

Recent Advances in the Enantioselective Synthesis of Chiral Amines via Transition Metal-Catalyzed Asymmetric Hydrogenation

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Abstract

Chiral amines are key structural motifs present in a wide variety of natural products, drugs, and other biologically active compounds. During the last decade, significant advances have been made with respect to the enantioselective synthesis of chiral amines, many of them based on catalytic asymmetric hydrogenation (AH). The present review covers the use of AH in the synthesis of chiral amines bearing a stereogenic center either in α , β or γ position with respect to the nitrogen atom, reported from 2010 to 2020. Therefore, we provide an overview of the recent advances in the AH of imines, enamides, enamines, allyl amines and *N*-heteroaromatic compounds.

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1. Introduction

Chiral amines are key structural motifs present in a wide variety of natural products, drugs, and other biologically active compounds (Figure 1).^{1,2} Around 40-45% of the small molecule pharmaceuticals and many other industrially relevant fine chemicals and agrochemicals contain chiral amine fragments. Moreover, chiral amines can be used as resolving agents, chiral auxiliaries or building blocks for the asymmetric synthesis of more complex molecules, including natural products.

Therefore, the great demand for enantiomerically enriched amines in the life sciences has driven the development of innovative and sustainable synthetic routes towards their efficient preparation.³

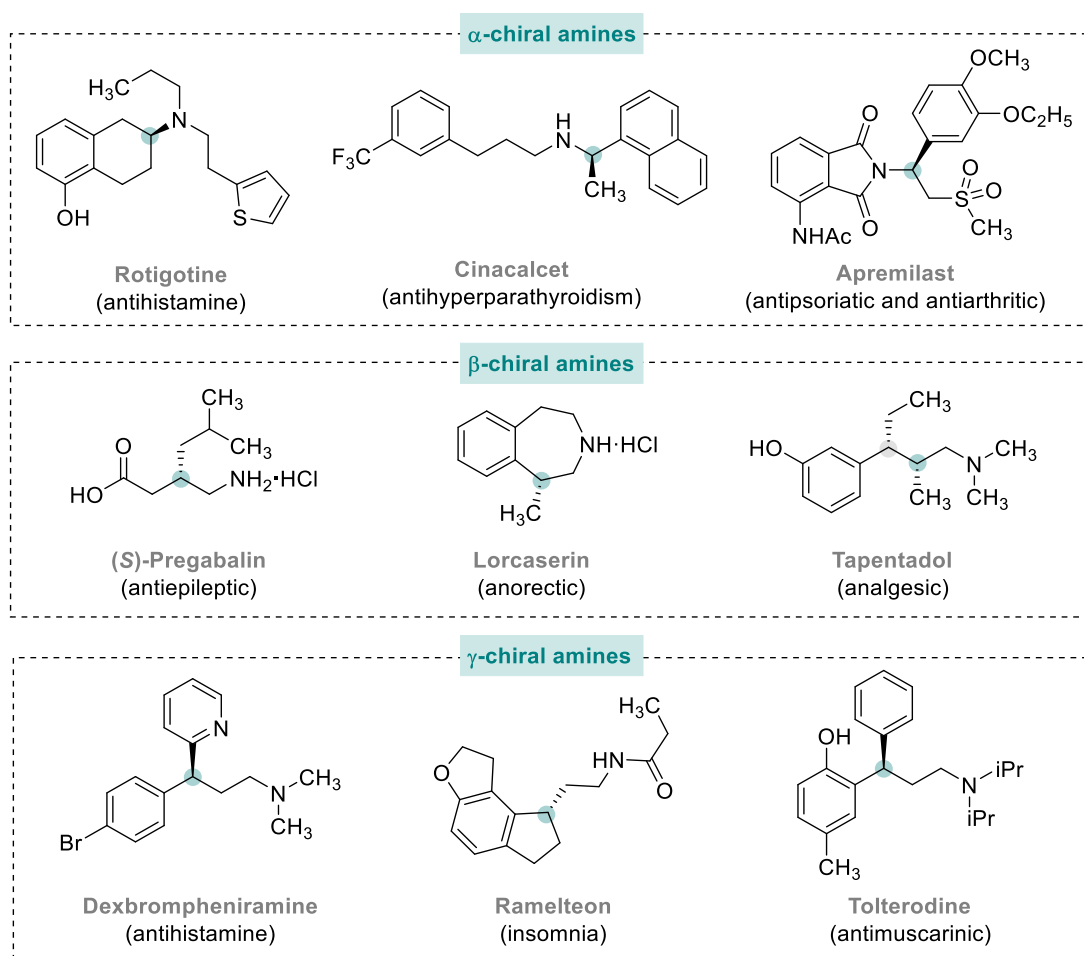


Figure 1. Selected pharmaceuticals with chiral amine fragments.

Despite the widespread relevance of chiral amines, traditional synthetic methods such as resolution are still being used. To overcome their intrinsic limitations, the use of catalytic methods has been widely investigated in recent decades, asymmetric catalysis being a key research field in modern synthetic chemistry.^{4,5} Although biocatalytic⁶ and organocatalytic⁷ strategies have gained importance, the catalytic approach based on transition metals is still, arguably, the method most widely used.⁸ The design and synthesis of modular chiral ligands have allowed the preparation of novel metal complexes whose properties have been fine-tuned to afford highly active and efficient catalysts.

A relevant number of new metal-catalyzed transformations for the synthesis of chiral amines have been reported. Important achievements have been made in enantioselective methods involving, among others, reductive amination,^{9,10,11,12} hydroamination,^{13,14,15} allylic amination¹⁶ or isomerization reactions.^{17,18} The metal-catalyzed enantioselective alkyl addition to imines has also been explored.¹⁹

Nonetheless, the asymmetric reduction of unsaturated compounds continues to be the most fundamental means of introducing chirality.²⁰ In this regard, the asymmetric reduction of imines^{21,22} (*via* hydrosilylation or transfer hydrogenation, for example) provides an attractive route to chiral amines. However, direct asymmetric hydrogenation (AH) of unsaturated nitrogenated compounds is probably the most powerful and efficient strategy. AH offers excellent atom economy, with almost no waste or byproducts, thus being a highly sustainable and “green” strategy for attaining optically active amines.²³ Due to all these advantages, AH has become one of the major disciplines in homogeneous catalysis.²⁴ Transition metal-catalyzed AH frequently shows excellent chemo-, regio- and enantio-selectivity and it is considered a versatile and a reliable tool for the synthesis of chiral drugs.²⁵ The AH of challenging organic substrates such as unfunctionalized olefins,^{26,27} non-aromatic cyclic alkenes,²⁸ tetrasubstituted olefins²⁹ and (hetero)arenes^{30,31,32,33,34} has been extensively studied, reaching high levels of enantiocontrol. However, and in spite of the long-standing problems being partially solved, many challenges remain. Moreover, the environmental need to use more economical and accessible first-row transition metals (Mn, Fe, Co, Ni) arises as a new complex task in a field dominated by Rh, Ir and Ru since its origins.

Focusing on the enantioselective synthesis of chiral amines, important advances have been reported in the last ten years, many of them based on the AH of imines,^{35,36,37,38,39} enamines and derivatives,^{39,40,41} and *N*-heteroarenes.^{30,31,32} These advancements are largely driven by a plethora of new chiral phosphorus ligands,⁴² including phosphino-oxazolines⁴³ and *P*-stereogenic phosphines.^{44,45} In addition, other chiral phosphine-free metal catalysts, bearing *N*-heterocyclic carbenes⁴⁶ or *C,N*- and *N,N*-based ligands, have also shown outstanding catalytic activity.⁴⁷ Thanks to these breakthroughs, a wide range of previously not easily accessible chiral amines have been obtained with excellent enantioselectivities.

The development of new efficient routes for chiral amine synthesis has a strong and direct impact on medicinal chemistry and the pharmaceutical industry.⁴⁸ Indeed, recent years have witnessed an increase in the synthesis of new chiral amino building blocks due to the great demand for expanding the chemical space in drug discovery platforms.⁴⁹ AH has also found widespread use at the industrial level. The pioneering work of Knowles,^{50,51} Horner⁵² and Kagan⁵³, followed by the great success of the Monsanto Company⁵⁴ with the production of L-DOPA, opened up industrial-scale synthesis using AH.^{55,56,57} In 2009, Merck implemented a highly efficient and sustainable enantioselective synthesis of sitagliptin *via* rhodium-catalyzed AH on a manufacturing scale.⁵⁸ In 2011, Pfizer developed the multi-kilogram synthesis of the amino acid imagabalin hydrochloride (PD-0332334), used for the treatment of generalized anxiety disorder (GAD), *via* AH.⁵⁹ Another landmark in the field was the

rhodium-catalyzed AH of β -cyanocinnamic esters⁶⁰ to produce pregabalin (Lyrica), which is an important drug for the treatment of fibromyalgia and epilepsy.⁶¹

The present review focuses on the syntheses of chiral amines bearing a stereogenic center either in the α , β or γ position with respect to the nitrogen atom reported between 2010-2020. Therefore, we provide an overview of the recent advances in the AH of the following substrates: (a) imines; (b) enamides; (c) enamines; (d) allyl amines and (e) *N*-heteroaromatic compounds (Figure 2). Despite asymmetric reductive amination (ARA) is one of the most convenient methods for the preparation of chiral amines this topic will not be covered specifically in this review since ARA has been extensively reviewed recently.^{10,11,12}

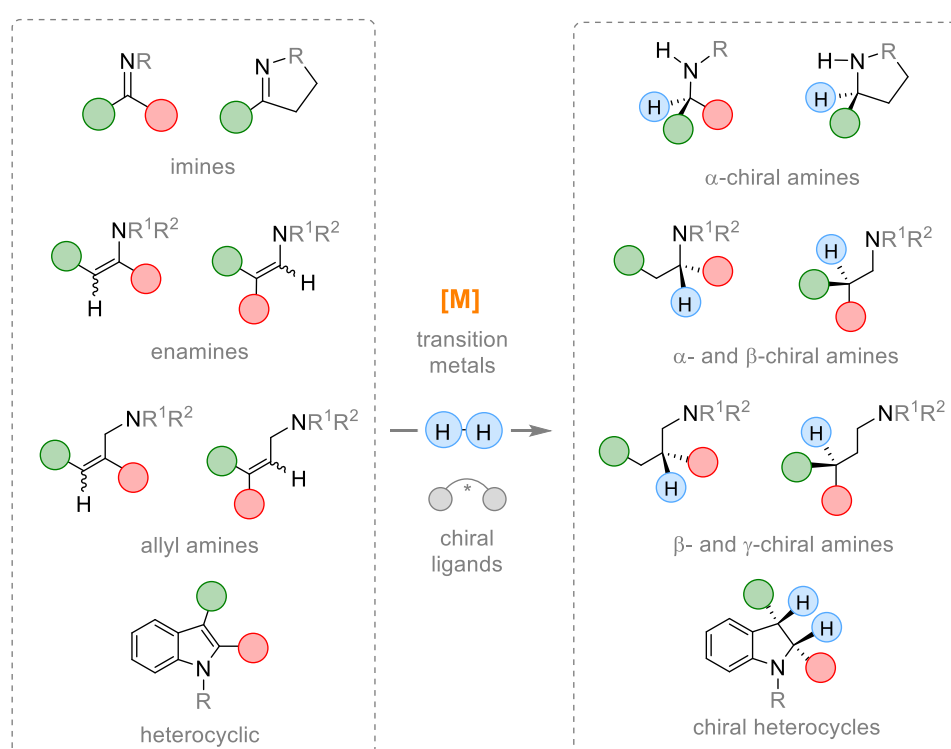


Figure 2. Synthesis of chiral amines *via* AH of unsaturated compounds using transition metal catalysis.

