2]OTf$	3.5	10	59	19 (-)
12	**80**	**67**	$[RhCODCl]_2$	3.5	11	9	63 (-)
13[e]	**80**	**67**	$[RhCODCl]_2$	30	100	100	82 (-)
14	**82**	**60**	$[Rh(NBD)_2]PF_6$	30	62	100	14 (+)
15	**82**	**60**	$[Rh(COD)_2]BF_4$	30	66	100	0
16	**82**	**60**	$[RhCODCl]_2$	30	1	76	17 (+)
17	**82**	**67**	$[Rh(NBD)_2]PF_6$	30	21	100	5 (+)

[a] Reaction conditions: 1% mol $[Rh(olefin)_2]X$, 0.5% mol $[Rh(COD)Cl]_2$, 2.5% mol ligand, 3.5 bar H_2, CH_2Cl_2, 25ºC, 16 h [b] absolute configuration was not determined [c] 0ºC, 7 h [d] 50ºC [e] 2.7% mol ligand, 24 h



Scheme 14

Although moderate to good enantioselectivities were obtained for the hydrogenation of α-arylenamides without substituents in the β-position, the β-substituted-α-arylenamide **82** was reduced with very low enantioselectivities (Table 14, entries 14-17).

3.3. Conclusions

It has been reported for the first time that *N*-aryl imine **74** can be efficiently hydrogenated by iridium catalysts bearing the D-mannitol derivative ligands phosphinite-phosphite **69a-b**. The catalytic systems Ir(I)/**69a** reached 100% conversion and 73% ee. Besides, the Ir(I)/D-xylose derivative ligand diphosphinite **5** succeeded in hydrogenating **74**. The optical yield, however, was only 46%.

In addition, the new C_2-mannitol diphosphinite ligands (**56a, 66a-b**) proved to be well suited for the Ir(I)-catalysed hydrogenation of *N*-aryl imine **76** and enantioselectivities were as high as 70%. Moreover, the iridium catalyst based on a diphosphite ligand can satisfactorily reduce imine **76** with ees up to 46% in the presence of Bu_4NI. Bulky *tert*-butyl groups in the *ortho* positions of the biphenyl

moiety of diphosphite **35b** have an extremely positive effect on enantioselectivity, as was previously found in the hydrogenation of dehydroaminoacid derivatives [27b].

The combination of the electronic and structural properties of the ligands and Ir(I) complexes must be optimal for each *N*-aryl imine.

The hydrogenation of imine **78** with rhodium and iridium systems bearing diphosphine and phosphinite-phosphite D-mannitol derivative ligands was not as successful as the hydrogenation of **74** and **76.** Conversions and enantioselectivities were low.

The catalytic systems Rh(I)/D-mannitol derivative diphosphinites reduced α-arylenamide **80** effectively but enantioselectivities were only moderate (up to 50%). However, the $[Rh(COD)Cl]_2$/D-mannitol and D-xylose monophosphinites proved to be more enantioselective systems, and provided ee's up to 82%.

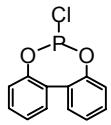
3.4. Experimental Section

General Comments. All reactions were carried out in an argon atmosphere using standard Schlenk techniques. Solvents were distilled and degassed prior to use.

^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini spectrometer at 300 and 400 MHz. Chemical shifts were reported relative to tetramethylsilane for ^{1}H and $^{13}C\{^{1}H\}$ as internal reference, H_3PO_4 85% for $^{31}P\{^{1}H\}$ and trichlorofluoromethane for $^{19}F\{^{1}H\}$ as external references. Elemental analyses were carried out on a Carlo Erba Microanalyser EA 1108. VG-Autospect equipment was used for FAB mass spectral analyses with 3-nitrobenzylalcohol as matrix. EI mass spectra were obtained on an HP 5989 A spectrometer at an ionizing voltage of 70 eV. Optical rotations were measured on a

Perkin-Elmer 241 MC polarimeter. Melting points were determined in an open capillary tube with a Tottoli-Büchi 510 melting point apparatus and are uncorrected. Single hydrogenation reactions were carried out in a Berghof or Parr 100 ml stainless steel autoclave and multi-screening hydrogenations were performed in a home-made 96-micro-titer plate in Bayer AG (Leverkusen-Germany)). The catalytic reactions were monitored by GC on a Hewlett-Packard 5890A. Conversion was measured in an Ultra-2 (5 % diphenylsilicone/95% dimethylsilicone) column (25 m x 0.2 mm Ø). The enantiomeric excess of *N*-(phenylethylidene)benzylamine (**21a**) was determined by ^{1}H NMR (with mandelic acid as the resolution agent) or by chiral chromatography after derivation into the trifluoroacetamide compound.. The enantiomeric excess of *N*-(phenylethylidene)aniline (**22a**) was determined by chiral chromatography after derivation into the acetamide compound. The enantiomeric excess of the 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline imine (**23a**) was determined by chiral chromatography.

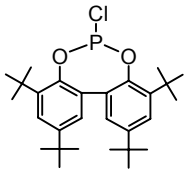
2,2'-Biphenylphosphorochloridite (62a) [24]



A 100-ml three-necked, round-bottomed flask equipped with a dropping funnel was filled with 6.2 ml of dry pyridine (76.5 mmol) and 1.34 ml of recently distilled PCl_3 (15.3 mmol). 1.2 g of 2,2'-bisphenol (6.4 mmol) was dissolved in 45 ml of dry toluene and added dropwise to the PCl_3/pyridine solution at 0ºC. When the addition was complete, the reaction mixture was refluxed overnight. The pyridine salts formed were removed by filtration under argon atmosphere. The reaction mixture was concentrated at reduced pressure. The product **62a** was used without purification in the following reaction step (1.1 g, 70% yield).

