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METAL-CATALYZED ASYMMETRIC HYDROGENATION OF C=N BONDS

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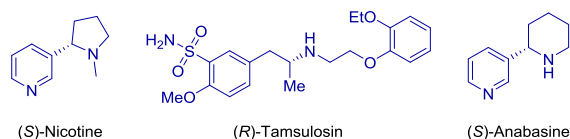
KEYWORDS. *Asymmetric Hydrogenation. Metal-Catalysis. Imine. Chiral Amine. Ligand.*

ABSTRACT: This review recaps the achievements in the field of metal-catalyzed asymmetric direct hydrogenation of non-activated and activated imines. A summary of the reported catalytic systems with the corresponding reactivity, selectivity, and limitations are given including a discussion about the effects of some reaction conditions on the enantioselectivity of imine hydrogenation. An analysis of proposed imine hydrogenation mechanisms is discussed.

Since the 1960s, homogenous catalytic asymmetric hydrogenation became an efficient and immensely useful methodology for the preparation of enantiopure compounds, both in academia and industry. Indeed, while starting from easily available prochiral substrates, asymmetric reductions of double bonds using hydrogen gas as a reductant or by transfer hydrogen process, provide chiral alcohols, alkanes, and amines in a sustainable manner. Therefore, the extraordinary potential of asymmetric hydrogenation reactions was recognized at the beginning of the 21st century by attributing the Nobel prize to the pioneers in this field, Knowles,¹ and Noyori.²

Regarding the ubiquity of chiral amines in natural products, these chiral molecules are key building blocks for pharmaceutical as well as agrochemical industries (Scheme 1).

Scheme 1. Several examples of drugs containing chiral amine motifs.

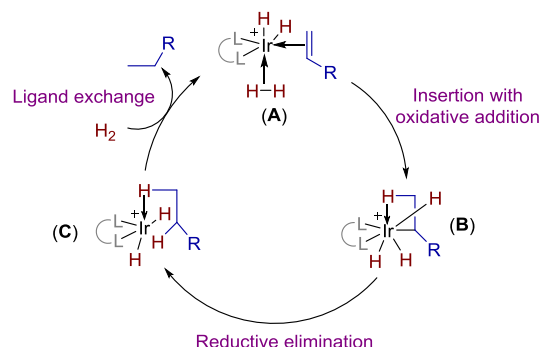


Asymmetric synthesis of enantiopure amines via stereoselective hydrogenation appears as the most appealing route to access these high value-added molecules. This reaction is not only characterized by 100% atom economy but also no waste generation may be expected while using a low loading of a finely selected catalyst. However, despite the earlier developments of asymmetric hydrogenation of alkenes and ketones, including their large scale industrial applications, the imine reduction is significantly less explored.³⁻¹³ Many efficient complexes designed for the reduction of alkenes and ketones performed poorly while compared to the related imines. It might be due to the C=N double bond properties and the impoverishment of the catalytic activity of the metal via possible coordination by the newly generated amine product. Moreover, factors such as the possible imine-enamine

tautomerization and the presence of the *E/Z* isomers of the acyclic imines can affect the enantioselectivity of the overall process.

From a mechanistic viewpoint, a clear gap between the current comprehension of olefin/ketone asymmetric reduction vs. imine hydrogenation is evident.¹⁴ A general mechanism of Ir-catalyzed olefin hydrogenation (Scheme 2) implies an Ir(III)/Ir(V) process starting by 1) olefin and hydrogen coordination to the Ir-precatalyst (**A**), followed by 2) oxidative addition of hydrogen to Ir and insertion of the olefin into Ir-H bond delivering Ir(V)-alkyl intermediate (**B**) and 4) final reductive elimination releasing the alkane product and the Ir(III) species (**C**) that undergoes ligand exchange with the new olefinic substrate and hydrogen to regenerate the active catalyst.

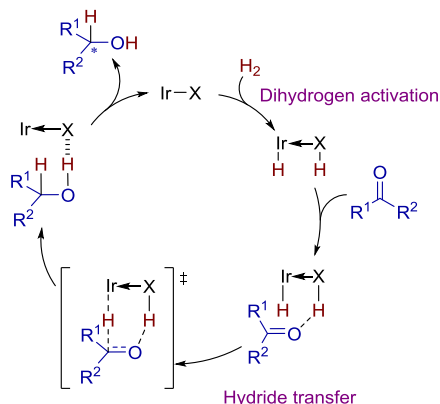
Scheme 2. Proposed mechanism for the Ir-catalyzed alkenes hydrogenation.



In the case of Ir-catalyzed hydrogenation of ketones, the common use of alkoxy or amino Ir(III) complex (Ir-X) results in the polarity-driven activation of hydrogen molecules, affording hydride coordination to Ir and a proton coordinating to the X atom (Scheme 3). Thus, the generated X-H moiety activates the carbonyl function inducing a strong polarization of the C=O bond, thus facilitating the hydride transfer for the

reduction of the carbonyl group. The release of the resulting alcohol regenerates the active Ir-X catalyst.

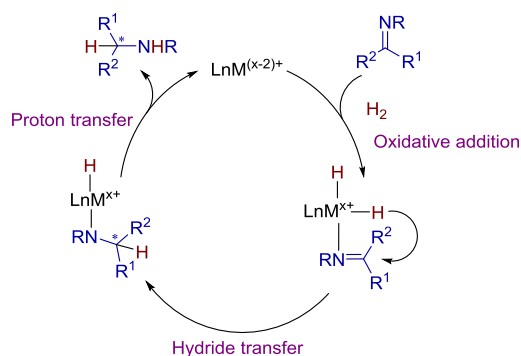
Scheme 3. Asymmetric hydrogenation of ketones by iridium catalyst.



While considering imine hydrogenation, several mechanistic scenarios have been envisioned and they can significantly diverge for different metals, catalysts, substrates, and even reaction conditions, thus rendering the generalization of this process illusive. However, two scenarios implying inner-sphere and outer-sphere mechanisms have been commonly proposed. The fundamental difference between these two scenarios concerns: 1) the mode of H₂ activation, that can be either homo or heterolytic, 2) the origin of the proton, 3) the coordination mode of the substrate, and 4) the oxidation state of the metal.

In the inner-sphere mechanism, the imine substrate coordinates to the metal through the lone pair of the nitrogen (η^1) or through the C=N double bond (η^2). In the initial step (migratory insertion of imine into M-hydride bond), a hydride transfer to the carbon center of the coordinated substrate takes place, furnishing the negative charge on the nitrogen atom and thus promoting (η^1)-coordination mode (Scheme 4). Subsequent proton transfer to the nitrogen center and reductive elimination release the amine product (reductive elimination) while the oxidative addition of H₂ warrants regeneration of the active catalyst.

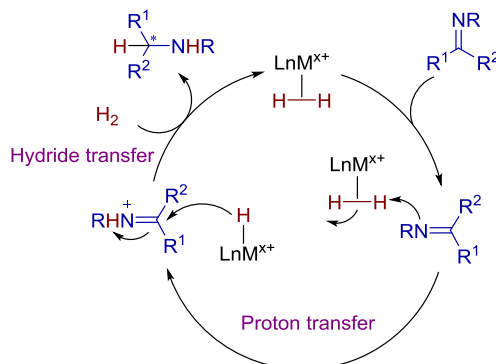
Scheme 4. Inner-sphere mechanism for transition metal catalyzed hydrogenation of imines.



In clear contrast, in the case of the outer-sphere mechanism, no coordination between imine and the catalyst is expected (Scheme 5). The H₂ coordinates in η^2 -fashion to the metal and is cleaved heterolytically by the unbounded imine substrate,

playing the role of the base. Accordingly, the proton transfer from M-H₂ (η^2) to the free imine takes place, generating simultaneously a free electrophilic iminium molecule together with a mono-hydride metal complex. In a final step, the hydride transfer to the free iminium completes the catalytic cycle, delivering the reduced amine while the coordination of H₂ regenerates the catalyst.

Scheme 5. Outer-sphere mechanism for transition metal catalyzed hydrogenation of imines.



Regarding the mechanisms of these transformations, it seems clear that achieving efficient chiral induction in the case of AIH (asymmetric imine hydrogenation) is far from trivial. If the transformation occurs via outer-sphere mechanism, without coordination of the imine to the metal center, the possibilities of the chiral information transfer from the stereogenic metal complex to the substrate seem restricted.

Therefore, it's not surprising that despite its great synthetic utility, the asymmetric hydrogenation of imines has remained a challenging field. Indeed, significantly fewer publications have been devoted to this topic and only since the beginning of this decade, more attention has been paid on AIH, targeting the design of efficient, highly stereoselective and general catalytic systems (Figure 1). Progressively substantial improvements have been achieved and powerful catalysts exhibiting higher enantioselectivity and larger substrate scope have been disclosed. Besides, a design of activated imine substrates, allowing more efficient chiral induction and delivering enantioenriched amines *via* post-functionalizations has also caught particular attention of the scientific community.

This review describes the advancements in metal-based catalyst systems that have been reported until mid-2020. Contrary to the others excellent reviews in the field,⁶⁻¹³ this manuscript is exclusively focusing on metal-catalyzed asymmetric imine hydrogenation.

The catalytic systems are classified according to the used metal and the nature of the substrate thus demonstrating the particular reactivity of different metals towards specific substrate classes. At the end, industrial applications of AIH have been stated.

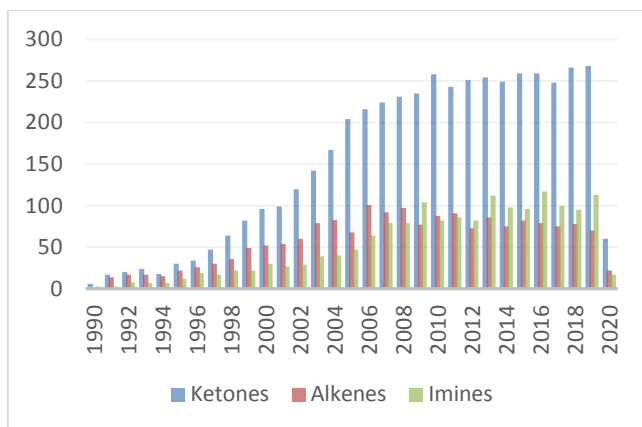


Figure 1. The evolution of published asymmetric hydrogenation of ketones, alkenes and imines per year (data compiled through web of sciences website in June 2020 using respectively AH of ketones, alkenes and imines as keywords).

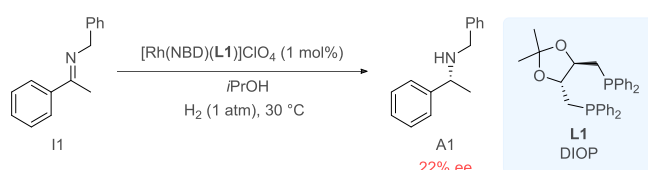
Asymmetric hydrogenation of non-activated imines

Rhodium-based catalysts

Rhodium is not only one of the first metals employed in olefin hydrogenation, but also one of the most efficient ones. Regarding its great potential in C=C and C=O bond reductions, its application in asymmetric imines hydrogenation has naturally caught substantial attention. Since the 70s, different research groups investigated various types of ligands in order to determine the optimal catalytic system for the synthesis of enantiopure amines.

The first attempts towards AIH date back to 1975 and the pioneering work of Scorrano.¹⁵ While using $[\text{Rh}(\text{NBD})(\text{DIOP})]^+\text{ClO}_4^-$ as catalyst under atmospheric pressure of hydrogen, reduction of an amino-acid derived olefin could be achieved with up to 85% ee. Conversely, the same catalysts performed poorly when challenged with acetophenone benzylimine **I1** (**I1**: Imine 1), delivering the expected amine **A1** (**A1**: Amine 1) with significantly lower 22% ee (Scheme 6). Remarkably, this early example already points out the huge gap between C=C and C=N asymmetric reductions.

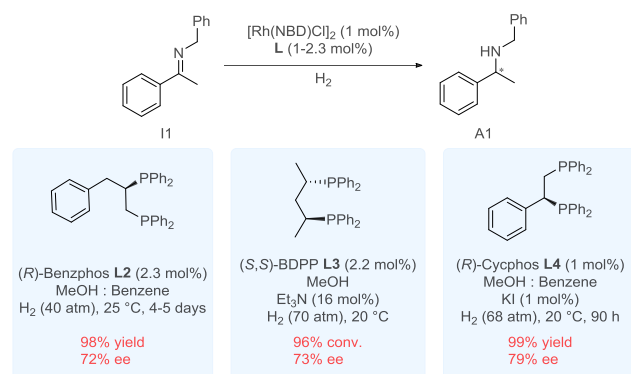
Scheme 6. The first Rh-catalyzed AIH.



In the 1980s, several research groups have investigated the ethylene bridged diphosphine ligands, focusing mainly on auxiliaries exhibiting C-stereogenic centers on the backbone (Scheme 7). Accordingly, reduction of the benchmark substrate **I1**, occurred with interesting ee, up to 72%, 73% and 79%, while using respectively Benzphos (**L2**),¹⁶ BDPP (**L3**),¹⁷ and Cycphos (**L4**)¹⁸ ligands, though higher H₂ pressures were required. A few key questions have been raised, i.e. reproducibility

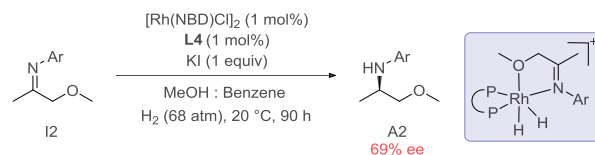
issues, the role of halide ligand, and related reactivity difference between isolated complex and *in situ* generated catalytic species. To answer at least some of these interrogations, Cullen, Fryzuk, James and collaborators have investigated in more detail the reaction catalyzed by Rh(I)/Cycphos (**L4**) system.¹⁹ The key role of halide additives could thus be confirmed as the isolated complex $[\text{Rh}(\text{NBD})(\text{R})\text{-L4}]\text{PF}_6$ furnished **A1** in a racemic mixture whereas *in situ* prepared complex generated under complexation of $[\text{Rh}(\text{NBD})\text{Cl}]_2$ with 2 equivalents of **L4** furnished **A1** in 67% ee. Furthermore, the addition of KBr or KI additives further improved the chiral induction, up to 79% ee. However, the halide additive effect could not be generalized to all substrates. More challenging dialiphatic and cyclic imines failed while using this catalytic system.

Scheme 7. Rhodium-catalyzed asymmetric hydrogenation of acetophenone benzylimine.



While regarding the inefficiency of this catalytic system versus aliphatic imines, the authors hypothesized that a careful substrate design could be a valuable solution. Accordingly, substrate **I2**, bearing an additional OMe coordinating motif was engaged in the AIH reaction and rewardingly, the expected product could be isolated with 69% ee. This result clearly suggests that the presence of a secondary basic site allows coordination of the imine in a bidentate manner, thus increasing the possibility of efficient chirality transfer between the chiral complex and the substrate (Scheme 8). This concept has been largely taken up in the following years, resulting in the design of a variety of more complex imine substrates.

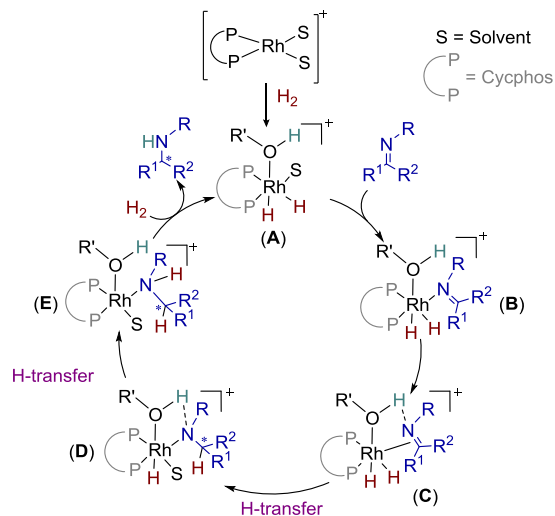
Scheme 8. The methoxy group of **I2** coordinated to the rhodium catalyst.



Based on the detailed mechanistic investigations,¹⁹ a mechanistic scenario has been proposed (Scheme 9). In the initial step, the catalytically active Rh(III)-species (**A**) is formed in the presence of hydrogen gas followed by coordination of the imine substrate *via* the nitrogen lone pair (**B**), which enables the formation of a complex with hydrogen bonds (**C**). Subsequently, the alcohol hydrogen bonding promotes the H-transfer and allows the formation of the Rh(III) intermediate (**D**). A second hydrogen transfer occurs, giving the coordinated amine (**E**), which is released under H₂ pressure. As stated above, the halide effect is substrate-dependent and hence its rationalization is far from trivial. A plausible hypothesis sug-

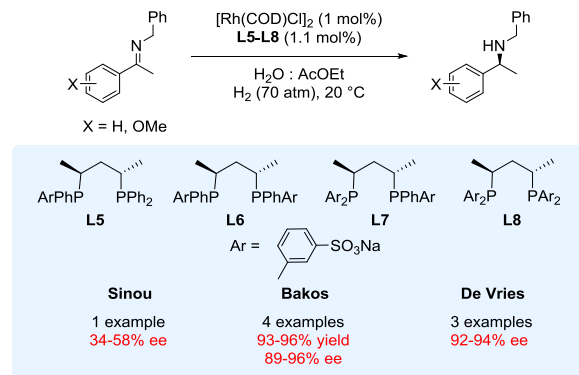
gests that in the absence of such an additive, two imine molecules can coordinate to the metal either in *syn* or *anti* geometries. The hydrogenation of the enantiotopic faces of such isomeric complexes results in decreased stereoselection. The addition of the iodine ion prevents such double coordination thus warranting the formation of a single specie of the key monocoordinated intermediate.

Scheme 9. Proposed mechanism for Rh-Cycphos hydrogenation of simple ketimines.



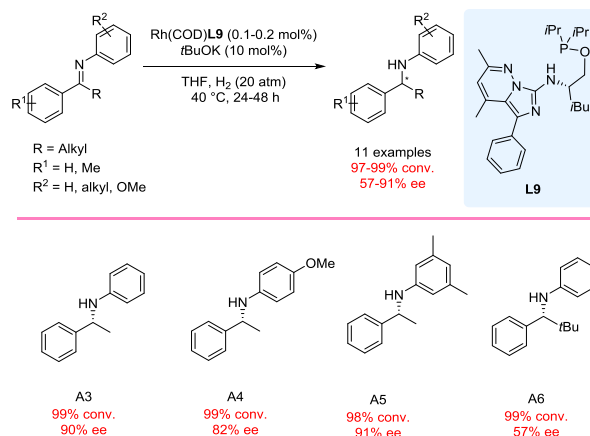
Targeting catalytic systems that might be easily recovered and recycled, Sinou and coworkers hypothesized that interesting reactivity could be observed while performing AIH using sulfonated phosphine ligand.²⁰ This water-soluble ligand should promote the reaction in aqueous-organic two-phase solvent systems, as the product can be easily recovered from the organic phase during work-up, thus paving a way towards a recyclable catalyst. Unfortunately, sulfonated (*S,S*)-BDPP ligand **L8** performed poorly in AIH of **I1**, delivering the expected product in modest ees (Scheme 10). Further investigations of these water-soluble Rh-complexes showed that remarkably higher enantioselectivity may be achieved while using only monosulfonated BDPP ligands **L5**, delivering the expected chiral amine with up to 96% ee.²¹ Substituents such as Cl⁻ and OMe are well tolerated, furnishing the corresponding amines in high optical purity. Although such catalytic systems are amongst the first ones allowing AIH with excellent levels of chiral induction, high pressure of H₂ (70 bars) limits considerably the synthetic applicability of this protocol.

Scheme 10. The effect of water-soluble sulfonated ligands on ketimines hydrogenation.



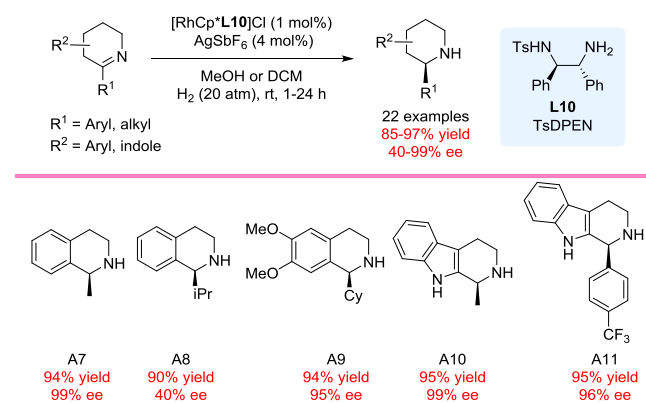
Although C-stereogenic diphosphine ligands have largely dominated the field of Rh-catalyzed AIH, several other families of ligands have also been evaluated in this challenging reaction. In 2010, Kempe's group designed an original imidazo azine-substituted amine ligand (Scheme 11). These ligands presenting three coordinating units, act as monoanionic N, N, P-tridentate amido-ligands recognized for their potential to stabilize metals of group 9. The corresponding chiral Rh-amido-complex **Rh(COD)L9**, generated in the presence of a catalytic amount of *t*BuOK, showed high reactivity and very good enantioselectivity in the reduction of *N*-aryl imines **I3-I6** delivering the expected **A3-A6** with enantioselectivities up to 91%.²² Remarkably, the dialkylphosphine-substituted complexes are particularly active as the catalyst loading as low as (0.1-0.2 mol%) and moderate H₂ pressure (20 bars), were sufficient to reach full conversion and high ee for the selected substrates.

Scheme 11. Asymmetric hydrogenation of *N*-arylimines.