2. Asymmetric hydrogenation of imines

The asymmetric hydrogenation of prochiral imines^{35,36,37,38,39,40} is the most direct and efficient approach to prepare valuable α -chiral amines.⁶² It has been used at industrial scale, exemplified by the multiton-scale production of the herbicide (*S*)-metolachlor.⁶³

Imines are more challenging substrates than their oxygenated analogs, namely ketones, due to the easy hydrolysis, the presence of *E,Z* stereoisomers and nucleophilicity. Thus, extensive efforts have

been devoted to the development of efficient synthetic procedures. In recent decades, considerable progress has been made in the AH of both *N*-protected and unprotected⁶⁴ imines. While ruthenium has provided excellent results in asymmetric transfer-hydrogenation reactions, iridium has shown better performance for the direct hydrogenation of imines.^{65,66,67} In addition, catalytic systems based on earth-abundant metals such as iron or cobalt have started to give competitive results.⁶⁸

2.1. *N*-Aryl imines

2.1.1. *N*-aryl aryl alkyl imines

Several examples of the AH of *N*-aryl imines derived from acetophenones have been reported, reaching excellent levels of enantioselectivity. The reduction of acetophenone phenyl imine (**S1**, Scheme 1) is the standard substrate for this chemistry.

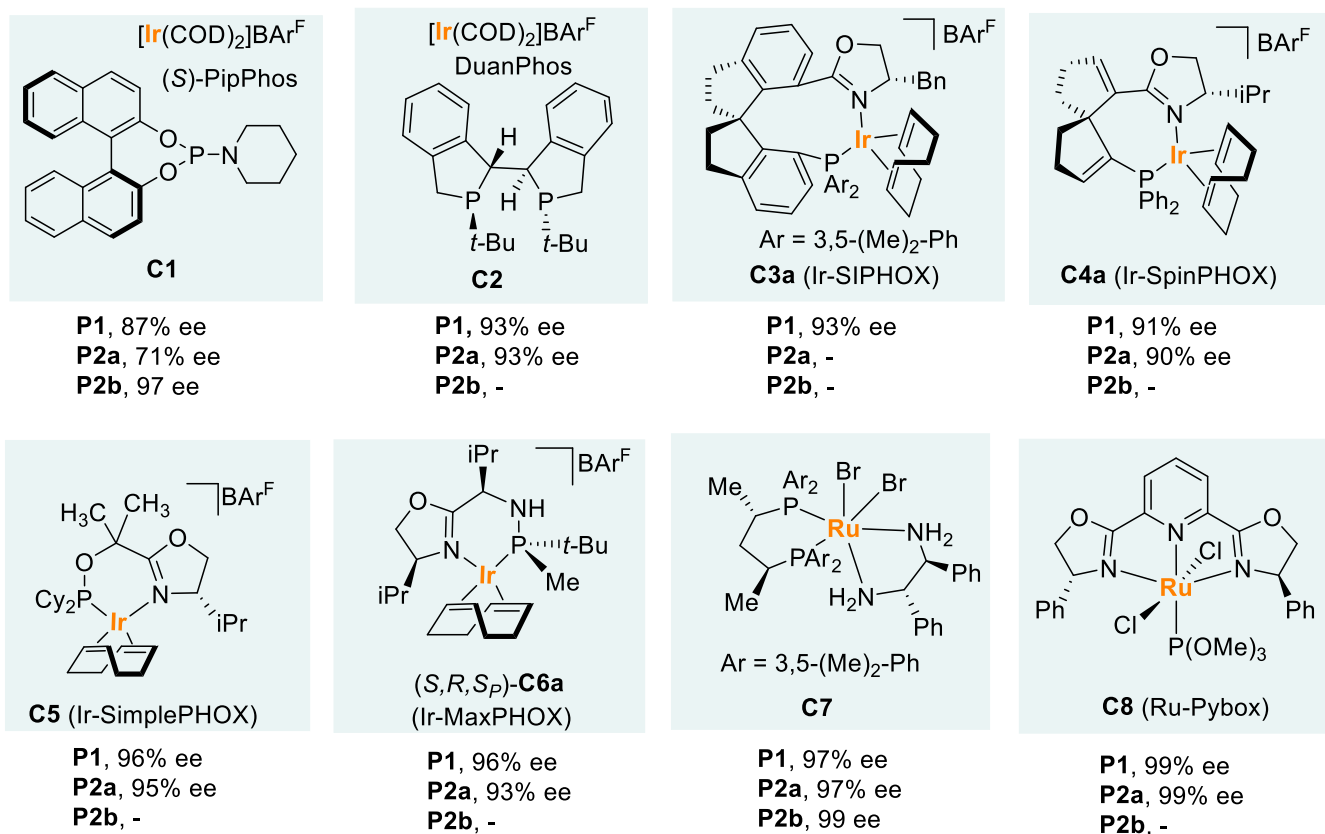
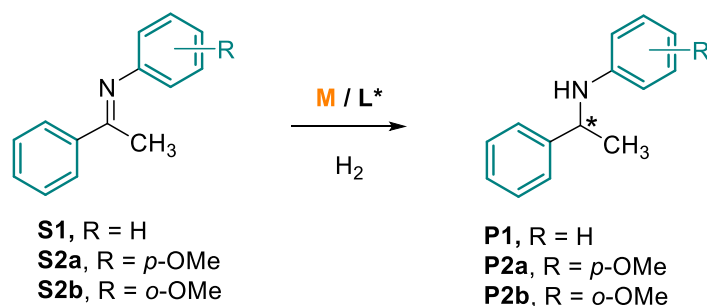
In 2009, de Vries, Feringa and co-workers reported the iridium-catalyzed AH of *N*-aryl imines using readily available (*S*)-PipPhos as chiral monodentate phosphoramidite ligand (**C1**, Scheme 1).⁶⁹ With the model substrate **S1**, they obtained a product of 87% ee but the selectivity increased significantly using *ortho*-methoxyphenyl imines (**S2b**) as substrates. This work demonstrated that, although bidentate chiral ligands were considered a superior class in AH, modular monodentate ligands might also be highly efficient in certain cases.⁷⁰

X. Zhang and co-workers used chiral diphosphine DuanPhos in the preparation of iridium catalysts **C2**.⁷¹ The AH of the standard substrate gave 93% ee. Similar substrates with substitutions in the aryl groups gave 90-93% ee.

Iridium complexes bearing phosphino-oxazoline chiral ligands have been widely used in the AH of *N*-aryl imines.^{72,73} Zhou's⁷⁴ and Ding's⁷⁵ groups respectively, developed chiral complexes with a spiranic backbone **C3a** and **C4a**. Both reported high activity and achieved chiral amines in up to 97% ee. Pfaltz also showed that phosphino-oxazoline ligands provide an excellent platform for the iridium-catalyzed reduction of *N*-aryl imines. In 2010, he reported a range of Ir-P,N chiral complexes (SimplePHOX, **C5**) that were readily accessible by a short and convenient synthesis.⁷⁶ The AH of **S1** with **C5** gave a product of 96% ee. In 2016, Riera & Verdaguer developed a novel family of chiral *P*-stereogenic phosphino-oxazoline ligands called MaxPHOX.⁷⁷ These modular ligands are prepared from three different building blocks: an amino alcohol, an amino acid, and a *P*-stereogenic phosphinous acid.⁷⁸ The key advantage of the Ir-MaxPHOX catalysts (**C6a**) resides in their structural diversity, which is conferred by four possible configurations and diverse substitution patterns. This feature allows fine-tuning of the catalyst for each specific reaction. Moreover, the absolute

configuration of the P-center is crucial and has a great impact on catalytic activity. Using these Ir-MaxPHOX complexes, the AH of acyclic *N*-aryl ketimines smoothly proceeded with high enantiocontrol (up to 96% ee) at 1 bar of hydrogen.⁷⁹

Scheme 1. Iridium- and ruthenium -catalyzed AH of *N*-phenyl 1-phenylethanamine.

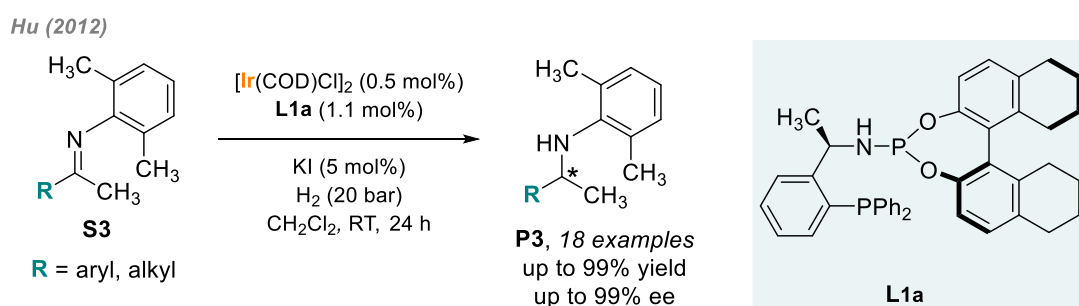


Ruthenium catalyst **C7**, first developed by Ohkuma and co-workers in 2012, afforded very high enantioselectivities on the model substrate **S1** (97% ee) (Scheme 1).⁸⁰ The Xyl-Skewphos/DPEN-Ru complex **C7** was applied to the AH of a range of imines derived from aromatic and heteroaromatic ketones with a TON as high as 18,000 to afford chiral amines in up to 99% ee.

Another ruthenium complex, Ru-Pybox (**C8**), developed by Pizzano and Gamasa,⁸¹ afforded the corresponding amines with excellent enantioselectivities. **C8** gave the best enantioselectivity for the model substrate **S1** (99% ee).

Sterically hindered *N*-aryl imines are difficult substrates. In 2001, X. Zhang and co-workers described Ir/f-binaphane as an excellent catalyst for the AH of sterically hindered *N*-aryl alkylarylamines.⁸² Later, in 2012, Hu reported an extended substrate scope by using the iridium complex derived from phosphine-phosphoramidite ligand **L1a** (Scheme 2).^{83,84} The corresponding chiral amines **P3**, which are important building blocks in organic synthesis and agrochemistry, were obtained in good to excellent enantioselectivities.

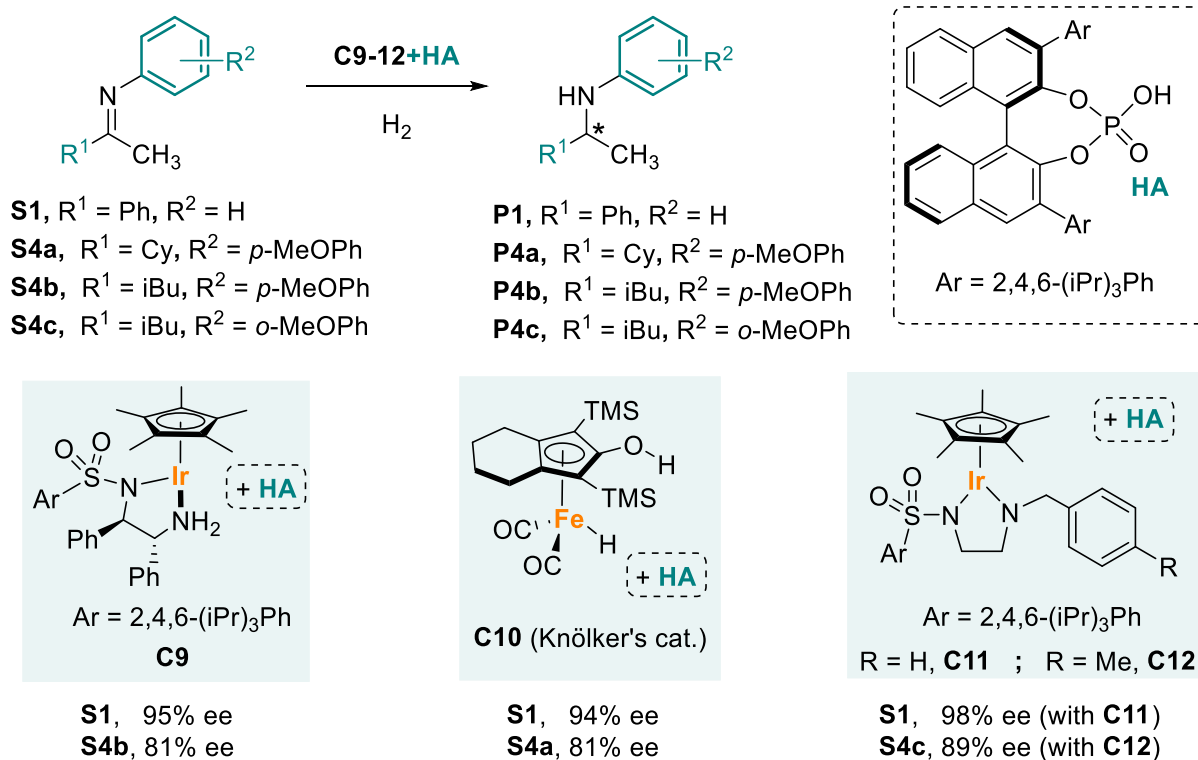
Scheme 2. Iridium-Catalyzed AH of sterically hindered *N*-aryl imines.