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.38-7.11 (m, 8H, arom.). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 180.6.

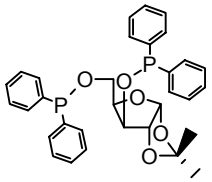
4,4',6,6'-Tetra-*tert*-butyl-2,2'-biphenylphosphorochloridite (62b) [24]



A 50-ml three-necked, round-bottomed flask equipped with a dropping funnel was filled with 3 ml of dry pyridine (37.1 mmol) and 750 µl of recently distilled PCl_3 (8.25 mmol). 3 g of 4,4',6,6'-Tetra-*tert*-butyl-2,2'-bisphenol (7.3 mmol) was dissolved in 15 ml of dry and degassed toluene and added dropwise to the PCl_3/pyridine solution at 0ºC. When the addition was complete, the reaction mixture was refluxed overnight. The pyridine salts formed were removed by filtration under argon atmosphere. The reaction mixture was concentrated at reduced pressure. The product **62b** was used without purification in the following reaction step (3.47g, 86% yield).

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.46 (d, *J*=2.4Hz, 2H, arom.), 7.17 (d, *J*=2.4Hz, 2H, arom.), 1.47 (s, 18H, *o*-$C_4\underline{H}_9$), 1.35 (s, 3H, *p*-$C_4\underline{H}_9$). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 147.8 (C arom.), 145.7 (C arom.), 140.6 (C arom.), 132.8 (C arom.), 126.9 (CH arom), 125.0 (CH arom.), 35.7 (C), 34.9 (C), 31.7 (CH_3), 31.1 (CH_3). NMR ^{31}P (161.9 MHz, $CDCl_3$, ppm) 172.1.

3,5-bis(diphenylphosphinite)1,2-*O*-isopropylidene-D-xylofuranose (5) [6]

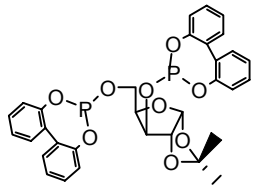


A total of 500 mg of 1,2-*O*-isopropylidene-D-xylofuranose (**61**) (2.6 mmol) was dissolved in dry and degassed THF (10 ml) to which 2 ml of dry pyridine (24 mmol) was added. 1 ml (5.28 mmol) of chlorodiphenylphosphine was added. The reaction mixture was stirred for 3 h. at room temperature. Ethyl ether (55 ml) was then added and the pyridine salts were precipitated and removed by filtration under argon atmosphere. Evaporation of the solvent gave 1.1 g (80% yield) of compound **5** as a yellow foam.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.55-7.24 (m, 20H, arom.), 5.91 (d, ^{3}J=3.2Hz, 1H, CH), 4.59 (m, 1H, CH), 4.44 (m, 2H, CH), 4.09 (m, 2H, CH_2), 1.40 (s, 3H,

CH_3), 1.23 (s, 3H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 141.4-127.7 (arom.), 111.3 ($\underline{C}(CH_3)_2$), 104.5 (CH), 83.2 (d, $^3J_{=}$24Hz, CH), 81.5 (d, $^2J_{=}$75.6Hz, CH), 79.6 (t, $^3J_{=}$27.2Hz, CH), 66.6 (d, ^2J=75.6Hz, CH_2), 26.6 (CH_3), 26.1 (CH_3). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 116.9, 115.1.

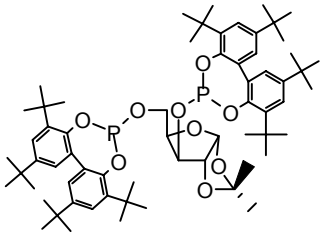
3,5-Bis[1,1'-biphenyl-2,2'-diyl)phosphite]-1,2-*O*-isopropylidene-D-xylofuranose (35a) [24]



A total of 380 mg of 1,2-*O*-isopropylidene-D-xylofuranose (**61**) (2 mmol) was dissolved in dry and degassed- toluene (12 ml) to which 1 ml of dry pyridine (12 mmol) was added. In 30 min the solution was added to a solution of **1** (5 mmol) in 5 ml of dry and degassed toluene and 1 ml of pyridine (12 mmol) at 0ºC. The reaction mixture was stirred for 2 h at room temperature. Filtration under argon atmosphere followed by evaporation of the solvent gave a yellow foam which was purified by flash column chromatography under argon atmosphere (dry and degassed toluene), affording 925 mg (75% yield) of compound **35a** as a white powder.

$[\alpha]_D$ ^{20} = + 0.045º (c=1, CH_2Cl_2). **NMR ^{1}H (**400 MHz, $CDCl_3$, ppm) 7.31-6.95 (m, 16H, arom.), 5.79 (d, $^3J_{H,H}$=3.6Hz, 1H, CH), 4.63 (dd, $^3J_{H,P}$=9.6Hz, $^3J_{H,H}$=2.8Hz, 1H, CH), 4.52 (d, $^3J_{H,H}$=3.6Hz, 1H, CH), 4.36 (td, $^3J_{H,H}$=6.8Hz, $^3J_{H,H}$=2.8Hz, 1H, CH), 4.2 (t, $^3J_{H,P}$=6.9Hz, 2H, CH_2,), 1.33 (s, 3H, CH_3), 1.15 (s, 3H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 149.9-121 (arom.), 112.3 ($\underline{C}(CH_3)_2$), 105.0 (CH), 79.1 (CH), 76.9 (d, $J_{P,C}$=18Hz, CH), 61.7 (d, $J_{P,C}$=178.8Hz, CH_2), 26.9 (CH_3), 26.4 (CH_3). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 140.5, 139.3.

