Iridium Catalyzed Asymmetric Hydrogenation

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Abstract

In this chapter, we describe the development in homogeneous Ir-catalyzed asymmetric hydrogenation with particular emphasis on the achievements made during the last 10 years. We also present their application to the synthesis of complex molecules. The first section deals with the hydrogenation of unfunctionalized olefins or with poorly coordinative groups. The second section includes the advances made in the hydrogenation of functionalized olefins. The last two sections cover the hydrogenation of imines and ketones, respectively.

Keywords

Iridium, Catalysis, Asymmetric Hydrogenation, (Un)Functionalized Olefins, Imines, Ketones

1. Introduction

Metal-catalyzed asymmetric hydrogenation offers some of the most sustainable and straightforward reactions for producing pharmaceuticals, flavours, fragrances, agrochemicals and fine chemicals due to its perfect atom economy and operational simplicity.[1] It is estimated that around 10% of all chemical steps in the synthesis of these compounds are hydrogenations. Despite the extensive research dedicated to the asymmetric hydrogenation and the important progress reached some issues still need to be solved. Most catalysts only work with a limited number of substrates and each type of substrates needs a specific catalyst for optimal enantioselectivity. For example, the asymmetric hydrogenation of functionalized alkenes is mostly carried out by Ru- and Rh-diphosphine catalysts,[2] while the asymmetric hydrogenation of unfunctionalized olefins or with poorly coordinative groups is mainly carried out with Ir-P,N catalysts[3]. Broad substrate scope are desirable to reduce the time dedicated to ligand/catalyst design and preparation. A desired additional condition is that the catalyst family should be synthesized from available starting materials and be easy to handle.

The number and types of functionalized substrates has been remarkably expanded and their use is commonplace, as illustrated in the commercial production of the Parkinson's L-DOPA drug,[4] the broad-spectrum antibiotics levofloxacin[5] and sitagliptin[6] and the pesticide (*S*)-metolachlor[7]. The success of catalysts relies on the ability of the substrate to form a metal chelate involving the double bond and a donor atom. Although the reduction of functionalized olefins has been thoroughly studied for decades, there are, some substrate types that are still a challenge. Among them it can been found the cyclic β-enamides, which have recently attracted attention because their hydrogenation products are found in many pharmaceutically and biologically active products. Two representative examples are rotigotine, used to treat Parkinson's disease, and alnespirone, a selective 5-HT1A receptor with antidepressant and anxiolytic properties.[8] In the last decade, it has been found that Ir-containing catalysts[9] can be used in their reduction with results that surpass the most studied Rh and Ru-catalysts[10]. Other challenging substrates were Ir-catalysts has shown to be superior or complementary to the Rh/Ru-catalysts are unsaturated carboxylic acids, nitroolefins among others (see below sections 3–5).

The introduction of chirality becomes a much greater challenge when the coordinative groups of the olefins are absent. So, compared to the AH of functionalized olefins, the reduction of unfunctionalized alkenes or with poor coordinative groups is much less mature.[3] The best catalysts have two characteristics in common: (i) they mainly contain P,N ligands[11] and (ii) their optimal structure is highly dependent on the geometry and substitution pattern of the olefin.[3] The consequence is that for each particular olefin type a different ligand family needs to be developed. It is also important to notice that catalysis has been developed in different grades for each olefin substitution pattern. The most successful cases have been reported for trisubstituted olefines and, to a less extend, for disubstituted. The asymmetric hydrogenation of tetrasubstituted unfunctionalized substrates is still underdeveloped.

In this book chapter we describe the development in Ir-catalyzed asymmetric hydrogenation with particular emphasis on the achievements made during the last 10 years. We also present their applications to the synthesis of complex molecules. Most of the work has been devoted to the hydrogenation of non-functionalized olefins or with poorly coordinated groups (section 2), with significant advances in both, substrate scope and mechanistic studies. However also notable advances has been made in improving the catalytic performance in the reduction of relevant and more challenging functionalized substrates, such as, unsaturated carboxylic acids, nitroolefins, cyclic β-enamides, imines, etc. (see sections 3–5)

2. Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins or with poorly coordinative groups

Among the most challenging substrates to date are the unfunctionalized olefins or olefins with poorly coordinative groups.[3] A breakthrough in the hydrogenation of this type of substrates came in 1997 when Pfaltz et al. used phosphine-oxazoline PHOX ligands **L1** (Figure 1) to design [Ir(**L1**)(cod)]PF_6 (cod = 1,5-cyclooctadiene), a chiral analogue of Crabtree's catalyst ([Ir(py)(PCy_3)(cod)]PF_6) that enantioselectively hydrogenated imines.[12] Although this catalyst also hydrogenated unfunctionalized olefins highly enantioselectively, it was unstable to the reaction conditions. Pfaltz and co-workers overcame this problem by changing the catalyst anion to [(3,5-$(F_3C)_2$-$C_6H_3)_4B]^-$([$BAr_F]^-$). The result was [Ir(**L1**)(cod)]BAr_F (Figure 1), an active, enantioselective, and stable catalyst library for olefin hydrogenation. Despite this

success, its scope was limited (mainly *E*-trisubstituted olefins).[13] It was also seen that the optimal catalyst was highly dependent on the geometry and substitution pattern of the olefin. This triggered the search for new catalysts that would reach a wider substrate scope.

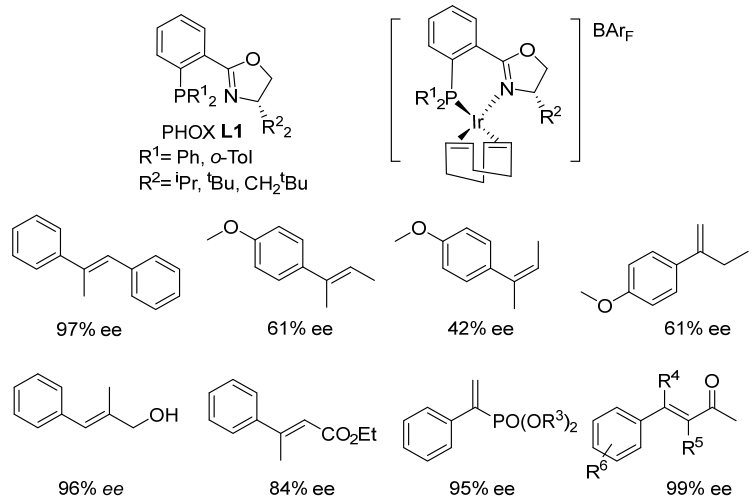


Figure 1. Selected Ir-catalyzed asymmetric hydrogenation results with [Ir(**L1**)(cod)]BAr_F.

In this respect, Pfaltz group continued to develop new versions of the PHOX complexes, modifying the ligand backbone, with the discovery of very efficient ligand libraries.[14] Successive work incorporated pyridine and quinoline rings instead of the oxazoline, which allowed the successful reduction of challenging purely alkyl-substituted substrates in high ee.[15] A notable application was the total synthesis of γ-tocopherol as a single diastereoisomer in 98% ee, controlling two stereocenters in one reductive step (see below).[15b] The various developed ligands also enabled the reduction of various type of substrates, such as allylic alcohols, α,β-unsaturated esters,[16] furan derivatives,[17] boronic esters,[18] and tetrasubstituted olefins.[19]

Other groups also provided new successful ligand libraries, by modifying the chiral backbone, by replacing either the P-group by a N-heterocyclic carbene moiety or the oxazoline moiety by other N-donor groups (such as oxazole, thiazole, and imidazole) and by O- and S-donor groups.[3e,f,20] All these modifications allows to further extend the substrate scope.

Concerning mechanistic aspects, although the mechanism of olefin hydrogenation by Rh-catalysts is well understood, the mechanism when Ir-catalysts are used has not been fully determined until recently. In this context, computational and experimental research with P,N- and C,N- ligands have shown that the hydrogenation of minimally functionalized olefins proceeds via and Ir^{III}/Ir^{V} migratory-insertion/reductive-elimination catalytic cycle (Figure 2).[21] Very recently, Pfaltz's group, based on mechanistic studies under hydrogenation conditions, was able to detect the Ir(III) dihydride alkene intermediates responsible for the catalytic performance for the first time.[22] They found that, similarly to the classical Halpern-mechanism for asymmetric hydrogenation with Rh-catalysts, the minor intermediate, which is less stable, is converted to the major product enantiomer.

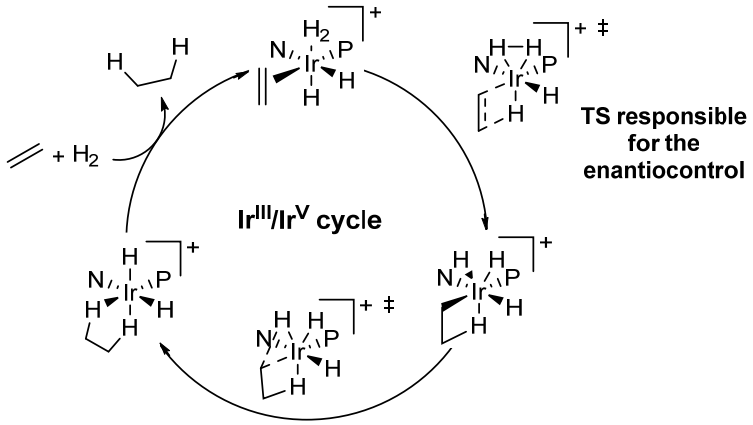


Figure 2. Ir^{III}/Ir^{V} catalytic cycle for the hydrogenation of minimally functionalized olefins.

In next sections we collect the catalytic results on the asymmetric hydrogenation of unfunctionalized olefins or with poorly coordinative groups.

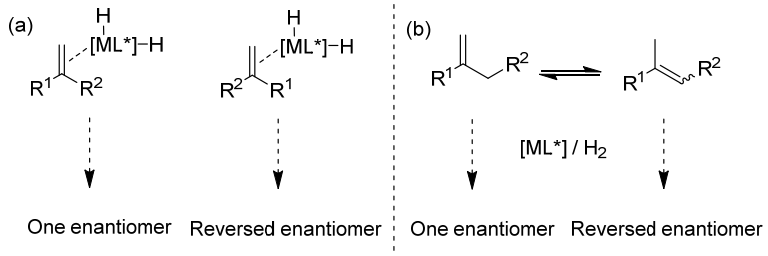
2.1. Di- and tri-substituted unfunctionalized olefins or with poorly coordinative groups

Aryl/alkyl trisubstituted alkenes have become the model substrates for evaluating the efficiency of new catalytic systems. In general, the hydrogenation of 1,2-diarylalkenes (i.e. *trans* α-methylstilbene) proceeded with higher enantioselectivities than monoarylated ones (such as *E*-2-(4-methoxyphenyl)-2-butene) for which only a limited number of catalysts provided high enantioselectivities.[3] The geometry of the olefin also

affects the catalytic performance. *Z*-Trisubstituted olefins are usually hydrogenated less enantioselectively than the related *E*-trisubstituted olefins. The lower enantioselectivities can be mainly attributed to a *Z*/*E* isomerization process to form the more stable *E*-alkene, which gives the opposite enantiomer of the hydrogenated product.[3] *Z*-2-(4-methoxyphenyl)-2-butene and dihydronaphthalenes (i.e. 7-methoxy-4-methyl-1,2-dihydronaphthalene) are frequently used to study the ligand scope in the hydrogenation of *Z*-alkenes. Dihydronaphthalenes have recently received much attention because the corresponding chiral tetraline motif is found in numerous natural products.[23] Trialkyl substituted alkenes have been much less studied. This is due in part to the difficulty in developing methods for ee-determination and also the lack of an aryl group that could direct the reaction via π-stacking interaction between the substrate and the chiral catalyst. The best results have been reported in the reduction of 1-methoxy-4-(3-methyl-pent-3-enyl)-benzene **S9** (ee's up to 95%).[15b]

Nowadays Ir-catalysts have also been able to reduce olefins with a variety of relevant neighboring polar groups such as α,β-unsaturated esters, ketones and lactames and vinyl boronates among others.[3] The effective hydrogenation of such a range of olefins is of great importance since their reduced products are key structural chiral units found in many high value chemicals (e.g. α- and β-chiral ketones and carboxylic acid derivatives are ubiquitous in natural products, fragrances, agrochemicals, and drugs). Substrate scope has also been extended to 1,1-diaryl or 1,1,2-triaryl substituted substrates (i.e. 1-(1,2-diphenyl-vinyl)-3,5-dimethyl-benzene) and more recently to 1,4- and cyclic dienes (i.e. 1,5-dimethyl-cyclohexa-1,4-diene), linear and cyclic sulfones and alkyl fluorides, which are present in several important drugs and natural products.

Unlike trisubstituted olefins, a large range of 1,1-disubstituted olefins have not been successfully hydrogenated until very recently.[3] This is because the catalyst has the added difficulty of controlling not only the face selectivity coordination (only two substituents compared with the three of trisubstituted olefins, Scheme 1a), but also the isomerization of the olefins to form the more stable *E*-trisubstituted substrates, which are hydrogenated to form the opposite enantiomer (Scheme 1b).



Scheme 1. Proposed reasons for the low enantioselectivities in the reduction of 1,1'-disubstituted olefins.

Next we compile the most representative catalytic results in the hydrogenation of di- and trisubstituted olefins organized by the type of ligands.

Phosphine-oxazoline ligands

Inspired by the work of Pfaltz et al. with PHOX ligands, many other phosphine-oxazoline ligands have been developed. Künding, Pfaltz et al. reported a modification in the oxazoline moiety with the phosphine-benzoxazine analogues **L2** (Figure 3, R= ^{t}Bu, ^{i}Pr).[14c] The enantioselectivities were lower than those recorded with PHOX ligands. The presence of a bulky substituent, a ^{t}Bu, at the oxazine group provided good enantioselectivities for *E*-trisubstituted olefins (ee's up to 89%) but low for trisubstituted allylic alcohols, *Z*-trisubstituted olefins, 1,1'-di- and tetrasubstituted olefins.

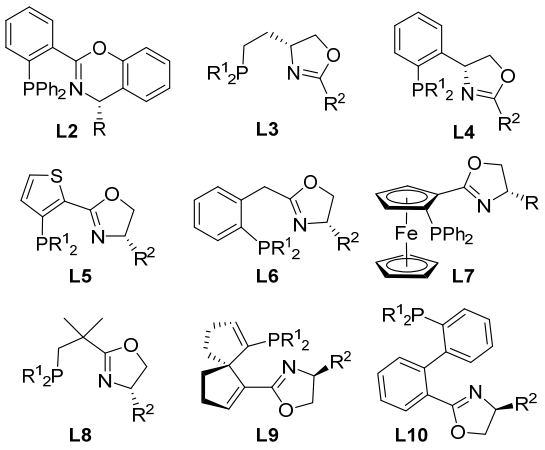


Figure 3. Selected phosphine-oxazoline ligand libraries developed for the Ir-catalyzed asymmetric hydrogenation of di- and trisubstituted olefins.

The rest of new developments in the ligand design were based on modifications of the ligand backbone. Ligands **L3**, developed by Burgess et al., were applied in the hydrogenation of several aryl-alkyl alkenes (Figure 3, R^1= Ph, *o*-Tol and R^2= Me, ^{t}Bu, 1-Ad, CPh_3).[24] These ligands proved to be superior to the PHOX ligands in the hydrogenation of *Z*-trisubstituted alkenes while ee's for *E*-trisubstituted alkenes were lower. The best enantioselectivities for *Z*-olefins were obtained with a ^{t}Bu group at the oxazoline and a diphenylphosphanyl group, while for *E*-olefins a bis(*o*-tolyl)phosphanyl group was needed (ee's up to 80%). A further modification of ligands **L3** was to introduce again the *ortho*-phenylene motif of the PHOX ligands. New ligands **L4** (Figure 3, R^1= Ph, Cy and R^2= ^{t}Bu, 1-Ad, $CHPh_2$, 3,5-^{t}Bu$_2$-C_6H_3), provided excellent results in the reduction of trans-α-methylstilbene derivates and trisubstituted α,β-unsaturated esters (ee's up to 99%).[25] Again bulky groups in oxazoline and phosphine moieties were needed (R^1= Cy; R^2= ^{t}Bu).