2.1.2. *N*-aryl dialkyl imines

In contrast to aromatic imines, successful examples of the AH of imines derived from aliphatic ketones (**S4**) are rare and usually with low chiral induction. In 2008, Xiao pioneered the field with the highly efficient cooperative catalysis between the ruthenium complex **C9** and a chiral phosphoric acid (HA) (Scheme 3).⁸⁵ In 2011, Beller and co-workers demonstrated that performing ligand-free AHs without the use of precious metal catalysts was possible.⁸⁶ The combination of an achiral iron complex (Knölker's catalyst, **C10**) with HAs enabled smooth hydrogenation for a wide range of *N*-aryl imines, including **S1** and the dialkyl imine **S4a**. Similarly, in 2013, Xiao reported a family of achiral iridium-(Cp*) complexes containing diamine ligands that, in combination with a chiral HA, gave access to highly active catalysts (**C11-C12**) for the AH of *N*-aryl imines derived from both aryl and aliphatic ketones.^{87,88} While **C11** was chosen as the best catalyst for **S1** (98% ee, Scheme 3), for imine **S4c** the highest enantioselectivity was observed using **C12**, which is the best catalyst reported to date for these substrates.

Scheme 3. AH of *N*-aryl dialkyl imines using binary catalysts of a metal complex and a chiral phosphoric acid (HA).



2.1.3. *N*-aryl α -imino esters

The synthesis of enantiomerically pure α -amino acids and their derivatives is of great importance in pharmaceutical and synthetic chemistry.⁸⁹ Chiral α -aryl glycines, in particular, have found wide applicability in the synthesis of significant antibacterial and cardiovascular drugs, such as amoxicillins and nocardicins.⁹⁰ Several highly efficient asymmetric catalytic methods such as the asymmetric Strecker⁹¹ or Sharpless aminohydroxylation have been developed.⁹² Despite being a logical approach, the AH of the corresponding α -imino esters has scarcely been addressed, presumably because of the relatively poor reactivity of these types of imino substrates toward hydrogenation.

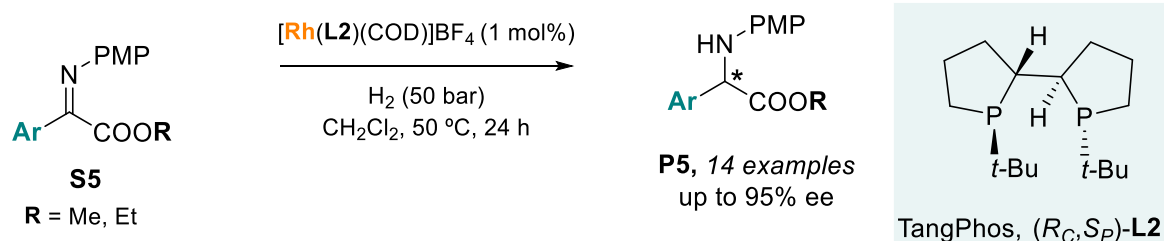
In 2006, X. Zhang and co-workers reported the first rhodium-catalyzed AH of **S5** using a *P*-stereogenic diphosphine **L2** (TangPhos), providing chiral glycines **P5** with high yields and enantioselectivities (Scheme 4).⁹³ However, the scope of this method was limited to *p*-methoxyphenyl (PMP)-protected α -imino esters. To overcome this constraint, Hu described the iridium-catalyzed AH of α -imino esters **S6** with unsymmetrical hybrid chiral ferrocenylphosphine-phosphoramidite ligand **L3** for the synthesis of optically active α -aryl glycines **P6** (Scheme 4).⁹⁴ The method features high

asymmetric induction (up to 96% ee), the iodo-substituent of the binaphthyl unit playing a fundamental role in the enantioselectivity.

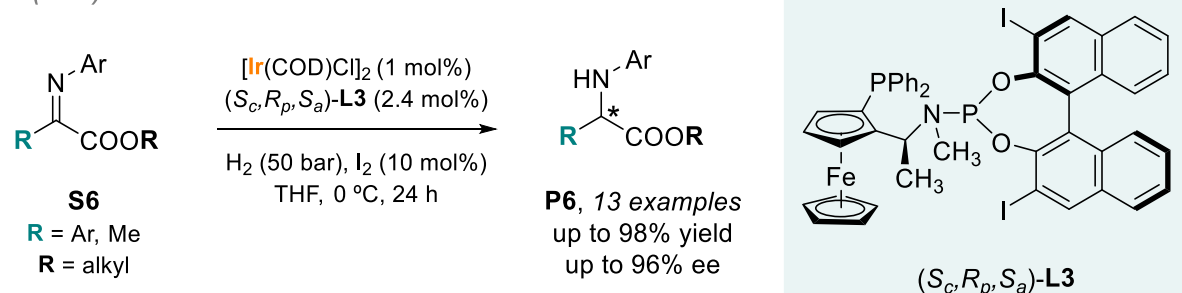
To avoid the use of precious metals, in 2020, W. Zhang and co-workers reported an efficient nickel-catalyzed AH of *N*-aryl imino esters **S7**, affording chiral α -aryl glycines **P7** in high yields and enantioselectivities (up to 98% ee) using a *P*-stereogenic dialkyl phosphine ligand, BenzP* **L4** (Scheme 4).⁹⁵ The reaction was performed on a gram scale at a low catalyst loading (S/C up to 2000). The preparation of two synthetic drug intermediates showcased the applicability of the method.

Scheme 4. AH of *N*-aryl α -imino esters.

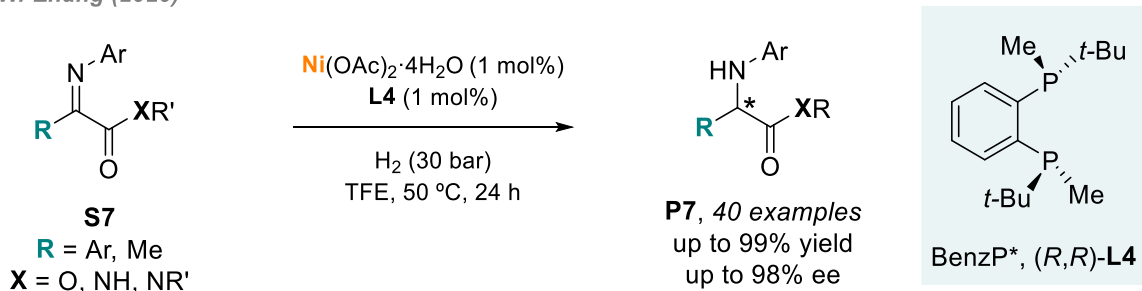
X. Zhang (2006)



Hu (2019)



W. Zhang (2020)

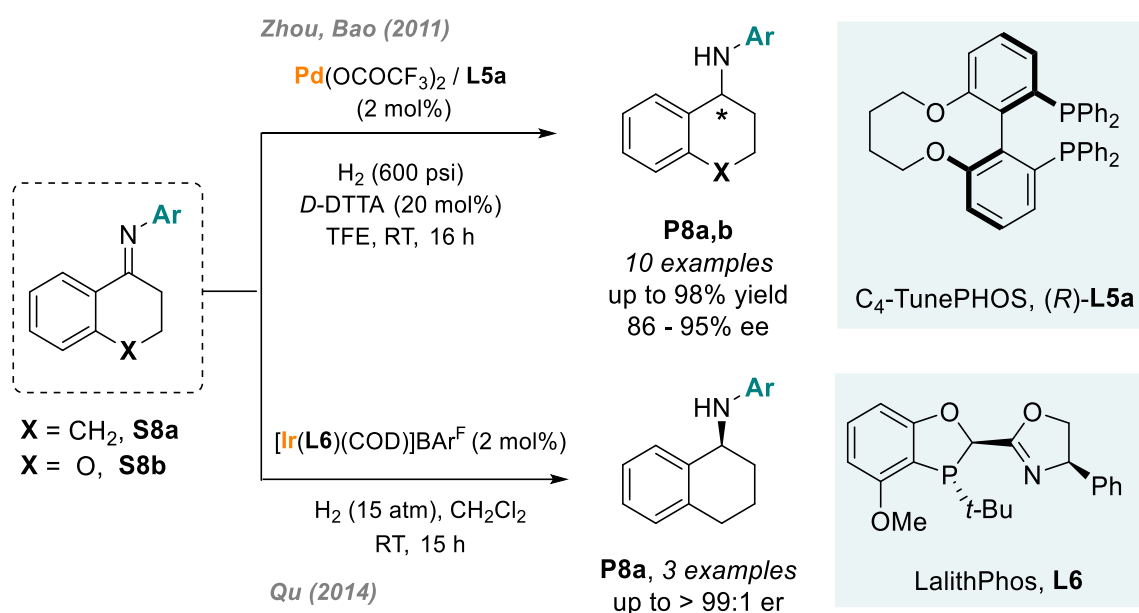


2.1.4. Exocyclic *N*-aryl imines

Typically, the AH of exocyclic ketimines derived from 1-tetralone or 4-chromanone exhibited low enantioselectivities, presumably due to the conformational strain upon metal coordination.^{96,97} In 2011, Zhou & Bao reported a highly enantioselective palladium-catalyzed hydrogenation using a catalytic amount of a Brønsted acid as activator (*D*-DTTA).⁹⁸ By using C₄-TunePhos **L5a** as a chiral

ligand, this catalytic system provided straightforward access to enantioenriched cyclic amines **P8a** and **P8b** (86-95% ee, Scheme 5), which are privileged structural motifs present in a large number of drugs and natural compounds.⁹⁹ Iridium-based catalytic systems were also used in this transformation. First, Bolm's group made a significant advance in the iridium-catalyzed AH of exocyclic imine **S8a**. They introduced a novel class of C₁-symmetry sulfoximines as chiral ligands that, once coordinated, yielded the corresponding chiral amine adduct in 91% ee.¹⁰⁰ Although it was a single example, the catalytic system also gave excellent results for acyclic *N*-aryl imines. Later, in 2014, Qu and co-workers reported a family of air-stable *P*-stereogenic dihydrobenzooxaphosphole oxazoline ligands (LalithPhos).¹⁰¹ In particular, Ir/**L6** was chosen as the best catalyst for the AH of **S8a**, which afforded up to three examples of **P8a** in enantiopure form (Scheme 5).

Scheme 5. AH of exocyclic *N*-aryl imines.