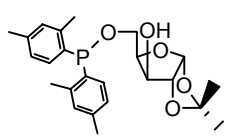
3,5-Bis[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-1,2-*O*-isopropylidene-D-xylofuranose (35b) [24]



A total of 500 mg of 1,2-*O*-isopropylidene-D-xylofuranose (**61**) (2.6 mmol) was dissolved in dry and degassed toluene (12 ml) to which 1 ml of dry pyridine (12 mmol) was added. The solution was added in 30 min to a solution of **3** (7.3 mmol) in 20 ml of dry and degassed toluene and 1 ml of pyridine (12 mmol) at 0ºC. The reaction mixture was stirred overnight at room temperature and the pyridine salts were removed by filtration under argon atmosphere. Evaporation of the solvent gave a white foam which was purified by flash column chromatography under argon atmosphere (dry and degassed- mixture of hexane/ethyl acetate 20:1), affording 2.2 g (78% yield) of compound **35b** as a white powder.

$[\alpha]_D^{20}$= + 0.838º (c=1, CH_2Cl_2). **MS FAB m/z (%)**: 1066.62 (1.67, M^+). **HRMS L-SIMS:** m/z, [$C_{64}H_{92}O_9P_2$] **Calculated** 1067.3574, **Found** 1067.6269. **NMR ^{1}H (**400 MHz, $CDCl_3$, ppm) 7.43-7.13 (m, 8H, arom.), 5.53 (d, $^3J_{H,H}$=3.2Hz, 1H; CH), 4.71 (dd, $^3J_{H,P}$=7.2Hz, $^3J_{H,H}$=2.4Hz, 1H, CH), 4.26 (dt, $^3J_{H,H}$=6.4Hz, $^3J_{H,H}$=2.4Hz, 1H, CH), 4.04 (m, 2H, CH_2), 3.92 (d, $^3J_{H,H}$=3.2Hz, 1H, CH_2), 1.47 (s, 18H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$), 1.38 (s, 9H, $C(CH_3)_3$), 1.35 (s, 27H, $C(CH_3)_3$), 1.33 (s, 3H, CH_3), 1.10 (s, 3H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 146.9-124.3 (arom.), 111.9 ($\underline{C}(CH_3)_2$), 104.9 (CH), 84.2 (CH), 79.0 (CH), 76.4 (CH), 61.9 (CH_2), 35.6 ($\underline{C}(CH_3)_3$), 35.5 ($\underline{C}(CH_3)_3$), 32.4 ($\underline{C}(CH_3)_3$), 32.3 ($\underline{C}(CH_3)_3$), 31.6 ($C(\underline{C}H_3)_3$), 26.9 (CH_3), 26.6 (CH_3). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 143.3, 134.7.

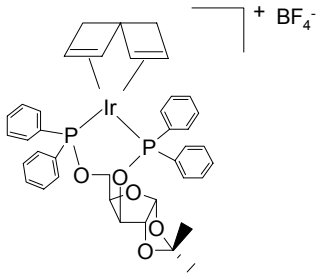
3-hydroxy-5-bis-*O*-(4-methoxyphenylphosphino)1,2-*O*-isopropylidene-D-xylofuranose (60)



A flask equipped with a magnetic stirrer was charged with 260 mg (1.35 mmols) of the 1,2-*O*-isopropylidene-D-xylofuranose (**61**), 7 ml of anhydrous THF and 0.34 ml (8.7 mmol) of anhydrous pyridine. A solution of 800 mg (2.89 mmols) of bis-(2,4dimethylphenyl)-chlorophosphine (**64c**) in 3 ml of anhydrous THF was added. The mixture was stirred at room temperature. Anhydrous Et_2O was added to facilitate the precipitation of the salts formed and filtered under argon. Purification by column chromatography under argon gave 203 mg (35% yield) of compound **60** as a foam.

$[\alpha]_D^{20}$= - 0.134º (c=0.67, CH_2Cl_2). **Elemental Analysis calculated for $C_{24}H_{31}O_5P_1$** (%): C, 66.96; H, 7.26, **Found** (%): C, 66.25; H, 7.28. **MS FAB m/z (%)**: 430.17 (4.16, M^+). **HRMS L-SIMS:** m/z, [$C_{24}H_{31}O_5P$] **Calculated** 430.1909, **Found** 430.1896. **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.15-7.08 (m, 6H, arom.), 5.82 (br, 1H, CH), 4.47 (br, 1H, CH), 4.31 (br, 1H, CH), 4.24 (br, 1H, CH), 4.19 (m, 2H, CH_2), 2.82 (br, 1H, OH), 2.41 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$) 136.0-130.1 (CH, C, arom.), 111.8 (C), 104.9 (CH), 85.4 (CH), 79.0 (d, ^3J=7.6 Hz, CH), 75.9 (CH), 67.8 (d, ^2J=20.5 Hz, CH), 27.1 (CH_3), 26.5 (CH_3), 21.5 (CH_3), 21.4 (CH_3), 20.5 (d, ^3J=8.4 Hz, CH_3),20.3 (d, ^3J= 8.4 Hz, CH_3) **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 108.9.