Latter, Cozzi's group developed ligands **L5**, in which the phenyl ring of the PHOX ligands was replaced by a thiophene group (Figure 3, R^1= Ph, *o*-Tol, Cy and R^2= ^{i}Pr, ^{t}Bu).[26] This modification also led to high enantioselectivities but only in the hydrogenation of *trans*-α-methylstilbene (ee's up to 99%). Hou et al. developed phosphine-oxazoline ligands **L6** in which the flat *ortho*-phenylene group in the PHOX ligands was replaced by a benzylic group (Figure 3, R^1= Ph, *o*-Tol, *p*-Tol and R^2= Me, ^{i}Pr, ^{t}Bu).[27] These ligands allows to extent the type of substrates successfully hydrogenated. High enantioselectivites were achieved with *E*-trisubstituted aryl/alkyl alkenes, allylic alcohols and α,β-unsaturated esters and ketones (ee's up to 98%). The best enantioselectitivies were obtained with an ^{i}Pr oxazoline group and a diphenylphosphanyl functionality.

Another modification was to introduce a ferrocenyl group (ligands **L7**, Figure 3, R^2= Me, ^{i}Pr, ^{t}Bu, Ph, Bn). The best results were obtained with the ligand that contain a small methyl substituent in the oxazoline group, that proved to be superior than PHOX in the *Z*-substrates (89% ee), while ee's for *E*-alkenes were lower (ee's up to 89%).[28]

Pfaltz et al. also further modified PHOX ligands by replacing the *ortho*-phenylene tether by a branched alkyl chain (ligands **L8**; Figure 3, R^1= Ph, *o*-Tol, Xyl and R^2= ^{i}Pr, ^{t}Bu, Bn).[23] These ligands provided higher enantioselectivities in the hydrogenation of trisubstituted *E*- and *Z*-aryl alkenes than the PHOX ligands (ee's up to 98%). The best

results were achieved with the ligand that contains bulky substituents at both phosphine and oxazoline groups (R^1= Xyl and R^2=*t*Bu). The authors showed its applicability with the synthesis of (*R*)-7-demethyl-2-methoxycalamenene, an antitumor natural product.

The spirocyclic phosphine-oxazoline ligands **L9** (Figure 3, R^1= *o*-Tol, Ph and R^2= Ph, Bn) were also successfully used in the hydrogenation of α,β-unsaturated amides,[29] and β,β-disubstituted enones[30].

Afterwards, Zhang et al. developed phosphine-oxazoline ligands **L10** with an axis-unfixed biphenyl backbone (Figure 3, R^1= Ph, 3,5-^{t}Bu$_2$-C$_6$H$_3$, 3,5-^{t}Bu$_2$-4-MeO-C$_6$H$_2$ and R^2= ^{i}Pr, ^{t}Bu, Ph, Me) which successfully hydrogenated exocyclic α,β-unsaturated carbonyl compounds (including ketones, lactones, and lactams),[31] 3-substituted 2,5-dihydropyrroles,[32] and 2,5-dihydrothiophene 1,1-dioxides[32].

Aminophosphine-oxazoline ligands

Some aminophosphine-oxazoline ligands have also showed comparable high efficiency that phosphine-oxazolines in the reduction of unfunctionalized olefins or with poorly coordinative groups. In this context, Pfaltz et al. modified the PHOX ligands by replacing the *ortho*-phenylene group by a pyrrole group leading to ligands **L11** (Figure 4, R^1= Ph, *o*-Tol, Cy and R^2= ^{i}Pr, ^{t}Bu).[33] Enantiomeric excesses surpassed those previously obtained with the PHOX ligands, with ligands bearing a bulky *tert*-buthyl oxazoline substituent and either a *ortho*-tolyl or cyclohexenyl P-group. Nevertheless, the enantioselectivities for *Z*-trisubstituted olefins were not above 80% ee. Then, Gilbertson et al. developed the proline-based aminophosphine-oxazoline ligands **L12** (Figure 4, R^1= Ph, *o*-Tol and R^2= ^{i}Pr, ^{t}Bu), related to previous ligands **L11**, however they provided lower enantioselectivities.[34] The best result were obtained with the ligand bearing a bulky *tert*-buthyl oxazoline substituent.

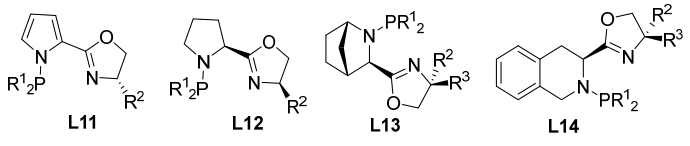


Figure 4. Selected aminophosphine-oxazoline ligand libraries developed for the hydrogenation of di- and trisubstituted olefins.

Andersson et al. developed ligands **L13** and **L14** (Figure 4, **L13**; R^1=Ph, *o*-Tol, Cy; R^2= H, ^{t}Bu, Ph and R^3= H, Ph; and **L14**; R^1= Ph; R^2= H, ^{i}Pr, Ph and R^3= H, ^{i}Pr, Ph).[35,36] Ligands **L13**, which are based on a rigid bicyclic backbone, provided higher enantioselectivities than ligands **L14**, with a more flexible backbone. Ir/**L13** catalyst (with R^1= R^2= R^3= Ph) afforded, for first time, high enantioselectivities in the hydrogenation of enol phosphinates,[35b,c] vinyl silanes,[35d] fluorinated olefins,[35e] vinyl boronates,[35f] α,β-unsaturated acryclic esters,[35g] α,β-unsaturated lactones[35g] and γ,γ-disubstituted and β,γ-disubstituted allylic alcohols[35h] (Figure 5).

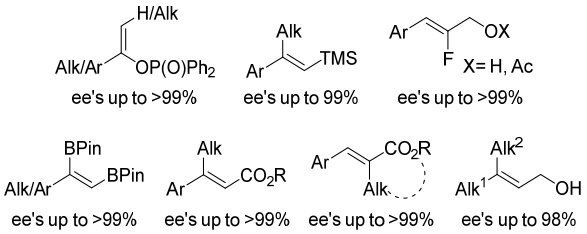


Figure 5. Representative hydrogenation results with Ir/**L13** catalyst.

Phosphinite-oxazoline ligands

It can been highlighted the family of phosphinite-oxazoline ligands **L15**, (Figure 6, R^1= Ph, *o*-Tol, Cy; R^2= ^{t}Bu, Ph, ferrocenyl, 2-Naph; R^3= H, Me, 3,5-Me_2-C_6H_3 and R^4= Me, ^{i}Pr, ^{t}Bu, Bn) developed by Pfaltz et al.[14d,f,37a-c] Ligands **L15** constitute one of the most privileged ligands for this process. They provided excellent enantioselectivities in the reduction of a broad range of both *E*- and *Z*-trisubstituted olefins, including α,β-unsaturated esters and for the first time, in a limited range of more challenging terminal olefins as well as in the reduction of 1,1'-disubstituted enamines (ee's up to 99%, Figure 7).[37a-d] More recently, Ir-catalysts containing ligands **L15** have also been successfully applied in the reduction of α,β-unsaturated nitriles (ee's up to 98%, Figure 7).[37c] The best enantioselectivities were achieved with ligands containing a methyl substituent at R^3, a benzyl substituent at R^4 and a phenyl at R^1. However, the appropriate substituent at the oxazoline and the configuration of the carbon of R^3 depend on the substrate to be hydrogenated. For *E*-trisubstituted olefins, ee's are best with ligands containing a Ph or a 3,5-Me_2-Ph and a *S*-configuration, while for *Z*-olefins the highest enantioselectivities were achieved using ligands with Ph and a *R*-configuration. In addition, these catalysts work efficiently in propylene carbonate as an environmental friendly solvent, and this allowed the Ir-catalysts to be reused maintaining the excellent enantioselectivities.[38]

Based on ligands **L15** Pfaltz group developed ligands **L16** (Figure 6, R^1= Ph, *o*-Tol and R^2= ^{i}Pr, ^{t}Bu) where the alkyl chain is bonded in the C-2 instead of the C-4 of the oxazoline moiety, which shifts the chirality from the alkyl chain to the oxazoline moiety.[14g,18] The scope of these ligands is narrower than with the privileged phosphinite-oxazoline ligands **L15**, however, they are complementary. Ligands **L16** provided high enantioselectivities for allylic alcohols and alkenes with heteroaromatic substituents.

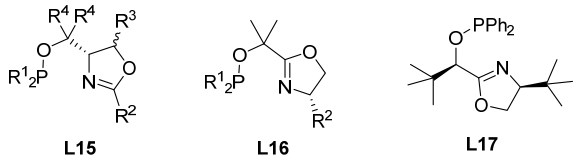


Figure 6. Selected phosphinite-oxazoline ligand libraries developed for hydrogenation of di- and trisubstituted olefins.

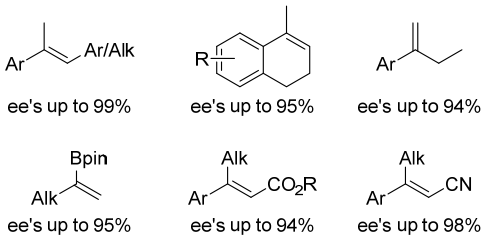


Figure 7. Representative catalytic hydrogenation results with Ir/**L15** catalyst.

Kazmeier et al. synthetized ligands **L17** (Figure 6) that provided excellent enantioselectivities for linear and cyclic α,β-unsaturated ketones (ee's up to >99%).[37d]

Phosphite-oxazoline ligands

Phosphite-containing ligands have shown to be particularly useful for asymmetric catalysis. They have a greater resistance to oxidation than phosphines and phosphinites, they are easily synthesized from readily available chiral alcohols, and their modular constructions is easy.[39] Despite this, it was not until 1999 that a publication reported their use in the reduction of unfunctionalized olefins using Ir-TADDOL-based phosphite-oxazoline catalysts (**L18**, Figure 8). However, their substrate scope and enantioselectivities were lower than their related Ir-phosphinite/phosphine-oxazoline catalysts. Additionally, the use of high pressures (100 bars) and high catalyst loadings (4 mol%) was required to obtain full conversions.[14h]

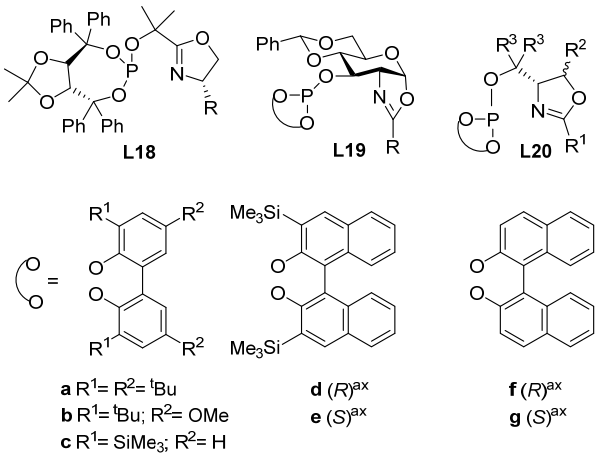


Figure 8. Selected phosphite-oxazoline ligand libraries developed for the Ir-catalyzed asymmetric hydrogenation of di- and trisubstituted olefins.

Our group contributed to the asymmetric Ir-catalyzed hydrogenation of unfunctionalized olefins with a new series of air stable ligands that are applicable to a wide variety of substrates (di- and trisubstituted). The key was the introduction of a flexible biaryl phosphite group in the ligand. We first developed the pyranoside phosphite-oxazoline ligand library **L19** (Figure 8, R= Me, ^{i}Pr, ^{t}Bu, Ph, Bn) synthetized from D-glucosamide, an inexpensive natural feedstock, that contains several biaryl phosphite groups.[21f,40] It was found that for enantioselectivities to be high the presence of bulky substituents in the biaryl phosphite group and less-sterically demanding substituents in the oxazoline moiety was required. Thus, it was possible to identify two general ligands (**L19c** and **L19e** with R= Ph) that provided high enantioselectivities. For comparative purpose, the related phosphinite-oxazoline analogues were also tested, but with lower success.[40b] With ligands **L19c** and **L19e**, high enantioselectivities and activities (ee's ee's up to >99%) in many trisubstituted olefins (25 examples, Figure 9), even in the reduction of the more challenging *Z*-isomers could be reached and triarylsubstituted substrates, which provides an easy entry point to diarylmethine chiral centers that are present in several important drugs and natural products.[41] High enantioselectivities could also be achieved in the reduction of many trisubstituted substrates with poorly coordinative groups, such as α,β-unsaturated esters and ketones, vinylsilane, allylic alcohol and acetates. Also to note the excellent enantioselectivities obtained in the hydrogenation of vinylboronates (ee's ranging from 92% to >99%). Their hydrogenation provides chiral borane compounds, which are useful building blocks in organic synthesis because the C-B bond can be readily converted to C-O, C-N

and C-C bonds with retention of the chirality. Even more remarkable were the high enantioselectivities obtained for the first time in the reduction of a broad range of 1,1'-disubstituted olefins (19 examples, Figure 9). It was found that the Ir/**19e** system was robust against variations in the electronic nature of the substrate aryl substituents (ee's up to 99% ee). Also high levels of enantioselectivity were obtained in the reduction of heteroaromatic terminal olefins (ee's up to 99%). Nevertheless, the enantioselectivities were affected by the nature of the alkyl chain and diminished in 1,1'-diaryl alkenes due to an isomerization process.

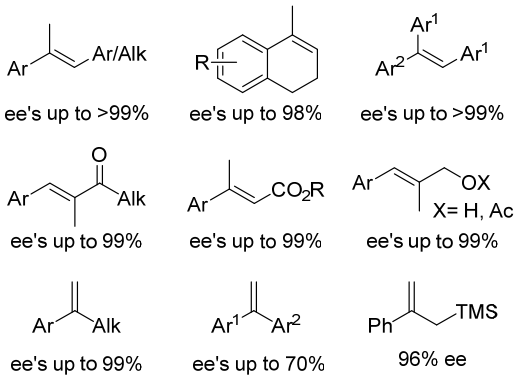


Figure 9. Representative hydrogenation results with Ir/**L19c,e** catalyst.

With the aim of understanding the catalytic performance of Ir/**L19** catalysts, a DFT computational study was performed in collaboration with Norrby et al.[21f] It was found, that the preferred reaction path is an Ir(III/V) cycle with migratory insertion of a hydride as the selectivity-determining step. In addition, the effect of the ligand parameters could be rationalized by using a simple quadrant model (Figure 10), where the phenyl oxazoline's substitutent occupies the upper left quadrant, and one of the aryls of the biaryl phosphite moiety partly blocks the lower right quadrant (Figure 10a). The other two quadrants are free. The calculated structure had a chiral pocket that fit perfectly *E*-olefins (Figure 10b). This quadrant model also explains the change of ligand (from **L19e** to **L19c**) to obtain a high enantioselectivity in *Z*-olefins (Figure 10c). Ligand **L19c** has bulky substituents in the *para* position, which increase the dihedral angle of the biaryl group and results in lower occupancy of the lower right quadrant than with ligand **L19e**. Therefore, the substituent in the biphenyl group can tune the occupancy of the lower right quadrant, and therefore *Z*-alkenes can also be successfully hydrogenated (Figure 10c). The same explanation accounts for the triaryl- and disubstituted substrates. In conclusion, the DFT studies confirm that the flexibility of the biaryl phosphite group

is a crucial parameter in the achievement of high enantioselectivities for substrates with different geometries and steric requirements.