During the preliminary studies, AIH of cyclic imines, such as **I7**, was considered as particularly challenging and several Rh complexes bearing diphosphine ligands failed to provide sufficient levels of enantioselectivity. A significant advance was achieved by Xiao who developed a complementary Rh-based catalytic system implying chiral diamine ligands, such as TsDPEN **L10** (Scheme 12).²³ The corresponding cationic Rh-TsDPEN complex, an efficient catalyst in asymmetric transfer hydrogenation reactions, turned out to be also a catalyst of choice for the hydrogenation. Enantioenriched tetrahydroisoquinolines (**A9**) and tetrahydrocarbolines (**A10-11**) could thus be prepared in excellent yields and enantioselectivities. The stereodiscrimination is believed to be controlled not only by the steric properties of **L10** but also via C-H interactions between the Cp* methyl group and the imine aromatic ring.

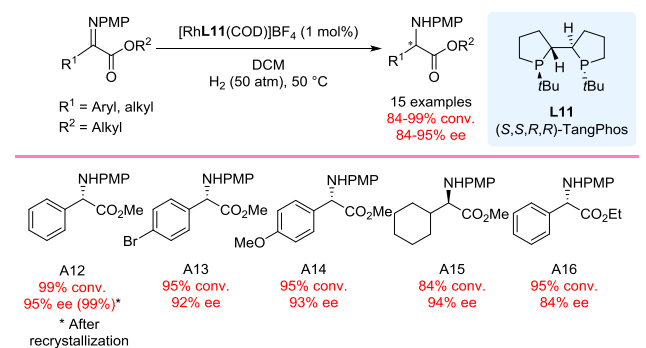
Scheme 12. Hydrogenation of cyclic imines catalyzed by Rh.



The improved reactivity of Rh-TsDPEN containing a Cp* moiety as the second ligand could arise from the high oxidation state of Rh in this precursor. Catalytically active cationic Rh(III) species, generated *in situ* via Ag-promoted Cl-abstraction, is believed to react quickly with H₂, thus generating the Rh-H hydride specie and promoting the overall transformation. Among several silver sources tested, AgSbF₆ outperformed due to the bulky and non-coordinating nature of the SbF₆ anion.

Based on these preliminary efforts concerning the functionalization of relatively simple amines, the following attempts have turned progressively to the application of this methodology towards the synthesis of more complex amine-derivatives, bearing different functional groups. While substrates containing a coordinating motif on the N-atom will be presented in part II of this review, the group of Zhang has focused on AIH of aryl imino esters (Scheme 13). Screening of several chiral diphosphine ligands revealed that (*S,S,R,R*)-Tangphos (**L11**) is the optimal choice. The expected chiral amino esters (such as A12-16) were afforded with up to 95% ee under H₂ pressure of 50 bars. This catalytic system, contrary to many others, tolerates a diversity of substrates, providing the products with constant ees. The synthetic utility of this reaction could be further highlighted by its large-scale application as the desired chiral amino acid (1 g) could be obtained using a catalyst loading as low as 0.1 mol% (TON > 820).²⁴

Scheme 13. Asymmetric hydrogenation of arylimine esters.



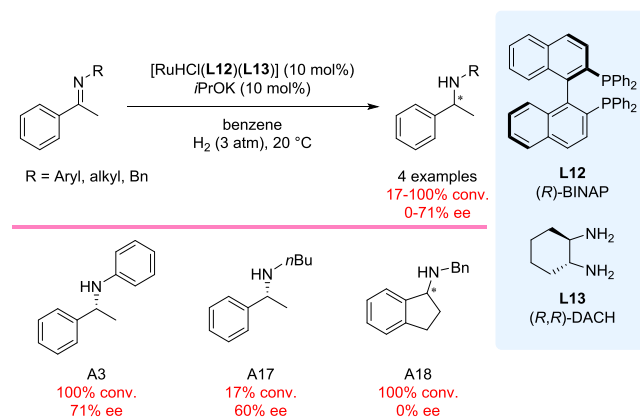
Ruthenium based catalysts

Despite the appealing reactivity of chiral Ru-complexes in asymmetric hydrogenation of C=C and C=O bonds, the applications of this metal for C=N reduction has emerged only at the beginning of this century and very different ligand design,

compared to the one used in Rh-catalyzed transformations, has been developed.

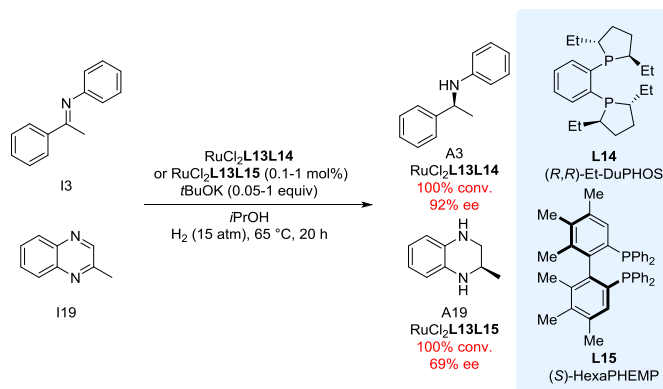
Drawing inspiration from Noyori's seminal contributions,² Abdur-Rashid and Morris established a family of mixed (diphosphine **L12**)(diamine **L13**) chiral RuHCl complexes for AIH. Such a complex is obtained using RuHCl(PPh₃)₃ precursor via sequential coordination of diphosphine and diamine ligand (Scheme 14).²⁵ The monohydride RuHCl(*R,R*-Binap)(*R,R*-cyclohexyldiamine) **L12** and **L13** complex, generated under basic conditions and low H₂ pressure (3 atm), promotes the asymmetric hydrogenation of ketones and imines, thus allowing the generation of amines A3 and A17 with moderate enantioselectivities (71 and 60% ee respectively). Unfortunately, *N*-benzyl imine turned out to be an extremely challenging substrate for this catalytic system as no chiral induction could be achieved for A18.

Scheme 14. Morris's ruthenium hydrogenation of imines.



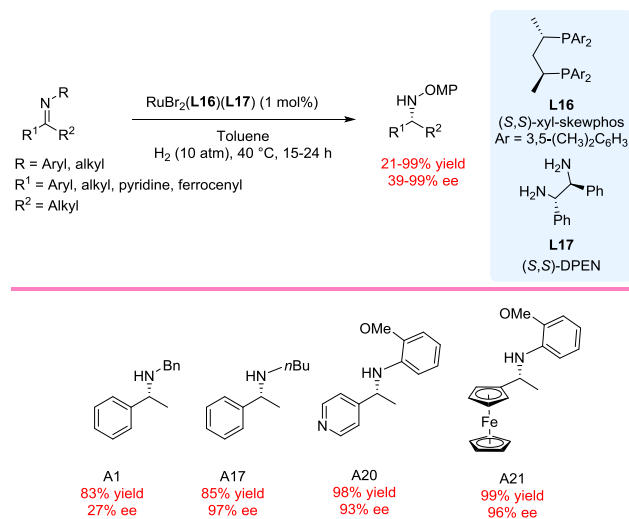
Subsequent efforts towards Ru-catalyzed AIH implied the use of RuCl₂(diphosphine)(diamine) air-stable complex.²⁶ This standard catalyst, after *in situ* activation with potassium *tert*-butoxide, promotes quantitative AIH of simple imines I3 and 2-methylquinoxalines II9 while using *i*PrOH as solvent (Scheme 15). Fine selection of both, chiral diphosphine and chiral amine permitted the design of the optimal catalyst: (*R,R*)-Et-DuPhos/(*R,R*)-DACH (**L14/L13**), able to reach up to 92% ee. However, this transformation suffers from a lack of generality, as the catalyst's optimization was required for different substrates. Also, the addition of *t*BuOK was critical to the stereoselectivity as in the presence of an equimolar amount, an equilibrium between imine and its aldimine tautomer was observed, thus seriously decreasing the chiral induction. From the mechanistic viewpoint it is interesting to highlight that, based on the deuterium labeling study, reduction of the imines could occur also *via* transfer hydrogenation, albeit this route is less selective and kinetically disfavored. Thus, this transformation illustrates unambiguously the complexity of the development of the general and highly enantioselective AIH system.

Scheme 15. Noyori type complex for ruthenium asymmetric hydrogenation of imines and 2-methylquinoxalines.



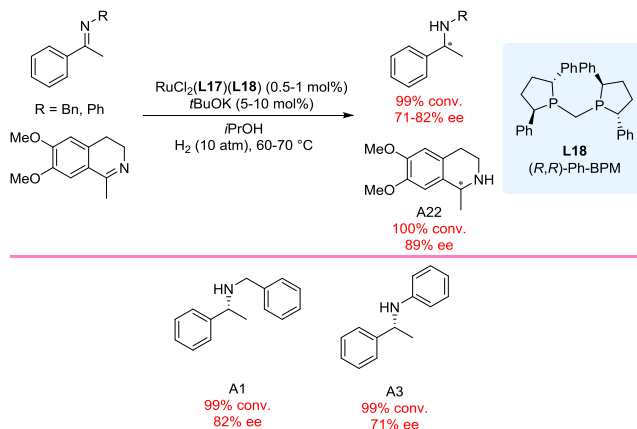
The potential and scope of AIH catalyzed by Ru(diphosphine)(diamine) ligand was further expanded by Ohkuma's group (Scheme 16).²⁷ $\text{RuBr}_2[(S,S)\text{-xyl-skewphos } \mathbf{L16}][(\text{S,S})\text{-DPEN } \mathbf{L17}]$ precatalysts features great reactivity and excellent enantioselectivity with respect to several different families of imines, including aromatic and heteroaromatic ones, as well as some ferrocenyl and vinylic derivatives. The reaction occurs under relatively low H_2 pressure of 10 atm and low catalyst loading is sufficient to promote the reaction (TON up to 18000), thus rendering this catalytic system industrially relevant.

Scheme 16. Ohkuma's hydrogenation of imines.



An alternative example of Ru-complex was also disclosed by Jackson (Scheme 17).²⁸ In this case, $\text{RuCl}_2[(R,R)\text{-Ph-BPM}][(\text{S,S})\text{-DPEN}]$ catalyzed the reduction of three imines in moderate to good enantioselectivities (71-89% ee).

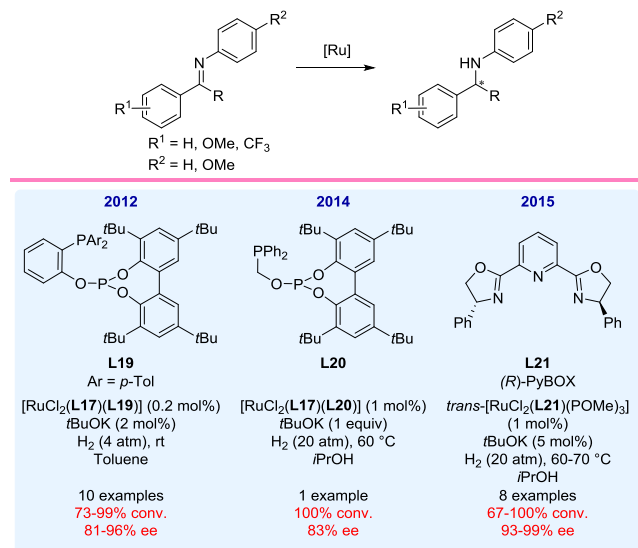
Scheme 17. Jackson's Ru-catalyzed hydrogenation of imines.



In 2012, Pizzano's group developed ruthenium achiral phosphane-phosphite / chiral diamine complexes and studied their performance in the enantioselective hydrogenation of *N*-(1-phenylethylidene)aniline **I3** (Scheme 18).²⁹ While studying the asymmetric hydrogenation of olefins and enamines, chiral DPEN diamine **L17** was used as chirality source in combination with several different phosphane-phosphinite achiral ligands. Interestingly, the structure of the phosphane-phosphinite impacts both, the catalytic activity and the stereoselectivity. The efficient catalyst was the one possessing a phosphite-based flexible unit, bearing the bulkier substituents (*t*Bu), essential for the highest catalyst activity. While using the optimal precatalyst **Ir-L19**, *N*-arylimines derivatives were hydrogenated under mild conditions (i.e. room temperature and 4 atm of H_2) furnishing the chiral amines with full conversion and high ee (81 – 96%). In some cases, with electron-poor substrates, higher pressure of H_2 was necessary to reach the full conversion of the starting substrates due to a lower reactivity and selectivity.³⁰

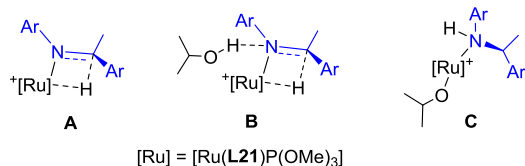
Interestingly, promising reactivity was observed while using much simpler $\text{P}(\text{OMe})_3$ monodentate phosphite ligand in combination with chiral pybox (2,6-bis(oxazoline)pyridine) **L21** ligand (Scheme 18).³¹ This ligand combination allows the generation of highly active Ru-complex, able to catalyze the highly enantioselective reduction of a small panel of *N*-aryl imines. Importantly, this catalyst seems relatively general as constant ees of 93-99% were measured for all tested substrates. Noteworthy, this reaction occurs under both hydrogenation and transfer hydrogenation conditions; similar results were obtained by using H_2 gas or *i*PrOH as proton sources.

Scheme 18. Pizzano's systems for imines hydrogenation.



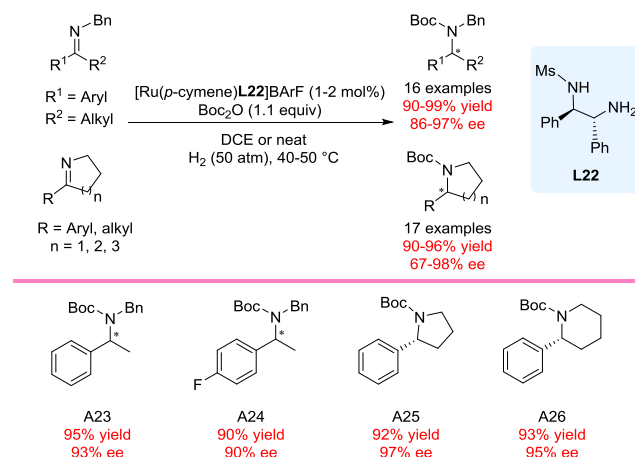
The *N*-aryl imines substrates were hydrogenated through an inner-sphere mechanism, which involves imine coordination (Scheme 19). From the mechanistic point of view, comparable enantioselectivities for both, hydrogenation and atom transfer route have been observed, suggesting the existence of a common enantiodetermining step. It can be hypothesized that the imine insertion into the Ru-H bond (A) is the stereoselective event. Possible coordination of the solvent during the imine insertion may also occur (B). The third intermediate (C) could be formed from (B) or via reaction of the amide complex generated from (A) with *i*PrOH. Subsequently, the amine decoordination in (C) gives the corresponding unsaturated alkoxide [Ru(O*i*Pr)(Ph-PyBOX)(P(OMe)₃)]⁺ which can release the active rhodium hydride species [Ru(H)(Ph-PyBOX)(P(OMe)₃)] under both hydrogenation or transfer hydrogenation conditions.

Scheme 19. Transition states for ruthenium hydrogenation in protic solvent.

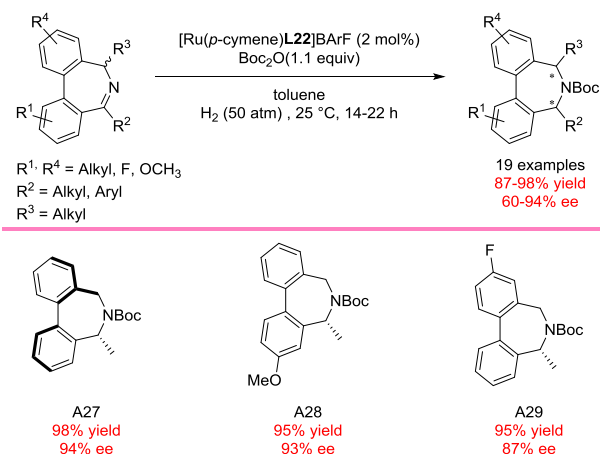


Regarding the success of mix Ru-complexes, as well as catalytic potential of η^6 -arene/TsDPEN-Ru(II) complexes in asymmetric ketones hydrogenation, other groups hypothesized that a comparable reactivity should also be accessible while designing a catalytic system bearing an achiral *p*-cymene ligand in combination with a chiral amine.³² Following this idea, Fan has reported phosphine free, cationic Ru(*p*-cymene)-MsDPEN **L22** catalyst (Scheme 20).³³ The optimization study revealed that counter anion impacts slightly the enantioselectivity of the reaction and under the optimal reaction conditions, hydrogenation of the imine **II** was achieved with up to 96% ee.³⁴ Interestingly, to avoid the catalyst poisoning by a small amount of benzylamine resulting from the decomposition of the substrate, (Boc)₂O was added in the reaction mixture and thus *N*-Boc protected chiral products were afforded. Subsequently, this work has been extended towards AIH of cyclic *N*-alkyl imines as well as dibenzo[*c,e*]azepines delivering a range of 2-aryl and 2-alkyl pyrrolidines and 6,7-dihydro-5*H*-dibenz[*c,e*]azepines in excellent yields and enantioselectivities (Scheme 21).³⁵

Scheme 20. Cationic Ru-complexes for enantioselective hydrogenation.



Scheme 21. Asymmetric hydrogenation of azepines.



Palladium based catalysts

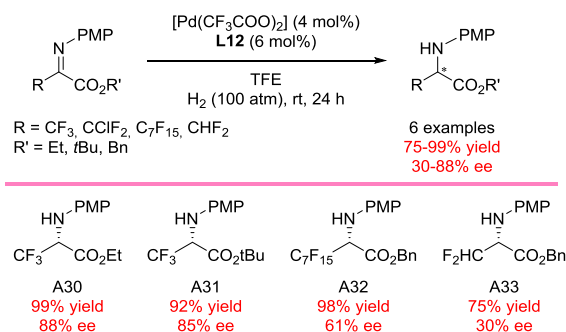
While palladium catalysts are frequently used for cross-coupling reactions to create C-C and C-N bonds, the applications of this metal in asymmetric hydrogenation reactions are scarce.

Amii, Uneyama *et al.* have proven that Pd is appealing in the context of asymmetric hydrogenation of challenging α -fluorinated iminoesters.³⁶ In general, the presence of a fluoroalkyl substituent on imines results in weaker coordination to the metal center, thus favoring nucleophilic reactions over hydrogenation. In addition, due to the increased acidity of the α -proton of the generated amine, the racemization might be expected. Surprisingly, a very simple catalytic system generated *via in situ* coordination between Pd(CF₃CO₂)₂ and (*R*)-BINAP **L12** turned out to be a promising solution, while performing the reaction in 2,2,2-trifluoroethanol (TFE) (Scheme 22). The particular role of TFE as the optimal solvent arises from possible weak coordination to the palladium center facilitating rapid exchange with the less coordinating fluorinated imines. Besides, imine activation by TFE *via* protonation or hydrogen bonding cannot be excluded.

Under these conditions, several enantioenriched fluorinated amino esters have been furnished. The catalytic system is highly selective while using trifluoromethylated or dichlorofluoromethylated iminoesters as substrates I30-I31,

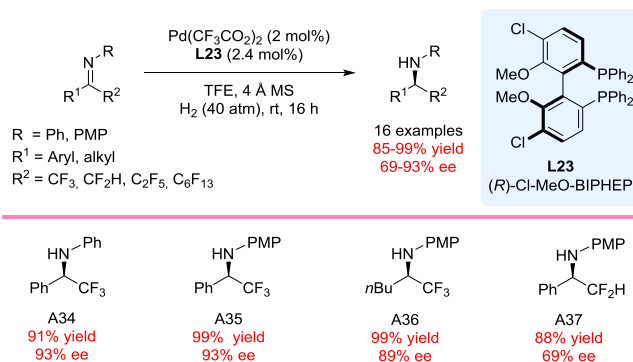
but significant drop in enantioselectivity was witnessed while evaluating esters bearing other fluorinated motifs, such as C₇F₁₅ and CHF₂ (I32-I33). Particularly disappointing stereoselection of only 30% was observed in the case of CH₂F-substituted iminoester and can be attributed to the possible *E/Z* isomerization. In contrast, the nature of the ester moiety has a limited impact on the reaction outcome.

Scheme 22. Pd-BINAP hydrogenation of fluorinated imines.



Perfluoroalkyl ketimines were also studied by the group of Zhou.³⁷ The hydrogenation of I34-I37 was achieved using Pd supported by privileged axially chiral phosphine ligand: (*R*)-Cl-MeO-BIPHEP L23. Similarly to the previous examples, Pd(CF₃CO₂)₂ and TFE were the best combination to promote these AIHs (Scheme 23). The addition of 4 Å MS was beneficial and the overall reaction could be conducted at room temperature under a pressure of 40 bars of H₂. Under the optimized reaction conditions, the desired trifluoromethylated amines were afforded with good to high enantioselectivities (69 – 93% ee). This improved catalytic system also tolerated other fluorinated motifs, such as CF₂H, CF₂Et, and C₃H₇ groups, though lower stereoselection was observed.

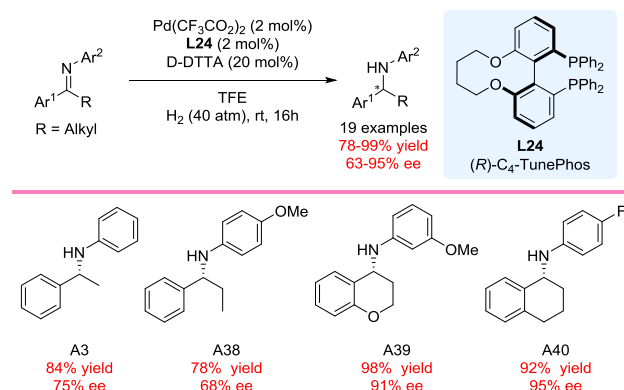
Scheme 23. Pd-catalyzed hydrogenation of perfluoroalkyl ketimines.