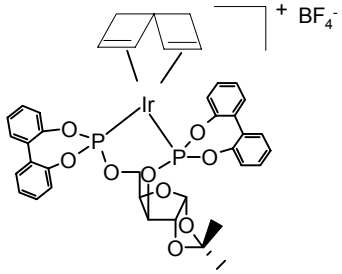
[Ir(COD)(5)]BF_4 (65a)



To a chilled (-80ºC) solution of [Ir(COD)$_2$]BF_4 (150 mg, 0.3 mmol) with dry and degassed dichloromethane (4 ml), a solution of **5** (250 mg, 0.4 mmol) with dry and degassed dichlorometane (5 ml) was added dropwise.The solution was allowed to warm to 0ºC and stirred for 15 min. Ethyl ether (30 ml) was then added to precipitate the desired compound **65a** as a pale purple solid (322 mg, 76% yield).

Elemental analysis calculated for.$C_{40}H_{44}O_5P_2IrBF_4$ (%):C 50.80; H 4.69, **Found** (%):C 50.65; H 4.85. **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 103.5 (d, $^2J_{P;P}$=78Hz), 101.0 (d, $^2J_{P;P}$=78Hz).

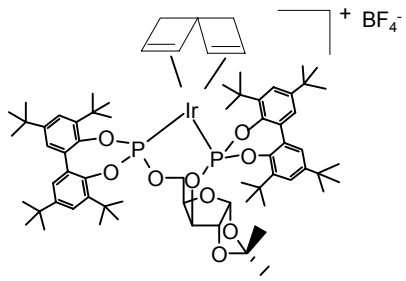
[Ir(COD)(35a)]BF_4 (65b) [25b]



To a chilled (-80ºC) solution of [Ir(COD)$_2$]BF_4 (104 mg, 0.2 mmol) with dry and degassed dichloromethane (4 ml), a solution of **35a** (128 mg, 0.2 mmol) with dry and degassed dichlorometane (5 ml) was added dropwise. The solution was allowed to warm to 0ºC and stirred for 15 min. Ethyl ether (30 ml) was then added to precipitate 68.3mg (68% yield) of the compound **65b** as a white solid.

Elemental analysis calculated for $C_{40}H_{40}O_9P_2IrBF_4$ (%): C 47.77; H 4.01, **Found** (%): C 47.45; H 4.09. **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 105.1 (br), 103.5 (br).

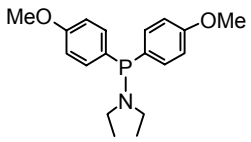
[Ir(COD)(35b)]BF_4 (65c) [25b]



To a chilled (-80ºC) solution of $[Ir(COD)_2]BF_4$ (103.3 mg, 0.2 mmol) with dry and degassed dichloromethane (4 ml), a solution of **35b** (213.7 mg, 0.2 mmol) with dry and degassed dichlorometane (5 ml) was added dropwise.The solution was allowed to warm to 0ºC and stirred for 15 min. Ethyl ether (30 ml) was then added to precipitate 194.8 mg (67% yield) of compound **65c** as a purple solid.

Elemental analysis calculated for $C_{72}H_{104}O_9P_2IrBF_4$ (%): C 59.45; H 7.21, **Found** (%): C 59.57; H 7.86. **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 112.01 (d, $^2J_{P;P}$=50Hz), 110.6 (d, $^2J_{P;P}$=50Hz).

(diethylamino)-bis(4-metoxyphenyl)phosphine (63a) [10g]

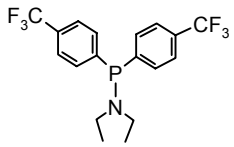


A flask fitted with a mechanical stirrer and an addition funnel was charged with 0.43 g (18 mmol) of magnesium turnings, 6 ml of THF and 6 ml of Et_2O. An iodine crystal was added to facilitate the initiation of the reaction. To this cooled suspension (0°C) 2.14 ml (17.1 mmol) of 4-bromo-anisole in 3 ml of anhydrous Et_2O was added. The reaction was allowed to warm to 22-28 °C and was stirred overnight. The reaction was then transferred into an addition funnel via canula and washed with 5 ml of THF to ensure that all the Grignard reagent had been transferred. The flask containing the addition funnel was charged with 1.2 ml (8.2 mmol) of Et_2NPCl_2 and 7 ml of THF and cooled to 0°C and the Grignard reagent was added for half an hour. The reaction mixture was stirred for 2 hours at 5-10°C. Then the reaction mixture was concentrated to the minimum amount in a vacuum pump. To the mixturee was added dry hexane (60 ml) and the solution was

filtered through dry celite under argon. A total of 1.48 g (57.2% yield) of the expected compound **63a** was obtained as a syrup.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.48 (dd, *Jortho*= 8.8 Hz, J_{PH}= 6.4 Hz, 4H, arom.), 6.88 (m, 4H, arom.), 3.81 (s, 6H, CH_3O), 3.06 (q, ^{3}J=7.2 Hz, 2H, CH_2), 0.96 (t, ^{3}J=7.2 Hz, 3H, CH_3). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 59.5.

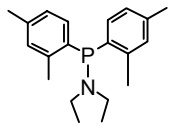
(diethylamino)-bis(4-trifluoromethylphenyl)phosphine (63b) [10g]



Prepared following the procedure described for **63a**. A total of 1.95 g (61.4% yield) of the expected compound **63b** was obtained as a syrup.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.48 (m, 4H, arom.), 7.37 (m, 4H, arom.), 2.99 (m, 2H, CH_2), 1.38 (t, ^{3}J=6.8 Hz, 3H, CH_3). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 59.4.