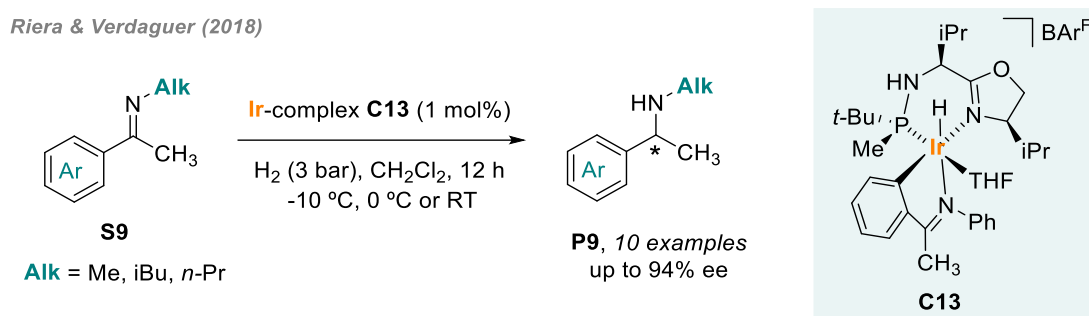


2.2. *N*-alkyl imines

Chiral *N*-methyl or *N*-alkyl amine is a frequent pharmacophore in many pharmaceuticals and drugs, and despite other successful approaches,^{102,103} direct AH is the most convenient process. In sharp contrast with the good results obtained with *N*-aryl ketimines, the development of the AH of *N*-alkyl ketimines has been more difficult. The high basicity and nucleophilicity of the corresponding *N*-alkyl amines as reaction products often results in catalyst deactivation. Pfaltz pioneered the use of Ir-PHOX catalysts for the AH of *N*-methyl imine of acetophenone, albeit with low enantioselectivity.⁷³ Later, in 2013, he discovered that the catalyst in the hydrogenation of *N*-aryl imine is actually an iridacycle

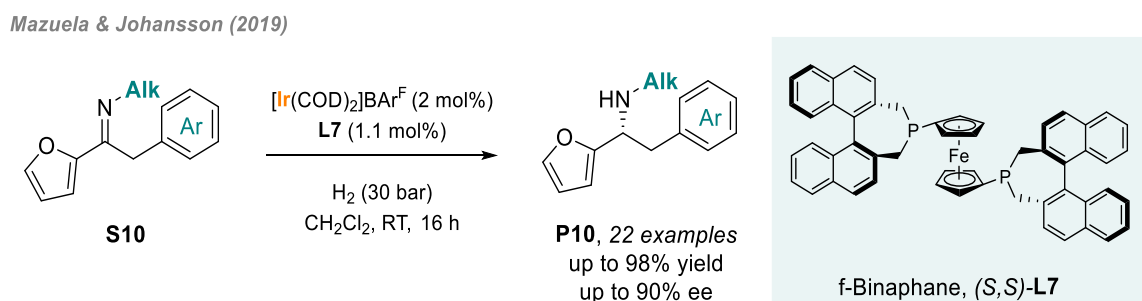
that forms upon reaction with the imine substrate.¹⁰⁴ Prompted by this finding, and inspired by the excellent activity that Ir-MaxPHOX catalysts showed in the AH of *N*-aryl imines,⁷⁹ Riera & Verdaguer's laboratory recently reported a highly efficient AH of *N*-alkyl imines **S9** using iridacycle **C13** prepared from MaxPHOX and the phenyl imine of benzophenone (Scheme 6).¹⁰⁵ This catalyst allowed the first direct hydrogenation of methyl and alkyl imines derived from acetophenones in very mild conditions and in high enantioselectivity (up to 94% ee).

Scheme 6. AH of *N*-methyl and *N*-alkyl imines using Ir(III)-H complex.



The AH of *N*-alkyl α -aryl furan-containing imines is a straightforward route to a wide range of unnatural *N*-alkyl aryl alanines. In this regard, Mazuela et al. reported that, using a Ir/(*S,S*)-f-Binaphane-**L7** as catalyst, up to 22 *N*-alkyl imines were efficiently hydrogenated, providing chiral amines **P9** (up to 90% ee), which can be further easily transformed into amino acids (Scheme 7).¹⁰⁶ The effect of substituents on the nitrogen was remarkable, as the use of large alkyl substituents led to a significant decrease of enantioselectivity.

Scheme 7. Iridium-catalyzed AH of *N*-alkyl α -aryl furan-containing imines.



Fan described the phosphine-free, chiral, cationic Ru/MsDPEN complex **C14a** which was a highly active catalyst for the AH of a range of acyclic and exocyclic *N*-alkyl ketimines (Scheme 8).¹⁰⁷ By

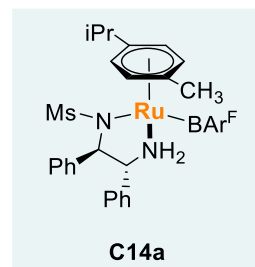
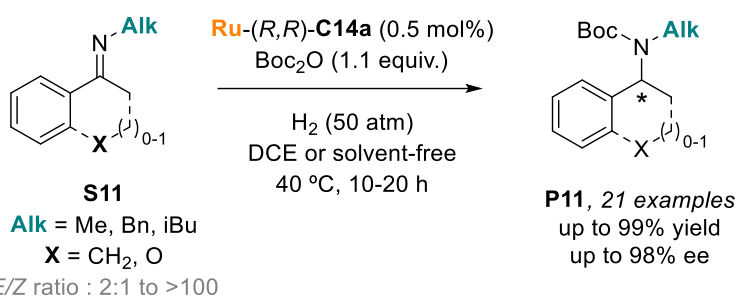
using BAr^{F} as counterion, a broad range of often problematic substrates **S11** were efficiently hydrogenated with low catalyst loadings, albeit with the use of Boc_2O to avoid catalyst inhibition. Moreover, this system also operates under solvent-free conditions, thus providing a highly sustainable platform to optically active amines **P10**. The same group later reported a similar ruthenium complex that, together with a phosphoric acid as additive via cooperative catalysis, was also an efficient catalyst for the hydrogenation of *N*-alkyl ketimines **S11** in the absence of Boc_2O .¹⁰⁸

Previously, in 2009, Ding and co-workers designed a new family of spiro phosphino-oxazoline chiral ligands that were successfully applied to the iridium-catalyzed AH of *N*-aryl imines.⁷⁵ Of note, the catalytic system is also applicable for *N*-alkyl imines (Scheme 8). Actually, both acyclic (**S12**) and exocyclic (**S13**) imines were efficiently hydrogenated with high levels of enantioselectivity using two distinct precatalysts (diastereoisomers **C4b** and **C4c**, respectively) and without the need of additives.

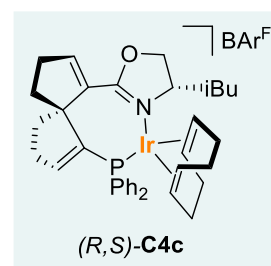
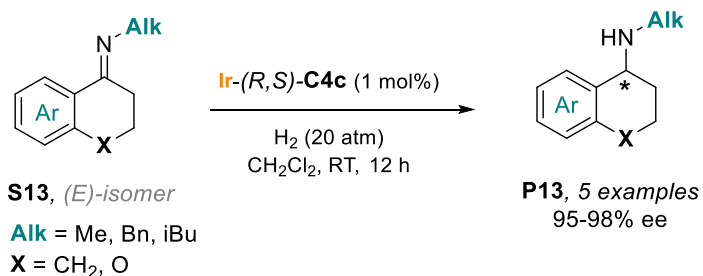
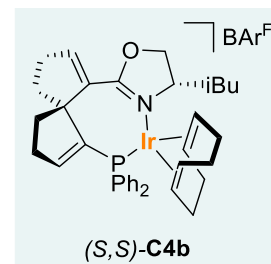
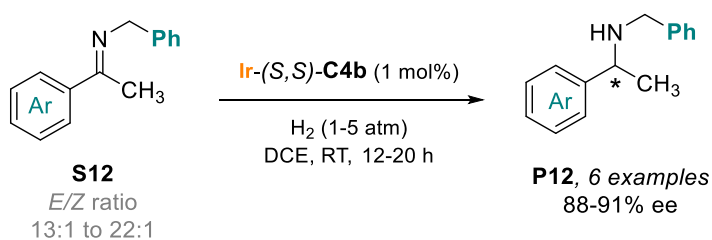
Phosphine ligands containing spiro scaffolds¹⁰⁹ such as f-spiroPhos **L8**, first reported by Hou and co-workers,¹¹⁰ emerged as a new and powerful class of chiral ligands for asymmetric catalysis. In 2016, this group reported a highly efficient AH of diarylmethanimines, which are challenging substrates due to the difficulties to distinguish between two sterically similar aryl groups (Scheme 9).¹¹¹ Hou detailed that, by using $\text{Ir}/\mathbf{L8}$ as catalyst, a variety of chiral diarylmethylamines **P14** were obtained with excellent enantioselectivities (up to 99% ee) and high TON. Previously, **L8** had also been successfully applied to the rhodium-catalyzed AH of α,β -unsaturated nitriles,¹¹² among other examples.

Scheme 8. Metal-catalyzed AH of *N*-alkyl imines.

Fan (2011)

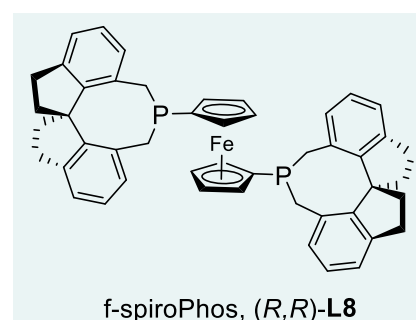
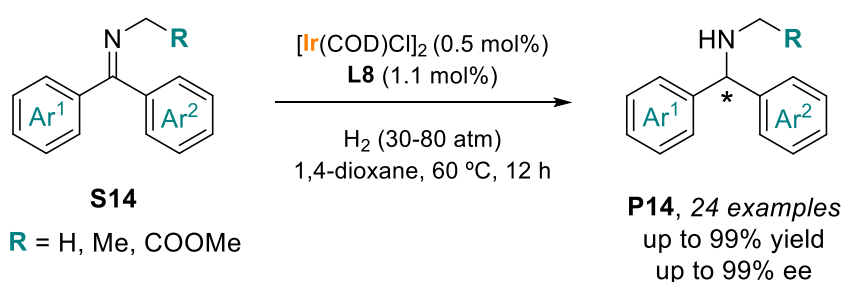


Ding (2009)



Scheme 9. Iridium-catalyzed AH of diaryl *N*-alkyl imines.

Hou, He (2016)

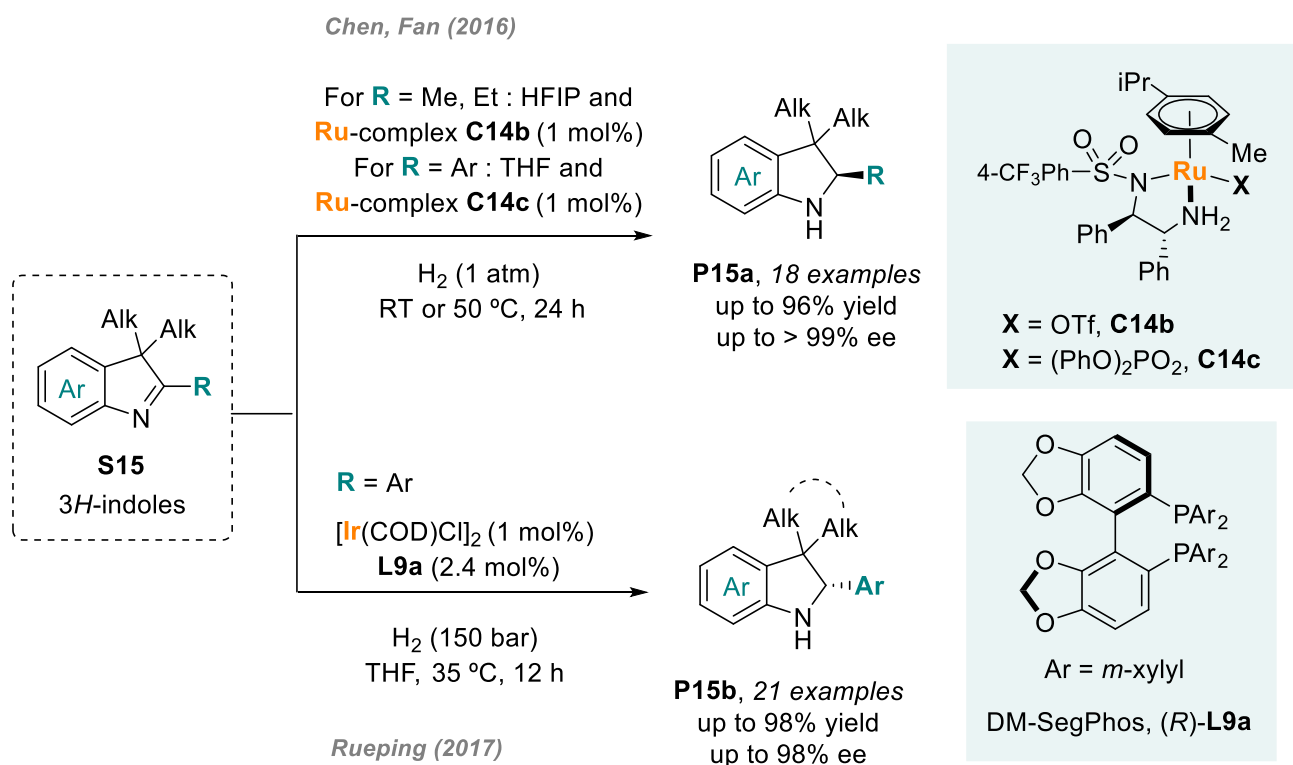


2.3. Cyclic *N*-aryl imines

The AH of *N*-heteroarenes is one of the most important ways to access chiral *N*-heterocyclic compounds (see Section 6). For instance, a direct strategy to obtain chiral indolines would be the direct AH of the corresponding indoles. However, indoles are a challenging class of substrates and