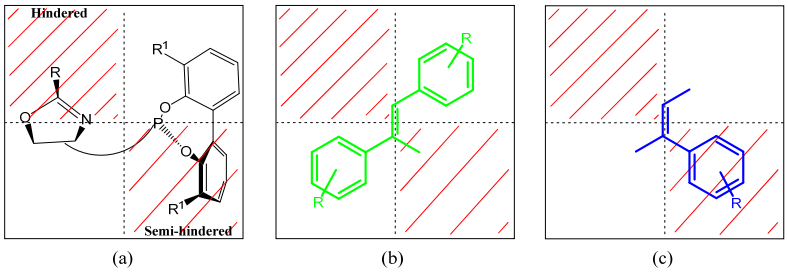


Figure 10. Quadrant diagram describing the enantioselective substrate-ligand interactions.

Following this contribution come the developments of new biaryl phosphite-oxazoline ligand libraries with the aim to increase even further the range of substrates successfully hydrogenated.[9c,42,43] Among them, we can highlight the application of phosphite-oxazoline ligands (**L20**, Figure 8),[42a,b] which were inspired in one of the best families developed for this transformation (previous ligands **L15**, Figure 6) by replacing the phosphinite groups by several biaryl phosphite moieties. Selecting the ligand parameters high enantioselectivities has been reported for trisubstituted olefins. Whereas Ir/**L20g** catalyst provided the best enantioselectivities for linear and cyclic olefins and a α,β-unsaturated ester, the best ee's for the more demanding *Z*-isomers and allylic alcohol and acetate were obtained with Ir/**20a** catalyst. This high catalytic performance was also extended to the hydrogenation of the more challenging 1,1'-disubstituted olefins (29 compounds, Figure 11), surpassing the previous family **L19** and becoming one of the best catalyst for the reduction of this type of substrates. High enantioselectivities were achieved in a broad range of aryl-alkyl (ee's up to >99%), even with substrates bearing decreasingly sterically alkyl substituents, and heteroaromatic-alkyl (ee's up to >99%) olefins. These catalyst precursors also tolerate very well the presence of neighboring polar groups. High enantioselectivities were achieved in the reduction of allylic alcohols and an allylic silane. Interestingly, the reaction showed no loss of enantioselectivity when dichloromethane was replaced by propylene carbonate. In addition, the use of propylene carbonate allowed the catalysts to be recycled up to five times by a simple two phase extraction maintaining the excellent enantioselectivities.

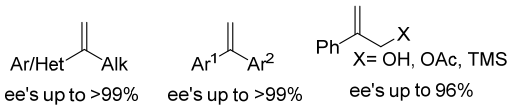


Figure 11. Representative results achieved with Ir/**L20** catalysts in the hydrogenation of 1,1'-disubstituted substrates.

Phosphorus-other nitrogen donor ligands

In the recent years, the research has also focused on the design of ligands containing more robust groups than oxazolines. A collection of the most representative phosphorus-other nitrogen donor ligands will be next presented.

As an alternative to P-oxazoline ligands, pyridine-containing ligands has attracted interest due to the robustness and the easy incorporation of pyridine group. Despite this few pyridine-containing ligands have provided outstanding results in terms of enantioselectivity and substrate versatility. For selected examples see Figure 12.[15a,17,44] Among them we can highlight the first pyridine containing ligand developed by Pfaltz et al. (phosphinite-pyridine ligands **L21**; Figure 12, R^1= Ph, *o*-Tol, Cy, ^{t}Bu and R^2= Me, ^{t}Bu, Ph, CPh_3), which was successfully used in a limited range of alkenes.[44d] The performance was subsequently further improved by the same group introducing a more rigid chiral bicyclic ligand backbone (ligands **L22**, Figure 12, R^1= Ph, *o*-Tol, Cy, ^{t}Bu; R^2= H, Ph, Me and R^3= H, Me). This ligand family with high rigidity was successfully applied in several kinds of trisubstituted olefins, including purely alkyl trisubstituted alkenes, furans, and benzofurans as well as trisubstituted pinacol derivates, α,β-unsaturated lactones, and N-protected indoles.[17,44e,g,h] The enantioselectivity was highest with a Ph substituent at the R^2 and bulky substituents at the phosphinite moiety (^{t}Bu or *o*-Tol). To obtain excellent enantiocontrol in the reduction of 7-methoxy-4- methyl-1,2-dihydronaphthalene, the introduction of a large aryl substituent at R^2 (2,4,6-tri-Me-Ph) was needed. Its applicability was demonstrated in the reduction of γ-tocotrienyl acetate to obtain γ-tocopherol, a principal component of vitamin E,[44i] resulting in enantioselectivity >98% for the *RRR* enantiomer. Another synthetic application can be found in the diastereo- and enantioselective hydrogenation of farnesol stereoisomers. By changing the bond's geometry, these catalysts give access to the four stereoisomers of the product in high selectivity.

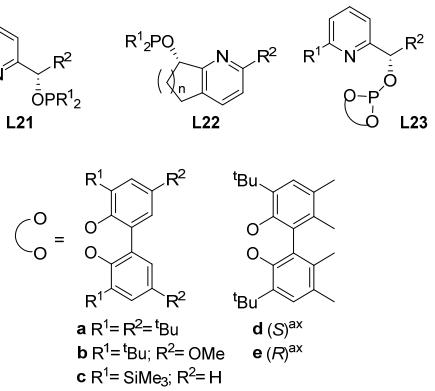


Figure 12. Most representative P-pyridine ligands for Ir-catalyzed asymmetric hydrogenation.

To benefit from the advantages of phosphite and pyridine moieties, our group replaced in ligands **L21** the phosphinite moieties by several biaryl phosphite groups increasing even further the substrate scope (Figure 12; ligands **L23**, R^1= H, Me, Br, Ph and R^2= Me, ^{t}Bu, Ph).[44o] Excellent enantioselectivities (ee's up to 99%) were obtained in a wide range of *E*- and *Z*-trisubstituted alkenes, including more demanding triarylsubstituted olefins and dihydronaphthalenes, and also terminal disubstituted olefins and to alkenes containing neighboring polar groups.

Another interesting change in the nitrogen donor group is the replacement of the oxazoline by imidazole, oxazole, thiazole, thiazoline and sulfoximine[45] groups. For selected examples see Figure 13. The first application was reported by Pfaltz et al. with the phosphine-imidazole ligands **L24** (Figure 13, R^1= Ph, *o*-Tol; R^2= ^{i}Pr, *t*Bu and R^3= ^{i}Pr, tBu, Cy, Ph, Bn, *p*-Tol).[14e] One advantage of the imidazoline group over the oxazoline is the possibility to introduce a new substituent R^3 at the nitrogen that could serve as a linker to attach the ligand to a solid support. Ligands **L24** provided better enantioselectivities in the hydrogenation of *Z*-trisubstituted olefins (ee's up to 88%) than PHOX ligands (ee's up to 42%). The best results were achieved with ligands containing bulky substituents at both R^1 and R^2 positions, while the substituent at R^3 had to be optimized for each substrate. Andersson group also developed the phosphine-imidazole ligands **L25** (Figure 13, R^1= Ph, *o*-Tol, 3,5-diMe-Ph), that gave high enantioselectivities for *E*-aryl/alkyl trisubstituted olefins (ee's up to 98%)[46,47] and cyclic dienes (ee's up to >99% for the *trans* isomer),[48] but was only moderate in the reduction of *Z*-olefins (ee's up to 72%).[47] The, enantioselectivities were best with ligand containing a bisphenylphosphanyl group except for the reduction of *trans*-α-

methylstilbene for which a bis-(*o*-tolyl)phosphanyl group was needed. More recently, they also showed its applicability in the enantioconvergent formal deoxygenation of racemic alcohols (Figure 5). This methodology was successfully used in the total synthesis of antidepressant sertraline and σ_2 receptor PB 28[35j].

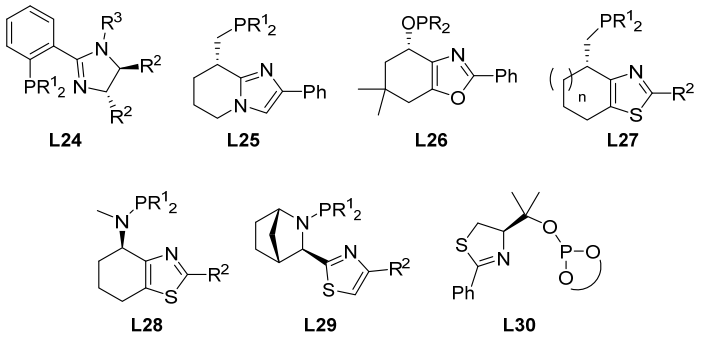


Figure 13. Most representative P-other N-donor ligands for Ir-catalyzed asymmetric hydrogenation.

Several classes of other P,N-ligands have been developed by Andersson et al. (Figure 13, ligands **L26**-**L29**; R^1= Ph, o-Tol … and R^2= Ph, ^{t}Bu …). The investigation of different bicyclic heteroaromatic rings led to highly enantioselective iridium catalysts containing oxazoles[23] and thiazoles[24] (Figure 13). These catalysts perform excellently on the typically tested trisubstituted nonfunctionalized olefins and also allow extending the substrate scope to vinyl allyl silanes,[35d] fluorinated olefins,[47,35e,49] vinyl boronates,[35f] enol phosphinates,[35b] and *E*- and *Z*-chiral sulfones,[50] allylic alcohols,[35h,51] and the monohydrogenation of 1,4-dienes.[52] Among the hydrogenation of dienes many purely alkyl-substituted were successfully hydrogenated (ee's up to 99%). In addition, they are able to selective hydrogenated only one of the double bonds leaving room for further synthetic manipulations. In this respect, Andersson group use this methodology to the total synthesis of (-)-Juvabione, a natural sesquiterpene exhibiting juvenile hormone activity using Ir/**L28** catalyst.[53]

Another interesting example of ligand design was the phosphite-thiazoline ligand **L30** (Figure 13), in which the oxazoline group in ligands **L20** was replaced by a thiazoline moiety. The introduction of a thiazoline moiety have not only provided enantioselectivities up to >99% for a range of α,β-unsaturated ketones, vinyl silane and trifluoromethyl olefins, but also have increased the enantioselectivities of *Z*-

trisubstituted olefins, while maintaining the excellent enantioselectivities for a range of *E*-trisubstituted and 1,1-disubstituted minimally functionalized olefins.[54]

P-carbene ligands

Another type of effective catalysts are the Ir/carbene-nitrogen complexes. An important advantage of N-heterocyclic carbene (NHC) catalysts compared to their phosphine analogues concerns their better tolerance for acid sensitive substrates. In 2001, Burgess' group reported for the first time that NHC-oxazoline based Ir-catalysts (ligand **L31**, Figure 14, R^1= 2,6-^{i}Pr$_2$-Ph and R^2= 1-Ad) can also be applied in the hydrogenation of unfunctionalized olefins with results comparable to the commonly used Ir-P,N catalysts.[55a,b] These catalysts afforded high enantioselectivities (up to 98% ee) in a limited group of unfunctionalized olefins, mainly trisubstituted and for the more challenging disubstituted olefins only one example was reported with low enantioselectivity. Since then, a few more carbene-N ligands have been developed but with less success,[55c-g] except for the family of Ir-NHC-pyridine catalysts[55h] developed in Pfaltz's group (with ligands **L32**, Figure 14, R=2,6-diisoprpoylbenzene) that showed similar enantioselectivities to the Burgess ones. So, high enantioselectivities (>90% ee) were observed, even for *Z*-trisubstituted (94% ee) and endocyclic substrates (96% ee).

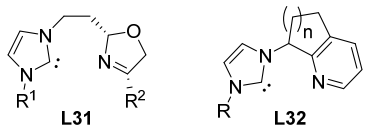


Figure 14. Selected P-carbene ligands for Ir-catalyzed hydrogenation of olefins.

Application of P-O/S ligands

In contrast to other catalytic processes and to the Rh/Ru-hydrogenation, for the reduction of unfunctionalized olefins the possibility of changing the nature of the N-donor atom in the ligand design of heterodonor ligands was not contemplated until recently. In 2011 Pfaltz successfully reported the application of proline-based P,O ligands **L33** in the asymmetric hydrogenation of trisubstituted alkenes (Figure 15, R^1 = Ph, ^{t}Bu, Cy, *o*-Tol and R^2 = ^{t}Bu, 1-Ad, CPh$_3$, 1Ad-NH, MesNH, CPh$_3$NH).[56] Phosphines bearing either a bulky amide or urea groups at the pyrrolidine N-atom

formed efficient Ir-catalysts for the asymmetric hydrogenation of several minimally functionalized olefins (ee's up to 99%).

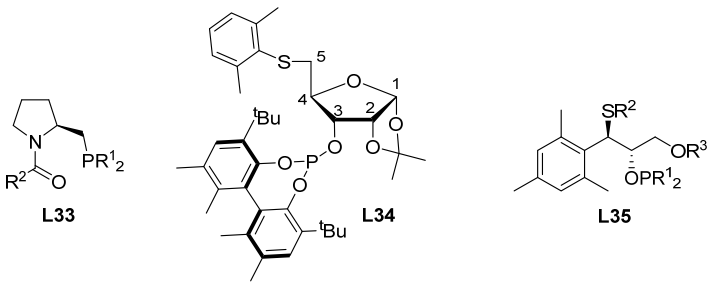


Figure 15. Selected P-O/S ligands for the Ir-catalyzed hydrogenation of olefins.

At the same time our group reported the application of a highly modular furanoside phosphite-thioether ligand library (ligands **L34**, Figure 15).[57] By selecting the ligand components in these furanoside-based ligands (position of the thioether group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3, the thioether substituent and the substituents/configuration in the biaryl phosphite moiety) we found that the best enantioselectivities were obtained using ligands with a 5-deoxy-ribofuranoside backbone **L34**. Excellent enantioselectivities were obtained (ee's up to 99%) in the reduction of a range of trisubstituted alkenes, including relevant examples with poorly coordinative groups (such us, α,β-unsaturated esters and vinylboronates). The results are comparable to the best ones reported in the literature except for the hydrogenation of 1,1'-disubstituted aryl/alkyl olefins. For this substrate class, our results indicated that enantioselectivity is dependent on the nature of the alkyl substrate substituent and much less affected by the electronic nature of the aryl ring. This has been attributed to an isomerization process that was supported by the fact that the hydrogenation of substrates bearing a *tert*-butyl group, for which isomerization cannot occur, provides high levels of enantioselectivity (ees up to 98%). We also studied the effect on catalytic performance of introducing either phosphinite or phosphine moieties with lower success.

Since then several other P-thioether ligands have been developed.[58] From them we can highlight the modular phosphite/phosphinite-thioether ligand library **L35** (Figure 15; R^1= Ph, Tol, Cy, Mes; R^2= Ph, 2,6-Me_2-Ph, 4-MeOPh, 2-Naph, ^{t}Bu, Ad, Cy; R^3= Me, Tr, Mes). In a simple 3 step procedure, several ligand parameters were easily tuned to maximize the enantioselectivities for each substrate (ee's up to 99% in 43 hydrogenated

products, Figure 16).[59] In contrast to the furanoside-based ligands mentioned above (**L34**), the best enantioselectivities were obtained with the phosphinite-S ligands, while results achieved with the phosphite-S analogues were less optimal. The crystal structures of the Ir-catalyst precursors indicate an equatorial disposition of the thioether group for the phosphite-based ligands, while an axial disposition is found in the analogues phosphinite ligands. The modularity of the ligands together with DFT studies were crucial to find which ligand parameters could be modified to generate more selective catalysts. In this respect, the use of a bulky mesityl group instead of a phenyl group in the ligand backbone improved enantioselectivity. With catalyst Ir/**L35**, with R^1= Tol, R^2= 2,6-Me_2-Ph and R^3= Me, excellent enantioselectivities (ee's up to >99%) were recorded for many trisubstituted olefins, including olefins with relevant neighboring polar groups such as α,β-unsaturated esters, ketones, vinyl boronates and allylic alcohols (Figure 16). High enantioselectivities were also achieved in the hydrogenation of 1,1'-disubstituted alkenes. Excellent enantioselectivities were also maintained by using propylene carbonate as an environmentally benign solvent, which allowed the Ir-catalyst to be reused up to three times. DFT studies also confirmed that the preferred reaction path is an Ir^{III}/Ir^{V} cycle where the selectivity-determining step is the migratory insertion of a hydride. DFT results also allowed the formulation of a quadrant model which explains the effect of the ligand parameters on selectivities. In this quadrant model the thioether substituent occupies the upper left quadrant and one of the P-substituents partly occupies the lower right quadrant, while the other two quadrants are free. This explains the high enantioselectivities obtained with the DFT-optimized guided design of thioether–phosphinite ligands in the reductions of (*E*)-olefins. In the case of the analogous phosphite–thioether ligands, the upper left quadrant is not enough blocked due to the equatorial disposition of the thioether group, which explains that their provided lower enantioselectivities than the related phosphinites.