Furthermore, asymmetric hydrogenation of non-fluorinated cyclic and acyclic imines using a Pd-based catalyst was investigated by the same group.³⁸ Initially, the combination of Pd salts and a commercial axially chiral diphosphine ligand (SYNPHOS) promoted the expected hydrogenation, albeit with moderate efficiency and very low enantioselectivity of 5%. A substantial stereoselection increase was observed in the presence of chiral acids, such as Di-*p*-toluoyl-L-tartaric acid (D-DTTA); the catalytic system combining Pd-precatalyst, TunePhos (L24) and D-DTTA delivered the expected amine A38 with 68% ee. Despite the fact that the addition of this chiral additive considerably impacts the stereoselection, the configuration of the final amine product is controlled by the absolute configuration of the chiral Pd-catalyst (Scheme 24).

Under these optimized reaction conditions, the synthesis of a wide range of enantioenriched amines was conducted with good to excellent yields and moderate to high ee.

Scheme 24. Enantioselective hydrogenation of *N*-arylimines with palladium complex.



Iridium based catalysts

Notwithstanding that some interesting catalytic systems for AIH have been designed using Rh, Ru, and Pd-based catalyst, Ir-based complexes clearly outperform in this type of reaction.

Two types of mechanisms for imine hydrogenation have been proposed: the inner-sphere and the outer-sphere. Both scenarios are based on various mechanistic studies involving mainly iridium catalyst, albeit similar pathways may also be envisioned in the case of ruthenium and rhodium-catalyzed transformations.

Two main differences exist between the inner- and the outer-sphere mechanism: in the later, the substrate is free and unbound during hydrogenation and the proton transfer to the substrate occurs first. In contrast, in the inner-sphere mechanism, the hydride transfer occurs after the proton transfer.

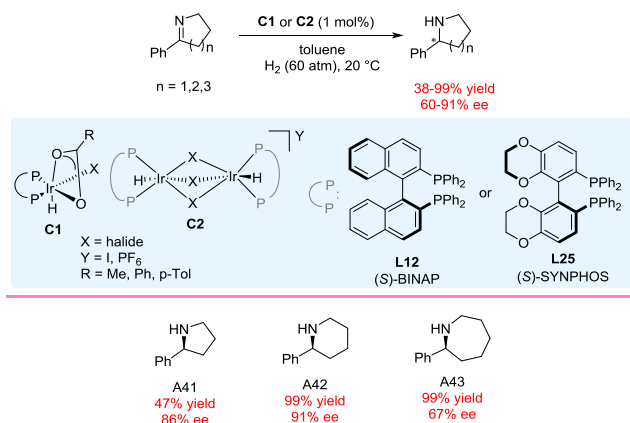
Diphosphine ligands

The seminal contributions on Ir-catalyzed AIH clearly illustrated the potential of Ir as the metal of choice for the synthesis of chiral amines. A complementary reactivity to the one observed in case of Rh and Ru-based catalysts have been delineated; in the case of Ir, the highest levels of optical purity have generally been observed for cyclic imines, while these imines performed poorly in case of other metals. Besides, very high pressure of H₂, typically 100 bar, was commonly applied to achieve high catalytic activity.

Regarding the importance of axially chiral diphosphine ligands in asymmetric homogeneous catalysis, it is not surprising that the initial investigations of the Ir-catalyzed AIH have been conducted using such well-established, privileged ligands. Accordingly, Mashima, Genet and co-workers synthesized mononuclear halide carboxylate and triply halogen-bridged dinuclear complexes, with BINAP L12 and SYNPHOS L25 ligands in order to investigate their performance in the hydrogenation of cyclic imines such as I41-I43 and 2-phenylquinoline. Good to excellent enantioselectivity was obtained by using these ligands under mild conditions in terms of temperature (Scheme 25). Complexes containing iodide demonstrate an increased catalytic activity compared to other halide complexes while the substitution of the carboxylic

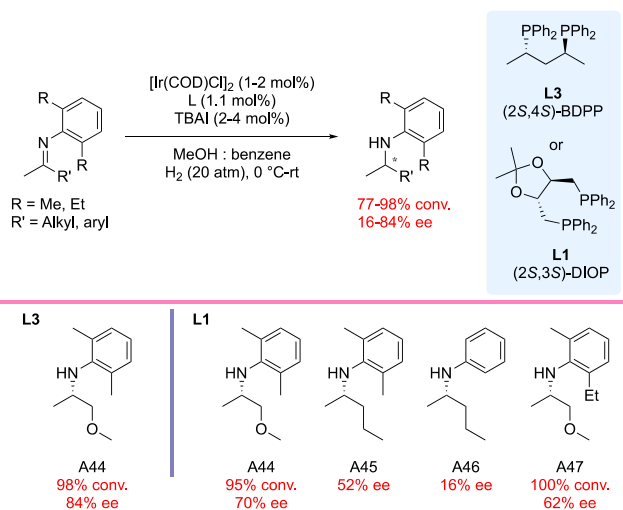
acid co-ligand seems to have a minor impact on the efficiency of this catalytic system.³⁹

Scheme 25. Asymmetric hydrogenation of cyclic imines using diphosphines ligands.



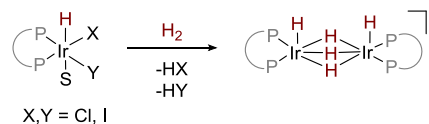
The first involvement of iridium metal in homogeneous asymmetric hydrogenation of *N*-aryl imines such as A44 was reported by Spindler's group.⁴⁰ Aiming for the synthesis of aniline derivatives, they used $[\text{Ir}(\text{COD})\text{Cl}]_2$ as a metal source to prepare *in situ* the catalyst in presence of a diphosphine ligand and halogen ions (Scheme 26). The evaluation of a small library of diphosphine ligands showed that the best activities and enantioselectivities were obtained with **L1** and **L3**, the ones that can form a conformationally flexible six- or seven-membered metallacycle. Likewise, in Rh-catalyzed AIH, iodide has a strong positive influence on both efficiency and selectivity of the catalytic system as the formation of inactive dinuclear iridium complexes might thus be prevented. The sterically hindered imine (I44) was reduced with the highest stereoselection, arguably due to the disfavored conformational freedom of motion of the imino group (hindered rotation about the *N*-aryl bond). Unfortunately, disappointing results were obtained while evaluating dialiphatic imines I45-46. Considering the potential of this catalytic system, its potential for the industrial synthesis of (*S*)-Metolachlor, an herbicide blockbuster, was investigated. Under the previously optimized reaction conditions, the (*S*)-Metolachlor's precursor A47 was obtained via hydrogenation of I47 with a moderate enantiomeric excess of 62%.

Scheme 26. The first iridium catalyzed enantioselective hydrogenation of acyclic imines.



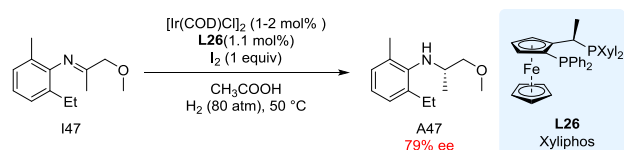
The lack of reactivity and enantioselectivity pushed Spindler and Togni to attempted to stabilize the Ir-catalyst with various additives.⁴¹ The deactivation of the Ir-diphosphine complex may indeed be attributed to the irreversible formation of hydride-bridged dimers that remain catalytically inactive (Scheme 27).

Scheme 27. Hydride bridged dimers.



Regarding the industrial importance of Metolachlor precursor I47, further investigations were conducted. In 1999, Blaser and Spindler employed Xyliphos (**L26**), a chiral ferrocenyl-based ligand in combination with Ir-precatalyst.⁴² In the presence of iodide and acetic acid, high activity was observed and the hydrogenation of I47 occurred with a good enantiomeric excess of 79% (Scheme 28).

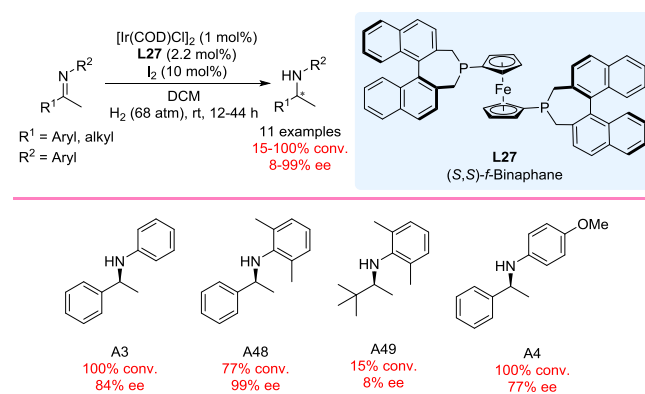
Scheme 28. Xyliphos ligand for MEA I47 hydrogenation.



Zhang and coworkers were also interested in the development of ferrocene-based chiral ligands for Ir-catalyzed AIH of acyclic *N*-arylimines.⁴³ Due to the low efficiency of the simple binaphane ligand in Rh- and Ir-catalyzed AIH, they hypothesized that the ferrocene-derived Binaphane should exhibit several advantageous features, such as increase of flexibility, larger bite angle as well as higher electron-donating properties.

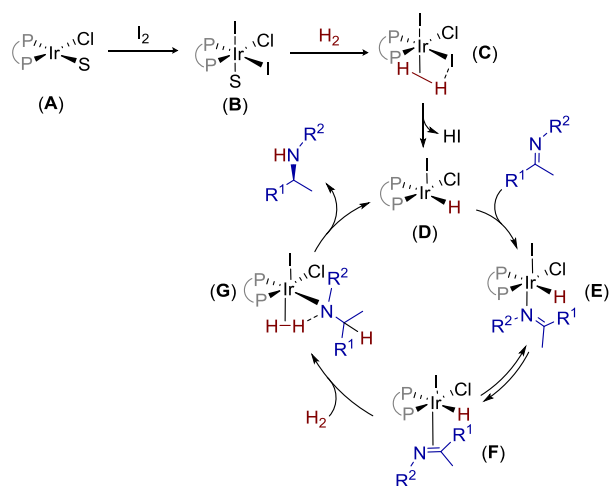
Accordingly, chiral and air-stable 1,1'-bisphosphanoferrrocene (*f*-Binaphane, **L27**) was synthesized. Direct asymmetric hydrogenation of *N*-arylimines was achieved in CH_2Cl_2 and under high H_2 pressure, furnishing efficiently the expected products (Scheme 29). Notably, similarly to other Ir-diphosphine complexes, hydrogenation of alkylimines was less efficient. The halogen-atom-additive effect, which usually prevents the catalyst deactivation *via* formation of $\text{Ir}(\text{P-P})\text{H}_2$, is less tangible than in other catalytic systems. Indeed, the enhanced enantioselectivity was observed only in some cases, thus suggesting that the catalytic process in presence of I_2 -additive differs from the process without the additive.

Scheme 29. Ir-*f*-Binaphane for the asymmetric hydrogenation of *N*-aryl imines.



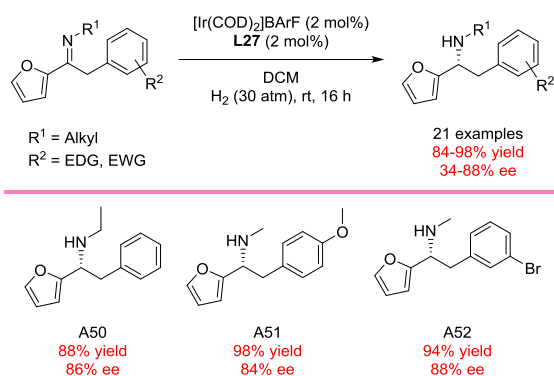
To rationalize the role of I₂, an inner-sphere mechanism was proposed where the oxidative addition of I₂ to the Ir(I) precursor generates the Ir(III) complex (B) (Scheme 30). After H₂ coordination, the heterolytic cleavage of H₂ occurs, furnishing the mono-hydride Ir(III)-H (D) simultaneously with the elimination of HI molecule. The imine substrate coordinates to the catalyst via two possible modes (via η¹ or η² coordination). The following step is the migratory insertion of the η²-imine into the Ir-H bond allowing the formation of Ir-amide complex (G). In the presence of H₂, the Ir-amide intermediate affords the chiral amine by heterolytic cleavage of H₂ and releases the active specie Ir(III)-H (D).

Scheme 30. The iodine role in the hydrogenation mechanism.



The *f*-Binaphane ligand (L27) has been also employed by Johansson and coworkers to achieve the enantioselective hydrogenation of *N*-alkyl α -aryl ketimines bearing a furyl moiety which are interesting scaffolds easily convertible into valuable chiral *N*-alkylated phenylalanine analogs (Scheme 31).⁴⁴ Large screening of various phosphine ligands revealed that L27 was the most efficient in AIH of this particular skeleton. Under 30 atm of H₂, the corresponding chiral amines were obtained with moderate to good enantioselectivities and with good to excellent yields.

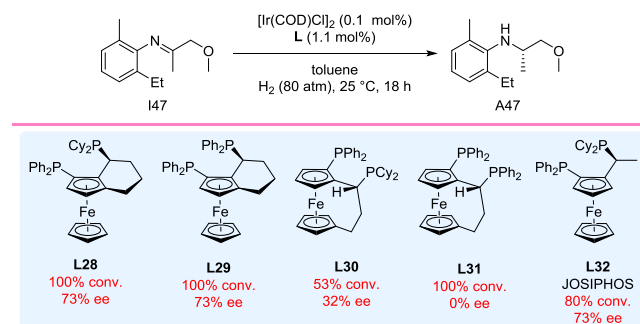
Scheme 31. Asymmetric hydrogenation of *N*-alkyl α -aryl ketimines.



Alternative architectures of ferrocene-based diphosphines, featuring planar chirality, were designed by Spindler-

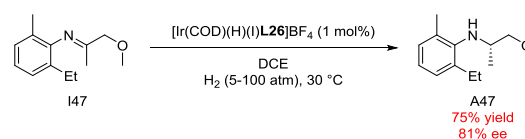
Weissensteimer-Jalon and coworkers and tested on the hydrogenation of I47, a Metolachlor precursor. Particularly, the synthesis of a library of such ligands with different flexibility has been undertaken to investigate the impact of the conformation of the ligand on its catalytic activity (the side chain to homo- or heteroannular bridge; Scheme 32).⁴⁵ Homoannular ligands L28 and L29 showed an interesting reactivity and selectivity but disappointingly, could not outcompete commercially available JOSIPHOS (L32) and XYLIPHOS (L26) ligand (Scheme 28).

Scheme 32. The efficiency of homo and heteroannularly bridged diphosphine ferrocene-based ligands.



In 2004, Dorta and coworkers prepared several cationic iridium-Xyliphos complexes to study their potential in the hydrogenation of the Metolachlor precursor, I47 (Scheme 33).⁴⁶ The Ir(I) complexes performed poorly whereas trivalent iridium precatalysts were more active in terms of yields. In contrast, the enantioselectivity was slightly impacted by the modification of the Ir-precatalysts. The halide free catalyst was inactive for the hydrogenation thus clearly showing how important the halide effect is. It was speculated that the H₂ activation step occurs subsequently with the elimination of H-halide molecule thus promoting the overall catalytic cycle. The best mononuclear single-component precatalyst was the Ir(III)-Xyliphos complex.

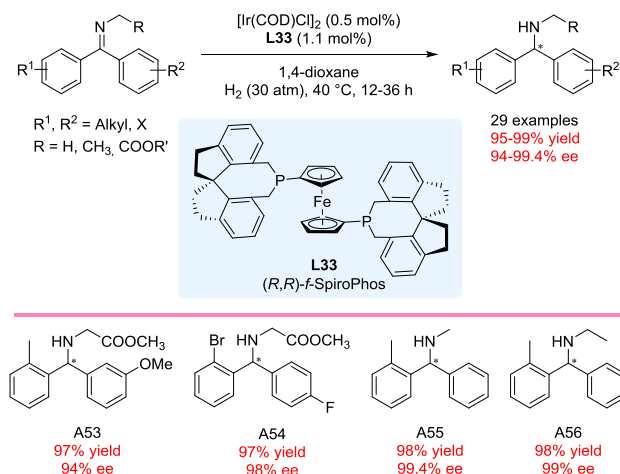
Scheme 33. Dorta's complex for the hydrogenation of MEA.



The next step forward in the AIH using ferrocene-based phosphine ligands was achieved while discovering the potential of *f*-SpiroPhos ligand L33. The group of He achieved in 2016 a challenging hydrogenation of *N*-substituted diarylmethanimines under mild conditions using an iridium catalyst with a chiral *f*-SpiroPhos ligand L33 containing a 1,1'-spirobiindane scaffold.⁴⁷ Remarkably, this catalytic system is compatible with a large panel of imines, providing a diversity of chiral diarylamines with high yields and excellent enantioselectivities (Scheme 34). Importantly, both *N*-alkyl and *N*-ester diarylimines successfully undergo the enantioselective hydrogenation. The *ortho*-benzene substituent is crucial to reach high activity and enantioselectivity, whereas with the non-*ortho*-substituted imines the interconversion of *Z/E* isomers of the imines is non-negligible, affecting the enantioselectivity. Noteworthy, this hydrogenation could be

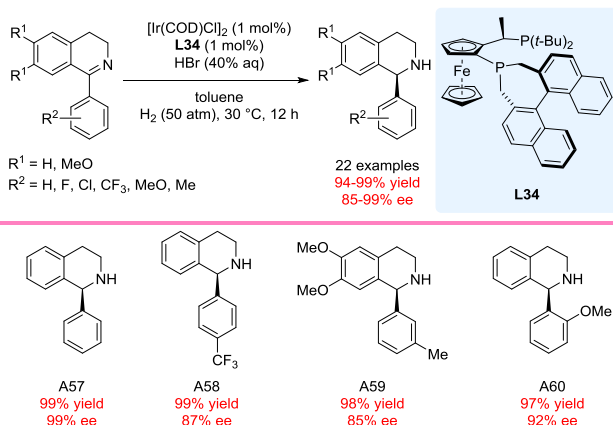
applied on a gram scale with low catalyst loading (TON up to 4K), proving the efficiency of this catalyst.

Scheme 34. Ir-SpiroPhos catalyzed enantioselective hydrogenation of diarylimines.



Alternative ligand design merging planar chirality of the ferrocene, central chirality and axial chirality was reported by Zhang. This ligand **L34** combines indeed the skeleton of Josiphos and the axially chiral phosphine moiety of *f*-Binaphane. This new type of ligand was evaluated in the Ir-catalyzed hydrogenation of 1-aryl-3,4-DHIQ (DHIQ = dihydroisoquinoline) substrates, delivering the desired products with up to 99% ee (Scheme 35).⁴⁸

Scheme 35. Josiphos-type binaphane ligands and their application in Ir-catalyzed hydrogenation of 1-aryl-3,4-DHIQs.

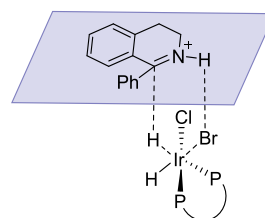


The atropisomerism of the binaphthalene backbone had a marked influence on the stereoreduction and lower chiral induction was observed while using a diphenyl derived ligand. A wide scope of chiral cyclic amines with differently substituted *N*-aryl groups was obtained with excellent yields and high ees. Superior stereoreduction was observed for the substrates bearing electron-donating groups, such as dimethoxy, on the benzene ring.

In this case, the halogen effect has also been witnessed, with the optimal results being achieved in the presence of HBr additive. The positive impact on the catalytic system was attributed to the imine's activation *via* hydrogen bonding. The catalyst performance is thus improved through a generation of

six-membered cyclic transition-state between the protonated imine and the catalyst (Scheme 36).

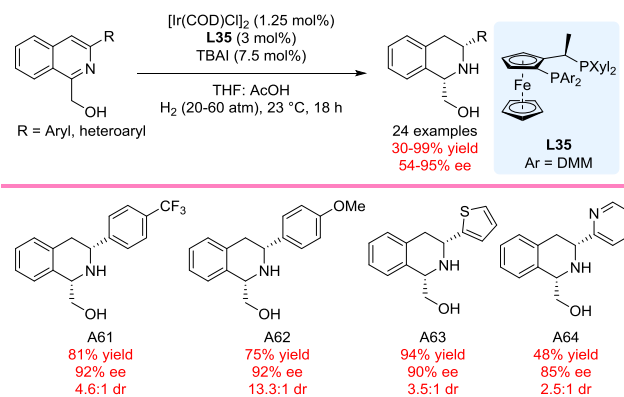
Scheme 36. Transition state for the hydrogenation of DHIQ.



Very recently, the potential of ferrocene-type ligands in the iridium catalyzed AIH was further expanded by Stoltz, who focused on the hydrogenation of *N*-heterocyclic imines.⁴⁹ A variety of isoquinolines were reduced under mild conditions by using the iridium dimer with 4-methoxy-3,5-dimethylphenyl (DMM)-Xyliphos **L35** ligand (Scheme 37).