their AH was unsuccessful for many years.¹¹³ In this field, Fan and Rueping's groups simultaneously reported two independent catalytic systems that were highly efficient for the AH of 3*H*-indoles (Scheme 10). Fan and co-workers described a highly efficient enantioselective synthesis of 2-alkyl and 2-aryl indolines (**P15a**) via AH using Ru diamine catalysts **C14b** and **C14c**, respectively.¹¹⁴ The catalytic reaction proceeded smoothly at low H₂ pressure and with a high enantioselectivity (>99% ee in the best cases). Both the counteranion and the solvent played a crucial role in catalytic performance. On the other hand, Rueping reported a highly enantioselective iridium-catalyzed AH of 3*H*-indoles **S15** by using chiral diphosphine ligand **L9a**.¹¹⁵ A wide range of valuable disubstituted and spirocyclic 2-aryl indolines **P15b** were prepared in excellent results, albeit at elevated H₂ pressure. Previously, the same group provided an operationally simple route to other biologically relevant heterocyclic compounds, such as dihydrobenzodiazepines, by AH.¹¹⁶

Scheme 10. Metal-catalyzed AH of 3*H*-indoles.



The enantioselective synthesis of seven-membered *N*-containing heterocycles has attracted considerable attention during recent decades, as they are versatile pharmacophores in medicinal chemistry. In 2012, Fan and co-workers, reported that two Ru/diamine catalysts were highly efficient

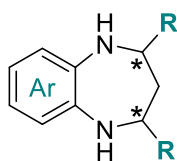
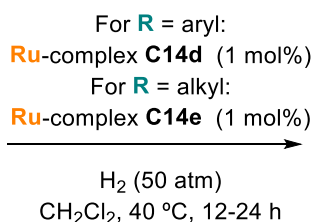
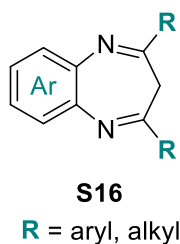
in the AH of benzodiazepines **S16** (Scheme 11).¹¹⁷ Interestingly, an achiral anion influenced both the nature and the coordination effect and reversed the sense of the asymmetric induction. After an exhaustive catalyst screening, **C14d** was chosen for benzodiazepine-bearing aryl substituents, while **C14e** was used for alkyl groups. In the first case, both enantiomers were obtained using the same ligand but in the presence of different achiral counteranions. Recently, they also reported that the iridium complex **C15** is a highly active catalyst for the AH of benzodiazepines **S17** bearing aryl substituents (Scheme 11).¹¹⁸ For both catalytic systems, the corresponding optically active dihydrobenzodiazepines were obtained with good to excellent diastereoselectivity and excellent enantioselectivity. The same group reported other catalysts, including dendritic phosphinoxazoline iridium complexes, which proved highly efficient for both the partial and total AH of benzodiazepines.^{119,120,121}

Zhou's group used Ir chiral complexes also for the AH of benzodiazepines. They reported that Ir/C₄-TunePhos-**L5a** is a highly active catalytic system for the AH of both pyrrole- and indole-fused benzodiazepines **S18**, reporting a moderate to excellent level of enantioselectivity (Scheme 11).¹²² Moreover, by switching to chiral ligand **L10**, outstanding results were also obtained for the AH of benzodiazepinones **S19**, thus offering a highly versatile catalytic approach for a range of chiral cyclic amines present in numerous important natural products and drugs. In addition, the same group later reported an iridium-catalyzed AH/oxidative fragmentation cascade for the synthesis of chiral dihydrobenzodiazepinones.

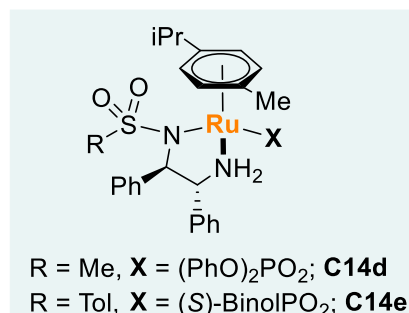
Scheme 11. Metal-catalyzed AH of benzodiazepines and benzodiazepinones.

Benzodiazepines

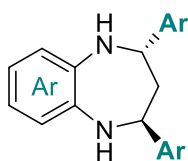
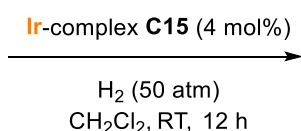
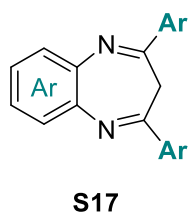
Fan (2012)



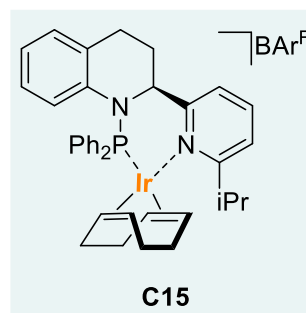
P16, 18 examples
5:1 to >20:1 dr
up to > 99% ee



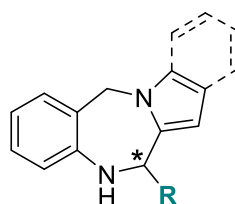
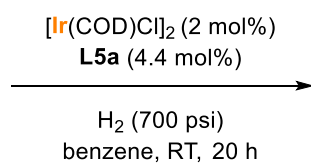
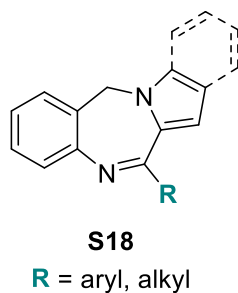
Fan (2019)



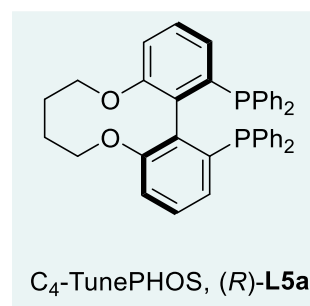
P17, 6 examples
4:1 to >20:1 dr
up to 99% ee



Zhou (2012)

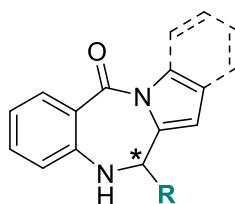
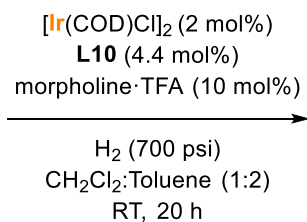
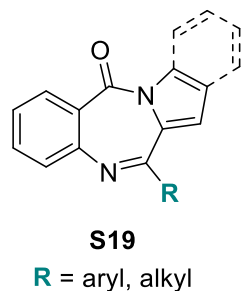


P18, 14 examples
up to 98% yield
77 - 96% ee

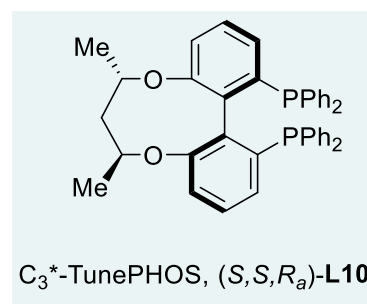


Benzodiazepinones

Zhou (2012)



P19, 20 examples
up to 99% yield
up to 96% ee

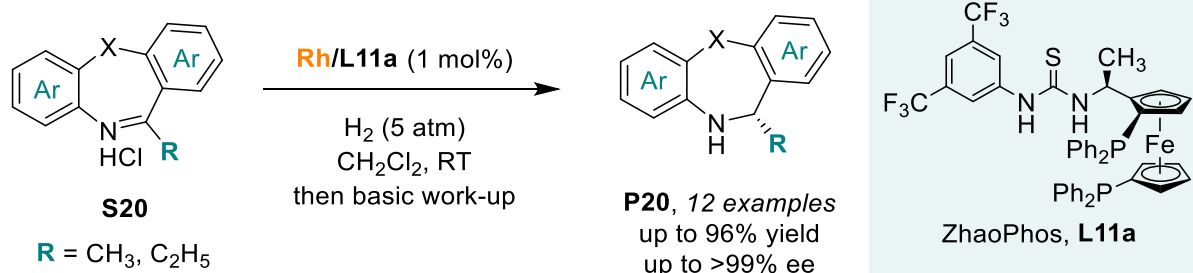


A number of successful examples of the AH of some benzo-fused seven-membered cyclic imines for the preparation of chiral benzazepines and benzodiazepines have recently been reported.^{123,124,125,126} X. Zhang and co-workers described a highly efficient AH of dibenzoazepine hydrochlorides **S20** catalyzed by Rh/ZhaoPhos-**L11a** (Scheme 12).¹²⁷ The corresponding chiral seven-member cyclic

amines **P20** were obtained in high yields and excellent enantioselectivities (>99% ee in the best cases). Interestingly, control experiments revealed that the anion-bonding interaction between the chloride ion of the substrate and the thiourea motif of **L11a** played a key role in enantioselectivity. The same reaction conditions were also useful for the AH of oxazepines.

Scheme 12. Access to chiral seven-membered cyclic amines via rhodium-catalyzed AH.

X. Zhang (2017)



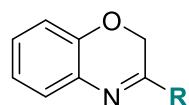
Another important family of C=N-containing heterocycles are benzoxazines and derivatives (**S21-22**). At the beginning of this decade, Beller,¹²⁸ Ohkuma¹²⁹ and Zhou's¹³⁰ groups reported advances in the transition-metal catalyzed AH of this class of compounds. Later, in 2014, Fan expanded the catalytic application of Ru/MsDPEN complexes. In fact, **C14f** and **C14g** were excellent catalysts for the highly enantioselective AH of 3-aryl and 3-styryl-substituted benzoxazines **S21**, respectively (up to 99% ee, Scheme 13).¹³¹ In contrast to previous work¹³⁰ where 3-styryl-substituted benzoxazines were completely hydrogenated, this catalytic system showed an exquisite 1,2-selectivity with an appropriate counterion (**C14g**). On the other hand, the main drawback of this method is that *ortho*-substituted aryl substituents in benzoxazines **S21** were not compatible. Unfortunately, when using these substrates, the reaction could not take place, probably due to undesired steric effects. In addition, the AH of 3-alkyl-substituted benzoxazines is underdeveloped.¹²⁹

Moving to iridium catalysis, Vidal-Ferran designed a new phosphine-phosphite ligand **L12** that, once coordinated to iridium, provided a highly active Ir(I) catalyst for the AH of 3-aryl substituted benzoxazines (**S21a**), benzoxazinones (**S22**) and benzothiazinones (**S23**) (up to 99% ee, Scheme 13).

132,133

Scheme 13. Metal-catalyzed AH of benzoxazines and benzoxazinones.