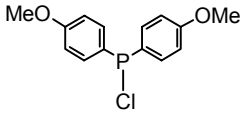
(diethylamino)-bis(2,4-dimethylphenyl)phosphine (63c) [10g]



Prepared following the procedure described for **63a**. A total of 1.37 g (59% yield) of the expected compound **63c** was obtained as a syrup.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.04 (m, 2H, arom), 6.94 (m, 4H, arom), 3.11 (m, 4H, $CH_{2)}$, 2.29 (s, 6H, CH_3), 2.28 (s, 6H, CH3), 0.86 (t, 6H, CH_3). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 47.2.

bis(4-methoxyphenyl)chlorophosphine (64a) [10g]

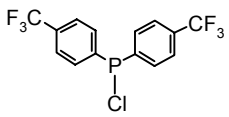


A flask fitted with a mechanical stirrer and an addition funnel was charged with 0.43 g (18 mmol) of magnesium turnings, 6 ml of THF and 6 ml of Et_2O. An iodine crystal was added to facilitate the initiation of the reaction. To this cooled suspension (0°C) 2.14 ml (17.1 mmol) of 4-bromo-anisole in 3 ml of anhydrous Et_2O was added. The

reaction was allowed to warm to 22-28 °C and was stirred overnight. The reaction was then transferred into an addition funnel via cannula and washed with 5 ml of THF to ensure that all the Grignard reagent had been transferred. The flask containing the addition funnel was charged with 1.2 ml (8.2 mmol) of Et_2NPCl_2 and 7 ml of THF and cooled to 0°C and the Grignard reagent was added for half an hour. The reaction mixture was stirred for 2 hours at 5-10°C. The reaction mixture was concentrated to the minimum amount in a vacuum pump. To the mixturee was added dry hexane (60 ml) and the solution was filtered through dry celite under argon. The filtrated dry HCl gas was passed through the solution for 1 hour. The reaction was mildly exothermic. The mixture was degassed by bubbling argon and the solid precipitate was filtered under argon. The filtrate was concentrated in a vacuum pump to give 1 g (45% yield) of compound **64a** as a syrup.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.48 (t, *Jortho*= 8.4 Hz, J_{PH}= 8.4 Hz, 4H, arom.), 6.88 (d, *Jortho*= 8.4 Hz, 4H, arom.), 3.75 (s, 6H, CH_3O). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 84.2.

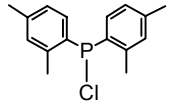
bis(4-(trifluoromethyl)phenyl)chlorophosphine (64b) [10g]



Prepared following the procedure described for **64a**. A total of 1.93 g (66% yield) of the expected compound **64b** was obtained as a syrup.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.33 (m, 8H, arom.). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 76.3.

bis(2,4-dimethylphenyl)chlorophosphine (64c) [10g]



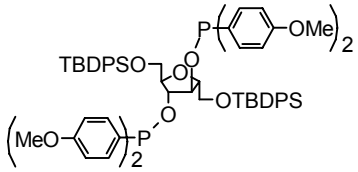
Prepared following the procedure described for **64a**. A total of 1.4 g (58.3% yield) of the expected compound **64c** was obtained as a syrup.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.40 (d, *Jmeta*= 4.4 Hz, 2H,

arom.), 7.2 (m, 4H, arom.), 2.5 (d, J_{PH}= 2 Hz, 6H, CH_3), 2.4 (s, 6H, CH_3). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 75.6.

2,3-bis-*O*-(4-methoxyphenylphosphino)-1,6-dideoxy-2,5-anhydro-D-Mannitol (66a)

Procedure A:



A flask equipped with a reflux condenser was charged with 100 mg (0.156 mmols) of the 1,6-dideoxy-2,5-anhydro-D-Mannitol (**70**). A solution of 109 mg (0.343 mmols) of (diethylamino)-bis(4-methoxyphenyl)phosphine **(63a**) in 2.2 ml of anhydrous toluene was added. The mixture was refluxed overnight and followed by TLC (Hexane/Ethyl Acetate 5:1 Rf=0,25). The residue was then purified by column chromatography with silica under argon to give 40 mg (22.7% yield) of compound **66a** as a foam.

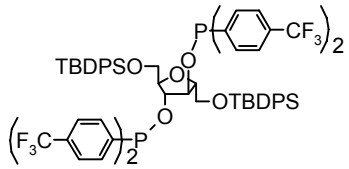
Procedure B:

A solution of 569 mg (1.79 mmols) of (diethylamino)-bis(4-methoxyphenyl)phosphine (**63a**) and 5.1 ml of a tetrazole (0.45M in CH_3CN) was stirred for 10 minutes at room temperature under argon. A solution of 288 mg (0.45 mmols) of 1,6-dideoxy-2,5-anhydro-D-Mannitol (**70**) in 3 ml of anhydrous dichloromethane was added and stirred for 30 minutes at room temperature. The reaction was followed by TLC (Hexane/Ethyl Acetate 5:1 Rf=0.25). The residue was then purified by column chromatography with silica under argon to give 301.2 mg (59% yield) of compound **66a** as a foam.

$[\alpha]_D^{20}$= 0.065º (c=0.83, CH_2Cl_2). **MS FAB m/z (%)**: 1129.31 (2.73, M^+). **HRMS L-SIMS:** m/z, $[C_{66}H_{74}O_9Si_2P_2]$ **Calculated** 1129.4069, **Found** 1129.4430. **NMR ^{1}H** (400 MHz, C_6D_6, ppm) 7.93 (m, 8H, arom.), 7.67 (m, 8H, arom.), 7.26 (m, 12H, arom.), 6.84 (m, 8H, arom.), 5.38 (dd, *J*=7.9 Hz, *J*=4 Hz, 2H, CH), 4.59 (m, 2H,

CH), 4.09 (dd, *J*=10.9 Hz, *J*=4.2 Hz, 2H, CH_2), 3.99 (dd, *J*=10.9 Hz, *J*=4.2 Hz, 2H, CH_2), 3.37 (s, 6H, CH_3O), 3.35 (s, 6H, CH_3O), 1.32 (s, 9H, CH_3), 1.27 (s, 9H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$) 160.7-113.9 (arom.), 85.0 (m, CH), 84.5 (CH), 64.1 (CH_2), 55.25 (CH_3O), 55.23 (CH_3O), 27.0 ($C(\underline{C}H_3)_3$), 19.4 ($\underline{C}(CH_3)_3$) **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 115.1.