This method tolerates numerous 1,3-disubstituted isoquinolines furnishing 1,2,3,4-tetrahydroisoquinolines (THIQs) with good yields, high enantio- and diastereoselectivities (up to 95% ee and >20:1 dr). The presence of hydroxymethyl motif as a directing group at the *C1*-position was crucial for the high reactivity and enantioselectivity. During the optimization of the reaction conditions it was found that the non-bulky ethereal solvents improve both, diastereoselectivity and efficiency, while additives such as acetic and TBAI are crucial to reach high conversions. In terms of the substrate scope, the electronic nature of the aryl substituent at *C3* position is crucial; electron-rich aromatics, such as *p*-anisole, afforded chiral THIQs with excellent yields, diastereoselectivity, and enantioselectivity while lower diastereoselectivity was observed for electron-poor aromatic substituents. It may be expected that the presence of electron-rich substituents at *C3* facilitates the coordination of the substrate to the iridium in a bidentate way thus enhancing efficient facial selectivity occurring in the second hydride addition step. The reaction of isoquinolines substituted with a heterocycle on the *C3* position such as furan, thiophene, pyrazole, and pyridine requires higher temperature and H_2 pressure.

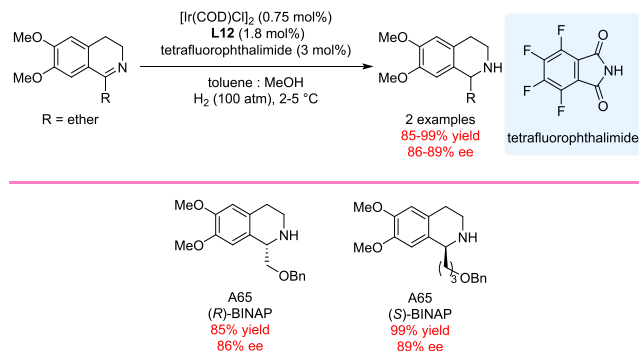
Scheme 37. Ir-catalyzed hydrogenation of isoquinolines.



Hydrogenation of other cyclic substrates, substituted dihydroisoquinoline, was investigated by Achiwa. Inspired by Noyori's Ru-BINAP complexes, Achiwa employed a catalytic amount of tetrafluorophthalimide as an additive in combination with the in situ generated Ir-**L12** complex (Scheme 38).⁵⁰ The additive will coordinate to the iridium center via the oxygen

thus improving the catalytic activity of the complex and promoting formation of chiral amine A65 with up to 89% ee. Noteworthy, A65 serves as an intermediate for the synthesis of isoquinoline alkaloids.

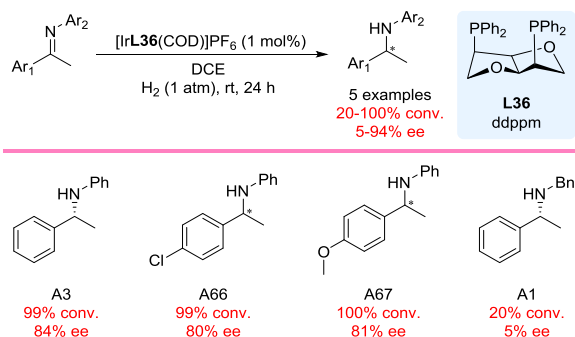
Scheme 38. Ir-BINAP system for the hydrogenation of cyclic imines.



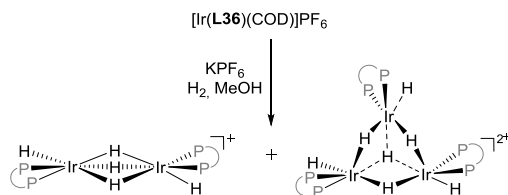
Dervisi *et al.* developed another approach to achieve the asymmetric hydrogenation of aryl imines using Ir(I) complex associated with ddppm ligand **L36** (

Scheme 39).⁵¹ This *endo*-diphosphine, initially designed for the Ru and Rh alkenes' hydrogenation, turned out to produce efficiently chiral amines while combined with Ir-precursor. This catalytic system is able to induce high enantioselectivity under atmospheric pressure of H_2 , while a significant drop of stereoselectivity was observed under H_2 overpressure. This negative impact of H_2 pressure could be rationalized by the saturation of the catalyst with hydrogen prior to the coordination of the imine, thus leading to the formation of inactive iridium-polyhydride clusters (Scheme 40). During the reaction progress, the decreasing amount of imine results in less efficient protection of the catalyst against the formation of dimeric and trimeric complexes thus favoring the catalyst's deactivation. Both, the substrate conversion and the enantioselectivity increased substantially in non-coordinating solvents and with weakly coordinating counter anions (such as PF_6^- and BF_4^-).

Scheme 39. Ir-ddppm complex for the enantioselective hydrogenation of aromatic imines.



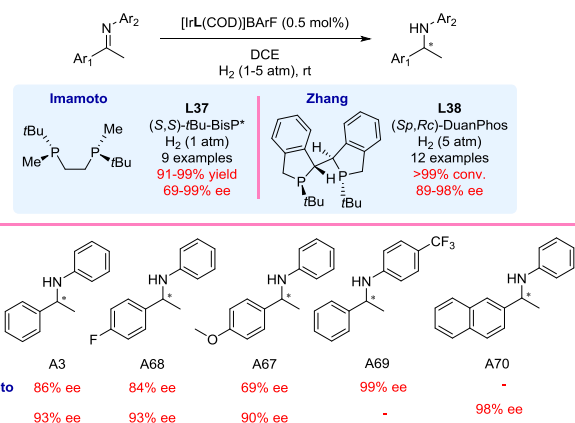
Scheme 40. Dimeric and trimeric Ir(III) polyhydride complexes.



Several others Ir-based catalytic systems perform well under low H_2 pressure. Imamoto has designed $[\text{Ir}(\text{L37}/\text{COD})]$ BARF complex (Scheme 41).⁵² Rewardingly, this complex bearing **L37**, strongly hindered P-stereogenic diphosphine, showed high reactivity for AIH of *N*-arylimines. Under atmospheric pressure of H_2 , at room temperature and while using only 0.5 mol% of the catalyst, the synthesis of the desired acyclic amines was achieved with up to 99% ee. The reaction tolerates various aromatic motifs on the *N*-aryl ring. Although the mechanism of this reaction has not been fully disclosed, the stereoselection seems to be generated during the migratory insertion step.

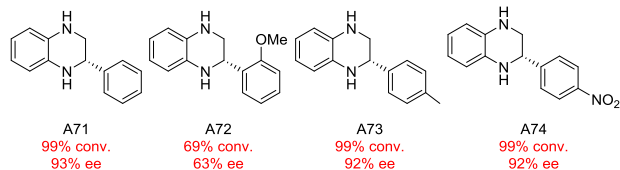
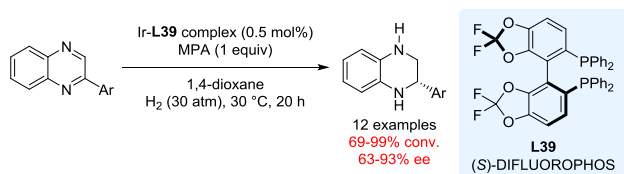
Excellent chiral induction during hydrogenation of imines was also achieved in the presence of DuanPhos **L38** (Scheme 41).⁵³ This alternative catalytic system furnished the *N*-aryl amines with ees up to 98% and TON up to 10000. However, significantly higher H_2 pressure of 50 bars was applied.

Scheme 41. Imamoto and Zhang's hydrogenation of *N*-aryl imines.



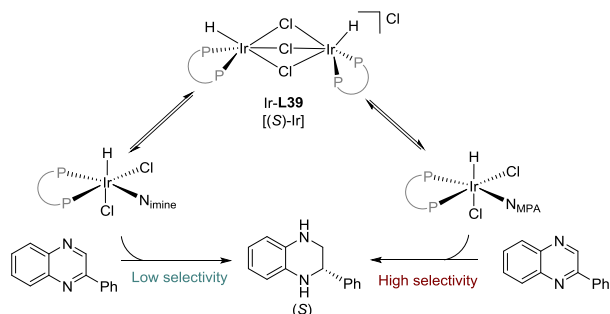
In 2012, Mashima *et al.* demonstrated the effect of the presence of *N*-methyl-*p*-anisidine (MPA) to enhance the reactivity and the enantioselectivity of the hydrogenation of 2-arylquinoxalines derivatives (Scheme 42).⁵⁴ This reaction is catalyzed by the dinuclear triply halide-bridged iridium complex associated to chiral DIFLUOROPHOS ligand **L39**. The presence of the additional ligand (MPA) contributes to the formation of a more active hydride catalyst, resulting from the Ir-MPA coordinated mononuclear complex, which is catalytically active for the reduction of 2-phenylquinoxaline (I71), delivering A71 with high enantioselectivity (93% ee).

Scheme 42. Hydrogenation of 2-arylquinoxalines derivatives in presence of *N*-methyl-*p*-anisidine (MPA) additive.



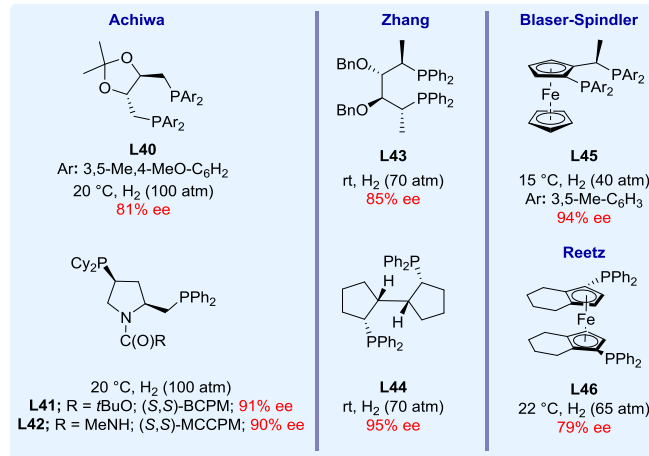
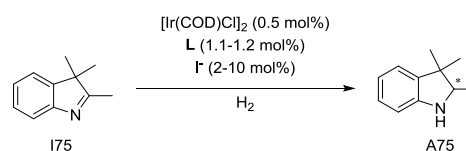
In contrast, lower yield and ee were observed in the absence of the MPA ligand. The replacement of MPA by the enantiopure hydrogenated product affords similar reactivity as with MPA (Scheme 43).

Scheme 43. The influence of the presence of MPA on the catalytic active specie.



Many groups reported the asymmetric hydrogenation of imines by associating iridium salts to several chiral diphosphine ligands, using 2,3,3-trimethylindolenine (I75) as a benchmark substrate (Scheme 44).⁵⁵⁻⁶⁰ Achiwa's group developed MOD-DIOP **L40** as a ligand that afforded the corresponding amine in 81% ee. One year later, the same group used BCPM **L41** and MCCPM **L42** ligands improving thus the ee up to 90-91%. Others diphosphines **L43** and **L44** were also employed by the group of Zhang and thus the indoline A75 could be obtained with a good enantiomeric excess (85% for **L43**) whereas using BCIP **L44** chiral ligand, ee of 95% was reached. The application of this reaction was extended also with Josiphos-type ligand **L45** and **L46** respectively by Blaser, Spindler and coworkers (76-94% ee) and by Reetz et al. (79% ee).

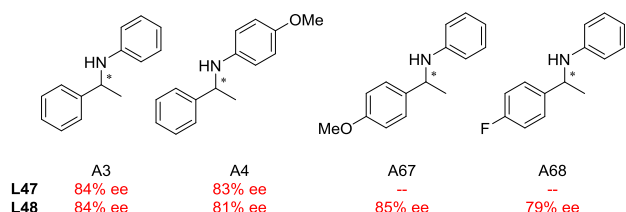
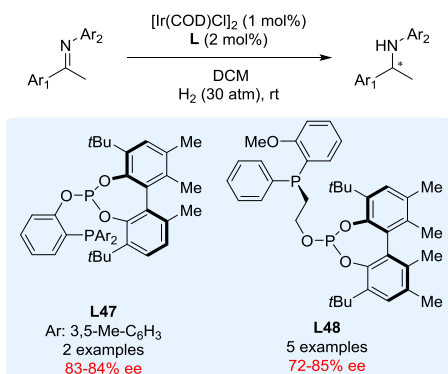
Scheme 44. Different complexes for the asymmetric hydrogenation of 2,3,3-trimethylindolenine.



Phosphine-Phosphite and phosphine-phosphoramidite ligands

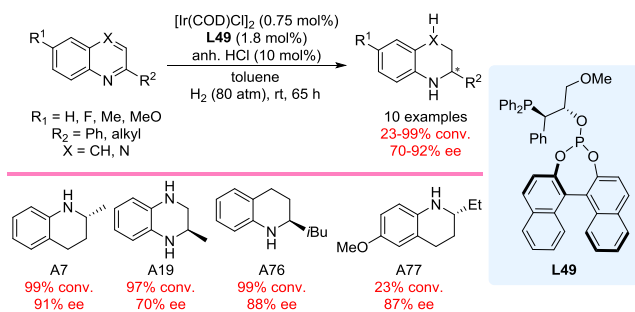
To further pursue the search of perfect chiral ligand for AIH, the attention has been turned towards phosphine-phosphites ligands (P-OP). These ligands possess an important feature compared to the simple diphosphine ligands. In both cases, two P-atoms are present but phosphine-phosphites are the ones possessing a good π -acceptor group. Inspired by the previous studies on the ferrocene-based catalyst, the strategy of Pizzano and coworkers consisted of exploring the ligand flexibility as an interesting parameter for catalyst optimization (Scheme 45).^{61,62} The oxophenylene bridged phosphine-phosphite ligand **L47** afforded moderate enantioselectivities in the catalytic hydrogenation of *N*-phenylimines. Based on these results, they developed a new dynamic ligand skeleton bearing an oxyethylene bridge as a flexible backbone **L48**. This ligand holds, in addition to the atropisomeric axis, a P-stereogenic phosphine group. This new catalyst afforded better enantioselectivity for the hydrogenation of *N*-arylimines (72-85% ee).

Scheme 45. Chiral phosphine phosphoramidite ligand in the Ir-catalyzed hydrogenation of arylimines.



An alternative structure of Ir-(P-OP) complexes was conceived by Vidal-Ferran while studying the asymmetric hydrogenation of *N*-heterocyclic imines (Scheme 46).⁶³ In this case, the ligand features two C-stereogenic centers on the ethylene backbone as well as atropisomerism on the BINOL moiety, with the atropchirality being the critical parameter for the enantioselectivity. Under hydrogen atmosphere, the combination of iridium with chiral phosphine-phosphite **L49** leads to the reduction of several substituted quinolines and one quinoxaline with high enantioselectivities (up to 93%). This catalytic system showed superior performance in terms of both reactivity and enantioselectivity in the presence of HCl additive.

Scheme 46. Enantioselective hydrogenation of *N*-heterocyclic imines.



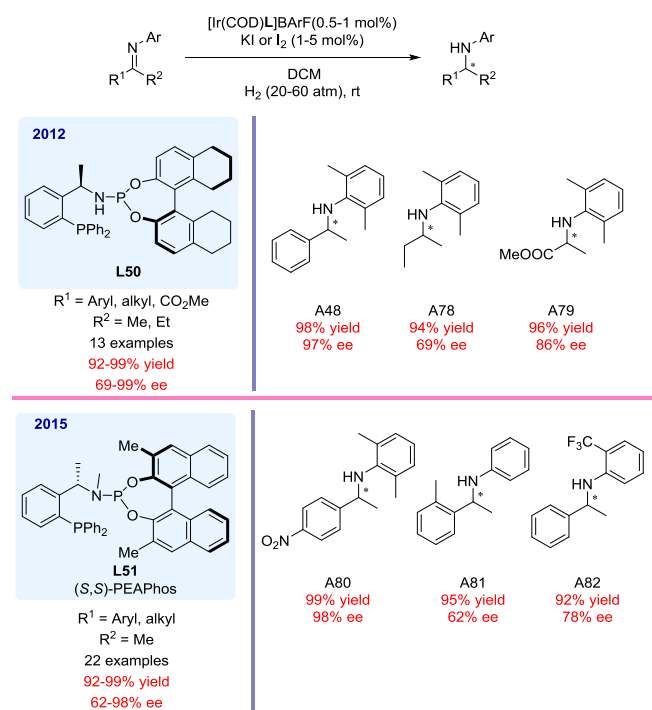
Moreover, Hu and coworkers developed a mild protocol for enantioselective hydrogenation of sterically hindered *N*-arylimines with BINOL-derived chiral phosphine phosphoramidite ligand (Scheme 47).⁶⁴

They suggested that the N-H and the H₈-binaphthyl moieties of the ligand (**L50**) are important to obtain high catalytic activity and enantioselectivity. The partially hydrogenated naphthalene scaffold contains sp³ hybridized carbons which increased the steric bulkiness of binaphthyl frameworks and changed the biaryl dihedral angle, leading to improved enantioselectivity. Possible hydrogen bonding occurs between the N-H motif of the ligand and the substrate. This catalytic system is characterized by high turnover numbers (up to 100k). Similar to several previously reported catalytic systems, the presence of halide additive improves the catalyst performance, as illustrated by

the synthesis of the chiral herbicide (*S*)-Metolachlor from the hydrogenated corresponding amine (total conversion, 80% ee).

The second generation of phosphoramidite ligands for AIH was further disclosed, represented by PEAPhos ligand **L51**.⁶⁵ The substitution on 3,3'-positions of the binaphthyl moiety showed an improvement of the enantioselectivity for a large panel of *N*-arylimines. In addition, two examples of alkylamines were hydrogenated under the same conditions with excellent yields and high ee. Ir-PEAphos complex presented high TON (up to 50K). The efficiency of this method was proven by the synthesis of (*R*)-metalaxyl which is a chiral fungicide.

Scheme 47. Chiral phosphine phosphoramidite ligand for the hydrogenation of *N*-arylimines.

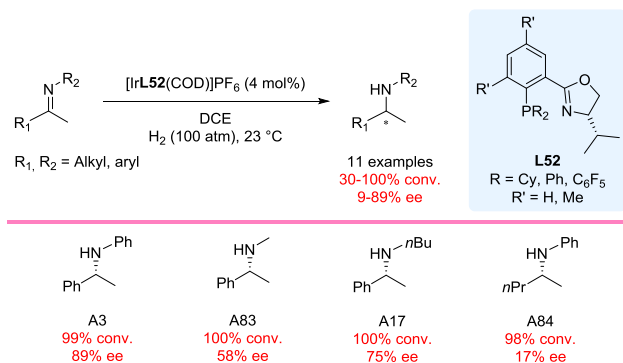


Phosphine-Oxazoline Ligands

In parallel to the development of a large library of diphosphine ligands for AIH, other families of ligands have also been used to achieve the same goal. Chiral P,N ligands, particularly phosphino-oxazoline (PHOX), used since 90s, have clearly emerged as a privileged chiral ligand for AIH.

In 1997, Pfaltz's group introduced the phosphanodihydrooxazoles PHOX ligand **L52** for imine hydrogenation (Scheme 48).⁶⁶ In this pioneering work, the cationic Ir(I) complex promoted the AIH furnishing the chiral amine with high ee (up to 89%), regardless of the imine (*E*)/(*Z*) configuration. Unfortunately, this catalytic system turned out to be less efficient while using imines featuring bulky aryl substituents as well as dialkyl and cyclic imines. Interestingly, the iodide additive has a negative effect, resulting in a significant enantioselectivity decline and the inversion of the configuration. Besides, while the nature of the Ir-complex counteranion has a minor impact on the reaction outcome, high concentration of the reaction mixture is crucial.

Scheme 48. The first PHOX ligand employed in asymmetric hydrogenation of imines.



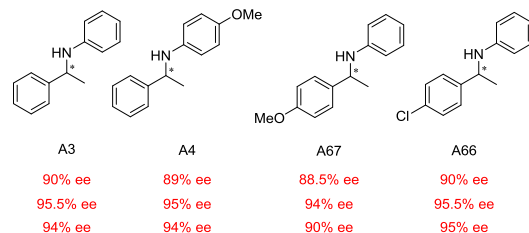
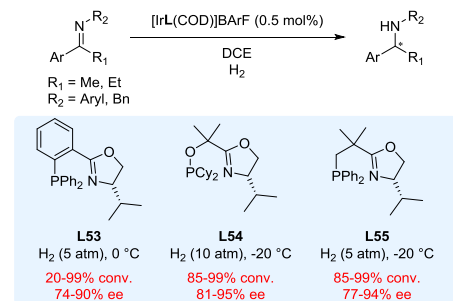
The following study showed that a modification of the counteranion from PF_6 to BARf permits this AIH to occur in scCO_2 as DCE solvent substitute, albeit lost in the enantioselectivity to 81% was observed for A3.⁶⁷

Following these seminal works, significant efforts have been devoted over the last decade to investigate and improve the Ir-phosphanodihydrooxazoles catalytic systems for AIH (Scheme 49).⁶⁸ The ligands with an isopropyl group **L53-55** (instead of large substituents such as *t*Bu) at the stereogenic center generally showed the optimal activity regardless of the ligand backbone. On the other hand, no clear conclusion concerning the substitution pattern of the P-atom could be drawn. In order to further optimize the AIH conditions, diverse additives were tested, including iodine and phthalimide, but the expected progress could not be reached. The use of the complexes bearing BARf counter anion was privileged, due to a better solubility of its salt in apolar media, reduced moisture sensitive and more convenient handling. In addition, decreased reaction temperatures were generally beneficial for the chiral induction.

Under the optimized reaction conditions, the scope of this catalytic system is relatively broad as both electron-rich and electron-poor imines could be used, furnishing the expected amines in high enantioselectivities and yields. The most promising results were reached with the Ir-SimplePHOX **L54** complex containing the electron-rich P-dicyclohexyl.