Fan (2014)

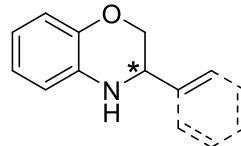


S21a-b

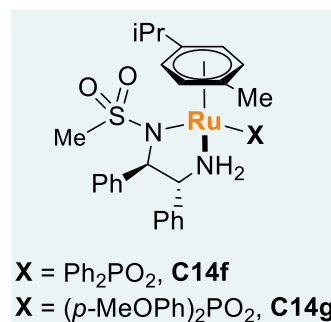
R = aryl, alkenyl

R = aryl,
Ru-complex **C14f** (0.5 mol%)
H₂ (50 atm)
toluene, 40 °C, 12 h

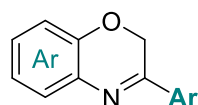
R = alkenyl,
Ru-complex **C14g** (0.5 mol%)
H₂ (80 atm)
toluene, RT, 12 h



P21a-b, 16 examples
up to 98% yield
up to 99% ee



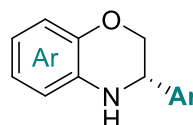
Vidal-Ferran (2013)



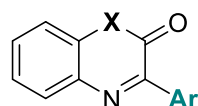
S21a

[{Ir(μ-Cl)(COD)}₂] (0.25 mol%)
L12 (0.55 mol%)

H₂ (40-80 bar)
THF, RT, 20 h



P21a, 8 examples
up to 95% ee

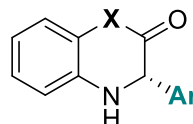


S22, X = O (benzoxazinones)

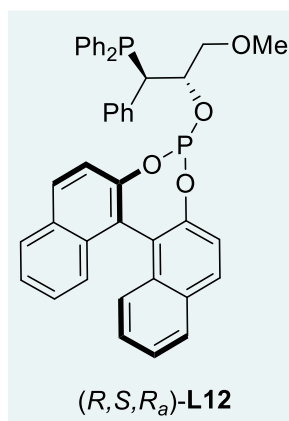
S23, X = S (benzothiazinones)

[{Ir(μ-Cl)(COD)}₂] (1 mol%)
L12 (2.2 mol%)

H₂ (80 bar)
THF, RT, 20 h



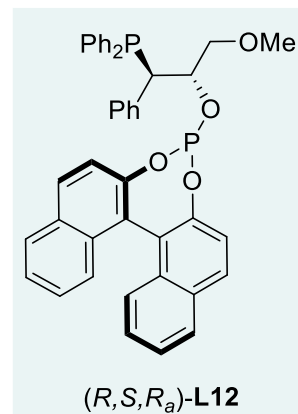
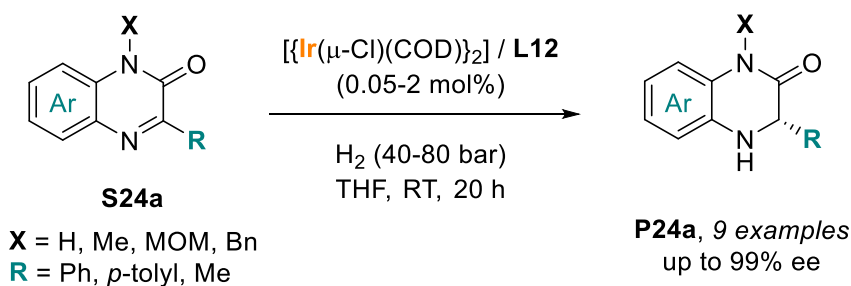
P22-23, 8 examples
up to 99% ee



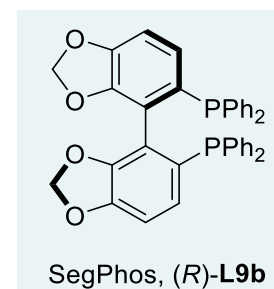
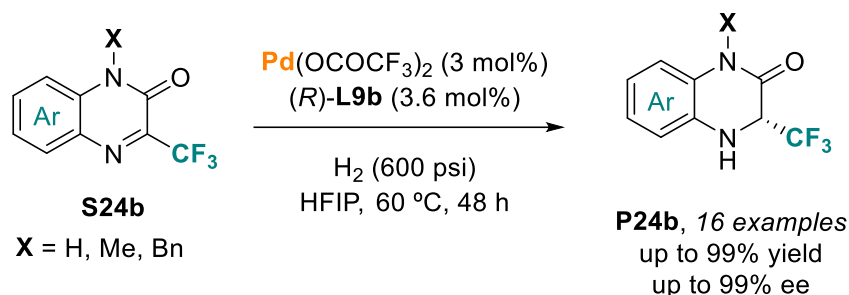
The iridium catalyst with **L12** was also the first-ever reported catalyst for the AH of quinoxalinones and *N*-substituted quinoxalinones **S24a** (Scheme 14). More recently, Peng and co-workers reported a highly enantioselective palladium-catalyzed AH of **S24b**.¹³⁴ Using (*R*)-SegPhos **L9b** as the chiral ligand, and performing the reaction in HFIP, a wide array of optically active 3-trifluoromethylated dihydroquinoxalinones **P24** were synthesized (>99% ee in the best cases, Scheme 14). However, the substituent on the aromatic ring impaired the reaction. In this regard, the introduction of a methyl group at the 5-position on the phenyl ring inhibited the reaction due to the steric effect.

Scheme 14. Metal-catalyzed AH of quinoxalinones.

Vidal-Ferran (2013)



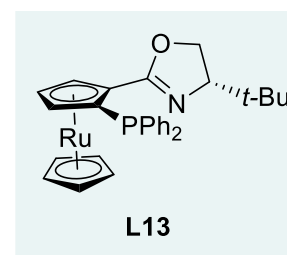
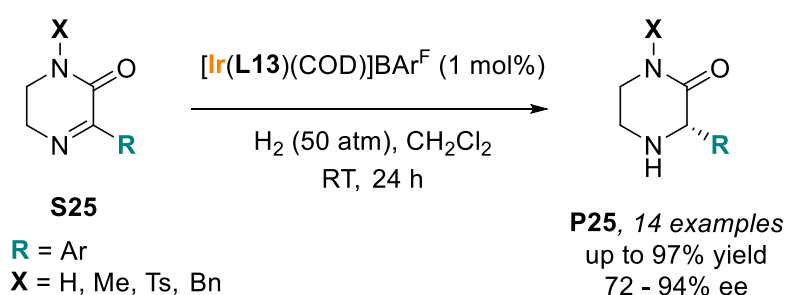
Peng (2019)



The AH of related non-aromatic systems such as 5,6-dihydropyrazin-2-ones **S25** was recently reported by Yang, W. Zhang and co-workers¹³⁵ using a phosphine-oxazoline RuPHOX ligand (**L13**). The corresponding chiral piperazin-2-ones **P25** were obtained in good yields and with moderate to good enantioselectivities (Scheme 15).

Scheme 15. Enantioselective synthesis of chiral piperazin-2-ones via AH.

Yang & W. Zhang (2017)

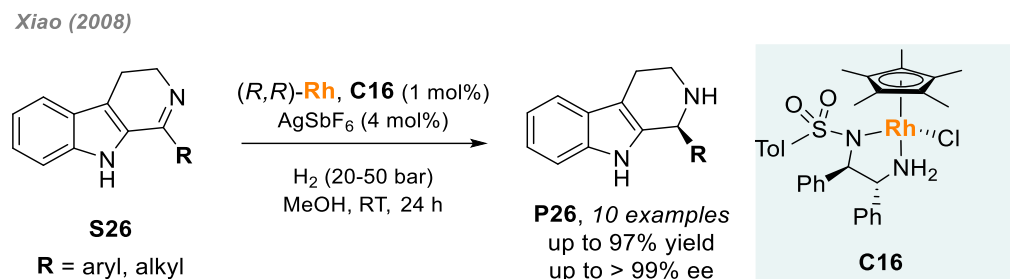


2.4. Cyclic *N*-alkyl imines

The great progress achieved in the AH of activated and *N*-aryl imines contrasts with the often problematic AH of *N*-alkyl imines. Buchwald's group reported the titanocene-catalyzed AH of cyclic *N*-alkyl imines back in 1994.¹³⁶ In 2008, Xiao and co-workers identified a Rh(III)-diamine complex (**C16**) as a highly active catalyst for the AH of cyclic *N*-alkyl imines **S26** to give bioactive tetrahydro-

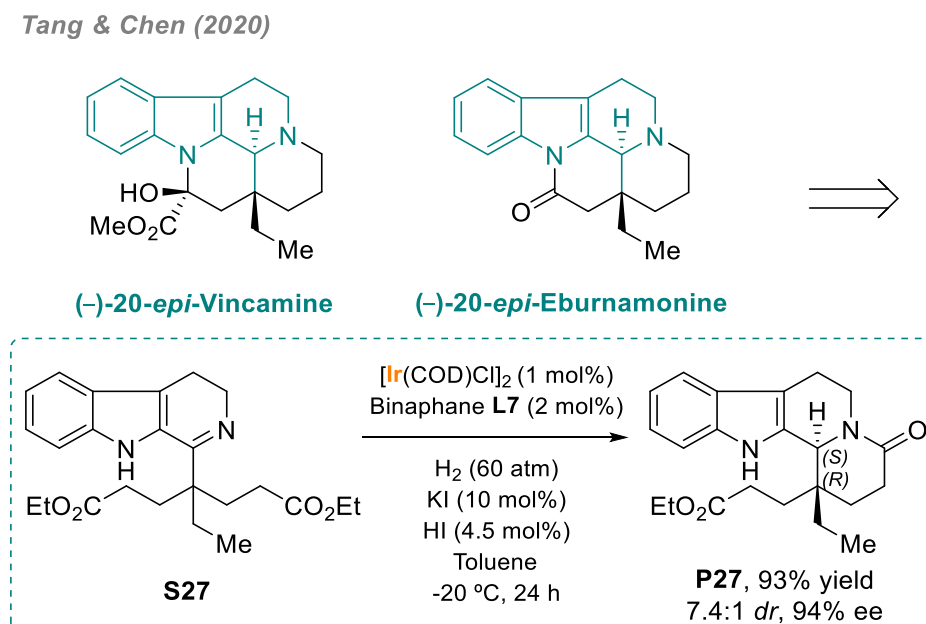
β -carbolines¹³⁷ **P26** in optically pure form (>99% ee in the best cases, Scheme 16).¹³⁸ Remarkably, both aryl and alkyl substituents were well-tolerated and mostly no differences in terms of enantioselectivities were observed.

Scheme 16. Rhodium-catalyzed AH of cyclic *N*-alkyl imines.



Dihydro- β -carbolines have been used to synthesize natural products. In 2020, Tang, Chen and co-workers reported a concise asymmetric total synthesis of two examples of the Eburnamine-Vincamine alkaloids (Scheme 17).¹³⁹ These syntheses featured a highly stereoselective iridium-catalyzed hydrogenation/lactamization cascade using f-binaphane **L7** as a chiral ligand, thus allowing a stereocontrolled assembly of the C20/C21 adjacent chiral centers in **P27**.