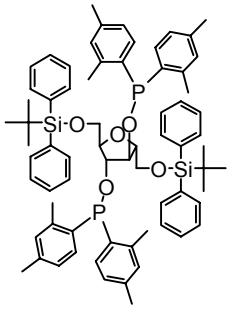
2,3-bis-*O*-((4-trifluoromethyl)phenylphosphino)-1,6-dideoxy-2,5-anhydro-D-Mannitol (66b)



A flask equipped with a reflux condenser was charged with 213 mg (0.332 mmols) of the 1,6-dideoxy-2,5-anhydro-D-Mannitol (**70**). A solution of 352 mg (0.897 mmols) of diethylamino-bis(4-trifluoromethylphenyl) phosphine (**63b**) in 2.5 ml of anhydrous toluene was added. The mixture was refluxed overnight and followed by TLC. The residue was then purified by column chromatography with silica under argon to give 40 mg (28% yield) of compound **66b** as a foam.

NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.65-7.25 (m, 36H, arom), 5.01 (m, 2H, CH), 4.18 (m, 2H, CH), 3.82 (dd, ^{2}J=11.2 Hz, ^{3}J=4 Hz, 2H, CH_2), 3.62 (dd, ^{2}J=11.2 Hz, ^{3}J=4 Hz, 2H, CH_2), 1.05 (s, 9H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$) 134.3-125.3 (arom.), 122.7 (CF_3), 86.2 (m, CH), 83.4 (CH), 63.6 (CH_2), 27.0 ($C(\underline{C}H_3)_3$), 19.5 ($\underline{C}(CH_3)_3$) **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 110.5.

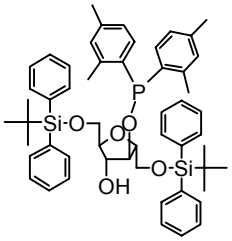
2,3-bis-*O*-(2,4-dimethylphenylphosphino)-1,6-dideoxy-2,5-anhydro-D-Mannitol (66c)



A solution of 3.4 g (10.9 mmols) of (diethylamino)-bis(2,4-dimethylphenyl)phosphine (**63c**) and 34 ml (15.3 mmols) of a tetrazole (0.45M in CH_3CN) was stirred for 10 minutes at room temperature under argon. To this solution, 878 mg (1.37 mmols) of 1,6-dideoxy-2,5-anhydro-D-Mannitol (**70**) was added and stirred for 2 hours at room temperature. The reaction was followed by TLC (Hexane/Ethyl Acetate 10:1 Rf=0.47). The residue was then purified by column chromatography with silica under argon to give 630 mg (41% yield) of compound **66c** and 446 mg (37% yield) of **67**.

$[\alpha]_D^{20}$= 0.080º (c=0.71, CH_2Cl_2). **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.55-6.70 (m, 32H, arom.), 4.66 (m, 1H, CH), 4.09 (m, 1H, CH), 3.65 (m, 2H, CH), 3.54 (m, 2H, CH), 2.14 (s, 6H, CH_3), 2.13 (s, 6H, CH_3), 2.12 (s, 6H, CH_3), 2.11 (s, 6H, CH_3), 0.74 (s, 18H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 141.0-126.7 (arom.), 85.5 (m, CH), 84.5 (CH), 64.2 (CH_2), 27 ($C(\underline{C}H_3)_3$), 20.7 (d, ^3J=7.74 Hz, CH_3), 20.5 (d, ^3J=6.84 Hz, CH_3), 20.5 (br, CH_3), 19.4 ($\underline{C}(CH_3)_3$). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 102.6.

2-*O*-(2,4-dimethylphenylphosphino)-1-6-dideoxy-2,5-anhydro-D-Mannitol (67)



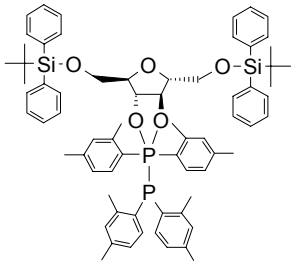
A flask equipped with a magnetic stirrer was charged with 300 mg (0.468 mmols) of the 1,6-dideoxy-2,5-anhydro-D-Mannitol (**70**) and 0.26 ml of anhydrous Et_3N. A solution of 337 mg (1.219 mmols) of bis-(2,4dimethylphenyl)-chlorophosphine (**64c**) in 2 ml of anhydrous THF was added. The mixture was stirred at room temperature. Anhydrous Et_2O was added to facilitate the precipitation of the

salts formed and filtered under argon. Purification by column chromatography under argon gave 180 mg (48% yield) of compound **67** as a foam and 157 mg (30% yield) of compound **73**.