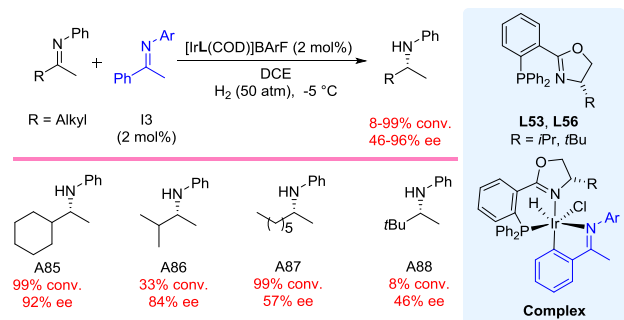
The limitation of this catalytic system was described when using imines derived from dialkylketones and cyclic imine substrates; low conversions and enantioselectivities were observed in the first case while moderate ee (56-82%) were achieved in the latter case.

Scheme 49. The evolution of the catalytic systems developed by Pfaltz.



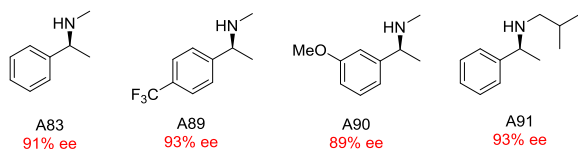
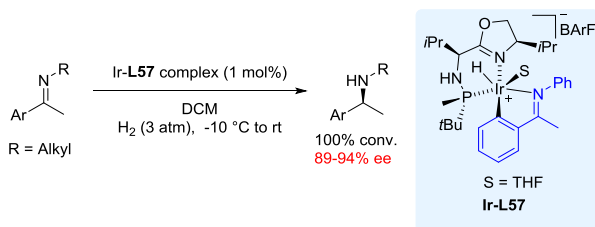
The major improvement, achieved by Pfaltz, was based on the discovery that iridacycles, obtained by cyclometallation of acetophenone imine **I3** with Ir-PHOX, are highly efficient catalyst.⁶⁹ Accordingly, a simple addition of **I3** to the Ir-PHOX promotes highly reactive and stereoselective AIH of a variety of alkyl- and arylimines (Scheme 50).

Scheme 50. Ir-PHOX catalyzed hydrogenation of alkyylimines. Souliguer oar couleur I3.



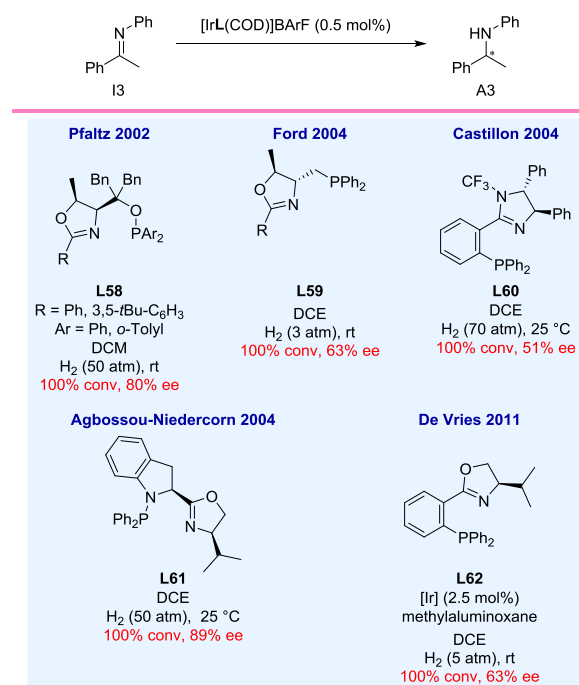
Likewise, the effect of an additional imine as the key additive has been shown by Verdaguer in 2018. His group developed the hydrogenation of *N*-methyl and *N*-alkyl imines by using a cyclometalated $[\text{IrH}(\text{THF})\text{L57}(\text{I3})]\text{BARf}$ complex with a P-stereogenic ligand **L57** (Scheme 51). The presence of THF as external ligand is crucial for a high catalytic activity even at low temperature (-10 °C), furnishing the corresponding chiral amines with high ee (up to 94%).⁷⁰

Scheme 51. AIH of N-alkylimines with cyclometalated Ir(III)H catalyst.



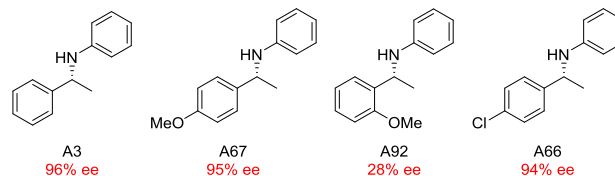
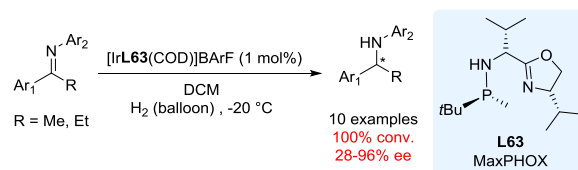
Inspired by these outstanding contributions of Pfaltz and benefiting from great modularity of this class of ligands, a library of structurally and electronically diversified phosphine oxazoline ligands has been designed **L58-L62** (Scheme 52).⁷¹⁻⁷⁵ Various strategies have thus been envisioned, such as modification of a linker between the oxazole and phosphine motifs, modification of the relative position between the two coordinating units, replacement of the oxazole moiety by an imidazole one, etc. Unfortunately, none of these modified ligands seems to outcompete the original catalytic system.

Scheme 52. Different PHOX ligands for the enantioselective hydrogenation of imines



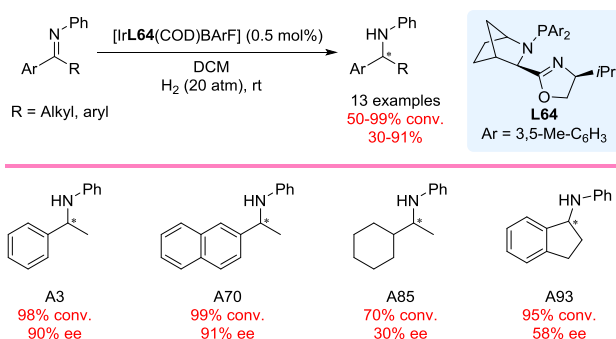
In contrast, excellent enantioselectivity in AIH of arylimines such as I3 and I67 could be achieved while using Ir-MaxPHOX (**L63**) complex, featuring two C-stereogenic centers, and one P-stereogenic motif. Riera and Verdager used this Ir-MaxPHOX **L63** catalyst to promote highly selective imine hydrogenation. The superior reactivity of such a catalytic system allows the application of atmospheric pressure of H_2 , while low temperature (-20°C) was crucial to insure optimal stereoselectivity (Scheme 53).⁷⁶ A panel of acyclic arylimines could thus be converted into the expected amines with good to excellent enantioselectivities. From the mechanistic perspective, this hydrogenation is believed to occur via an outer-sphere mechanism.

Scheme 53. Ir-MaxPHOX for imines hydrogenation.



During the following years, a diversity of chiral phosphine-oxazoline have been evaluated in AIH.⁷⁷⁻⁷⁹ Andersson and coworkers reported 2-azanobornane-oxazoline as an efficient chiral inductor in the hydrogenation of acyclic aromatic *N*-arylimines (Scheme 54).^{80,81} Following the previous conclusions, *i*Pr was selected as the optimal substituent on the C-stereogenic center of the oxazoline moiety. Besides, the ligand design showed that substituents of the P-atom have only a limited effect on the reaction outcome and the best chiral induction was reached with ligand **L64** bearing 3,5-dimethylbenzyl substituent. The imines substituted with neutral, electron-rich or electron-poor aromatics were reduced with similar enantiomeric excess. While enantioselectivity up to 91% was observed using the standard substrates, sterically encumbered dialkyl- and aryl-alkylimines turned out to be much more challenging substrates for which in general the catalyst is neither efficient nor stereoselective. When C=N bonds are directly connected to EWGs, the catalyst is inactive due to the decrease of the ability to coordinate to iridium.

Scheme 54. Ir-catalyzed for *N*-phenyl imines hydrogenation.

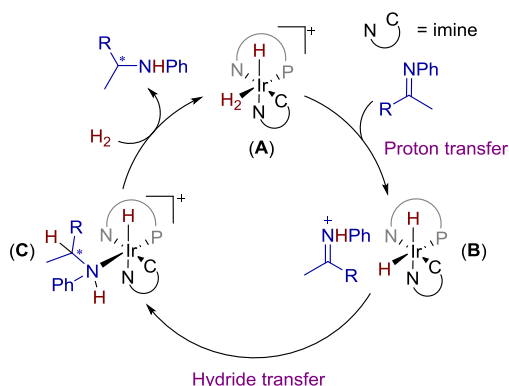


In terms of mechanistic investigations, Andersson and coworkers proved that metallacyclic Ir-species are catalytically active.⁸² Besides, the chiral induction is believed to arise in the outer-sphere transfer of a hydride from the neutral Ir(III) complex to a cationic iminium ion.

In order to investigate the mechanism of this transformation and compare this catalytic system with the Ir-PHOX catalyst, Wiest, Norrby, Andersson and coworkers have performed in-depth mechanistic studies.⁸² Different mechanistic scenarios have been evoked, including inner-sphere and outer-sphere scenarios. The DFT calculations suggested that the reaction goes through an outer-sphere mechanism in presence of an iridacycle beginning with binding of H_2 to the catalyst fol-

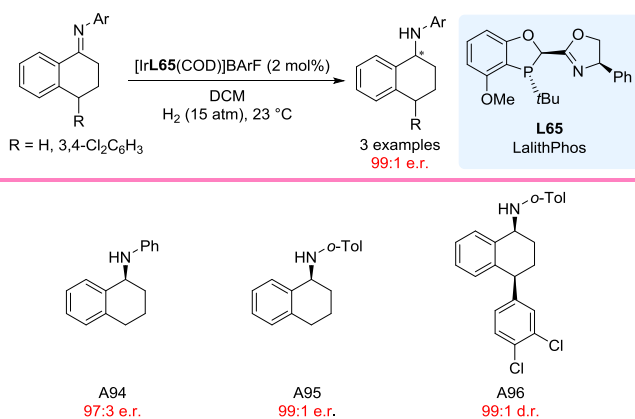
lowed by the transfer of a proton to the free imine (**B**) allowing the formation of iminium (Scheme 55). Then, a hydride transfer occurs affording the coordinated amine-Ir complex (**C**). The latter releases the chiral amine in the presence of H₂ and regenerates the active catalytic species (**A**).

Scheme 55. Proposed mechanism for Ir-PHOX imines hydrogenation.



Furthermore, Qu's group designed and synthesized the air-stable P-chiral dihydrobenzooxaphosphole oxazoline ligand **L65** to test its performance in the iridium-catalyzed asymmetric hydrogenation of alkenes.⁸³ This ligand, showed an outstanding reactivity towards exocyclic *N*-aryl-dihydronaphthalene ketimines I94-I96, particularly challenging substrates in AIH (Scheme 56). Ir-LalithPhos (**L65**) complex is able to promote the hydrogenation of these substrates under an atmospheric pressure of H₂ and at room temperature, delivering the expected products with up to 98% ee.

Scheme 56. Asymmetric hydrogenation of exocyclic *N*-aryl-dihydronaphthalene ketimines.



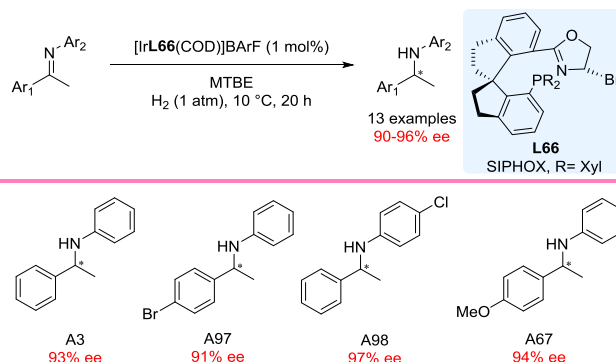
Spiro Phosphine-Oxazoline

Amongst the privileged chiral architectures for ligand design spiro structures developed by Zhou occupy an important place.⁸⁴ Therefore, it's not surprising that spiro-PHOX ligand established itself as an appealing ligand for Ir-catalyzed AIH. In 2006 the group of Zhou synthesized the cationic Ir-SIPHOX (**L66**) complex coordinated with BARF counteranion (

Scheme 57).⁸⁵ The catalyst design showed that the substitution of the oxazoline ring is critical for the enantioselectivity with the optimal results being obtained with a benzyl motif, while the *i*Pr group, optimal in the case of Pfaltz's ligand, performed poorly. In contrast, the substitution pattern of the phosphorus

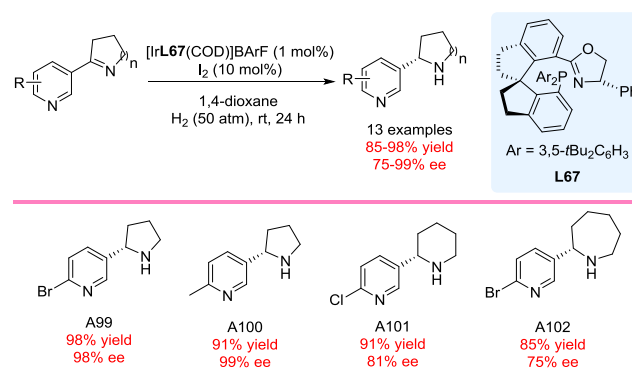
atom does not affect significantly the stereoselectivity, but it is critical to achieve high reactivity, particularly when using low catalyst loading (0.5 mol%) under 1 bar of H₂. Excellent enantioselectivities up to 97% ee have been obtained while reducing *N*-aryl ketimines.

Scheme 57. Mild conditions for the hydrogenation of *N*-arylimines.



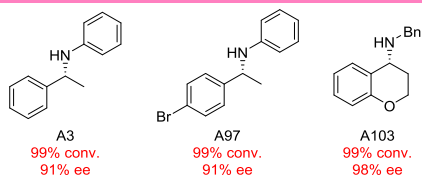
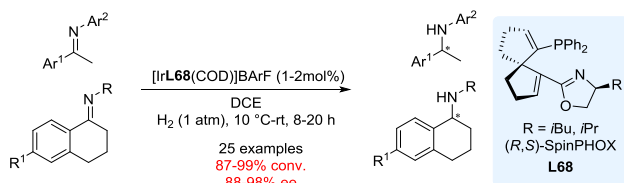
Subsequently, the efficiency of this catalytic system was evaluated while studying hydrogenation of very challenging substrates such as 2-pyridyl cyclic imines I99-I102 (Scheme 58).⁸⁶ The difficulty in this reaction is connected to the catalyst poisoning resulting from the coordination of pyridine moiety to the catalyst. Remarkably, while using Ir-SpiroPHOX (Ir-**L67**) complex, the corresponding pyridyl-containing amines were afforded with up to 99% ee although increase of the reaction pressure (50 bar) was crucial. The synthetic hint to access a highly reactive substrate is the introduction of an additional substituent *ortho* to the pyridine *N*-atom. Thus, increased steric hindrance in close proximity to the coordination site prevents the pyridine-metal association and resulting catalyst poisoning. This excellent chirality transfer induced by the Ir-SpiroPHOX complex can be attributed to the rigidity of the backbone, the large bite angle, and its bulky chiral environment around the metal.

Scheme 58. Ir-SpiroPHOX catalyzed hydrogenation of cyclic imine.



An alternative architecture of spirocyclic oxazoline complexes was designed by the group of Ding: SpinPHOX with different bulky alkyl substituents (**L68**) (Scheme 59).⁸⁷ These ligands, besides being very active in direct hydrogenation of *N*-aryl ketimines such as I3 and I97, performed equally well with more challenging and poorly explored, substrates, *N*-alkyl ketimines, with up to 98% ee. As previously, low H₂ pressure of 1 bar is enough to trigger the expected reactivity.

Scheme 59. Asymmetric hydrogenation of imines with SpinPHOX ligands.

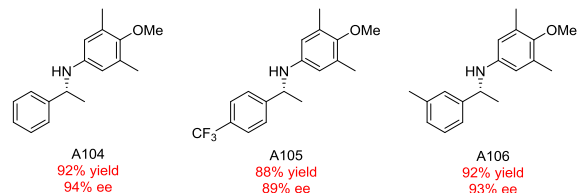
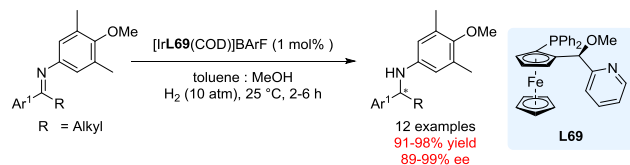


Miscellaneous P,N ligands

In addition to oxazoline, some other nitrogen donors have been used in P,N ligands.

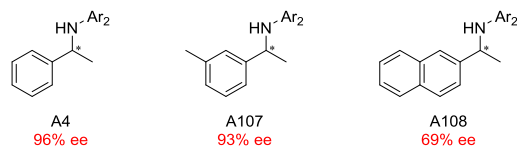
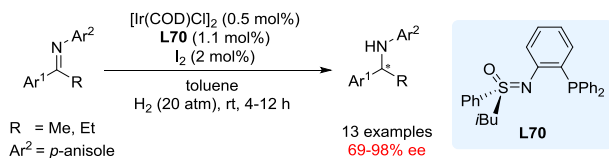
The group of Knochel reported the asymmetric hydrogenation of *N*-arylimines by using iridium cationic complex associated to a ferrocene based phosphino-pyridine ligand **L69**.⁸⁸ While using this new chiral ligand the desired chiral amine is formed with excellent yield and enantiomeric excess (Scheme 60).

Scheme 60. Knochel's system for AIH.



In 2005, Bolm's group developed the first *CI*-symmetric sulfoximine ligand **L70** in the iridium-catalyzed asymmetric hydrogenation of *N*-aryl imines (Scheme 61).⁸⁹ In this case, the addition of I₂ is crucial to generate the catalytically active Ir-species. The design of sulfoximine ligand revealed that increase of the steric hindrance on the sulfur atom was essential as excellent chiral induction up to 96% ee was observed while using isobutyl-substituted sulfoximine ligand. This catalytic system is efficient even while using a low catalyst loading of 0.5 mol%.

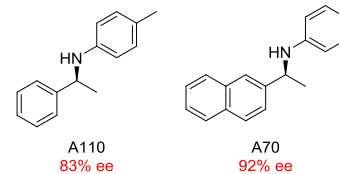
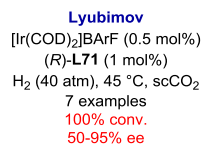
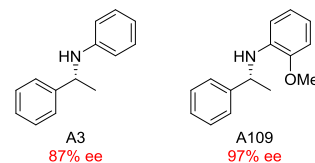
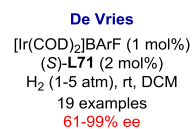
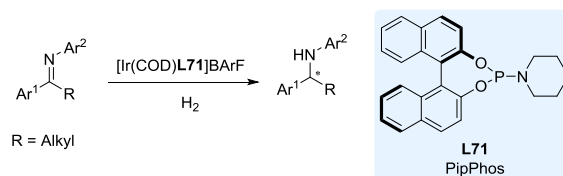
Scheme 61. Ir-catalyzed hydrogenation of aryl imine derivatives.



Phosphite and phosphinite ligand

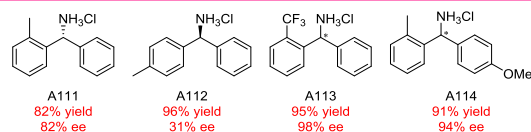
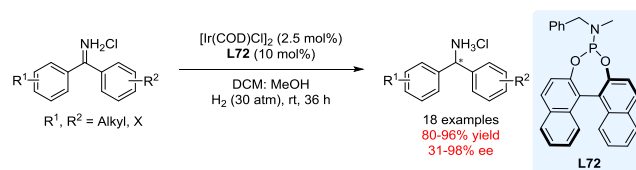
De Vries and Lyubimov reported independently the reduction of *N*-arylimines by employing monodentate phosphoramidite ligand PipPhos (**L71**) with iridium precursor (Scheme 62).^{90,91} In the work reported by De Vries, such a catalytic system allowed the hydrogenation of a wide scope of imines with modest to excellent enantioselectivities under mild conditions and low H₂ pressure. While using a comparable catalytic system, Lyubimov performed the reaction in *sc*CO₂ medium, thus affording the expected products with a comparable chiral induction albeit high H₂ overpressure was needed.

Scheme 62. Monodentate phosphoramidite ligand for imines hydrogenation.



A series of non-protected diarylmethylamines have been synthesized through the asymmetric hydrogenation of benzophenone *N*-H imines by using iridium catalyst associated with a chiral phosphoramidite ligand **L72** (Scheme 63). The presence of an *ortho* substituent is crucial to obtain high enantioselectivities.⁹²

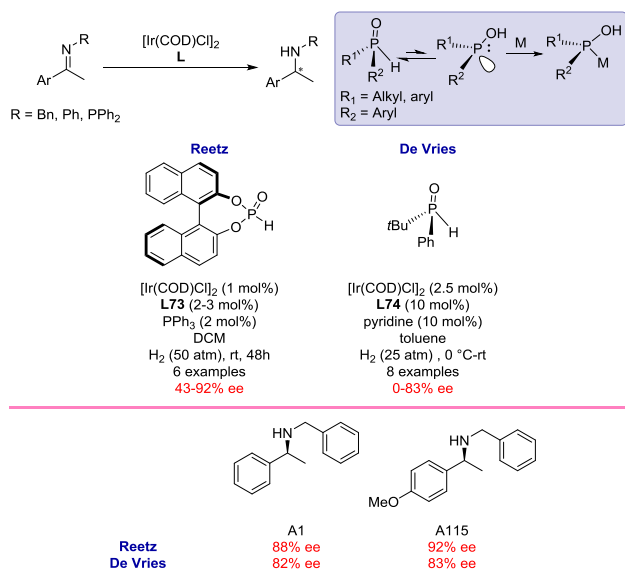
Scheme 63. AIH of unprotected diarylmethylamines.