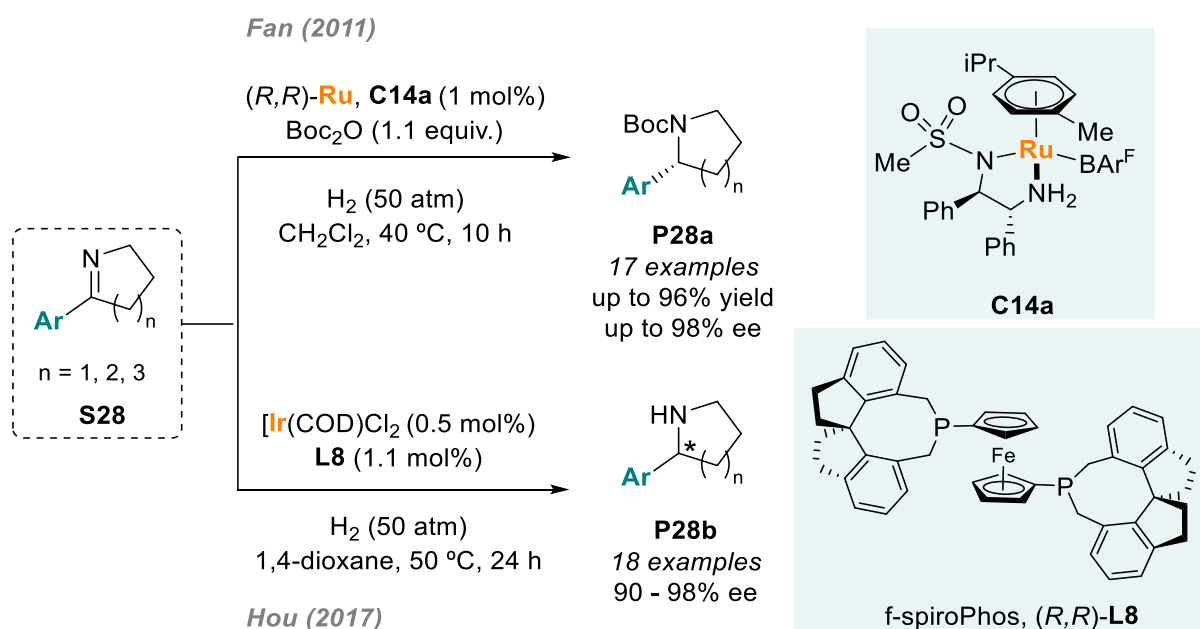
Scheme 17. Iridium-catalyzed enantioselective imine hydrogenation/lactamization cascade.



Chiral cationic Ru-MsDPEN complexes have also been employed in the AH of cyclic *N*-alkyl imines. In particular, Fan disclosed that **C14a** was an efficient catalyst for the AH of **S28** to provide chiral cyclic amines **P28a** in excellent yields and enantioselectivities (Scheme 18).¹⁴⁰ The same authors

used a similar catalytic system for the AH of dibenzo[*c,e*]azepine derivatives to afford seven-membered cyclic amines with moderate to excellent enantioselectivity.¹⁴¹ However, in both cases, the use of Boc₂O was required to prevent *in situ* catalyst deactivation. To circumvent this issue, Hou recently reported that the complex of iridium and (*R,R*)-*f*-spiroPhos **L8** as the catalyst allowed the smooth hydrogenation of a range of 2-aryl cyclic imines **S28** to **P28b** under mild conditions without any additive (Scheme 18).¹⁴² Hou also reported the synthesis of free cyclic amines via intramolecular reductive amination using a chiral iridium complex derived from **L8**.¹⁴³ Previously, in 2010, X. Zhang reported an iridium-based catalytic system for the direct AH of **S28** without *in situ* *N*-protection, albeit with lower enantioselectivities.¹⁴⁴

Scheme 18. Synthesis of chiral 2-aryl pyrrolidines and piperidines via AH.



Optically active 2-aryl pyrrolidines and piperidines are an important class of structural units in many natural products and pharmaceuticals (Figure 3).^{145, 146} In particular, chiral amines containing a pyridyl moiety, such as nicotine and its derivatives,¹⁴⁷ are very common in alkaloid natural products and pharmaceuticals. However, the transition metal-catalyzed AH of pyridyl-containing unsaturated compounds remained a great challenge due to the strong coordinating ability of the pyridine moiety, which led to catalyst deactivation. To overcome this limitation, in 2015, Xu, Zhu, Zhou and co-workers reported a highly efficient protocol to facilitate the exploration of nicotine-derived bioactive compounds.¹⁴⁸ By using iridium catalyst **C3b** with a chiral spiro phosphine-oxazoline ligand (SIPHOX), a wide variety of chiral amines **P29** were attained in excellent yields and enantioselectivities via direct catalytic AH of 2-pyridyl cyclic imines **S29** (Scheme 19).

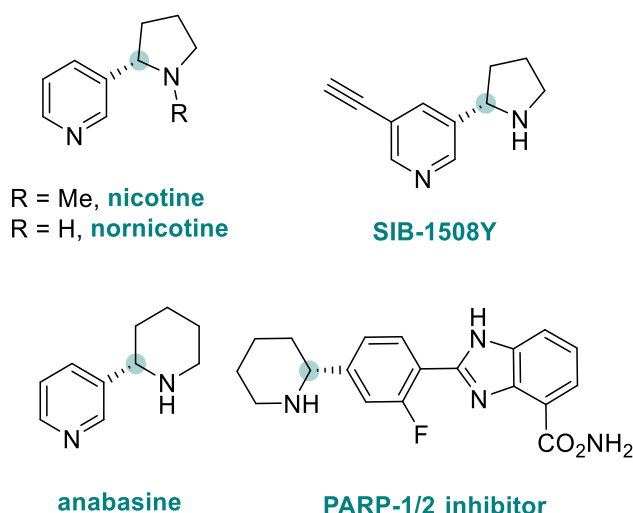
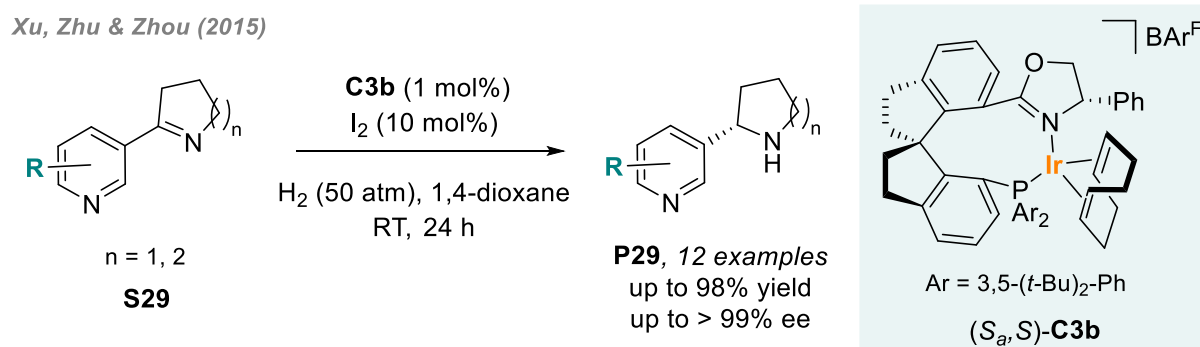


Figure 3. Structures of biologically active compounds and pharmaceutical drugs containing cyclic 2-aryl amine moiety.

Scheme 19. Iridium-catalyzed AH of 2-pyridyl cyclic imines.



Tetrahydroisoquinolines (THIQs) are an important class of alkaloids present in many pharmaceutical drugs (Figure 4).^{149,150} Therefore, the development of new enantioselective methods for their synthesis is highly desired. To this end, Zhou's group used ligand **L14** from the family of spiro-ligands SIPHOS for the enantioselective synthesis of THIQs. In 2012, they developed a highly efficient iridium-catalyzed AH of 3,4-dihydroisoquinolines (DHIQs) **S30** with good to excellent enantioselectivities (Scheme 20).¹⁵¹ The scope of the reaction was limited to alkyl substituents.^{138,152} X. Zhang's laboratory developed an alternative catalytic system using the iodine-bridged dimeric iridium complex with (*S,S*)-f-Binaphane **L7**.¹⁵³ This catalyst was applied to the AH of a wide range of 3,4-dihydroisoquinolines (**S30**) including, for the first time, those bearing aryl substituents. The corresponding THIQs **P30b** were afforded with excellent enantioselectivities and high TON (Scheme 20). Unfortunately, due to steric hindrance, the enantioselectivities varied dramatically with the substrates bearing a 1-*ortho*-substituted phenyl ring. To overcome this limitation, several catalytic

systems were reported as alternatives.^{154,155,156} Of note, Wang, Jiang, S. Zhang and co-workers reported a direct, simple and efficient protocol towards enantioenriched chiral 1-aryl substituted THIQs **P30c**.¹⁵⁷ For this purpose, they applied novel JosiPhos-type binaphane ligand (*t*-Bu-ax-JosiPhos) **L15** to the iridium-catalyzed AH of 1-aryl-substituted DHIQs **S30** (Scheme 20). Interestingly, the new ligand adopted the privileged properties of both JosiPhos and f-binaphane in terms of rigidity and electron-donating ability. Moreover, the use of 40% HBr (aqueous solution) as an additive dramatically improved the asymmetric induction of the catalyst. In 2020, the same catalytic system was applied to the AH of sterically hindered cyclic imines **P30d**, achieving with good to excellent enantioselectivities (74-99% ee) (Scheme 20).¹⁵⁸ This novel family of chiral ligands was also applied to the iridium-catalyzed AH of acyclic *N*-aryl imines.¹⁵⁹

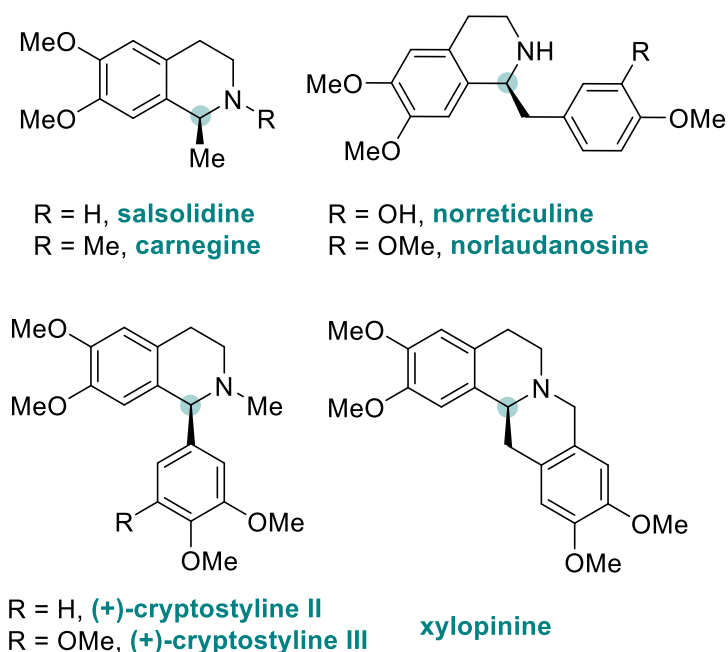
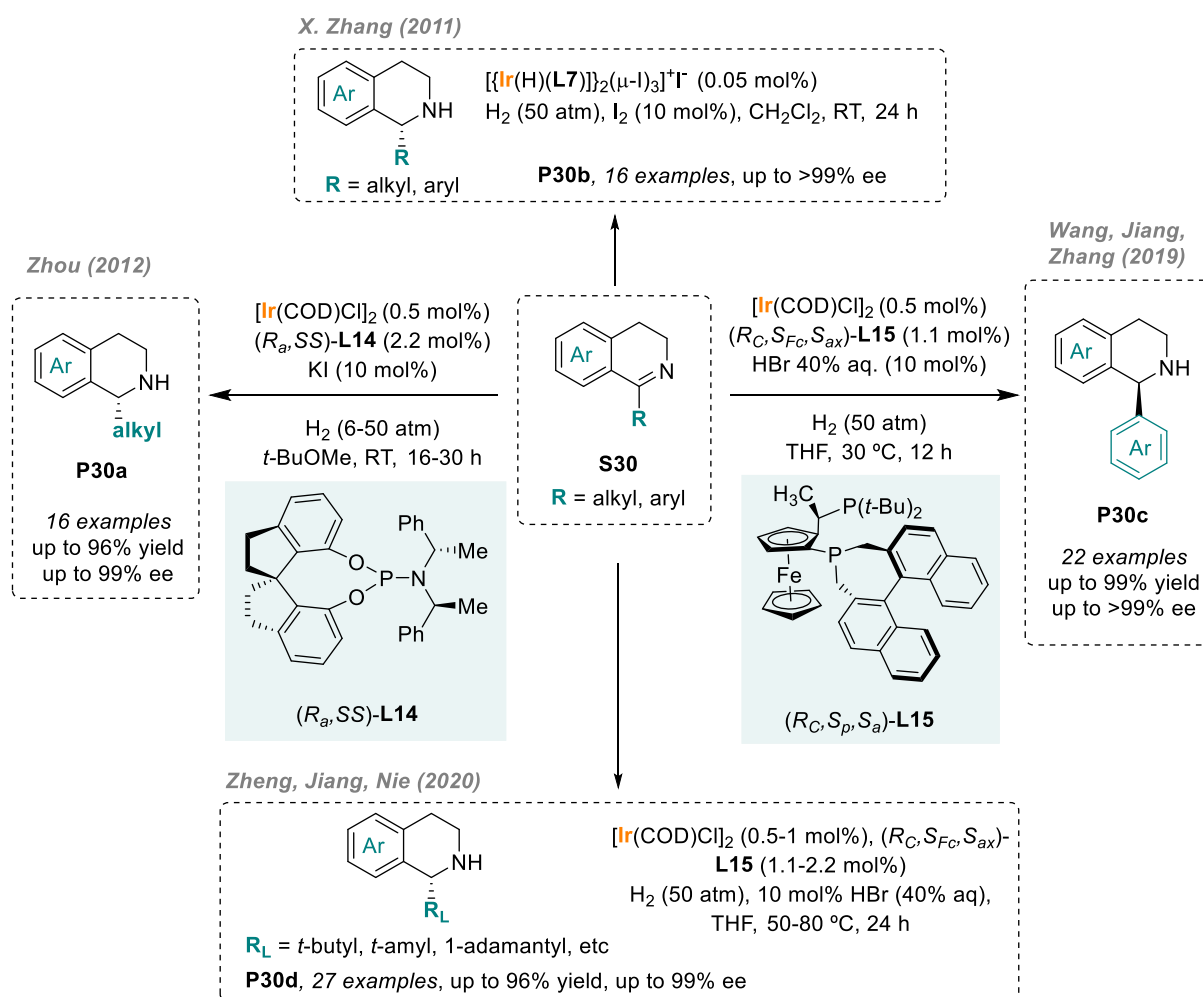