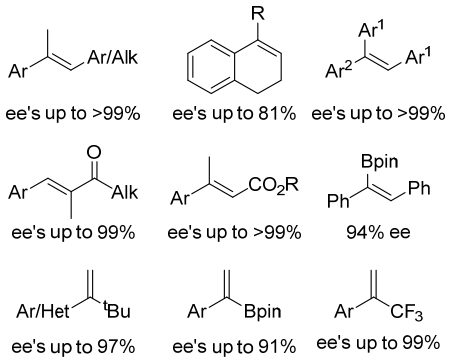


Figure 16. Representative hydrogenation results with Ir/**L35** catalysts.

2.2. Tetrasubstituted unfunctionalized olefins or with poorly coordinative groups

Despite the advances during the last 10 years in the hydrogenation of unfunctionalized olefins with the development of ligand libraries that allowed a significantly increase in the range of substrates that can been successfully hydrogenated, the reduction of tetrasubstituted olefins remains a challenge. The range of such substrates that can be efficiently hydrogenated is still narrow.[60]

In 1999 Buchwald's group reported the first successful asymmetric hydrogenation of tetrasubstituted unfunctionalized olefins.[61] Although high enantioselectivities were achieved for substituted indenes using the zirconozene catalyst **1** (Figure 17; ee's in the range 52–99%), the high catalyst loading (8 mol %), high H_2 pressure (typically >110 bar) and the low stability of the catalyst hampered their broad use. Much more recently, Zhang's group reported a Rh-catalyst **2** (Figure 17), containing a P-stereogenic diphosphine ligand synthesized in nine steps, that provided 85–95% ee's in the reduction of some indenes.[62] But it still required high catalyst loading (10 mol%), 60 °C and longer reaction times (4 days). Again, Pfaltz's group made an important breakthrough in this field. In 2007, they found that the stability and/or the harsh reaction conditions issues of the Zr/Rh-catalysts can be overcame with Ir/P-N catalysts. Another important finding was that the optimum ligand structures for tri- and tetrasubstituted olefins differed strongly.[19] Using Ir-catalysts **3** (Figure 17), containing ligands that form a 5-membered chelate ring, a wide range of indenes were hydrogenated with ee's in the range 94–96%, under milder reaction conditions and low catalyst loading (typically 1-2 mol%). Nevertheless, ee's diminished for non-cyclic olefins and for 1,2-dihydro-napthalenes (ee's between 89-97% and up to 77%, respectively). It should be mentioned that these catalysts were unsuccessful in the hydrogenation of trisubstituted olefins.

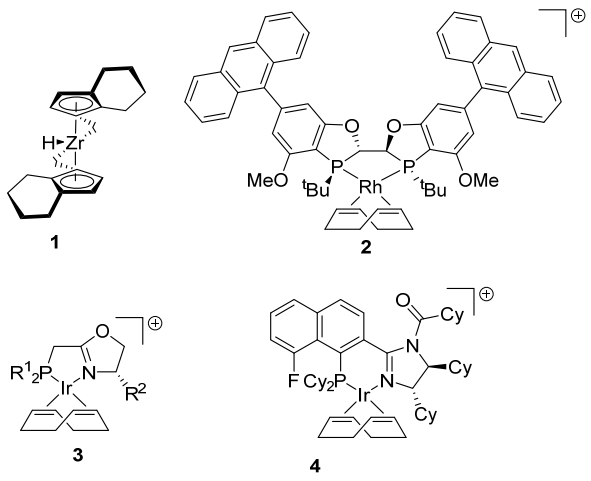


Figure 17. Representative catalysts for the Ir-catalyzed hydrogenation of tetrasubstituted olefins.

This finding prompted the interest in the design of new specific ligands for Ir-hydrogenation of unfunctionalized tetrasubstituted olefins. In 2013 Busacca's group found that the Ir-catalyst **4** could hydrogenate two cyclic substrates with ee's up to 96% at low catalyst loading. An inconvenience was that low temperature (0 °C) was required.[63]

Several more successful reports have appeared in the last few years. Notably, Andersson's group showed the efficient asymmetric hydrogenation of the challenging acyclic tetrasubstituted olefins. They successfully hydrogenated a broad range of tetrasubstituted vinyl fluorides using one of their privileged Ir-P,N catalysts for the reduction of trisubstituted olefins, with a small modification in the P group (ligand **L23** with R^1= *o*-EtPh; R^2=H; R^3= ^{i}Pr see above Figure 12).[64] The challenge of these substrates is that the catalyst must not only control de face selectivity, but also avoid the side defluorination reaction. Advantageously, the reaction proceeded smoothly without defluorination in high diastereo- and enantioselectivities. Various aromatic, aliphatic, and heterocyclic systems with a variety of functional groups were efficiently hydrogenated. The successful asymmetric hydrogenation of these substrates opens up a direct, atom-efficient, path to synthesize of chiral fluorine molecules with two contiguous stereogenic centers. However, the catalyst was not successful for other classes of cyclic and acyclic tetrasubstituted olefins, and also required the use of high H_2 pressure (20-100 bar).

Our group in collaboration with Riera's group reported the application of an Ir/P-stereogenic aminophosphine-oxazoline catalyst library **L36**, (Figure 18, R= Ph, ^{i}Pr, ^{t}Bu), with a simple, modular architecture, in the asymmetric hydrogenation of a broad range of different types of unfunctionalized tetrasubstituted olefins.[65] Improving previous results reported until now, the same family of catalysts is able to efficiently reduce indenes and the challenging 1,2-dihydro-napthalene derivatives (ee's up to 96%) and also a broad range of the elusive acyclic olefins with enantioselectivities up to 99% under mild reaction conditions. Moreover, the excellent catalytic performance is maintained for a range of aryl and alkyl vinyl fluorides (dr's > 99% and ee's up to 98%), where two vicinal stereogenic centers are created.

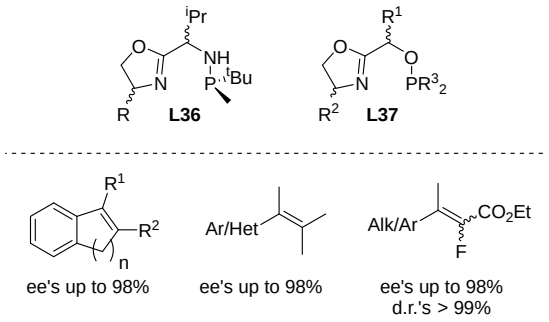


Figure 18. Selected catalytic results obtained with Ir/**L36**-**L37** catalysts in the reduction of tetrasubstituted olefins.

Then, by substitution of the aminophosphine group by simple readily available phosphinite groups (Ir/**L37** catalyst, R^1= Ph, *o*-Tol, Cy; R^2= Ph, ^{i}Pr, ^{t}Bu, Figure 18) we could also efficiently reduce many unfunctionalized tetrasubstituted olefins (ee's up to 98%) under mild reaction conditions.[9c] It should be noted that the more rigid the tetrasubstituted olefin is, the less bulky phosphinite moieties are required to reach the maximum enantioselectivity. For the more rigid cyclic indene derivatives, the best catalytic performance is therefore reached with the phosphinite-based ligand with Ph phosphinite substituent, while for the less rigid cyclic substrate, the phosphinite ligand with a bulkier *o*-tolyl group is needed. Finally, the even less rigid acyclic substrates require the ligand with the bulkiest cyclohexenyl phosphinite group. Even more interestingly, maintaining the same skeleton of the ligand by simple changing the phosphinite functionality by the right phosphite group (ligands **L37a-c**, Figure 19) we could also efficiently reduce many unfunctionalized tri- and disubstituted olefins (ee's up to 98%, Figure 19). In summary, from a common simple skeleton, the correct choice

of either phosphite or phosphinite groups gives for the first-time ligands that are suitable for di-, tri- and tetrasubstituted unfunctionalized substrates and also for cyclic β-enamides (62 examples, with ee's up to 99%).

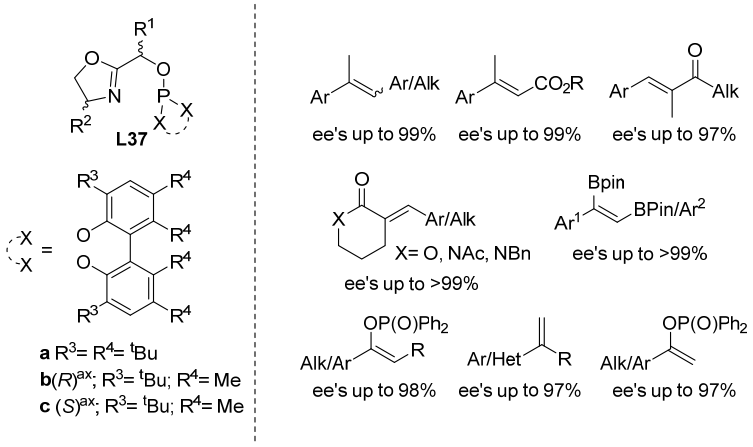


Figure 19. Selected results obtained with phosphite-oxazoline of ligands **L37a-c** in the Ir-catalyzed hydrogenation of di- and trisubstituted olefins.

A notable last contribution is the identification of an Ir-catalyst that is able to successfully hydrogenated a very broad range of diverse acyclic unfunctionalized tetrasubstituted olefins (around 30 examples).[66] A first parallel screening of a set of 34 different Ir-catalysts, found previous Ir-catalyst **3** (Figure 17, R^1= *o*-Tol; R^2= ^{i}Pr) to be the best candidate. A subsequent optimization of its structure (phosphine and oxazoline substituent) identified **3** with R^1= Cy and R^2= 3,5-bis-^{t}Bu-Ph as the optimal catalyst.

3. Ir-catalyzed asymmetric hydrogenation of olefins containing coordinating groups

As already mentioned the hydrogenation of olefins with strongly coordinating groups has been predominantly performed using Rh- or Ru- catalysts bearing chiral diphosphine ligands. They still constitute the optimal choice for the synthesis of optically active α-amino acids and many pharmaceutically relevant compounds. Nowadays, excellent enantioselectivities can be achieved for N-acyl α-dehydroamino acid derivatives, enamides and acrylates or itaconates among others.[2] However, in the last decade Ir-based catalysts have appears as a good alternative in the reduction of challenging functionalized olefins, providing higher catalytic performance than the Rh and Ru-catalysts. In this respect, we next show the improved catalytic performance in

the reduction of carboxylic acids and nitroolefins using Ir-catalyst. Chiral carboxylic acids are important intermediates for the preparation of biologically active compounds.[67] On the other hand, enantiomerically pure nitroalkanes can be easily converted to other versatile building blocks, such as amines, aldehydes, carboxylic acids, nitrile oxides, and denitrated compounds.[68]

3.1. Ir-catalyzed asymmetric hydrogenation of carboxylic acids

Although only few Ir-catalysts have been studied for this transformation, they have allowed to overcome the limitations of most studied Rh- and Ru-catalysts. Indeed, most of the reported Rh- and Ru-catalysts showed a scope limited to acrylic and cinnamic acids and especially with Ru-catalysts, high pressures and catalyst loadings are usually needed.[2] Scrivanti and co-workers explored for the first time the Ir-PHOX catalyst in the hydrogenation of 2-phenethylacrylic acid, recording enantioselectivities not higher than 81% ee.[69] Later, Burgess applied a chiral N-heterocyclic carbene-oxazoline **L31** (Figure 14) in the hydrogenation of tiglic acid with only 55% ee.[70] The inefficiency of these iridium catalysts was partly attributed to their tendency to aggregate into inactive trimers under a hydrogen atmosphere.[71]

Zhou et. al. showed for the first time that Ir-catalysts, the spiro phosphine-oxazoline (SIPHOX) Ir-catalysts (Figure 20a)[72], could efficiently hydrogenate unsaturated carboxylic acids with the presence of a base.[73] The addition of a base results in the formation of a carboxylate anion, which act as a strong coordinating group. Under mild reaction conditions, excellent yields (90−97%) and enantioselectivities (96−>99% ee) could be achieved for a broad range of α-aryloxy and α-alkyloxy substituted α,β-unsaturated acids, with TONs up to 10.000 (Figure 20a). It was found that the best catalysts contained a ligand with a bulky P-aryl group (Ar= $^{t}Bu_2Ph$), which was the best choice for most of the substrates studied afterwards. The hydrogenation protocol was efficiently used for the preparation of α-benzyloxy-carboxylic acid, a key intermediate in the syntheses of rhinovirus protease inhibitor rupintrivir (Figure 20b).[74] In contrast to previous Ir-catalysts, the rigidity and bulkiness of the spiro scaffold on SIPHOX ligands, seemed to prevent the Ir-catalysts to trimerize under hydrogenation conditions. The authors also found that while Ir-SIPHOX catalysts were not effective for the hydrogenation of α,β-unsaturated esters[75], the Ir-PHOX analogue did provide excellent enantioselectivities.[3b] Thus, both catalyst types have complementary substrate scope.

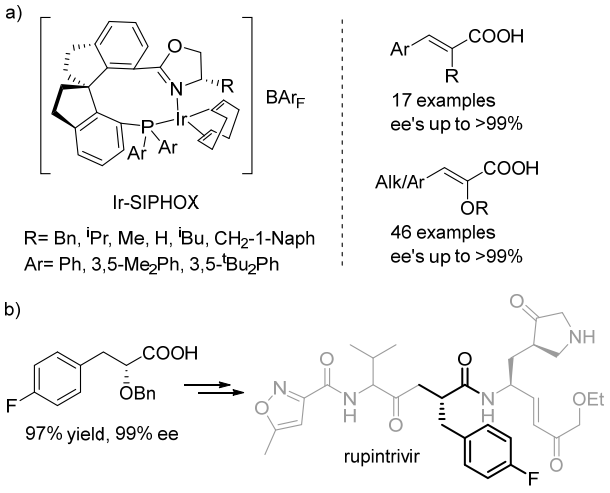


Figure 20. a) Ir-SIPHOX catalysts and their application in the asymmetric hydrogenation of α-alkyl, α-aryloxy- and α-alkyloxy-substituted α,β-unsaturated carboxylic acids. b) Synthesis of rupintrivir a rhinovirus protease inhibitor.