Enantiopure monodentate secondary phosphine oxide (SPO) was also studied as ligand for AIH.^{93,94} SPOs are easily prepared from available phosphine chloride derivatives. By tautomerization, the pentavalent structure is in equilibrium with the trivalent one (phosphinite). The later form coordinates to the transition metal at room temperature thus providing the active catalyst. Using these very simple ligands **L73-L74**, enantioenriched amines were delivered with appealing enantioselectivity, albeit pressure of 25 bars was necessary (Scheme 64). The presence of pyridine as additive allows the

decrease of the iridium and ligand's loading while simultaneously increasing the chiral induction.

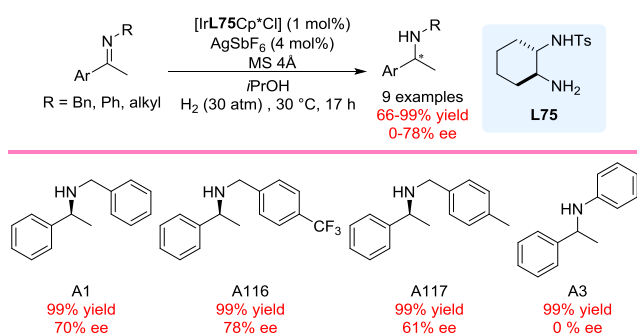
Scheme 64. Monodentate secondary phosphine oxide for imines hydrogenation.



N,N ligands

Diamine ligands have been used sparingly in the iridium-based catalytic system for the AIH. In 2009, Ikariya and coworkers explored a chiral monosulfonylated diamine ligand **L75** (Scheme 65).⁹⁵ The combination of the metal complex and silver salts enhances the catalyst activity and selectivity.

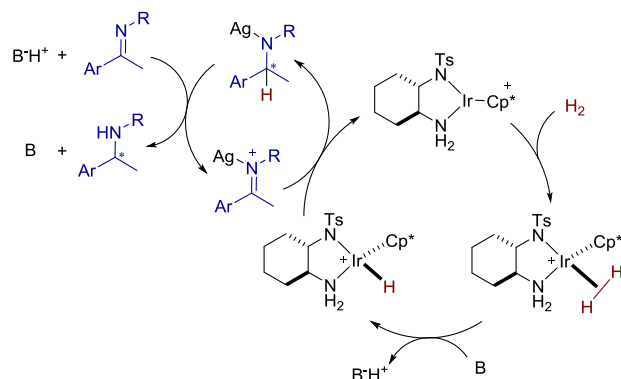
Scheme 65. Imines hydrogenation with monosulfonylated diamine ligand.



While considering the mechanism, [Cp*Ir(Tsycdn)(CH₃CN)]SbF₆ generated *in situ* from neutral catalyst precursor, Ir-Ligand, via ionization with AgSbF₆, is believed to be the active catalytic species (Scheme 66). This complex activates H₂, hence generating a hydride intermediate that undergoes the hydrogen transfer to the imine substrate *via* an outer-sphere mechanism.

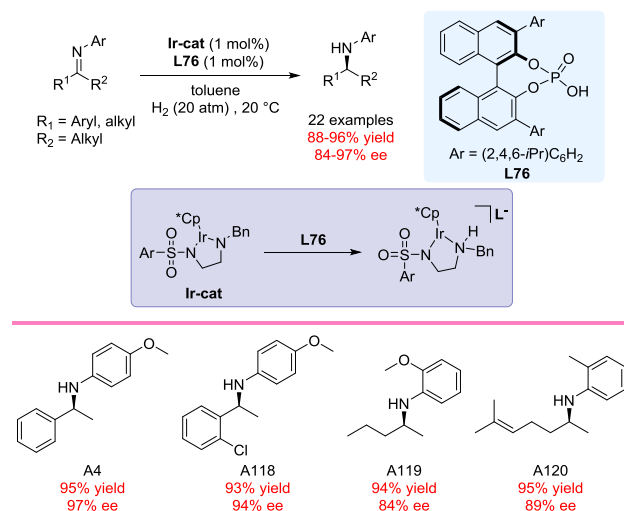
In addition, the silver salt is also believed to play a role as a Lewis acid that interacts with the nitrogen atom of the imine. This role was evidenced based on an NMR study. Upon imine activation, the hydrogenation occurs smoothly and with superior enantioselectivity.

Scheme 66. Proposed mechanism for imines hydrogenation with diamine ligands in presence of silver salts.



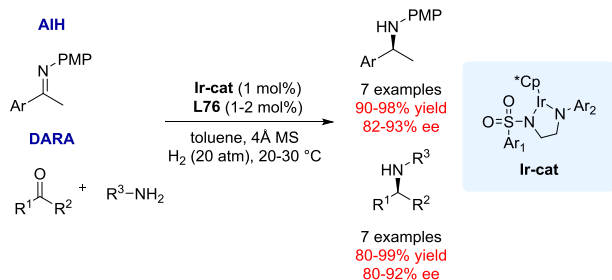
Moreover, Xiao and coworkers developed AIH using chiral-achiral catalyst combining an axially chiral phosphoric acid and an achiral diamine with Ir-precursor (Scheme 67).⁹⁶ Hydrogenation of aryl and alkylimines using an achiral diamine-Cp*–iridium complex with a chiral phosphoric acid occurred smoothly. The reactivity and stereoselectivity studies have been conducted and showed that the active catalyst is formed *in situ* by mixing the phosphoric acid **L76** with the iridium complex. The chiral information is thus transferred from the enantiomerically pure anionic moiety. This reaction is very efficient for a large panel of acyclic imines, including both, aromatic (A4, A118) and aliphatic (A119-120) ones.

Scheme 67. The chiral phosphoric acid's role.



Very recently, Kobayashi has reported a remarkable technological advance in AIH.⁹⁷ The author and his collaborators have designed a catalytic system combining heterogeneous iridium complex based on the polymer-supported diamine ligand, and a sterically encumbering atropisomeric phosphoric acid (TRIP, **L76**). This heterogeneous catalyst is promoting highly enantioselective direct reductive amination (DARA) of ketones under continuous flow conditions (Scheme 68).

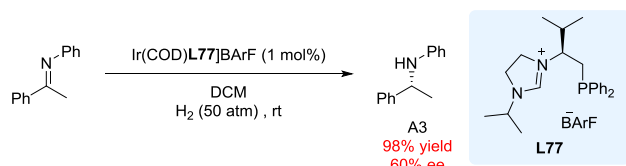
Scheme 68. Iridium catalyzed AIH and DARA.



NHC ligands

Regardless of the common use of NHC ligands in organometallic homogenous catalysis, the application of these ligands in AIH is very limited and include a single literature example. In 2006, Pfaltz and Nanchen developed an iridium cationic complex with phosphino *N*-heterocyclic carbene ligand **L77** for the hydrogenation of alkenes (Scheme 69).⁹⁸ This complex was applied in the hydrogenation of one aryl imine with a moderate enantiomeric excess of 60%.

Scheme 69. Ir-NHC system for the hydrogenation of an imine.

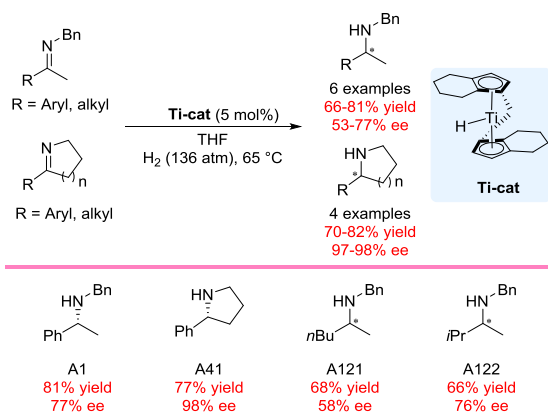


Titanium base catalysts

Early transition metals have also been involved in the asymmetric hydrogenation of imines at a relatively early stage.

The pioneering contribution in this field was disclosed in 1992 by Buchwald and coworkers. Ti(III) hydride catalyst, featuring ansa-metallocene structure was synthesized *in situ* from 1,1'-binaphth-2,2'-diolate derivative in presence of *n*-BuLi and phenylsilane.^{99,100} This catalytic system turned out to be highly selective while using cyclic imines (**I41**). However, a drastic decrease in the enantioselectivity was observed in the case of aliphatic *N*-benzylimines (**I1**, **I21**) (Scheme 70). Despite the clear advantage of this system using a cheap Ti-based catalyst, extremely high pressure of H₂ (136 atm) was required.

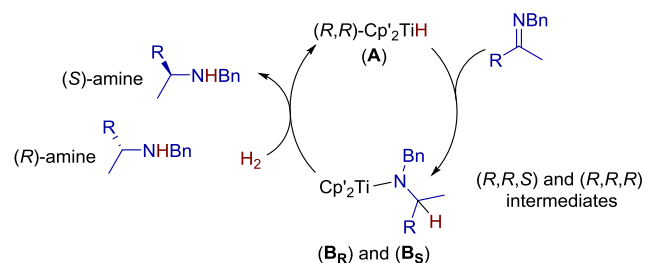
Scheme 70. Buchwald's system for imines asymmetric hydrogenation.



A mechanism has been proposed (Scheme 71). The titanium hydride (**A**) reacts with the imine to give two diastereomeric titanium intermediates (**B_R**) and (**B_S**) through an insertion. Then, these intermediates undergo hydrogenolysis to afford

two amines enantiomers and to regenerate the Ti(III)-H species (**A**). The catalytic system showed high tolerance to various organic functions such as alkenes, acetals, and alcohols.

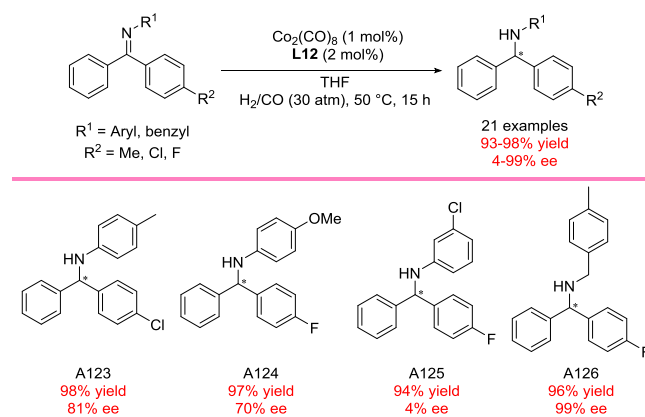
Scheme 71. Proposed mechanism for Ti(III) hydride catalyzed imines hydrogenation.



Cobalt based catalysts

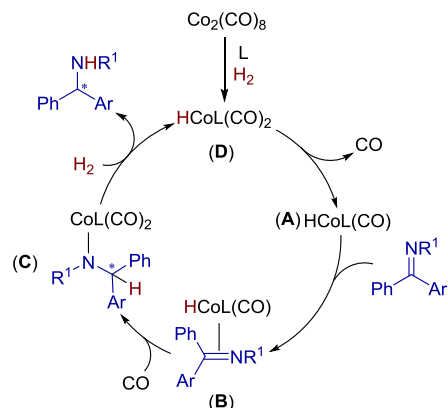
Although great advances have been achieved in the field of Rh, Ru, and Ir-catalyzed AIH, the use of poorly abundant and expensive noble metals somehow limits the synthetic utility of this approach, even though in some cases relatively low catalysts loading are sufficient to complete the reaction. To provide a more sustainable solution, Cabrera and Amézquita-Valencia introduced the first cobalt catalytic system for the enantioselective hydrogenation of arylketimines.¹⁰¹ They associated the dicobalt octacarbonyl with (*R*)-BINAP to reduce with excellent yields and moderate to good enantioselectivities a large panel of imines derived from benzophenone (Scheme 72). This reaction occurs under CO/H₂ gas atmosphere to warrant high yields; it is suggested that the partial CO pressure stabilizes the catalytic species. The study of the aromatic ring substituent effects revealed that the presence of electron-withdrawing groups negatively impacts the chirality transfer.

Scheme 72. The first Co-catalyzed hydrogenation of imines.



Based on the isolation and the characterization of different intermediates, the proposed mechanism starts with the formation of cobalt hydride (**A**) that is the catalytic active species (Scheme 73). The later coordinates the imine to form the complex (**B**). Subsequently, the insertion of the imine into the Co-H occurs in presence of CO to form the amino-cobalt complex (**C**) that under hydrogen pressure produces the enantiopure amine and releases the active catalyst (**D**).

Scheme 73. Mechanism for Co-catalyzed hydrogenation.

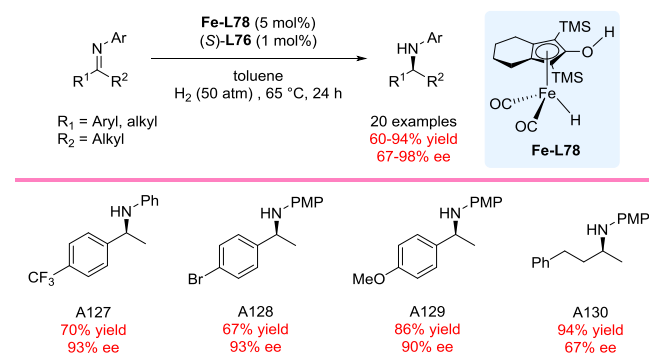


Iron based catalysts

Aiming more sustainable alternatives for AIH, Beller's group investigated a catalytic system based on cooperative transition-metal and chiral Brønsted acid catalysis for Fe-catalyzed stereoselective reduction.¹⁰² Accordingly, they developed the first combination of iron cyclopentadienone-based catalysts and chiral phosphoric acids **L76** for AIH. The Brønsted acid catalyst and the metal complex work in a cooperative way to afford the corresponding amine with high enantioselectivity. The dicarbonylhydro[2,5-di(trimethylsilyl)-3,4-butylene-1-hydroxy(η^5 -cyclopentadienyl)] Fe-complex **Fe-L78** which was explored by Knolker¹⁰³ gave the highest conversion and the best optical yields (Scheme 74).

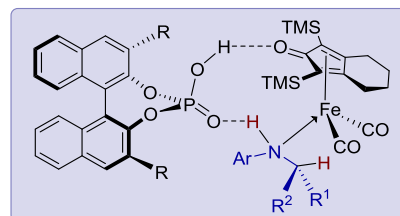
The tolerance of this cooperative system was evaluated on different aromatic ketimines. With imines bearing neutral, electron-rich and electron-poor aryl moiety, the hydrogenation occurs with excellent enantioselectivity (up to 98% ee). As well, the more challenging alkyl imines underwent this reduction to afford the enantiopure amine with moderate to good enantioselectivity (67–83% ee).

Scheme 74. Cooperative system for imines hydrogenation.



Regarding the mechanism, the Brønsted acid is believed to activate the substrate thus generating the activated intermediate that interacts with the non-chiral organometallic complex thus promoting the enantioselective hydrogenation (Scheme 75).

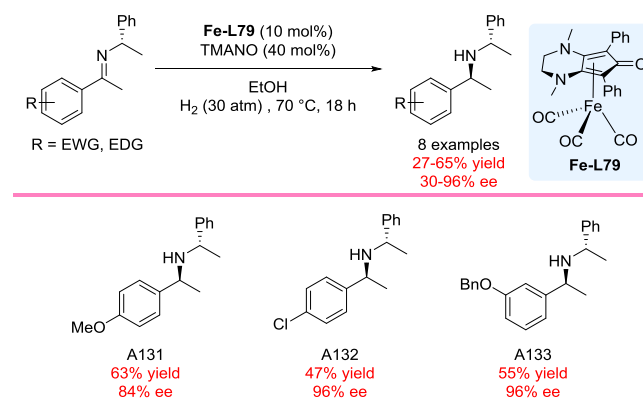
Scheme 75. The activated intermediate.



Inspired by this work, Benaglia and coworkers reported an iron-catalyzed diastereoselective hydrogenation of chiral imines.¹⁰⁴ Both Knolker and Renaud's complexes were tested and showed the highest activity, after *in situ* activation with trimethylamine *N*-oxide (TMANO), under hydrogen pressure (Scheme 76).

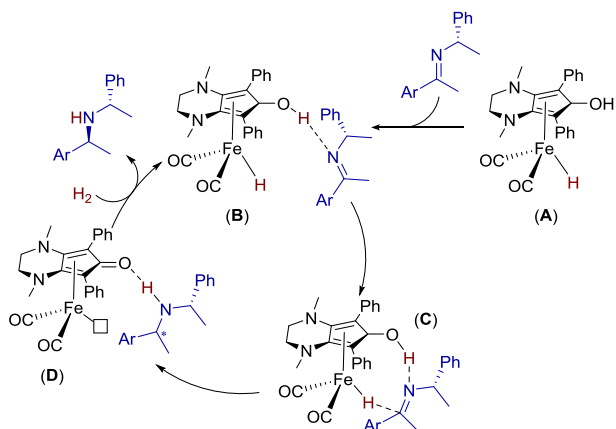
Contrariwise to Beller's system, the pre-activation of the imine substrate with a Brønsted acid has a dramatic negative effect. With the optimized conditions, the substrate scope was investigated. With EDG substituents, the chiral amine is formed with moderate yields while in presence of EWG lower yields were observed.

Scheme 76. Diastereoselective hydrogenation of chiral imines.



Mechanistic studies were subsequently conducted to elucidate the chemical and stereochemical outcome (Scheme 77). The reaction starts by the imine's coordination to the hydride-iron complex (**A**) hence providing the corresponding adduct (**B**). In the following step, a concerted and asynchronous process takes place: a proton transfer occurs from the hydroxyl group of the catalyst to the imine nitrogen (**C**) followed by the hydride transfer from the complex to the imine carbon to afford the intermediate (**D**). Based on these studies, the tolerance of electronic effect is explained. The *N*-protonation step is easier with electron-rich imines due to higher nitrogen basicity.

Scheme 77. Iron-catalyzed imines hydrogenation.



Substrate's design: Activated imines

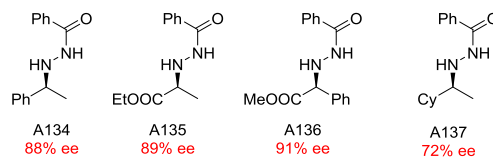
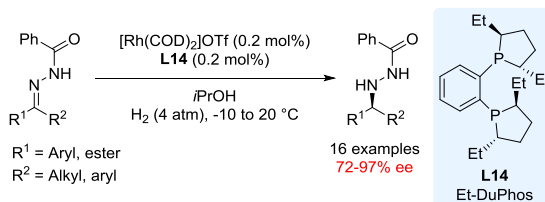
Despite the outstanding success of AIH, major challenges, such as catalyst poisoning and the *E/Z* isomerization, still persist causing enantioselectivity and/or reactivity losses. Different efforts have been devoted to improving the catalyst activity and thus the stereoselection. In addition to a fine selection of additives, substrate's design is an alternative strategy that has been investigated to develop highly enantioselective and efficient chiral catalysts for AIH.

In order to modify the electronic properties of the imine substrate and the amine product, significant attention has been focused over the last years on the substrate design, and the various imine-derivatives bearing coordinating motifs on the *N*-atom have been evaluated. The additional coordinating motif on a substrate may be able to accelerate the rate of AH through the chelation to the metal atom. Finally, the presence of a second coordination site on a substrate should enhance generation, within the catalytic cycle, of well-organized intermediates, hence enhancing highly stereoselective transformations. Noteworthy, these *N*-substituents should be easily removable after the key reduction step to afford the enantiopure primary amine.

Rhodium based catalysts

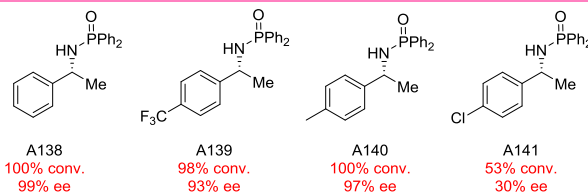
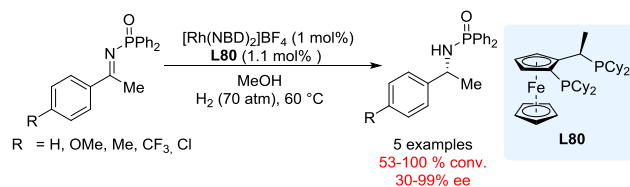
Burk's group was among the first to employ rhodium to achieve the hydrogenation of activated imines such as the *N*-benzoylhydrazones (Scheme 78).¹⁰⁵ Comparing to the other ligands from DuPhos family, Et-DuPhos **L14** afforded the expected *N*-benzoylhydrazine with the highest enantioselectivity. Remarkably, the benzoyl carbonyl function is crucial for the hydrogenation as this system was not efficient with *N*-phenylhydrazones. Indeed, the chelation of the substrates to the cationic rhodium center occurs *via* both, the oxygen of the carbonyl and the nitrogen of the hydrazone moiety. To reach optimal chiral induction, this reaction was performed under low pressure of H₂, at low temperature and in 2-propanol. The potential of this transformation is however limited to imines bearing electron-rich aryl motifs. Importantly, hydrazines may be considered as an interesting source of chiral amines because the N-N bond cleavage occurs smoothly and with no loss of the chiral information while using samarium iodide.

Scheme 78. Ru-catalyzed hydrogenation of *N*-benzoylhydrazones.