Spectroscopic Data of 67

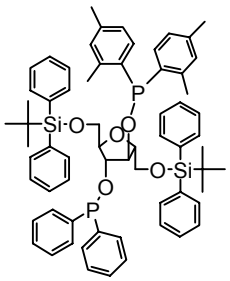
$[\alpha]_D^{20}$= 0.178º (c=0.89, CH_2Cl_2). **MS FAB m/z (%)**: 881.46 (4.39, M^+). **HRMS L-SIMS:** m/z, [$C_{54}H_{65}O_5Si_2P$] **Calculated** 881.2357, **Found** 881.2385. **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.59-6.87 (m, 26H, arom.), 4.47 (m, 1H, CH), 4.31 (m, 1H, CH), 3.99 (m, 2H, CH), 3.69 (m, 3H, CH_2), 3.54 (dd, 1H, CH_2), 2.79 (s, OH), 2.30 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.06 (s, 3H, CH3), 0.96 (s, 9H, CH_3), 0.94 (s, 9H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 138.1-127.6 (CH, C, arom.), 86.0 ($^2J_{C\text{-}P}$=18 Hz, CH), 84.9 (CH), 83.9 ($^3J_{C\text{-}P}$=6.13 Hz, CH), 78.0 ($^3J_{C\text{-}P}$=4.5 Hz, CH), 64.7 (CH_2), 64.1 (CH_2), 27.2 (C($\underline{C}H_3)_3$), 27.0 (C($\underline{C}H_3)_3$), 21.44 ($\underline{C}(CH_3)_3$),21.45 ($\underline{C}(CH_3)_3$), 20.5 (d, ^3J=12.17 Hz, CH_3), 20.3 (d, ^3J=12.27 Hz, CH_3), 19.6 (s, CH_3), 19.5 (s, CH_3). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 102.7.

Spectroscopic Data of 73



NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.73-6.77 (m, 32H, arom.), 4.15 (m, 2H, CH), 4.05 (m, 2H, CH), 3.78 (dd, ^2J=11.2 Hz, ^3J=3.4 Hz, 2H, CH_2), 3.66 (dd, ^2J=11.2 Hz, ^3J=3.4 Hz, 2H, CH_2), 2.12 (d, J=2 Hz, 6H, CH_3), 2.05 (s, 6H, CH_3), 1.98 (s, 6H, CH_3), 1.88 (d, J=2 Hz, 6H, CH_3), 0.97 (s, 18H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 140.0-127.5 (arom.), 86.3 (CH), 79.4 (CH), 65.5 (CH_2), 27.0 (C($\underline{C}H_3)_3$), 21.3 (CH_3), 21.2 (CH_3), 21.9 (CH_3), 20.7 (CH_3), 19.4 ($\underline{C}(CH_3)_3$). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 42.6 (d, $^1J_{P\text{-}P}$=234.2 Hz, P(III)), -44.2 (d, $^1J_{P\text{-}P}$=234.2 Hz, P(V)). **MS m/z (%):** 1120.5 (M^+)

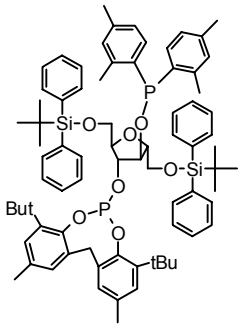
2-*O*-(2,4-dimethylphenylphosphino)-3-*O*-(diphenylphosphino)-1-6-dideoxy-2,5-anhydro-D-Mannitol (68)



A total of 58 mg (0.06 mmols) of 2-*O*-(2,4-dimethylphenylphosphino)-1-6-dideoxy-2,5-anhydro-D-Mannitol (**67**) was dissolved in 0.5 ml of anhydrous THF and 32 µl of anhydrous Et_3N. To this solution, 12.5 µl (0,066 mmols) of chlorodiphenylphosphine was added. The reaction mixture was then allowed to react for 1 hour, following the reaction by TLC (Hexane/Ethyl Acetate 20:1 Rf= 0.36). The salts formed were removed by filtration through celite under argon. Evaporation of the solvent gave a solid, which was purified by column chromatography with silica under an atmosphere of argon to give 29.4 mg (45.9% yield) of compound **68** as a foam.

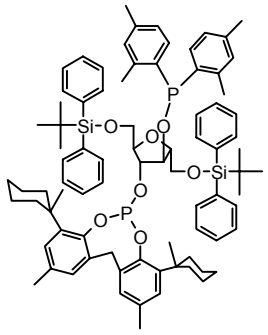
NMR ^{1}H (400 MHz, $CDCl_3$, ppm) 7.67-6.91 (m, 36H, arom.), 4.89-4.79 (m, 2H, CH), 4.15 (m, 2H, CH), 3.75 (m, 2H, CH_2), 3.57 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.19 (s, 3H, CH3), 2.14 (s, 3H, CH_3), 1.10 (s, 9H, CH_3), 1.00 (s, 9H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 139.3-127.9 (CH, C, arom.), 85.6 (m, CH, CH), 84.3 (m, CH, CH), 64.1 (CH_2), 63.9 (CH_2), 26.8 ($C(\underline{C}H_3)_3$), 21.3 (CH_3), 20.7 (br, CH_3), 20.6 (br, CH_3), 19.4 ($\underline{C}(CH_3)_3$). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 114.2, 102.7.