With the use of Ir-SIPHOX catalysts, Zhou and co-workers have largely unblocked the amount of unsaturated carboxylic acid derivatives that can be hydrogenated enantioselectiviely,[75,76] and for which Rh- and Ru-catalysts showed no success. Thus, they further expanded its application to the reduction of other trisubstituted α,β-unsaturated carboxylic acids, such as α-aryl- and α-oxymethyl-substituted cinnamic acids (Figure 21). The hydrogenation of both types of substrates were used as a key step for the total synthesis of two natural products. Thus, the enantioselective reduction of α-arylcinnamic acid (Ar^1=2,4-MeO$_2$Ph, Ar^2= 4-MeOPh)[77] and α-oxymethylcinnamic acid (Ar= 4-MeOPh, R= 3,4-(OCH$_2$O)Ph) was used for preparing (*S*)-Equol and (*S*)-(+)-homoisoflavone.[78] Similarly, a range of N- and O-heterocycles of different ring sizes could be also hydrogenated with enantioselectivities ranging from 89 to 99% ee (Figure 21). The methodology allowed the direct preparation of (*R*)-nipecotic acid and (*R*)-tiagabine in excellent yields and enantioselectivities.[79] Again, with a ligand containing a 3,5-^{t}Bu$_2$Ph substituent in the phosphine, a range of tetrasubstituted acrylic acids with α-aryl, α-alkyl, α-aryloxy, or α-alkyloxy substituents were reduced in high enantioselectivities (90-99%) (Figure 21). It should be noted that some of the hydrogenated products are key intermediates of chiral drugs, such as Mibefradil and Fenvalerate.[80]

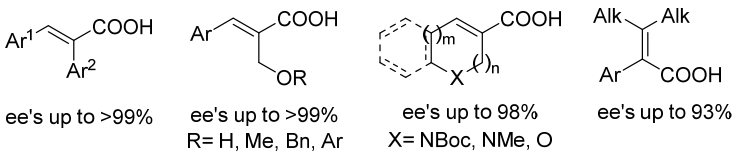


Figure 21. Ir-catalyzed asymmetric hydrogenation of trisubstituted α,β-unsaturated carboxylic acids and acrylic acids with SIPHOX ligands.

The excellent results of spiro phosphine-oxazoline ligands (SIPHOX) are not only limited to α,β-unsaturated acids. The authors also explored the reduction of several β,γ-unsaturated acids, which gives access to molecules with a chiral centre at the γ-position. A range of 4-alkyl-4-aryl-3-butenoic acids could be hydrogenated in up to 97% ee with a ligand containing an α-naphthylmethyl group on the oxazoline ring and a 3,5-Me_2Ph as a phosphine substituent (Figure 22). With this asymmetric hydrogenation as the key step, the concise total syntheses of the natural products (*R*)-aristelegone-A, (*R*)-curcumene, and (*R*)-xanthorrhizol were accomplished.[81] It should be noted that β,γ-unsaturated ester (*E*)-methyl 4-phenylpent-3-enoate was inert under hydrogenation conditions, thus indicating that the functional carboxy group is crucial for the reaction by acting as a directing group. The use of a carboxy directing group was also extended to the hydrogenation of terminal 1,1-dialkyl, 1,1-diaryl and 1-aryl-1-alkyl γ,δ-unsaturated acids (Figure 22, ee's up to 99%).[82] This strategy is particularly useful for the reduction of 1,1-diaryl and 1,1-dialkylethenes, in which most of the catalysts fail in differentiate the *Re*- and *Si*-faces due to the similarity on size of both substituents of the olefin. In addition, it was shown that the directing carboxy group on these substrates can be subsequently removed or easily transformed to other useful functional groups if desired.[82a] A range of α-alkyl-α-aryl terminal olefins were also reduced in excellent enantioselectivities (98->99%; Figure 22), yielding valuable compounds with a chiral benzylmethyl centre. The developed hydrogenation process was also used as a key step for preparing (*S*)-curcudiol and (*S*)-curcumene in excellent enantioselectivities and overall yields.[82b] Finally, the authors further confirmed the role of the carboxylate moiety as a directing group by showing that when no free carboxylic acid was present or no basic conditions were used, the reaction didn't proceed.[82a] Moreover, it was found that for substrates having an extra C=C double bond in the alkyl side chain, the presence of the carboxy directing group makes the reaction chemoselective towards the α-alkyl-

α-aryl double bond (Figure 22), even when the additional double bond was placed in the terminal position.[82b]

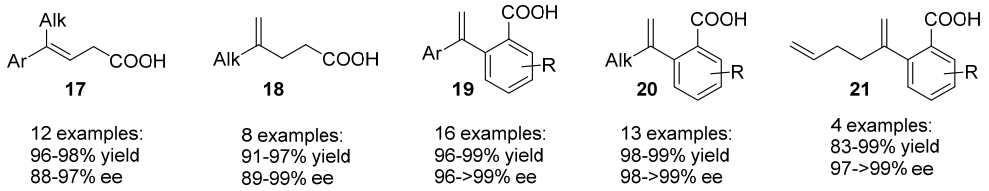


Figure 22. Ir-catalyzed asymmetric hydrogenation of β,γ-unsaturated acids and γ,δ-unsaturated acids using SIPHOX-ligands.

As found with Rh- and Ru-catalysts, the Ir-SIPHOX catalysts showed unsatisfactory results for the hydrogenation of 2-substituted α-arylacrylic acids. To overcome this limitation, Zhou and co-workers developed a new series of spiro P,N-ligands (SpiroBAP), with a benzylamino moiety instead of the oxazoline group (Figure 23a). The new generation of ligands exhibited extremely high reaction rates (TOFs up to 6000 h^{-1}) and excellent enantioselectivities (94−98% ee) in the reduction of α-aryl- and α-alkyl acrylic acids to the corresponding chiral carboxylic acids, including ibuprofen, naproxen, and flurbiprofen, which are widely used nonsteroidal anti-inflammatory drugs (Figure 23a). As for SIPHOX ligands, ligands with a bulky P-aryl group (Ar= 3,5-^{t}Bu$_2$Ph) gave the best catalytic results.[83]

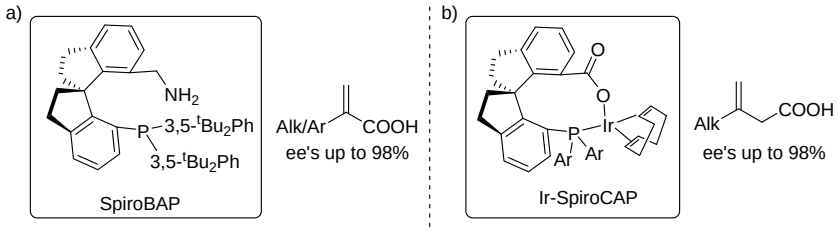


Figure 23. Ir-catalyzed asymmetric hydrogenation of a) α-substituted acrylic acids using a SpiroBAP ligand and b) 3-alkyl-3-methylenepropionic acids with Ir/SpiroCAP catalysts.

Zhou et. al have also recently developed a neutral version of spiro-based Ir catalysts (Ir-SPiroCAP, Figure 23b), by replacing the oxazoline moiety on SIPHOX ligands by an anionic carboxy group. The resulting Ir-complexes do not require the use of a tetrakis[3,5-bis(tri-fluoromethyl)phenyl]borate (BAr_F^-) counterion, which is necessary for stabilizing chiral cationic Crabtree-type catalysts, while remaining highly stable for

a long time in air. These new generation of catalysts exhibited an unprecedented high enantioselectivity (up to >99% ee) in the hydrogenation of the challenging 3-alkyl-3-methylenepropionic acids (Figure 23b). To demonstrate its potential application in organic synthesis, the synthesis of (*S*)-14-methyloctadec-1-en, a female sex pheromone of the peach leafminer moth (Lyonetia clerkella), was carried out. The new catalysts were also effective (ee's up to 99.4%) in the reduction of other α-methyl cinnamic acid, tiglic acid and α-substituted acrylic acids, among others.[76]

The authors also performed a mechanistic study including DFT studies that strongly supported an Ir(III)/Ir(V) cycle. The high stability of the chiral spiro-iridium catalysts under reaction conditions[72] allowed the trapping of the active intermediates and facilitated the mechanistic study.[84] To mimic the basic conditions used in the hydrogenation reactions the authors used sodium (*E*)-2-methyl-3-phenyl acrylate as a model substrate. The isolation of the monohydride intermediate **5** (Figure 24), resulting from the migratory insertion of **6** (Figure 24) was key to understand the mechanism. Dimeric species **7** and **8** (Figure 24), which are off-cycle species, were also isolated and characterized by X-ray diffraction. Both dinuclear intermediates have the carboxy group acting as a bridge of the two Ir-centers. The isolation of intermediates **5-8** confirms the coordination of carboxy group to Ir when the reaction is performed under basic conditions. It should be noted that in contrast to Ir-hydrogenation of unfunctionalized olefins, the Ir-dihydride olefin complex **5** can undergo migratory insertion in the absence of H_2.[22] This mechanistic divergence could indicates that the mechanism of Ir-catalyzed hydrogenation of alkenes may vary depending on the type of substrate and/or catalyst.

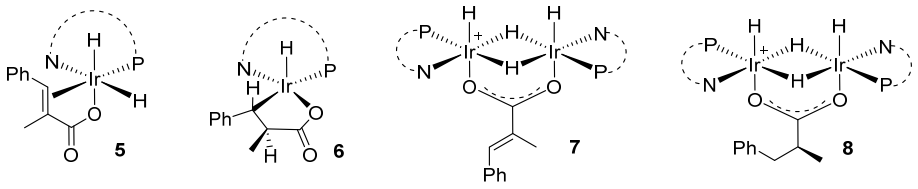


Figure 24. Structures of isolated intermediates **5-8** in the model reaction of sodium (*E*)-2-methyl-3-phenyl acrylate with the Ir-SIPHOX catalyst (Ar= 3,5-^{t}Bu$_2$Ph, R= H).

Two other Ir-catalysts have been studied for this transformation. Already in 2010, Ding et. al tested the spiro-based P,N-ligands **L9** (Figure 3) in the reduction of α-aryl-β-substituted acrylic acids. Enantioselectivities up to 96% ee were achieved, leading to the

production of a series of biologically interesting carboxylic acids, such as those containing a β-tetrahydro-2H-pyran-4-yl moiety.[85] These ligands were also applied in the hydrogenation of (*E*)-2-(hydroxymethyl)-3-arylacrylic acids in good to high enantioselectivities (Figure 25a).[86]

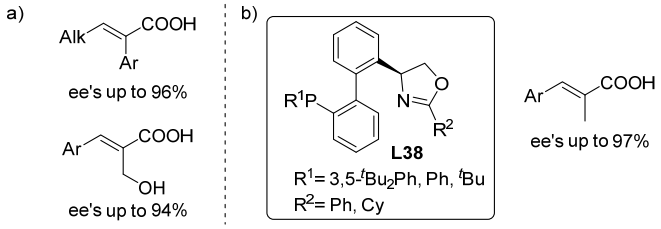


Figure 25. Ir-catalyzed asymmetric hydrogenation of a) α-aryl-β-substituted acrylic acids and α-hydroxymethyl cinnamic acids using ligand **L9** and b) α-methyl cinnamic acids with **L38** ligand.

Recently Zhang et. al reported the application of the phosphine-oxazoline ligands **L38** (Figure 6b), with an axial-unfixed biphenyl moiety, which has the advantage of a simple synthesis from the readily available (*S*)-(+)-2-phenylglycinol. Ir/**L38** (Ar= 3,5-^{t}Bu$_2$Ph, R= Ph) provided high yields and enantioselectivities in the widely studied α-methyl cinnamic acids (Figure 25b, up to 97% ee, 98% yield, 2.000 TON).[31]

3.2. Ir-catalyzed asymmetric hydrogenation of nitroolefins

Despite the synthetic utility of reduced chiral nitroalkanes, the direct asymmetric hydrogenation of these type of substrates was not achieved until quite recently, by using diphosphine-based Rh-catalysts.[87] Although these catalysts were quite efficient in the hydrogenation of β,β-disubstituted nitroolefins, they were sensitive to the steric hindrance of the substrate. Hou and co-workers developed an Ir-(*R*,*R*)-f-SpiroPhos complex for the reduction of β-acylamino nitroolefins (Figure 26). This newly developed Ir-catalysts allowed the preparation of a range of β-amino nitroalkanes in high yields and excellent optical purities (up to >99% ee), including substrates with *ortho*-substituted phenyl groups in the β-position.[88] The substrates studied contained a NH-acyl group which by chelation could facilitate the enantioselective hydrogenation. However, the authors showed later that Ir-(*R*,*R*)-f-SpiroPhos-catalyst was also highly enantioselective without the presence of this additional chelating group. Thus, excellent enantioselectivities (up to 98% ee, Figure 26) were also achieved in the reduction of

β,β-disubstituted nitroalkenes, including nitroalkenes with an *ortho*-substituted phenyl ring and thus, overcoming the limitations of the catalytic systems developed by Zhang and co-workers.[89] After this, the groups of Zhang and Zhou have also explored the enantioselective Ir-catalyzed reduction of nitroolefins without an extra chelating group, obtaining also high enantioselectivities. [90,91]

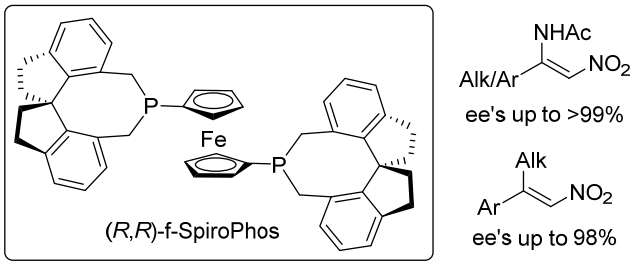


Figure 26. Ir-catalyzed hydrogenation of β-acylamino nitroolefins and β,β-disubstituted nitroolefins using (*R*,*R*)-f-SpiroPhos ligand.

3.3. Ir-catalyzed asymmetric hydrogenation of enamines, enamides and allylic amines

Ir-catalysts have also been used in the hydrogenation of amino-functionalized alkenes, albeit to a lesser extent than other alkenes.[44a,92,93] Nevertheless, they proved to be useful in the asymmetric hydrogenation of very attractive and challenging substrates, such as enamide esters, cyclic β-enamides, etc. In this context, the asymmetric hydrogenation of β-enamine esters is a straightforward way to prepare enantiopure β-amino acids and their derivatives. However, the methodology has been largely limited to the involvement of an N-acyl group that assists the reaction by chelation to the metal and facilitates to achieve high reactivity and enantioselectivity. The direct hydrogenation of unprotected enamine esters would be a more high-atom economical approach to obtain these valuable building blocks. Some Ir-catalysts modified with chiral monophosphoroamidites or diphosphine ligands, have been applied in the hydrogenation of some unprotected NH- and N-aryl enamine esters with good-to-high enantioselectivies (ee's up to 97%).[94] Recently, Dong, Zhang et al. disclosed the highly effective asymmetric hydrogenation of tetrasubstituted α-fluoro-β-enamino esters using bisphosphine−thiourea ZhaoPhos ligand (Figure 27).[95] A series of valuable chiral α-fluoro-β-amino esters containing two adjacent tertiary stereocenters were afforded with high yields and excellent diastereo- and enantioselectivities (d.r.'s up to >25:1, ee's up

to >99% ee and TON values up to 8600). Importantly, no defluorinated by-product was detected.

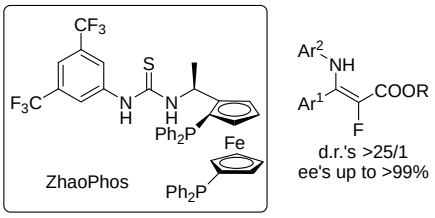


Figure 27. Hydrogenation of tetrasubstituted α-fluoro-β-enamino esters catalyzed by Ir-ZhaoPhos catalyst.

Ir-catalysts have also shown to be very useful for the enantioselective hydrogenation of cyclic β-aryl enamides. The reduction of this type of substrates constitutes a direct route to 2-aminotetralines and 3-aminochromanes, which are key structural units found in numerous therapeutic agents and biologically active natural products.[8] However, their hydrogenation have provided unsatisfactory results and only few Rh- and Ru-catalysts have been successful.[10] In 2012 a neutral Ir-complex, with a sulfonimidamido based phosphoramidite (SIAPhos) ligand, catalyzed the reduction of three cyclic β-enamides with promising enantioselectivities (up to 92% ee; Figure 28). However, this catalyst showed low activities (55-81% conversion after 18 h at rt and at P_{H2}=50 bar).[96]

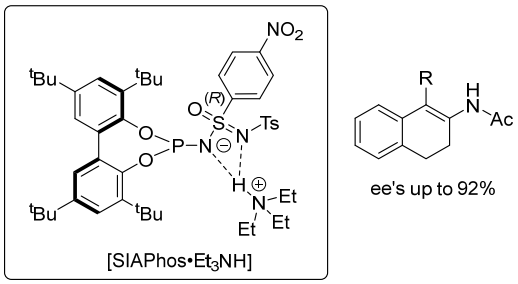


Figure 28. Ir-catalyzed hydrogenation of β-aryl cyclic enamides using SIAPhos ligand.