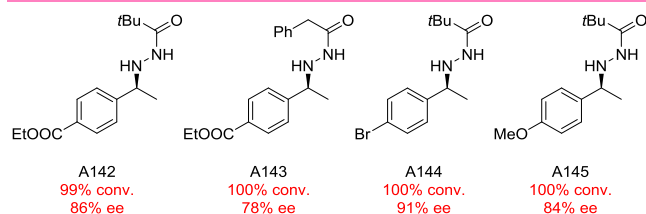
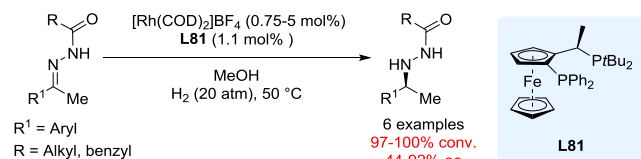
In 2001, Blaser and Spindler developed cationic Rh-ferrocenyldiphosphine catalyst for the enantioselective hydrogenation of *N*-diphenylphosphinylketimines (Scheme 79).¹⁰⁶ This family of substrates is easily accessible from the corresponding oxime while the straightforward cleave of the N-P bond under acidic conditions allows removal of the phosphorous-motif. The N-P=O group is believed to display the key role of an anchoring group to control the selectivity within the hydrogenation event. Many diphosphines were tested and the Josiphos-type ligand outcompeted other ligands, furnishing the expected products with high enantioselectivity (99% ee with *N*-diphenylphosphinylacetophenone imine (A138)).

Scheme 79. Ru-Josiphos catalyzed of *N*-Diphenylphosphinylketimines.



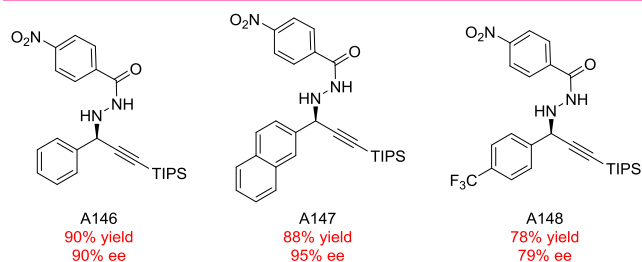
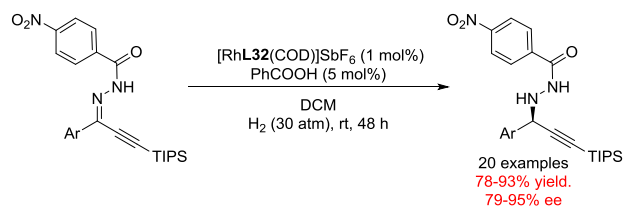
In order to access enantiopure protected hydrazines, Yoshikawa's and Tan's group developed a rhodium(I)-based catalytic system for the asymmetric hydrogenation of *N*-alkoxycarbonyl hydrazones (Scheme 80).¹⁰⁷ Among the studied diphosphines, Josiphos-type ligands **L81** established itself as the most suitable in terms of selectivity and reactivity. By using low catalyst loading, the hydrazines were formed with total conversion and moderate to good enantioselectivity in methanol.

Scheme 80. Hydrazones's asymmetric hydrogenation.



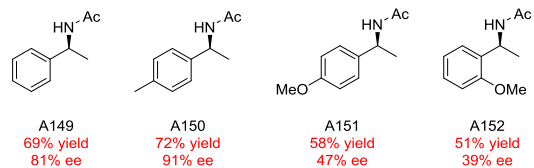
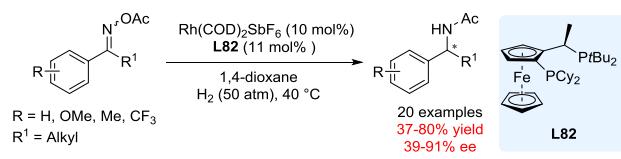
Another example of enantioselective hydrogenation of hydrazones using a combination of Rh-metal and Josiphos-type ligand was disclosed by Jiang and Zhang.¹⁰⁸ In this case, alkynyl-aryl hydrazones were used as substrates, thus targeting the synthesis of relevant enantiopure propargylamines. Substrates bearing terminal silyl groups underwent the hydrogenation with excellent chemoselectivity (selective reduction of C=N bond in a presence of alkyne motif) and enantioselectivities while using **L32** in combination with benzoic acid additive. The desired products were obtained with up to 95% ee and in general, slightly less efficient stereoreduction was observed for substrates bearing electron-poor aromatic rings. Importantly, 3-step hydrazine cleavage occurs efficiently, thus delivering the targeted enantioenriched propargylamines with only a minor enantiopurity decrease (Scheme 81).

Scheme 81. Rhodium-catalyzed asymmetric hydrogenation of alkynyl arylhydrazones.



Josiphos-type ligands have also been employed by the group of Zhang to promote the enantioselective hydrogenation of oximes acetate (Scheme 82).¹⁰⁹ During the work-up, acetic anhydride is added to the free amine obtained to form the chiral amide with good enantioselectivities. Among the different tested ligands, the optimal results were obtained while using electron rich **L82**. The catalyst is the most efficient when the reaction occurs in coordinating solvents such as THF or 1,4-dioxane delivering the desired amides with good to high enantioselectivities and yields.

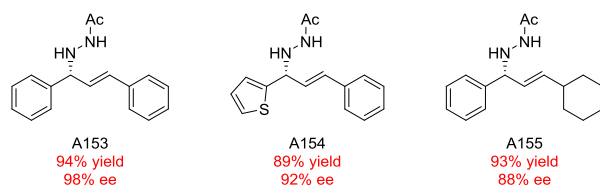
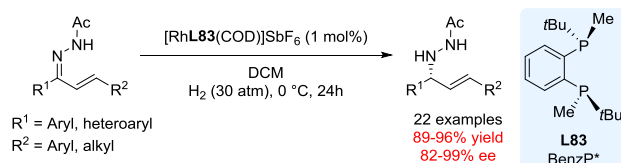
Scheme 82. Rh-catalyzed hydrogenation of acetyloxime.



Alternative Rh-based catalytic systems for asymmetric hydrogenation of oximes, such as indanone oxime was disclosed by Maj and Agboussou-Niedercom.¹¹⁰ The chiral amine is formed with good to quantitative yields, but only modest level of enantioselectivity could be reached.

Zhang's group designed a P-stereogenic diphosphine-rhodium complex and studied its performance for the selective hydrogenation of allylic hydrazones (Scheme 83). Different directing groups present on the imine were screened to enhance the hydrogenation event. Weakly coordinating *N*-protecting groups, such as Ts and Boc, failed delivering the expected products. Rewardingly, with Bz and Ac groups chemo- and enantioselective hydrogenation took place, affording the chiral allylic hydrazine with high yield and enantioselectivity together with a small amount of the over-reduced by-product.¹¹¹ The corresponding chiral amines are hence easily accessible *via* reductive cleavage. The best results in terms of reactivity and stereoreduction were achieved with *N*-NHAc. A gram scale reaction could be performed using low catalyst loading (0.2 mol%), clearly illustrating the synthetic potential of this methodology.

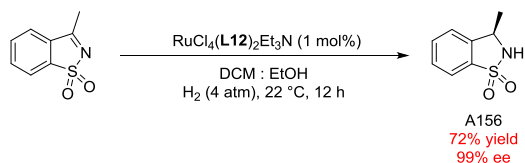
Scheme 83. Selective hydrogenation of allylic hydrazones



Ruthenium based catalysts

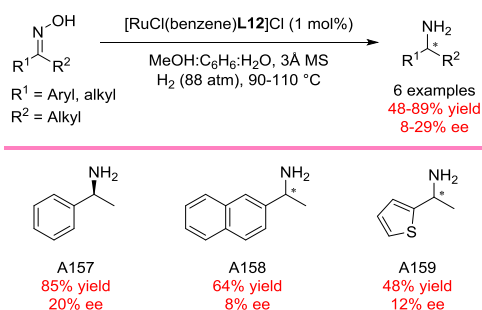
Enantiomerically pure sultams were synthesized by ruthenium-based catalytic system starting from the corresponding prochiral imine, as disclosed by Oppolzer's group.¹¹² The active catalytic complex is pre-synthesized *in situ* from the commercial $[RuCl_2(COD)]$ and the enantiopure BINAP **L12** in presence of triethylamine (Scheme 84).

Scheme 84. Synthesis of sultam by using ruthenium-catalyst.



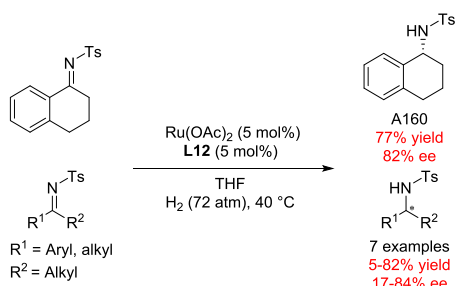
Some efforts have also been devoted to asymmetric hydrogenation of alkyl aryl ketoximes. Unfortunately, while using [Ru(benzene)Cl₂]₂-(*R*)-BINAP complex, the stereoselection remains very modest (Scheme 85).¹¹³

Scheme 85. Ruthenium-catalyzed hydrogenation of oximes.



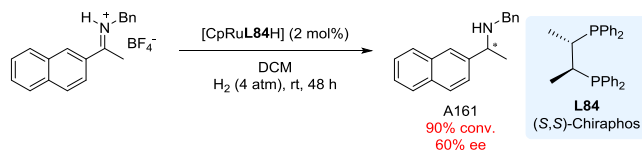
In contrast, the Ru-Binap complex performed much better when challenged with *N*-sulfonylimine derivatives (Scheme 86).¹¹⁴ Not surprisingly, the complexation of the oxygen atom of the tosyl group to the metal center is a key parameter, promoting efficient stereoselection. Following this concept, α -aminotetralin has been afforded in good yield and moderate ee of 82%, while others tosylamines have been generated with moderate to good yields and enantioselectivities.

Scheme 86. Ru-catalyzed hydrogenation of *N*-sulfonyl imines.



By using a ruthenium hydride complex, Norton and Magee reported the hydrogenation of iminiums. The reaction of an iminium cation which is generated *in situ* from the corresponding imine and HBF₄•OMe₂ affords, after the basic workup, the chiral amine with excellent conversion and moderate enantioselectivity (60% ee) (Scheme 87).¹¹⁵

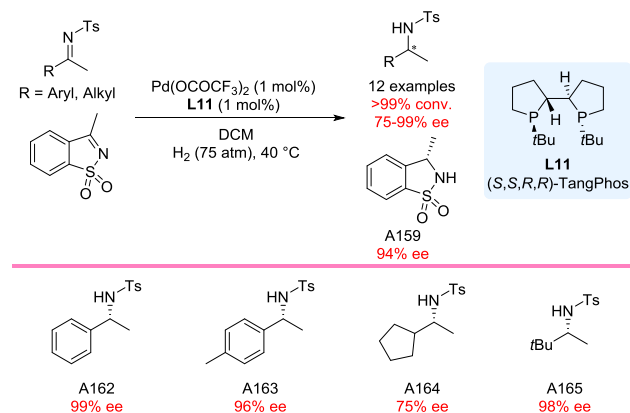
Scheme 87. Ruthenium catalyzed hydrogenation of an iminium salt.



Pd(OCOCF₃)₂ and (*S,S,R,R*)-TangPhos (**L11**) promoted this transformation efficiently and with high stereoselectivity. Due to its electron-donating and rigid character, TangPhos ligand appeared to be the optimal ligand. Interestingly, CF₃CO₂⁻ ion turned out to be critical in this catalytic system as a complete loss of reactivity was observed in the presence of other ions.

The reaction occurs under high hydrogen pressure, whereas both conversion and enantioselectivity decreased at lower pressure. It tolerates both electron-donating and electron-withdrawing substituents on the aryl moiety of the imines. Furthermore, this system provided quantitatively the sultam with excellent ee of 94% from the corresponding prochiral imine.

Scheme 88. Pd-catalyzed hydrogenation of *N*-sulfonyl imines.



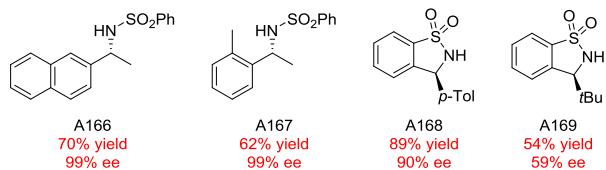
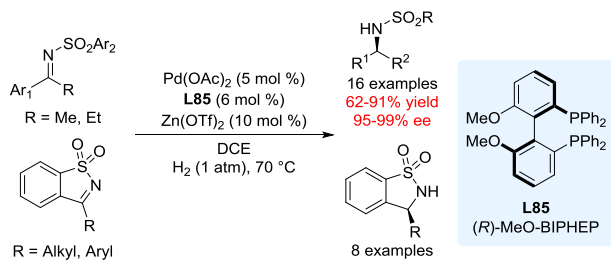
In 2018, Laishram, Fan, and coworkers developed an alternative catalytic system for the palladium-catalyzed enantioselective hydrogenation of cyclic and acyclic *N*-sulfonylimines (Scheme 89).¹¹⁷ Contrary to the previous examples, Pd(OAc)₂ was more efficient than Pd(CF₃CO₂)₂ while the best enantioselectivities were reached using (*R*)-MeO-BIPHEP **L85**. Furthermore, the reactivity of this catalytic system could be enhanced adding Lewis acid and Zn(OTf)₂ turned out to be the optimal additive.

This co-catalytic system tolerates a wide range of functional groups regardless their electronic effects with the highest yield and ee for the neutral aryl *N*-tosylimines. Interestingly, the hydrogenation of *N*-benzyl and *N*-phenyl imines gave the corresponding amines with low yields and moderate ees.

Scheme 89. Pd-catalyzed reduction of *N*-sulfonyl imines.

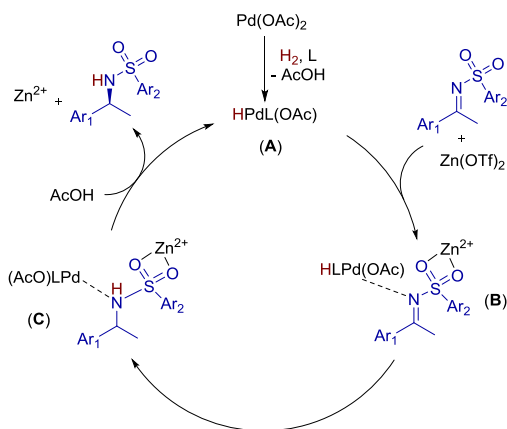
Palladium based catalysts

An interesting protocol for the asymmetric hydrogenation of *N*-tosylimines, using Pd-complex, was described by Zhang (Scheme 88).¹¹⁶ The complex system combining



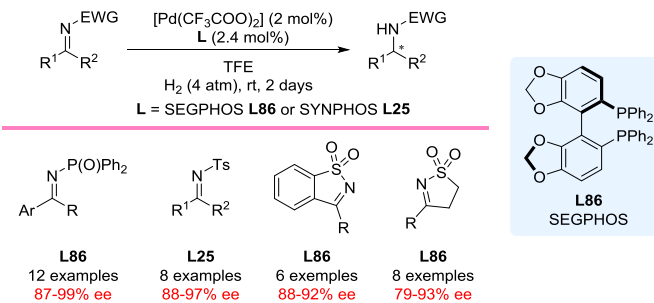
A mechanism has been proposed (Scheme 90). Under dihydrogen pressure, the palladium hydride **A** is formed which is the catalytic active species that coordinates to the nitrogen. Meanwhile, zinc coordinates to the sulfonyl oxygens (**B**) which facilitates the hydride transfer to the carbon atom and the proton transfer to the nitrogen atom, thus furnishing the intermediate (**C**). In presence of hydrogen, the sulfonamide is released and the catalytically active **A** is regenerated.

Scheme 90. Proposed mechanism for the Pd-Zn co-catalyzed hydrogenation.



As an extension of their work on Pd-catalyzed asymmetric hydrogenation of functionalized ketones, Zhou's group developed the enantioselective hydrogenation of several different activated imines, such as *N*-diphenylphosphinyl ketimines and *N*-sulfonyl imine. Pd(CF₃CO₂)₂ associated with SEGPHOS **L86** afforded the expected products with excellent optical purities (87- 99% ee) and could be an appealing solution for the synthesis of both cyclic and acyclic amine derivatives (Scheme 91).^{118,119} TFE, the weakly coordinating solvent, is the most efficient reaction medium while the addition of 4Å molecular sieves rendered the overall system more robust. Series of commercially available chiral diphosphine ligands were also tested under the same conditions to find the appropriate combination of Pd and ligand for each family of substrates. The developed catalytic systems showed high tolerance for various substrates exhibiting different electronic and steric properties.

Scheme 91. Pd-catalyzed hydrogenation of different activated imines.

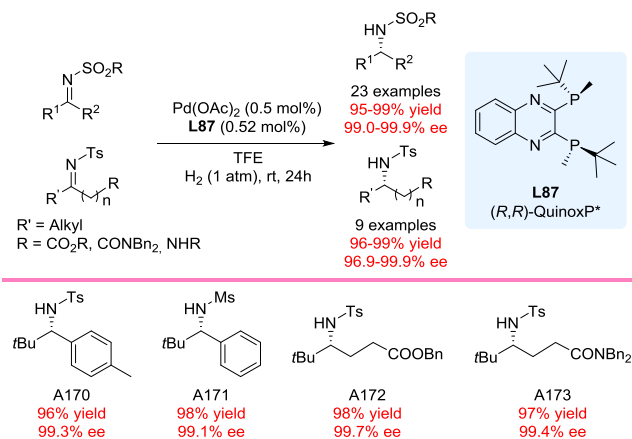


Recently, a major advance in AIH of activated imines has been achieved by Zhang.¹²⁰ While considering asymmetric hydrogenation of sterically hindered *N*-tosylimines, excellent results have been obtained using electron-rich, P-stereogenic diphosphine (*R,R*)-QuinoxP* **L87** in combination with Pd(OAc)₂ (Scheme 92). Under mild reaction conditions, i.e. 1 bar of H₂, room temperature, and TFE solvent, the desired protected amines were afforded with up to 99,9% ee.

Excellent yields and enantioselectivities were obtained with both electron-donating and withdrawing substituents at the 3- or 4-position of the aryl ring. Besides, these conditions are also compatible with alkyl imines. A series of functionalized *N*-tosylimines bearing various ester groups and different aliphatic moieties underwent the asymmetric hydrogenation smoothly. Similar results were also achieved while investigating bulkier imines bearing *t*-Bu substituent.

From the mechanistic viewpoint, both, inner-sphere hydrogenation with direct coordination of the C=N bond to Pd, and outer-sphere hydrogenation with the direct involvement of the solvent, employing a Pd-H complex as a catalyst, might be envisioned.

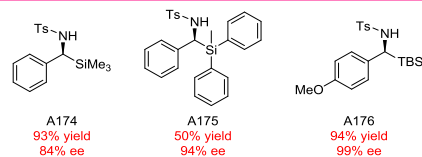
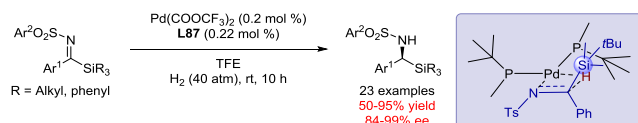
Scheme 92. Asymmetric hydrogenation of sulfonyl imines with QuinoxP* ligand.



Subsequently, the first asymmetric hydrogenation of sulfonylimines, bearing a silyl moiety, and affording chiral α -aminosilanes was reported using Pd-catalyst with P-stereogenic diphosphine (Scheme 93).¹²¹ QuinoxP* **L87** outcompetes other chiral ligands delivering the silylated sulfonylamines with excellent enantioselectivities.

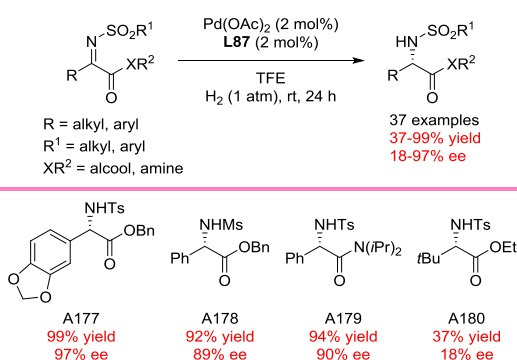
The excellent selectivity arises from the generation of a privileged transition state when the sulfonyl group is placed on the opposite side to the bulky silyl group. Both groups are adjacent to the smaller P-substituent that is the methyl (comparing to the *tert*-butyl group) (Scheme 93).

Scheme 93. Asymmetric hydrogenation of silylated sulfonylimines.



The potential of this Pd/QuinoxP* catalytic system for asymmetric hydrogenation goes even further, as recently illustrated in the context of the synthesis of enantiopure α -arylglycines.¹²² While using Pd(OAc)₂ in combination with L87, hydrogenation of a large panel of α -iminoesters was achieved with excellent efficiency and stereoselectivity, under remarkably mild reaction conditions (1 atm of H₂ and room temperature). Use of TFE (trifluoroethanol) medium is crucial as the decomposition of the substrate was observed in MeOH, while the racemic product was obtained in EtOH. The scope of this reaction is very broad; a diversity of electron-donating and electron-withdrawing substituents are tolerated on the aromatic ring and heterocycles are also compatible. In contrast, deceiving results were obtained for alkyl iminoesters (Scheme 94).

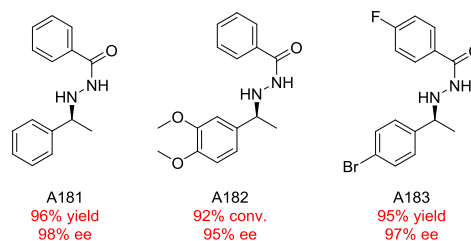
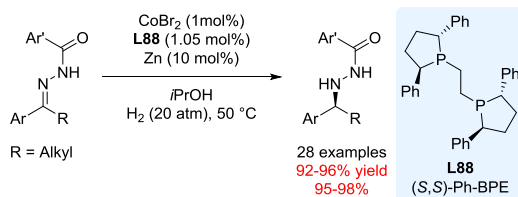
Scheme 94. Asymmetric hydrogenation of iminoesters with QuinoxP* ligand.