2-*O*-(2,4-dimethylphenylphosphino)-3-*O*-(4,8-ditert-butyl-2,10-dimethyl-12h-dibenzo[δ,γ][1,3,2]dioxaphosphocine)-1-6-dideoxy-2,5-anhydro-D-Mannitol (69a)



A total of 178 mg (0.202 mmols) of 2-*O*-(2,4-dimethylphenylphosphino)-1-6-dideoxy-2,5-anhydro-D-Mannitol (**67**) was dissolved in 1 ml of anhydrous toluene and 100 µl of anhydrous pyridine and cooled at 0°C. A solution of 100 mg (0,252 mmols) of 4,8-ditert-butyl-6-chloro-2,10-dimethyl-12h-dibenzo[δ,γ] [1,3,2] dioxa_ phosphocine in 1 ml of anhydrous toluene and 100 ul of anhydrous pyridine was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred, following the reaction by TLC (Hexane/Ethyl Acetate 10:1 Rf= 0.55). Purification by column chromatography with silica gave 100 mg (39.6% yield) of compound **69a** as a foam. **$[\alpha]_D^{20}$=** 0.174º (c=0.42, CH_2Cl_2). **MS FAB m/z (%)**: 1249.12 (3.91, M^+). **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.69-6.73 (m, 30H, arom.), 5.79 (m, 1H, CH), 4.92 (m, 1H, CH), 4.67 (m, 1H, CH), 4.30 (m, 1H, CH_2), 4.13 (d, ^2J=12.4 Hz, CH_2), 3.98-3.72 (m, 4H, CH_2), 3.15 (d, ^2J=12.4 Hz,1H, CH_2), 2.31 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.26 (s, 9H, CH_3), 2.19 (s, 3H, CH_3), 1.29 (s, 9H, CH_3), 1.22 (s, 9H, CH_3), 1.04 (s, 9H, CH_3), 0.98 (s, 9H, CH_3). **NMR ^{13}C** (100.6 MHz, $CDCl_3$, ppm) 145.6-126.8 (CH, C, arom.), 85.9 (m, CH), 85.4 (CH), 85.2 (CH), 80.3 (m, CH), 64.3 (CH_2), 63.9 (CH_2), 34.8 (CH_2), 31.2 ($C(\underline{C}H_3)_3$), 31.1 ($C(\underline{C}H_3)_3$), 27.0 ($C(\underline{C}H_3)_3$), 26.9 ($C(\underline{C}H_3)_3$), 21.5 (CH_3), 21.4 (CH_3), 21.3 (CH_3), 20.8 (d, ^3J=13.7 Hz, CH_3), 20.6 (d, ^3J=13.7 Hz, CH_3), 19.5 ($\underline{C}(CH_3)_3$), 19.4 ($\underline{C}(CH_3)_3$). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 127.9, 102.8.

2-*O*-(2,4-dimethylphenylphosphino)-3-*O*-(2,10-dimethyl-4,8-bis(1-methylcyclohexyl)-12H-dibenzo[δ,γ][1,3,2]dioxaphosphocine)-1-6-dideoxy-2,5-anhydro-D-Mannitol (69b)



A total of 145 mg (0.164 mmols) of 2-*O*-(2,4-dimethylphenylphosphino)-1-6-dideoxy-2,5-anhydro-D-Mannitol (**67**) was dissolved in 0.5 ml of anhydrous toluene and 100 µl of anhydrous pyridine and cooled at 0°C. A solution of 100 mg (0.252 mmols) of 6-chloro-2,10-dimethyl-4,8-bis(1-methylcyclohexyl)-12H-dibenzo[δ,γ][1,3,2] dioxaphosphocine in 1 ml of anhydrous toluene and 100 µl of anhydrous pyridine was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred. To the mixture was then added dry hexane and the solution was filtered under argon. Purification by column chromatography under argon with silica gave 71 mg (32.4% yield) of compound **69b** as a foam.

$[\alpha]_D^{20}$= 0.226º (c=0.50, CH_2Cl_2). **MS FAB m/z (%)**: 1328.16 (1.45, M^+). **NMR ^{1}H** (400 MHz, $CDCl_3$, ppm) 7.71-6.74 (m, 30H, arom.), 5.67 (m, 1H, CH), 4.85 (m, 1H, CH), 4.62 (m, 1H, CH), 4.30 (m, 1H, CH), 4.12 (d, ^2J=12.8 Hz, 1H, CH_2), 4.01-3.74 (m, 4H, CH_2), 3.15 (d, ^2J=12.8 Hz, 1H, CH_2), 2.36 (s, 3H, CH_3), 2.29 (s, 2h, CH_3), 2.28 (s, 3H, CH_3), 2.27 (br, 6H, CH_3), 2.24 (s, 3H, CH_3), 1.54-1.12 (m, CH_2), 1.16 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.05 (s, 9H, CH_3), 0.97 (s, 9H, CH_3). **NMR ^{31}P** (161.9 MHz, $CDCl_3$, ppm) 127.8, 103.2.

General procedure for the Ir-catalysed hydrogenation of imines

$[Ir(COD)Cl]_2$ (0.022 mmol) or $[Ir(COD)_2]BF_4$ (0.045 mmol) was dissolved in 10 ml of dry, degassed CH_2Cl_2 in a Schlenk tube. The corresponding ligand (0.055 mmol) was then added, followed by the corresponding imine (4.4 mmol for a 100:1

imine:Ir ratio). The solution was transferred under argon to the autoclave via a syringe.

The reaction mixture was stirred overnight at room temperature under 70 bar of H_2 pressure

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CERTIFIQUEN:

Que la memòria que du per títol "TUNABLE CHIRAL LIGANDS FOR Ir AND Rh HYDROGENATION PROCESSES. SYNTHESIS OF ENANTIOMERICALLY ENRICHED AMINES", que presenta Ester Guiu i Rozas per a optar al grau de Doctora en Química, ha estat realitzada sota la nostra direcció en els corresponents Departaments de la Universitat Rovira i Virgili.

Tarragona, Octubre del 2003

Prof. Dra. Carmen Claver Cabrero Prof. Dr. Sergio Castillón Miranda

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