It has not been until very recently that Ir-catalysts have shown their high efficiency in the reduction of this type of challenging substrates. In 2016 two reports appeared demonstrating the potential of Ir-catalysts modified with P,N-ligands and showing that Ir-P,N catalysts can be also efficient in the reduction of alkenes bearing metal-coordinating groups.[9a,b] Riera and Verdaguer et. al. found that bulky P-stereogenic phosphine-oxazoline ligands **L36** (Figure 18) provided the highest selectivity ever reported for the reduction of cyclic enamides derived from α- and β-tetralones (Figure

29a, ee's up to 99% ee at only 3 bars of H_2), surpassing the results obtained with the widely studied Rh and Ru-catalysts.[9a] The same year, Diéguez and co-workers also reported the successful application of PHOX derived phosphite ligands **L39** (Figure 29b) to the hydrogenation of cyclic β-enamides.[9b] A range of 2-aminotetralines and 3-aminochromanes were obtained in high yields and excellent enantioselectivities (ee's up to 99%, Figure 29b). The hydrogenation of cyclic α-enamides also proceeded in high enantioselectivities (ee's up to 96%). In addition, the reactions could be carried out in environmentally friendly solvents, propylene carbonate, with no loss of selectivity.

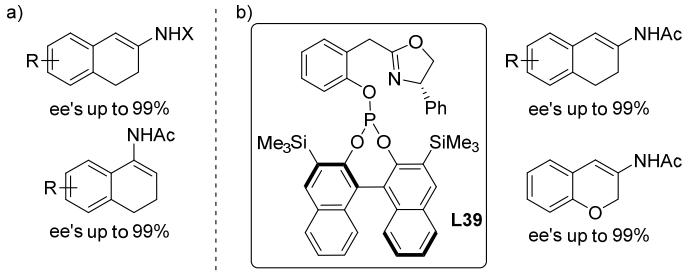


Figure 29. Ir-catalyzed hydrogenation of α- and β-aryl cyclic enamides using a) (*S*,*R*,R_P)-**L36** and b) **L39** ligands.

The already mentioned ligands **L37** (Figure 18) that were successful for di-, tri- and tetra-substituted unfunctionalized olefins, also provided excellent enantioselectivities in the hydrogenation of various cyclic β-enamides (6 examples, ee's up to 99%).[9c] Moreover, both enantiomers of the reduced products could be access with the correct choice of the phosphite-based ligand.

Finally, it has been recently shown that Ir-phosphite-thioether catalysts can also successfully catalyze the hydrogenation of cyclic β-enamides. The sugar-derived phosphite-thioether ligands (**L40**, Figure 30) provided a range of 2-aminotetralines and 3-aminochromanes with excellent enantioselectivities (Figure 30, ee's up to 99%).[97] Interestingly, both enantiomers of the hydrogenated products were obtained by simply switching from Rh to Ir. Moreover, low hydrogen pressure (10 bar) and environmentally friendly propylene carbonate could be used, with no loss of selectivity.

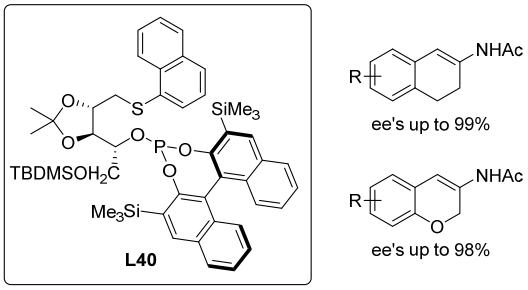


Figure 30. Ir-catalyzed hydrogenation of β-aryl cyclic enamides using P,S-ligand **L40**.

Very recently it has been reported that Ir-catalysts can also successfully catalyze the hydrogenation of N-sulfonyl allyl amines[98] and aryl allyl phtalimides.[99] The hydrogenation of both types of substrates is another way to produce valuable chiral amines, such as β-aryl propanamines, which are important precursors for the synthesis of several pharmaceutical drugs.[100] The commercially available threonine-derived phosphinite (UbaPHOX) iridium catalysts were found to be the best candidates for the hydrogenation of several N-sulfonyl allyl amines (Figure 31a). A range of β-methyl amines were afforded with good to excellent ee's of up to 94%. The synthetic potential of this methodology was shown with the synthesis of the biologically active compounds (*R*)-Lorcaserin and LY-404187.

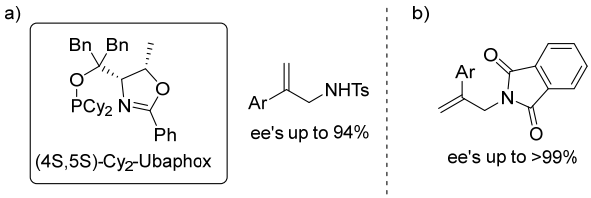


Figure 31. Ir-catalyzed hydrogenation of a) N-sulfonyl allyl amines using Ubaphox ligand and b) 2-aryl allyl phtalamides using **L36** ligand.

Concerning the reduction of aryl allyl phtalimides, the previously mentioned Ir-**L36** catalysts were the best choice. Various enantioenriched β-aryl-β-methyl amines were yielded with excellent enantiomeric excess values (up to >99% ee) and using a low catalyst loading (1 mol%) and low hydrogen pressure (1 bar H_2) (Figure 31b). The utility of the methodology was exemplified with the formal synthesis of (*R*)-Lorcaserin, OTS514, and enantiomerically enriched 3-methyl indolines.

4. Asymmetric Ir-catalyzed hydrogenation of imines

The asymmetric hydrogenation of imines is a high-atom economical way to prepare chiral amines. Despite all the advances made, their hydrogenation still remains a challenging task and most of the reported catalysts present low reactivity and enantioselectivity, harsh reaction conditions and narrow substrate scope. The reason is probably due to instability of certain imines, coordination of substrates, which can take place through both the nitrogen donor atom and the double bond and *E/Z* imine interconversion in the case of acyclic imines.[101] The first catalysts developed for this reaction were based mostly on Rh-diphosphine catalysts and they showed only moderate enantioselectivities (60-70%).[102] Later, some Ir-, Ru- and Ti-catalysts also appeared improving enantioselectivities. Among the early applications, it should be highlighted the iridium-Xyliphos catalyst, which led to the large-scale production of the amine herbicide (S)-Metolachlor (Figure 32).[103] Later Pfaltz's PHOX ligand (**L1**)[12] and Zhang's (*S*,*S*)-f-Binaphane ligand[104] also exhibited excellent results for catalytic enantioselective hydrogenation of imines. This inspired several groups to explore the asymmetric hydrogenation of imines and to date, Ir-complexes are among the most efficient catalysts for this transformation.[101]

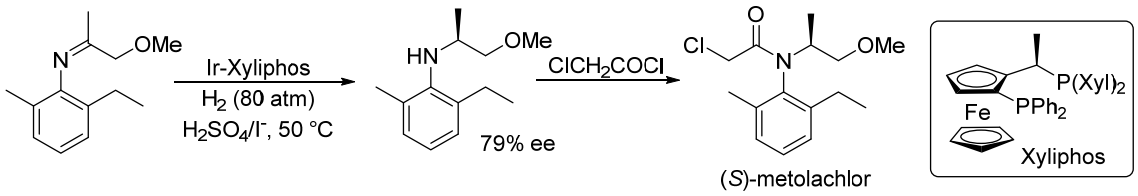


Figure 32. Early synthesis of metalochlor using Ir-Xyliphos catalyst.

Both cyclic and acyclic imines provide useful chiral amines but usually, specific catalysts are required for each type of substrates. The reason is that acyclic imines might exist as Z/E mixtures while cyclic imines usually have a fixed configuration imposed by the cycle. For the asymmetric hydrogenation of acyclic imines, in general, two types of iridium precursors are used, neutral and cationic complexes. Neutral complexes are generated from [{Ir(μ-Cl)(cod)}$_2$] precursor and are usually combined with diphosphine, monophosphoramidite or phosphoramidite-N ligands. Some additives are also usually added, such as I_2, KI. Cationic complexes are prepared from [Ir(cod)$_2$]X catalyst precursor and P-oxazoline ligands. Although cheaper counterions (X^-) were studied,[105] usually BAr_F has been the most used counterion.

Asymmetric hydrogenation using cationic catalyst precursors

Phosphine-oxazoline PHOX ligands **L1** (Figure 1) and **L8** (Figure 3), are among the most efficient ligands for the enantioselectivie hydrogenation of acyclic N-aryl imines. Excellent activities and enantioselectivities (up to 96% ee; Figure 33) were obtained by using low catalyst loadings (0.1–0.5 mol%) at -20 °C and 5–50 bar hydrogen pressure in the reduction of aryl/alkyl N-aryl ketimines (Figure 33a).[106] Other related P,N ligands, such as **L6** (Figure 3) and **L16** (Figure 6), have also been applied albeit with moderate success.[27a,44m] A few years later, the success of PHOX-based catalytic systems was extended to dialkyl ketimines.[107] A key to these improvement was the addition of the appropriate imine as additive. Mechanistic investigation revealed that the active species is a cyclometalated complex **9** (Figure 33b). Thus, a range of N-aryl dialkyl imines were hydrogenated in high enantioselectivities (up to 92% ee; Figure 33a). Nevertheless, N-alkyl aliphatic imines were only hydrogenated in moderate ee's (up to 77%; Figure 33a).

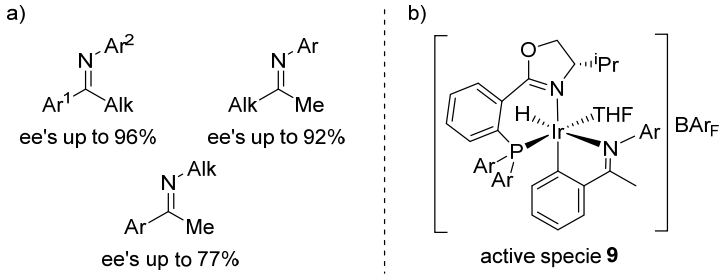


Figure 33. a) Ir-catalyzed asymmetric hydrogenation of N-aryl and N-alkyl imines. b) Cyclometallated active species **9**.

Recently, cyclometallated complex **10** containing the P-stereogenic-oxazoline ligand **L36** proved to be successful in the asymmetric of a wide range of N-alkyl amines, including the more challenging N-methylated ones (ee's up to 94%; Figure 34).[108] Interestingly, high ee's (up to 96%) were also achieved in the reduction of N-aryl ketimines (Figure 34).[109]

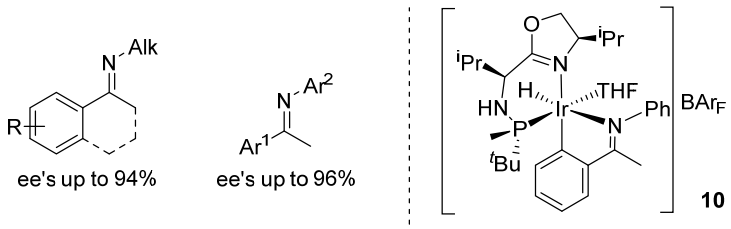


Figure 34. Ir-catalyzed asymmetric hydrogenation of N-aryl and N-alkyl imines using Ir-**L36** catalytic system.

Cationic iridium complexes based on the already mentioned **L9** ligands (Figure 3), were found to be highly efficient in the hydrogenation of a broad range of aryl alkyl N-benzyl imines (ee's up to 93%). Importantly, even higher enantioselectivities were obtained for various exocyclic N-alkyl imines (ee's up to 98%).[110] The protocol was successfully employed in the synthesis of the antidepressant chiral drug sertraline.[111] High enantioselectivities in the reduction of some exocyclic N-aryl-dihydronaphthalene imines were also achieved using P-chiral dihydrobenzooxaphosphole-oxazoline Lalithphos ligand (ee's up to 99%).[112]

Asymmetric hydrogenation using neutral catalyst precursors

Neutral catalyst modified with Xyliphos and (*R*,*R*)-f-binaphane ligands early proved to be suited for the AH of sterically hindered N-aryl imines.[104,103] More recently, Hu et al. improved previous results with the use of phosphine-phosphoroamidite ligand **L41** (Figure 35).[113] A range of sterically hindered N-aryl imines were therefore hydrogenated featuring high ee's (up to 99%) and turnover numbers (up to 100.000; Figure 35). Later, the same group disclosed that the steric effect of substituents on the *o*-postions of the binaphthyl showed a significant influence on the enantioselectivity and found that **L42** (Figure 35) was also highly enantioselective in the Ir-hydrogenation of sterically hindered N-aryl imines (ee's up to 98%).[114] The utility of this methodology was demonstrated in the synthesis of the chiral herbicide (*S*)-Metolachlor and the chiral fungicide (*R*)-metalaxyl.

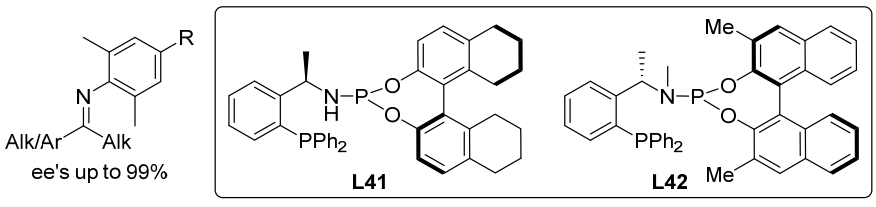


Figure 35. Ir-catalyzed asymmetric hydrogenation of sterically hindered N-aryl imines using phosphite-phosphoroamidite ligands **L41** and **L42**.

Neutral Ir-catalysts have also shown excellent enantioselectivities in the asymmetric hydrogenation of diarylmethanimines, whose hydrogenation products are found in

numerous biologically active compounds of pharmaceutical relevance.[115] In this context, two catalytic systems should be highlighted. Ir/**L43** catalytic system provided high enantioselectivities in the reduction of benzophenone N−H iminium salts with one of the aryl groups *ortho*-substituted (ee's up to 98%; Figure 36a).[116] More recently, (*R*,*R*)-f-SpiroPhos ligand (Figure 26) allowed the enantioselective hydrogenation of N-alkylester substituted diarylimines under mild reaction conditions (ee's up to >99%; Figure 36b).[117] A feature of this catalyst was that the presence of an *ortho*-substituent in one of the aryl groups was not required to achieve high enantioselectivities.

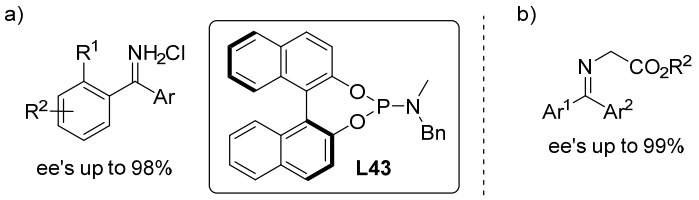


Figure 36. Ir-catalyzed asymmetric hydrogenation of a) diaryl iminium salts using Ir/**L43** catalysts and b) N-alkylester substituted diarylimines using Ir/(*R*,*R*)-f-SpiroPhos catalyst.