Cobalt based catalysts

In 2019, Zhang and coworkers reported an efficient cobalt-catalyzed hydrogenation of imines derivatives.¹²³ A wide scope of chiral hydrazines was obtained with excellent yields and ees. The presence of NHC(O)Ar motif is crucial to reach high reactivity (Scheme 95). This moiety enhances and directs the coordination of the cobalt to the C=N bond thus improving the catalytic performance and enhancing efficient chirality transfer. The zinc dust was used to reduce the Co(II) precatalyst. This Co-L88 complex tolerates various arylketimines with different electronic effect and features a high turnover number (up to 2000) even under a moderate H₂ pressure.

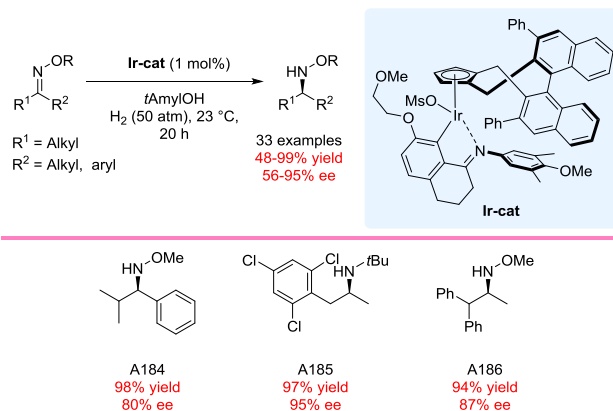
Scheme 95. Cobalt-catalyzed hydrogenation



Iridium based catalysts

Recently, Cramer's group developed a challenging, asymmetric hydrogenation of oximes delivering the corresponding chiral hydroxylamines without the cleavage of the weak N-O bond (Scheme 96). They employed a cyclometalated iridium (III) complex bearing a robust chiral cyclopentadienyl ligand. The catalyst reveals great chemoselectivity for the reduction of C=N bonds and shows a high turnover number (up to 4000), furnishing the expected products with up to 95% ee.¹²⁴

Scheme 96. Asymmetric hydrogenation of oximes by iridium-based catalysts.

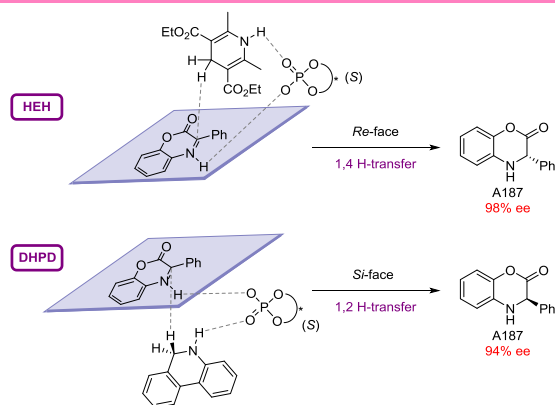
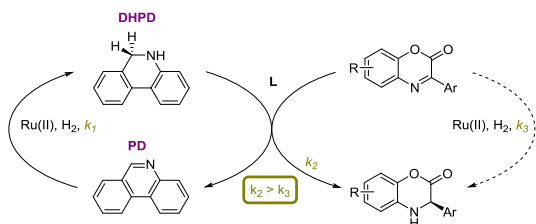
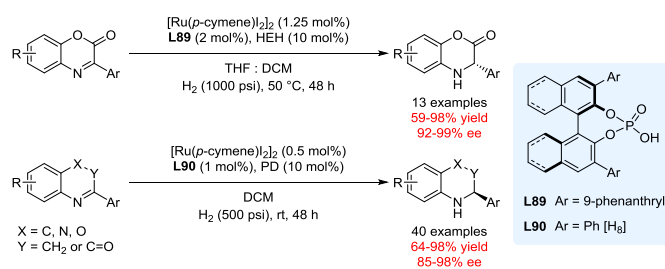


Biomimetic Asymmetric Imine hydrogenation

Regarding the importance of the redox metabolism process in the living organisms controlled by coenzymes such as NADH and NADPH, it is not surprising that the development of biomimetic reductions has attracted significant scientific attention. Indeed, it could be imagined that if *in situ* regenerable NAD(P)H model mimics are found, an alternative strategy towards the mild reduction of various compounds could be imagined. Following this hypothesis, Zhou has designed the first biomimetic hydrogenation of benzoxazinones, using Hantzsch ester (HEH) as recyclable NAD(P)H-mimic (Scheme 97).¹²⁵ Despite the originality of this work and excellent chiral induction reached using L89, harsh reaction conditions (1000 psi of H₂) hampered the synthetic utility of this reaction. A major step forward was achieved by the same group while discovering the potential of dihydrophenanthridine (DHPD) to act as efficient NAD(P)H

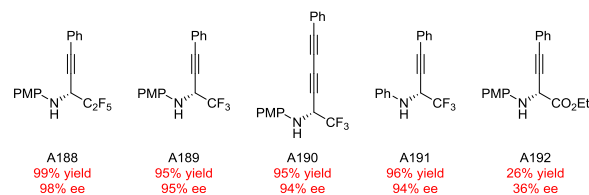
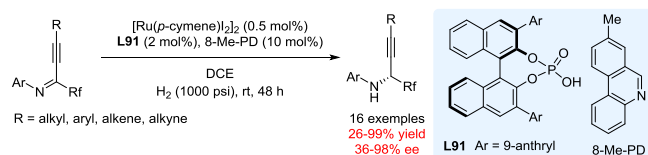
model, thanks to the mild Ru-hydrogenation under a low pressure of H₂.¹²⁶ The biomimetic asymmetric reduction of benzoxazinones thus occurs via easy hydride transfer from DHPD, with the stereoselection being induced via participation of a chiral phosphoric acid. It can be speculated that the substrate and DHPD interact with the phosphoric acid through two hydrogen bonds, thus generating a “contact central model”. Such a complex, biomimetic catalytic system is compatible with a diversity of heterocyclic substrates, including benzoxazinones, benzoxazines, and quinoxalines, delivering the chiral products in excellent yields, generally superior to 90%. The mechanism of this transformation implies synergistic action of two cycles; while Ru-catalysts allow mild hydrogenation of phenanthridine, the hydride transfer from DHPD to the imine, mediated by the phosphoric acid, furnishes the expected amine. The reduced phenanthridine may be regenerated under H₂ pressure.

Scheme 97. First biomimetic hydrogenation of benzoxazinones.



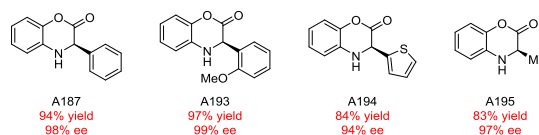
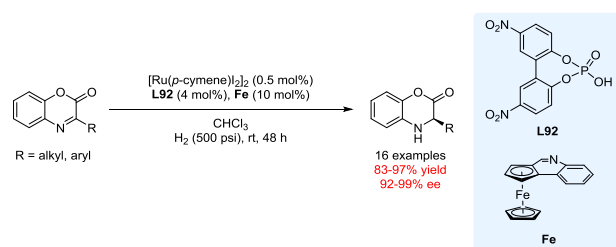
Subsequently, the concept of biomimetic imine hydrogenation has been expanded further. Alternative NAD(P)H mimics have been developed¹²⁷ and the applicability of such process was extended towards fluorinated propargylamine-type compounds (Scheme 98).¹²⁸

Scheme 98. Biomimetic hydrogenation of fluorinated propargylamine derivatives.



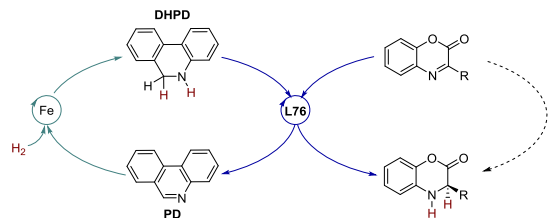
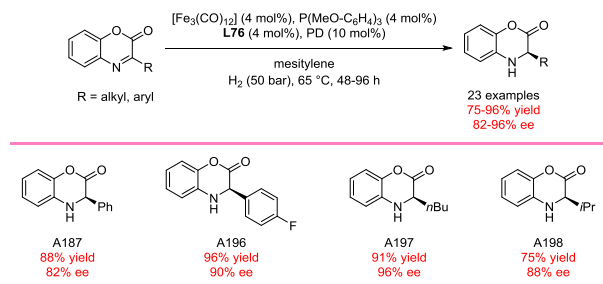
Very recently, the design of a chiral NAD(P)H model was investigated.¹²⁹ Remarkably, planar-chiral ferrocene-based model turned out as efficient and stereoselective hydride transfer agent, promoting benzoxazinones reduction in a presence of a simple, achiral Brønsted acid. Notably, the desired products were isolated in excellent yields and very high enantioselectivities (Scheme 99).

Scheme 99. Asymmetric hydrogenation in presence of achiral Brønsted acid.



Aiming more sustainable transformation, Beller and coworkers have investigated the potential of iron catalysis to perform closely related biomimetic hydrogenation. After establishing the potential of Fe₃(CO)₁₂ to catalyze the reduction of commercially available phenanthridine, they discovered that the catalytic systems combining this Fe-catalysts with the NAD(P)H mimics and chiral Brønsted acid, allow efficient benzoxazinones hydrogenation.¹³⁰ Under optimized reaction conditions, 3-aryl and 3-alkyl-substituted benzoxazinones were converted smoothly into the desired amines with high stereocontrol. The proposed mechanistic scenario suggests Fe-catalyzed reduction of PD to DHPA, followed by synergistic, Brønsted acid mediated hydride transfer to the imine substrate, furnishing the expected amine with excellent stereoselectivity (Scheme 100).

Scheme 100. Biomimetic hydrogenation of benzoxazinones catalyzed by an iron catalyst.



Accordingly, this original bioinspired methodology should be recognized as a valuable alternative strategy providing original chiral amines.

Applications of AIH in pharmaceutical and agrochemical industry.

While considering large-scale production of enantiopure molecules, asymmetric hydrogenations are extremely appealing transformations. Indeed, use of H_2 as the sole reagent together with a catalytic amount of a chiral catalyst furnishes the desired enantiopure compound with 100% atom economy while avoiding generation of any side product. In addition, relatively simple protocols, straightforward isolation of the products and expected very efficient chiral induction, render asymmetric hydrogenations the most frequently used asymmetric catalytic industrial process.

However, the development of large-scale asymmetric hydrogenation process requires optimization of various parameters, such as choice of the catalyst, catalytic loading, turnover number and turnover frequency, availability and prize of the catalyst (including both, a metal and a ligand), H_2 overpressure, etc.

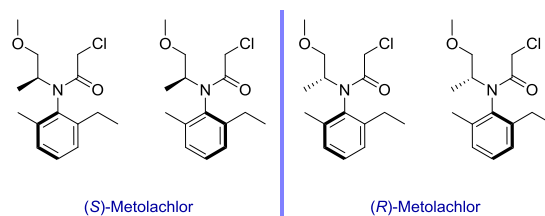
Chiral amines are key motifs in pharmaceutical and agrochemical industries and therefore their straightforward, large-scale synthesis is an important topic, perfectly addressed by the development of asymmetric hydrogenation protocols. In particular, asymmetric hydrogenation appears as a perfect solution for both, large-scale production of key building blocks of the commercially available products, and R&D sector.

Several papers, already cited above, highlighted the synthesis of skeletons or interesting building blocks in different fields. Herein, few examples are discussed in more details.

The key intermediate of the Metolachlor, an herbicide blockbuster developed by Novartis and commercialized by Syngenta, produced on the scale of 10K tons per year, illustrates the real success story of the industrial asymmetric hydrogenation of imines. This reaction was presented as the largest enantioselective catalytic process.¹³¹

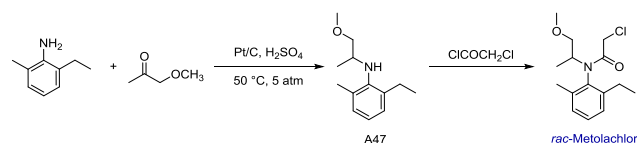
Metolachlor possess an atropisomeric axis and a stereogenic center, leading thus to four possible stereoisomers (Scheme 101).

Scheme 101. Structures of Metolachlor's stereoisomers.



Metolachlor was first synthesized in 70's via reductive alkylation process and commercialized in 1976 as a racemic mixture (Scheme 102). Rapidly, it was discovered that (1*S*)-diastereomers (C-N axial bond is not controlled) is the particular active form, accounting for 95% of its herbicidal activity. Following this discovery, design of new synthetic and technological solutions to access selectively the desired diastereomer has attracted a major interest.

Scheme 102. The first industrial route for the synthesis of racemic Metolachlor.



Different routes have been considered for the synthesis of the (*S*)-Metolachlor, including enamide hydrogenation and nucleophilic substitution reaction. The unavailability of the starting materials rendered these strategies inapplicable. Consequently, significant efforts have been focused on the development of asymmetric imine hydrogenation-based strategy. In such a case, MEA (I47) was designed as an easily available starting material. Although extremely tempting, the scarcity of literature precedents concerning AIH at this period demonstrated its high-risk / high-gain character.

The first encouraging result (69% ee, with TOF= 15 h⁻¹) was obtained by using the catalytic system previously developed for the olefin hydrogenation, i.e. Rhodium complex bearing Cyphos **L4** as the chiral ligand. Improved chiral induction was achieved in a presence of the Ir-based catalyst in combination with BDPP **L3** (84% ee). Unfortunately, even in a presence of iodide ions the catalyst deactivation was observed, thus resulting in low catalytic activity.

To prevent the catalyst's poisoning, a series of non-classical diphosphine ligands such as ferrocenyl diphosphine derivatives (developed previously by Togni and Spindler¹³²) were investigated. The iridium ferrocenyl diphosphine complexes performed well, delivering the desired product A47 in 80% ee and 80% yield, while using a low catalyst loading of 10⁻⁶ mol% (TOF of 1.8x10⁶ h⁻¹).¹³³

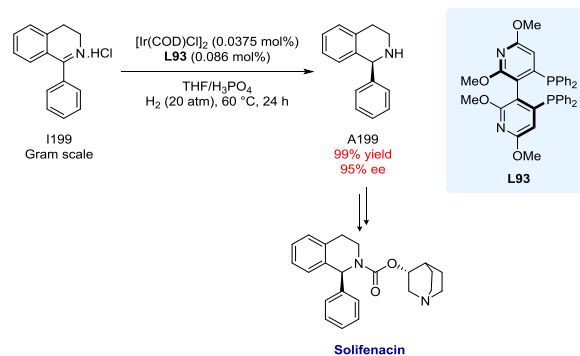
Still today, this catalytic system is used by Syngenta in production, and hence represents the largest scale enantioselective catalytic process in the industry.¹³⁴

The possible applications of AIH go far beyond and a diversity of drugs and agrochemical precursors may now be rapidly afforded using such protocols. Therefore, many important biologically active compounds and their direct precursors were

synthesized, on laboratory scale, *via* AIH. Unfortunately, information concerning the large-scale production procedures remain scarce.

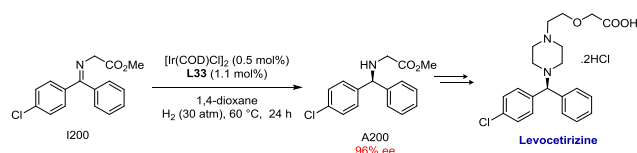
Among these compounds, Solifenacin is an important anticholinergic drug for the treatment of overactive bladder.¹³⁵ The gram-scale synthesis of (*S*) enantiomer of the key intermediate was achieved by Ruzic and coworkers *via* enantioselective hydrogenation of tetrahydroisoquinone using Ir-(*S*)-P-Phos **L93** catalytic system with a very low catalyst loading and a moderate hydrogen pressure of 20 atm (Scheme 103).

Scheme 103. Synthesis of Solifenacin's precursor.



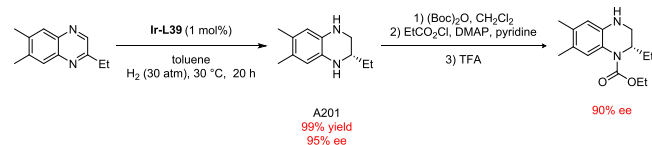
The iridium-SpiroPhos complex developed for the asymmetric hydrogenation of prochiral diarylmethylimines established itself as an attractive solution for the synthesis of Levocetirizine, a known histamine H1-receptor antagonist.⁴⁶ The AIH of I200 delivered the desired chiral amine with 96% ee. However, a catalyst loading of 1.1 mol% is crucial to reach full conversion of the starting material, thus delivering the advanced precursor with 96% ee (Scheme 104).

Scheme 104. Synthesis of Levocetirizine's precursor.



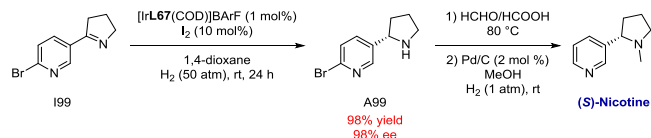
A series of 2-substituted tetrahydroquinoxaline was synthesized by Ohshima, Mashima, Ratovelomanana-Vidal and coworkers *via* iridium-catalyzed hydrogenation of the corresponding quinoxalines. This method is considered as a pathway for the enantiopure intermediate of cholesterylester transfer protein CETP inhibitor, which is a family of drug used for cardiovascular disease (Scheme 105).¹³⁶

Scheme 105. Synthesis of CETP inhibitor.



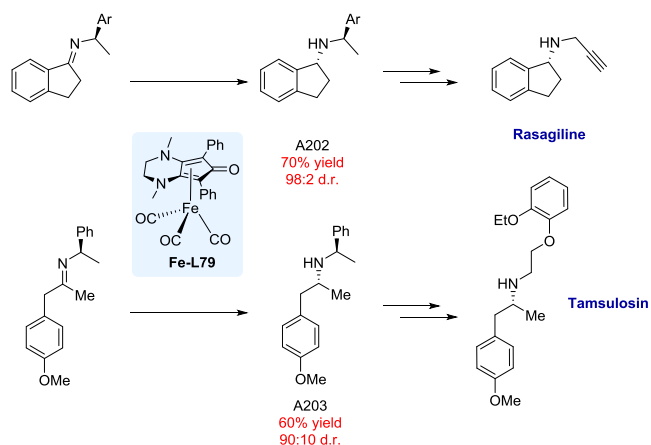
AIH of pyridyl cyclic imines has also attracted significant interest while regarding the possible industrial applications. Zhou's group developed a method for the hydrogenation of pyridyl cyclic imines I99, thus illustrating the utility of this method to access various natural alkaloids, such as (*S*)-Nicotine (Scheme 106).⁸⁶

Scheme 106. Synthesis of (*S*)-Nicotine through the hydrogenation of a pyridyl cyclic imine.



Synthesis of enantiopure chiral amines, key precursors of biologically active molecules, is not only limited to the use of expensive and poorly abundant noble metals as recently illustrated by Benaglia and coworkers. This research group was interested by the synthesis of Rasagiline, an anti-Parkinson treatment. Remarkably, use of the Fe-based catalyst, previously developed by the same group, promoted asymmetric hydrogenation of I202, delivering the expected amine A202 with 96% de, while using 10 mol% of the catalyst and applying high pressure of H₂ (Scheme 107). The same protocol is also applicable for the synthesis of A203, direct precursor of Tamsulosin, used for benign prostatic hyperplasia treatment.¹⁰⁴

Scheme 107. Synthesis of Rasagiline and Tamsulosin precursors.



This overview showed that the asymmetric hydrogenation of imines with chiral transition-metal complexes is among the most powerful approaches for the elaboration of chiral amine structures with high level of enantiocontrol. These examples are proving that despite the fact that AIH still needs further improvement, it can be clearly considered as a strategic methodology for the pharmaceutical and agrochemical industries.

Conclusion

Asymmetric hydrogenation is a perfect atom-economic reaction, commonly effective under mild conditions, and usually furnishing appealing and high-value-added enantiopure amines in high yields. Despite intrinsic challenges related to this reaction, a diversity of chiral complexes, using different metal precursors, have been designed over the recent years. Therefore, a diversity of benchmark acyclic and cyclic imines may now be hydrogenated with excellent enantioselectivities. In addition, alternative approaches, such as the design of activated substrates have been elaborated to further expand the portfolio of enantiopure nitrogenated compounds accessible *via* hydrogenation of C=N bonds.

However, despite the great achievements accomplished in the field of asymmetric imine hydrogenation, several challenges persist. The majority of catalytic systems are relatively substrate-dependent and therefore, for various families of substrates, excellent enantioselectivities generally could not be reached with a single catalyst. Consequently, a fine catalyst

design might be required to warrant an optimal stereoselectivity for a precise product of interest. Besides, frequently relatively high catalysts loadings are still used, non-omitting the prevalence of noble, poorly available, and expensive metal precursors (mainly Ir, Rh and Ru). Therefore, the development of 3d-metal-catalyzed AIH will certainly catch significant attention within the next years. Alternatively, the sustainability of the overall process might be further improved if recyclable catalytic systems are accessible. Besides, flow protocols might offer additional advantages over classic batch-type reactions, rendering it even more attractive for large-scale productions. Accordingly, the field of AIH is expected to rapidly evolve and the advanced industrial process will unquestionably flourish.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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