Hu et al. have also disclosed the Ir-hydrogenation of α-imino esters. A range of optically active α-aryl glycines were synthesized using Ir-**L44** catalytic system (ee's up to 96%; Figure 37a).[118] Very recently a high throughput experimentation (HTE) at Astrazeneca enabled the identification of highly enantioselective catalytic systems for the hydrogenations of N-alkyl α-aryl ketimines containing a furyl moiety.[119] After an extensive screening of Ru-, Rh- and Ir- catalysts, Ir-catalytic system bearing the (*S*,*S*)-f-Binaphane ligand was found to be the most enantioselective (ee's up to 90%; Figure 37b).

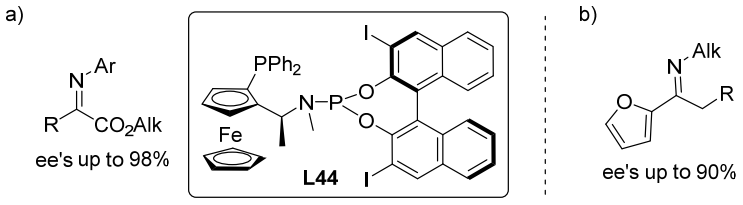


Figure 37. Ir-catalyzed asymmetric hydrogenation of a) α-imino esters using Ir/**L44** catalysts and b) furyl-based N-alkyl α-aryl ketimines using Ir/(*S*,*S*)-f-Binaphane catalyst.

Neutral complexes generated from $[Ir(I)(COD)Cl]_2$ and activated by addition of halogen-based oxidants such as iodine are among the most successful systems for the asymmetric hydrogenation of cyclic amines. Among the cyclic imines studied, the hydrogenation of isoquinolines and 3,4-dihydroisoquinolines is the most desired since they provide a straightforward synthetic route towards valuable chiral compounds with a 1,2,3,4-tetrahydroisoquinoline motif, which is present in several natural alkaloids and pharmaceutical molecules. However, the strong coordination ability of isoquinolines and their enhanced stability due to their aromaticity, makes them less reactive towards hydrogen. In this context, Zhou et. al developed the first example of highly enantioselective hydrogenation of quinoline derivatives with a (*R*)-MeO-BIPHEP [6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl] as the ligand.[120] However, these systems were restricted only to quinolines. Importantly, the protocol was later expanded to isoquinolines, which is a very challenging class of substrates, but stoichiometric amounts of chloroformate as a substrate activator were needed.[121] In 2012, a more efficient $Ir(COD)Cl]_2$/(*R*)-SynPhos catalytic system was disclosed, which used 1-bromo-3-chloro-5,5-dimethylhydantoin (BDCMH) as a catalyst activator, and therefore, only catalytic amounts of activator were required.[122] A range of chiral 3,4-disubstituted tetrahydroisoquinoline derivatives were obtained with ee values as high as 96% (Figure 38). The scope of this catalytic system was extended to other aromatic imines, such as polycyclic nitrogen-containing heteroaromatics pyrrolo/indolo[1,2-a]quinoxalines and phenanthridines,[123] sulfur-containing dibenzo[b,f][1,4]thiazepines,[124] activated N-benzyl-pyridinium bromides[125] and fluorinated isoquinoline derivatives[126] (Figure 38). Finally, the authors also reported the use of (*R*)-SynPhos ligand in the deracemization of secondary and tertiary amines with a tetrahydroisoquinoline core.[127] The process consisted in a redox N-bromosuccinimide oxidation of the amines and the subsequent Ir-catalyzed asymmetric hydrogenation. A range of chiral 1-substituted 1,2,3,4-tetrahydroisoquinolines were generated with up to 98% ee in 93% yield.

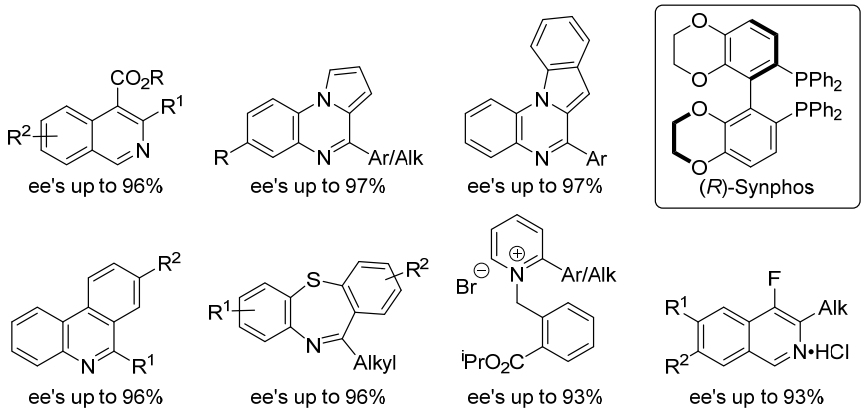


Figure 38. Iridium-catalyzed enantioselective hydrogenation of cyclic imines using Ir/(*R*)-Synphos catalyst.

Other diphosphine-based catalysts have also been successfully used in the asymmetric hydrogenation of aromatic iminium salts. Thus, for instance, a range of 1- and 3-substituted isoquinolinium salts,[128] 2,6-disubstituted pyridinium hydrochloride (3·HCl)[129] and pyrrolo[1,2-a]pyrazines[130] were successfully hydrogenated using (*S*,*S*,*R*^{ax})-C3*-TunePhos ligand (ee's up to 96%, Figure 39). Ir/(*R*,*Sp*)-Josiphos catalyst also provided excellent ee's in the hydrogenation of a range of pyrazinium salts (ee's up to 96%, Figure 39).[131] It should be noticed that recently, an efficient catalytic system for the hydrogenation of pyrrolo[1,2-a]pyrazines without the need of formation of the corresponding salts or the addition of any additive has been reported using Ir/(*R*)-BTFM-Garphos catalyst (ee's up to 96%, Figure 39).[132] A highly enantioselective hydrogenation of heteroaromatics bearing a hydroxyl group, 3-hydroxypyridinium salts, has been successfully developed using Ir/(*S,S*)-f-Binaphene catalyst, providing a direct access to *trans* 6-substituted piperidin-3-ols with up to 95% ee.[133] Another interesting examples can be found in the succefull hydrogenation of iminium salts of N-alkyl tetrahydroisoquinolines (ee's up to 96%, Figure 39)[134] and of N-alkyl-2-arylpyridium salts (ee's up to 98%, Figure 39)[135] using SegPhos-type ligands. Recently a new strategy has been developed, in which pyridinium and isoquinolinium salts are generated *in situ* by employing halogenide trichloroisocyanuric acid as a traceless activation reagent. Mechanistic studies indicated that hydrogen halide generated in situ acted as an activator. This method allowed the Ir/(*R*)-SegPhos-mediated hydrogenation of a range of isoquinolines and pyridines in excellent yields and enantioselectivities (up to 99% ee, Figure 39), while avoiding tedious steps of installation and removal of the activating groups.[136] Finally, it should be mentioned that not only Ir/diphosphine catalysts are able

to catalyze the reduction of iminium salts. Thus, it should be highlighted the recent works of Qu's group in the use of dihydrobenzooxaphosphole-pyridine ligand MeO-BoQPhos for the asymmetric hydrogenation of 2-alkyl-pyridinium salts including examples containing an α-heteroaryl substituent.[137,138]

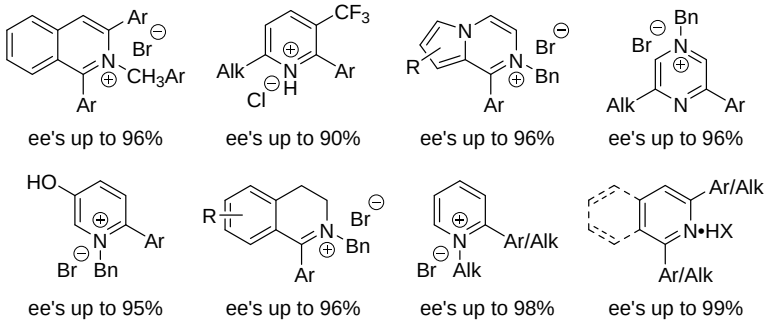


Figure 39. Representative examples of iminium salts successfully hydrogenated.

Similarly, the successful hydrogenation of 6-membered ring cyclic imines has not been only limited to the use of Synphos-based system. Thus, for instance, a range of quinoline derivatives have been successfully hydrogenated with diphosphines and monophosphoroamidites. (*S,S*)-f-Binaphene ligand has been also efficiently used in the reduction of 1-substituted 3,4-dihydroisoquinolines (ee's up to >99%).[139] Similarly, a range of 1-aryl-substituted tetrahydroisoquinolines were obtained in ee's of up to >99% and good TON (up to 4.000) using Josiphos-type binaphane ligand.[140] Higher TON's (up to 43.000) were achieved in the reduction of a range of quinolines using both Ir/(*R*)-Difluorphos[141] and Ir/(*R*)-P-Phos[142] catalytic systems. A successful example of the use of monophosphoroamidite ligand can be found in the use of (R^{ax},*S*,*S*)-Siphos-pe ligand in the hydrogenation of 1-alkyl-dihydroisoquinolines with ee's of up to 96%. The usefulness of the latter reaction was demonstrated with the synthesis of the tetracyclic alkaloid (*S*)-xylopinine in 85% yield and 96% ee.[143]

Besides quinoline derivatives, the range of 6-membered ring cyclic amines successfully hydrogenated has been extended. Thus, for instance, Ir-Segphos catalyst was successfully used in the hydrogenation of 1,4-benzoxazines[144] and quinazolines[145] (ee's up to 98%, Figure 40). The utility of the method was demonstrated with the synthesis of the bioactive compounds Eg5 inhibitor and (−)-SDZ 267-489 in excellent enantioselectivities (>99% and 99% ee, respectively).[145] Another example can be found in the use of cationic dinuclear iridium(III) chloride catalyst {[IrH((*S*)-Difluorphos)]$_2$(μ-

Cl)$_3$}Cl for the reduction of 2-alkyl and 2-aryl- substituted dihydroquinoxalines[146] and tosylamido-substituted pyrazines[147] (ee's up to 95%, Figure 40). Ir-catalyst modified with phosphine-phosphite ligand **L45** proved to be highly efficient in the asymmetric hydrogenation of benzoxazines, benzoxazinones, benzothiazones and quinoxalinones (ee's up to 99%; Figure 40).[148]

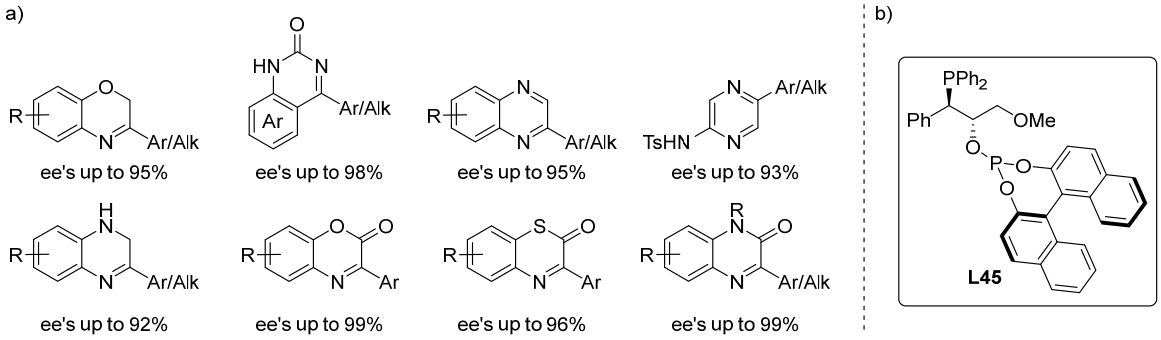


Figure 40. Representative examples of 6-membered cyclic imines other than quinoline derivatives and iminium salts successfully hydrogenated using Segphos, Difluorphos and phosphine-phosphite ligand **L45**.

Most of the literature dealing with the hydrogenation of cyclic imines reports examples on 6-membered ring systems. Examples on the successful hydrogenation of 7-membered cyclic imines are rare. In particular, Ir/C3*-Tunephos catalysts proved to be highly efficient in the asymmetric hydrogenation of substituted dibenzo[b,f][1,4]oxazepines, benzodiazepinones and benzodiazepines (ee's up to 96%, Figure 41a).[149] More recently, Zhou et al. reported the asymmetric hydrogenation of 6-substituted 5H-benzo[d]benzofuro[3,2-b]azepines using a Biphep-type ligand **L46** (ee's upo to 91%, Figure 41b).[150] 2,4-Diaryl-1,5-benzodiazepines and 2,4-diaryl-3Hbenzo[b]azepines has been also successfully hydrogenated (ee's up to 99% and d.r.'s up to >20:1) using aminophosphine-pyridine ligand **L47** (Figure 41c)[151] and a dendritic PHOX-derivative[152,153]. Benzoxazinones derivatives have also been recently reduced using ZhaoPhos ligand (Figure 27) achieving excellent enantioselectivities (up to 99% ee).[154]

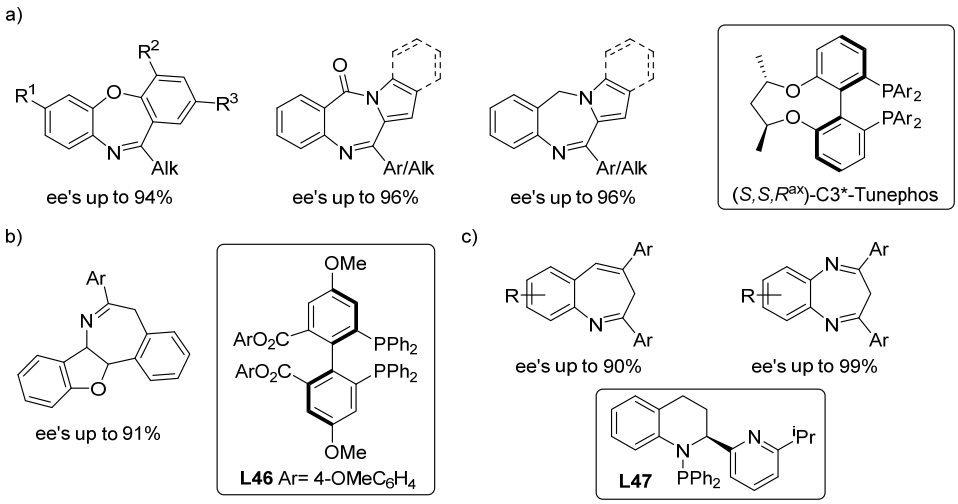


Figure 41. Representative examples of 7-membered cyclic imines successfully hydrogenated using a) C3*-Tunephos ligands, b) Biphep-type ligand **L46** and aminophosphine-pyridine ligand **L47**.

There are very few examples on the asymmetric hydrogenation of 5-membered ring cyclic imines. In this context the use of iodine-bridged dimeric [{Ir(H)[(S,S)-(f)-binaphane]}$_2$(μ-I)$_3$]I complex catalyzed the asymmetric hydrogenation of a series of 2-aryl-1-pyrrolines in good ee's (up to 86%) and high tornover numbers (TON's up to 5.000).[155] More recently, the use of (*R*,*R*)-f-SpiroPhos ligand (Figure 26) improved enantioselectivities to up to 98% (Figure 42).[156] In contrast to Ir/(*S*,*S*)-f-Binaphane catalyst, the enantioselectivity was only affected when a 2-alkyl substituent was present on the imine instead of an aryl group (ee's up to 77%). Moreover, this method was successfully applied to the synthesis of (+)-(6S,10bR)-McN-4612-Z, a potent inhibitor for the uptake of important central neurotransmitters norepinephrine, dopamine and serotonin into nerve cells. Very recently a bifunctional bisphosphine–thiourea ZhaoPhos ligand (Figure 27) was successfully applied in the Ir-catalyzed asymmetric hydrogenation of cyclic sulfamidate imines (ee's up to 99%; Figure 42).[157]

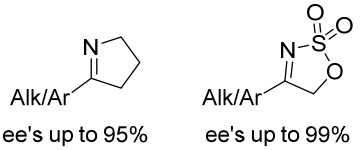


Figure 42. Representative examples of 5-membered cyclic imines hydrogenated.

5. Ir-catalyzed asymmetric hydrogenation of ketones

Over the last decades, the Ir-catalyzed asymmetric hydrogenation of ketones has experienced a huge advance. Thus, a range of Ir-catalysts have demonstrated to be highly efficient, achieving excellent enantioselectivities and activities for a range of ketones. Such progress has made Ir-catalyst good alternatives to the most commonly used Ru-catalysts. Most of the key ligands are phosphine-based, although there are some important examples that do not contain a P-donor group.

P-donor based ligands

One of the key P-containing ligands was disclosed by Poli's group.[158] They developed a ferrocenyl-based phosphine-thioether ligand **L48** that provided high enantioselectivities (ee's up to 99%) for a range of alkyl aryl ketones (Figure 43), albeit activities (TOF's up to 250 h^{-1}) do not compare well with the current state of the art.

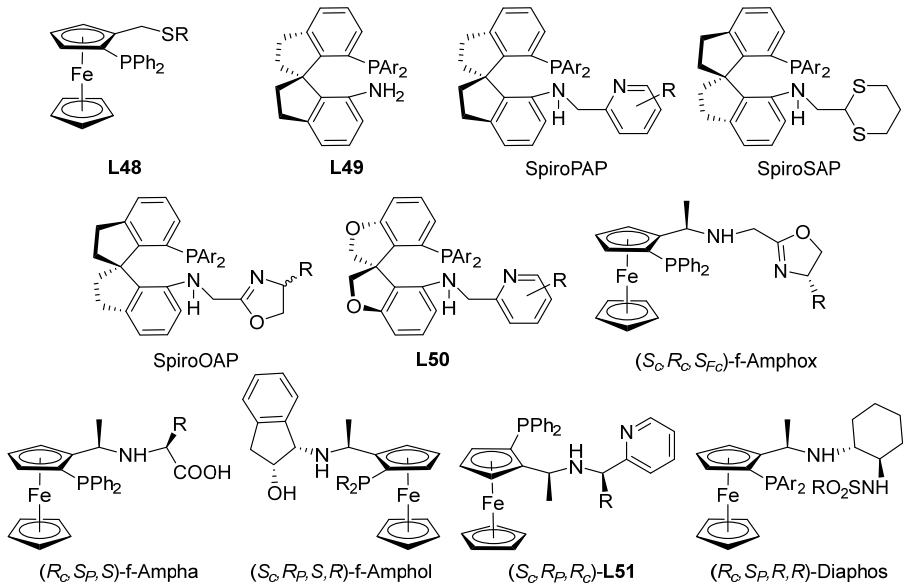


Figure 43. Selected P-containing ligands developed for the Ir-catalyzed asymmetric hydrogenation of ketones.

In 2010, Xie, Zhou et al. developed chiral spiro aminophosphine ligands **L49** (Figure 43).[159] The use of Ir/**L49** catalyst provided high ee's (up to 97%) and activities (TOF's up to $3.7x10^4$ h^{-1}) in the hydrogenation of aryl alkyl ketones and exo-cyclic α,β-unsaturated ketones. Nevertheless, the catalyst deactivates under hydrogenation

conditions. Mechanistic investigations indicated that the deactivation was due to the formation of $[IrH_2(\mathbf{L49})_2]^+$ complex.[159b]

To prevent the formation of such inactive species, the same group introduced in **L49** a pyridine group as a third coordinating position, leading to the tridentate P,N,N spiro pyridine-aminophosphine ligands SpiroPAP (Figure 43).[160] Ir/SpiroPAP (Ar= 3,5-^{t}Bu$_2$-C$_6$H$_3$ and R= 3-Me) system proved to be highly efficient in the AH of aryl alkyl ketones and aryl β- and δ-ketoesters (ee's up to 99.8% and TON's up to 4.550.000; Figure 44).[160] The excellent performance of SpiroPAP ligands has been further extended to acyclic α,β-unsaturated acyclic ketones,[161] α-, γ- and δ-keto acids,[162] α-amino ketones[163] and α,β-unasaturated α-ethoxy carbonyl β-substituted cyclic ketones[164] (Figure 44). This catalytic system has been also used in the deracemization of α-substituted lactones[165] (Figure 44) via dynamic kinetic resolution (DKR) as well as in the kinetic resolution of aliphatic alcohols[166]. The synthetic versatility of Ir/SpiroPAP catalyst was demonstrated with the synthesis of drugs and natural products such as (-)-mesembrine, rivastigmine, (-)-Hamerigan B.[161,167]

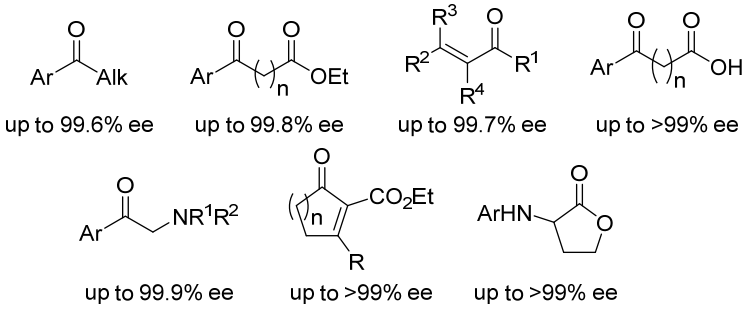


Figure 44. Representative ketones successfully hydrogenated with Ir/SpiroPAP catalyst.

The Xie's and Zhou's group developed a P,N,S variant (SpiroSAP; Figure 43) with a 1,3-dithiane group instead of the pyridine group.[168] Ir/SpiroSAP catalyst proved to be highly efficient in the asymmetric hydrogenation of β-alkyl-β-ketoesters[168] as well as in the dynamic kinetic resolution (DKR) of β-ketolactams[169] (Figure 45). Ir/SpiroSAP catalyst was also used in the formal total synthesis of (-)-cyanolide A and (-)-doluculine.[170] Recently, a new SpiroPAP variant has been developed by replacing the pyridine group by an oxazoline moiety (SpiroOAP; Figure 43).[171] SpiroOAP ligands proved to be efficient in the reduction of α-ketonamides (ee's up to 98%).

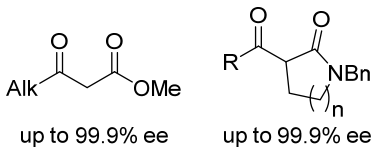
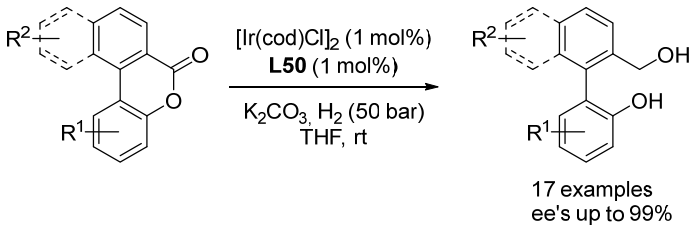


Figure 45. Representative ketones successfully hydrogenated with Ir/SpiroSAP catalyst.

Yin, Zhang et al. developed a variant of SpiroPAP ligands containing an oxa-spirocyclic ligand **L50** (Figure 43).[172] Ir/**L50** catalyst was successfully used in the asymmetric hydrogenation of Bringmann's lactones via DKR to yield enantiopure chiral biaryl diols in high ee's (up to >99%; Scheme 2).



Scheme 2. Asymmetric hydrogenation of Bringmann's lactones via DKR with Ir/**L50**.

Dong, Zhang et al. developed novel tridentate ferrocene aminophosphoxazoline ligands (f-Amphox, Figure 43). Ir/f-Amphox catalyst proved to be highly efficient in the reduction of simple aryl alkyl and dialkyl ketones (ee's up to >99% and TON's up to 1.000.000; Figure 46).[173] f-Amphox-based catalytic systems were also successfully used in the hydrogenation of α-, β-, γ- and δ-keto amides,[174] α-amino ketones,[175] α-hydroxy ketones,[176] b-ketoesters,[177] styrylglyoxylamides,[178] halohydrins[179] as well as in the deracemization of α-amino β-unfunctionalized ketones via DKR[180] (Figure 46). Hou's group also developed a modification in which the Uggi's amine was replaced by phenethylamine.[181] However, only moderate ee's were achieved in the reduction of β-ketoesters.

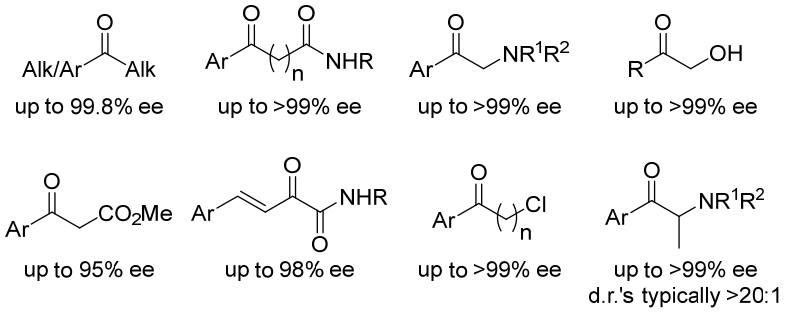


Figure 46. Representative ketones successfully hydrogenated with the Ir/f-Amphox catalyst.

The Dong's and Zhang's groups developed a P,N,O variant (f-Ampha; Figure 43) with a chiral carboxylic acid instead of the oxazoline moiety.[182] f-Ampha ligands exhibited excellent catalytic performance for a range of aryl alkyl ketones,[182] α-ketoesters[183] as well as in the desymmetrization of cyclic 1,3-diketones[184]. For these catalytic systems the hydroxyl group of the carboxylic acid group is involved with the formation of O-H···substrate interaction with a new catalytic bifunctional mode. At the same time a new ferrocene-based amino-phosphine-alcohol was developed (f-Amphol; Figure 43).[185] Ir/f-Amphol catalysts also showed excellent enantioselectivities for simple aryl alkyl ketones,[185,186] albeit the turnover numbers are lower than for Ir/f-Amphox catalysts. Ir/f-Amphol ligands were also successfully used in the asymmetric hydrogenation of β-keto sulfones[187] and of α-substituted β-ketoesters via DKR[188]. For these catalytic systems, DFT studies indicated that the hydroxyl group of the f-Amphol ligands play a key role in the reduction process.

Hou's group developed a sterically hindered ferrocenyl P,N,N-ligands in which the oxazoline in the f-Amphox ligands was replaced by a pyridinylmethyl group with an extra coordinating stereogenic center (ligands **L51**; Figure 43).[189] Ir/**L51** (R= 2-tolyl) catalyst demonstrated to be highly efficient in the asymmetric hydrogenation of α-alkyl substituted β-aryl-β-ketoesters via DKR yielding the corresponding alcohols in high diastereo- and enantioselectivities (d.r's up to >95/5 and ee's up to 99%).

Zhong's group developed tridentate ferrocene-based diamine-phosphine sulfonamide ligands (f-Diaphos; Figure 43).[190] The f-Diaphos ligands provided excellent reactivity and enantioselectivities in the Ir-catalyzed hydrogenation of diaryl and 2-pyridyl aryl ketones (ee's up to >99%; TON's up to 19600).[190,191]

Non P-donor based ligands

Ir complexes bearing chiral phosphine-free ligands have also been successfully used in the asymmetric hydrogenation of ketones. Albeit such catalytic systems are able to induce high enantioselectivities, the turnover numbers are still lower than the most active P-based ligands such as SpiroPAP and f-Amphox.

In this context Ohkuma's group demonstrated that Cp*Ir(III) complex containing MsDPEN ligand **L52** (Figure 47) efficiently hydrogenated α-hydroxy ketones.[192] A range of 1-aryl-1,2-ethanediols were therefore achieved in high ee's (up to 99%) with TON's as high as 6000. Latter their high performance was extended to the use of aromatic (hetero)cyclic ketones (e.g. indanones, benzofuranones, chromanones…) achieving an excellent enantiocontrol (ee's up to >99%).[193] At the same time, Ikariya's group developed a bifunctional triflylamide-tethered CpIr version of [Cp*Ir(OTf)**L52**], albeit it provided only good ee's (up to 93%) in the reduction of benzophenone.[194]

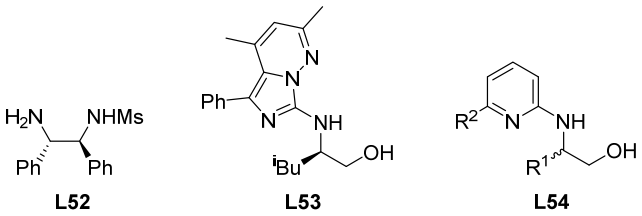


Figure 47. Non-Pdonor based ligands for the Ir-catalyzed asymmetric hydrogenation of ketones.

Kempe's group introduced an imidazo[1,5-b]pyridazine-type ligand **L53** (Figure 47) for the Ir-catalyzed hydrogenation of simple ketones.[195] A range of aryl alkyl and aryl aryl ketones were therefore efficiently hydrogenated providing excellent ee's (up to >99%) and TON's (up to 200.000) using Ir/**L53** catalyst. It should be pointed out that the catalyst precursor [Ir(cod)**L53**] rapidly evolve under catalytic conditions to the formation of Ir-K catalyst complex **11** in which **L53** is coordinated thought the amino-alcohol (Figure 48). In 2016 Kempe et al. developed the pyridylalkylamine ligands **L54** (Figure 47).[196] Nevertheless, the efficiency of Ir/**L54** catalysts proves to be somewhat lower than Ir/**L53** catalyst in the reduction of simple ketones (ee's up to 96%).

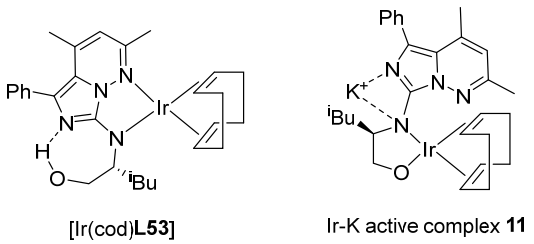


Figure 48. Catalyst precursor [Ir(cod)**L53**] and its bimetallic active species **11**.

6. Conclusions

Due to perfect atom economy and simplicity, the metal-catalyzed asymmetric hydrogenation continues to be one of the most sustainable and straightforward reactions for creating stereogenic centers in target molecules. In the asymmetric hydrogenation of unfunctionalized olefins or with poorly coordinative groups Ir containing heterodonor P,X ligands continues to be the catalysts of choice. Examining the last progress in this field, the substrate scope has been largely extended, with the successful hydrogenation of challenging and relevant substrates such as polyene substrates, with the formation of multiple stereocenters, olefins that contain non-coordinating groups such as halides avoiding the dehalogenation side reaction, and allylsilanes. Also efficient catalysts have been found for the reduction of heteroarenes and benzene. A lot of progress has also been achieved in the regio- and stereoselective monohydrogenation, as an efficient route for preparing natural products and complex organic molecules (e.g. juvabione). This has been achieved thanks to the recent development of powerful catalytic systems that have also allowed to advance in the search of a single catalysts able to tolerate a large number of olefins types. However, some limitations have still to be solved such as the necessity to work with pure geometrical isomers (e.g. *E*- and *Z*-trisubstituted alkene produced opposite enantiomers of the hydrogenated products). Other demanding substrates are hindered tetrasubstituted olefins, whose hydrogenation can generate two vicinal stereocenters in a single reaction and thus give rise to products of higher stereochemical complexity. The first significant progress has been made in the past five years, but the scope of the substrate needs to be further improved, and this area of research is likely to expand in the future as well. The advances of Ir-catalysts in the last 10 years has not only been limited to unfunctionalized olefins, the development of Ir-catalysts has also notably expanded the field of the asymmetric hydrogenation of unresolved functionalized substrates, providing in some cases complementarity to Rh and Ru-catalysts and in other cases surpassing the widely used Rh- and Ru-catalysts.

7. Acknowledgements

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