Figure 4. Pharmaceuticals and alkaloids containing chiral 1-substituted THIQs.

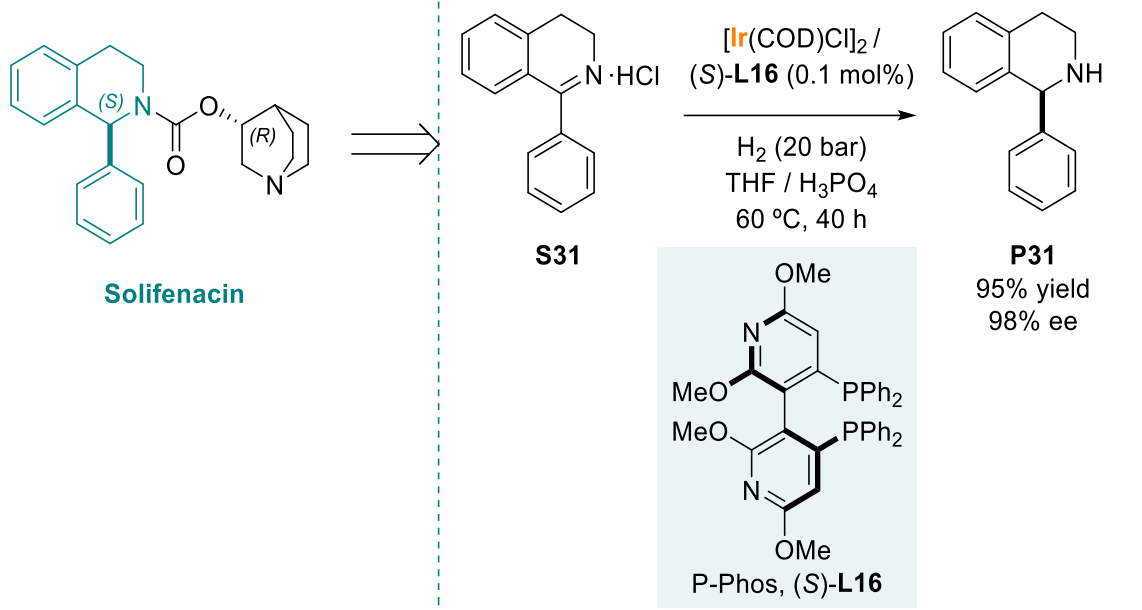
Scheme 20. Enantioselective synthesis of THIQs via iridium-catalyzed AH.



In 2013, Zanotti-Gerosa's group (Johnson-Matthey) described a novel approach to the synthesis of the urinary antispasmodic drug solifenacin (Scheme 21).¹⁶⁰ After an exhaustive optimization process, the group demonstrated the feasibility of the process for the AH of the hydrochloride salt **S31**. The use of this salt increased reactivity in the presence of the iridium catalyst with chiral ligand (*S*)-P-Phos (**L16**). The robustness of the protocol was proved by reproducing it on 200 g scale to give **P31** in 95% yield and 98% ee.

Scheme 21. Asymmetric synthesis of solifenacin via iridium-catalyzed AH.

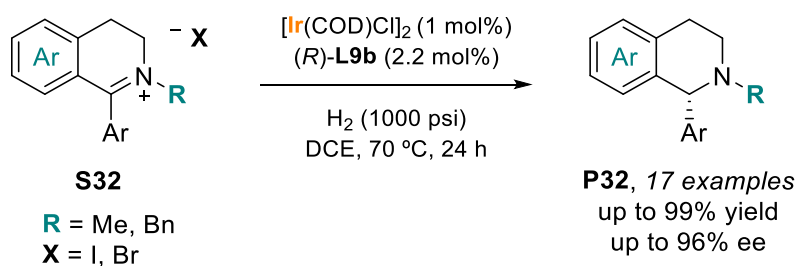
Johnson Matthey (2012)



The AH of iminium salts is the method of choice for obtaining tertiary amines in terms of simplicity and atom economy. In this regard, Zhou's group described an efficient and convenient method using Ir/(*R*)-SegPhos **L9b** for the AH of cyclic iminium salts bearing a dihydroisoquinoline moiety **S32** (Scheme 22).¹⁶¹ The corresponding chiral tertiary amines **P32** were afforded in good to excellent yields and with up to 96% ee.

Scheme 22. Iridium-catalyzed AH of cyclic iminium salts.

Zhou & Shi (2017)



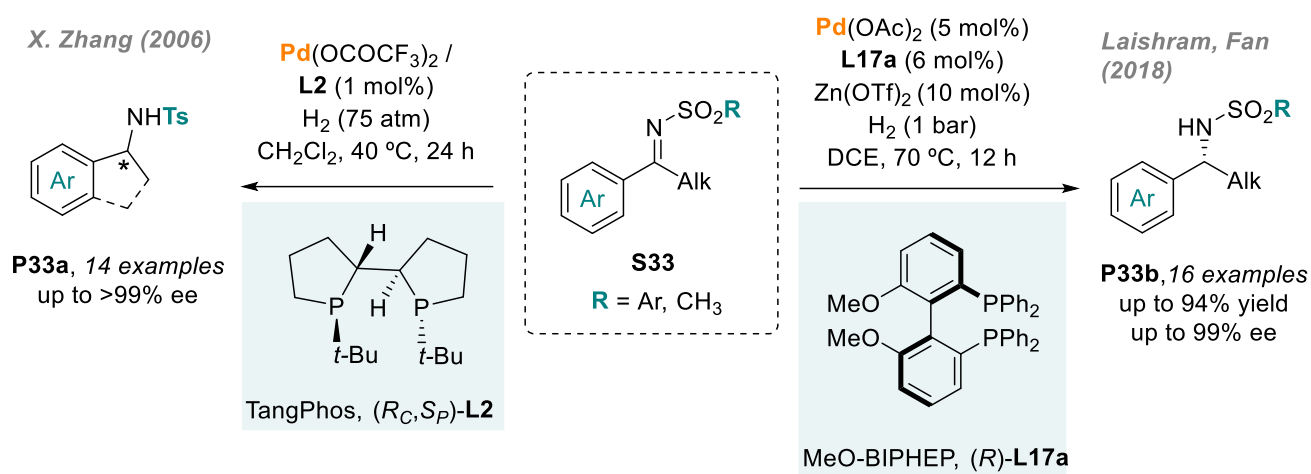
2.5. *N*-sulfonyl imines

2.5.1. Acyclic or exocyclic *N*-sulfonyl imines

At the beginning of this decade, the instability of some imines prepared from ketones and the inhibitory effect of the amine products on the metal catalysts partially prevented their widespread use in AH. To overcome these limitations, *N*-sulfonyl imines, which are more stable than aryl or alkyl imines, emerged as a useful alternative. Moreover, the strong electron-withdrawing character of the

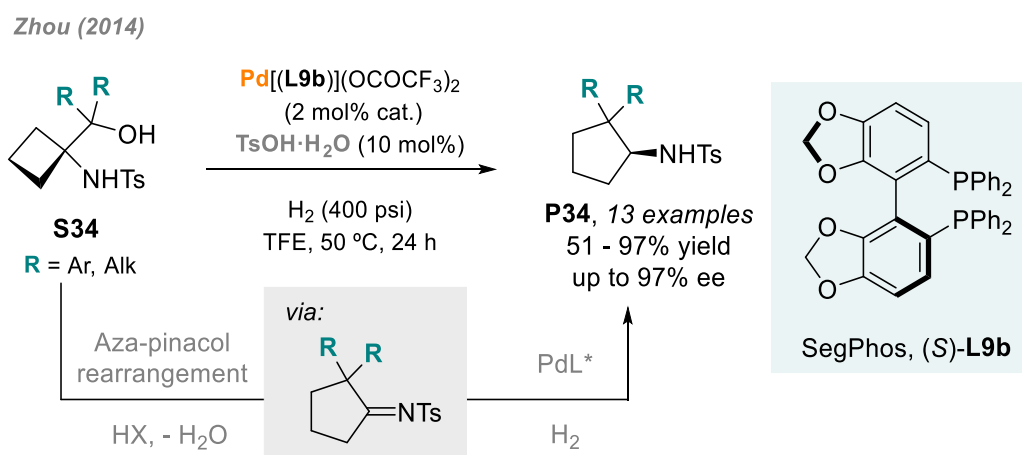
sulfonyl group reduces the probability of eventual catalyst deactivation. In 2006, X. Zhang and co-workers reported an important breakthrough in the field: palladium-catalyzed AH using TangPhos (**L2**).¹⁶² *N*-sulfonyl imines **S33** (including exocyclic imines) were efficiently hydrogenated with high levels of enantioselectivity (>99% ee in the best cases, Scheme 23). However, high H₂ pressure was required to hydrogenate the C=N bond with full conversion. Aiming to design a catalytic system able to work at low pressure, Laishram, Fan and co-workers recently reported a co-catalytic system based on Pd and using Zn(OTf)₂ as an essential additive.¹⁶³ The combination of this Lewis acid, Pd(OAc)₂ and the axially chiral diphosphine MeO-Biphep (**L17a**) furnished the corresponding *N*-sulfonyl amines **P9b**, which show high activity and optical purity working under 1 bar of H₂ (Scheme 23).

Scheme 23. Palladium-catalyzed AH of aryl alkyl *N*-sulfonyl imines.



Palladium-based catalysts had a strong impact on AH.¹⁶⁴ Furthermore, palladium-catalyzed processes involving tandem or cascade reactions are advantageous for the exploration of highly reactive intermediate species. In 2014, Zhou's group reported an efficient palladium-catalyzed AH *via* hydrogenation of an intermediate generated from the acid-catalyzed aza-Pinacol rearrangement of **S34** (Scheme 24).¹⁶⁵ Using the axially chiral ligand (*S*)-SegPhos **L9b**, up to 13 examples of chiral five-membered exocyclic amines **P34** were obtained in moderate to high yields and excellent enantioselectivities (up to 97% ee).

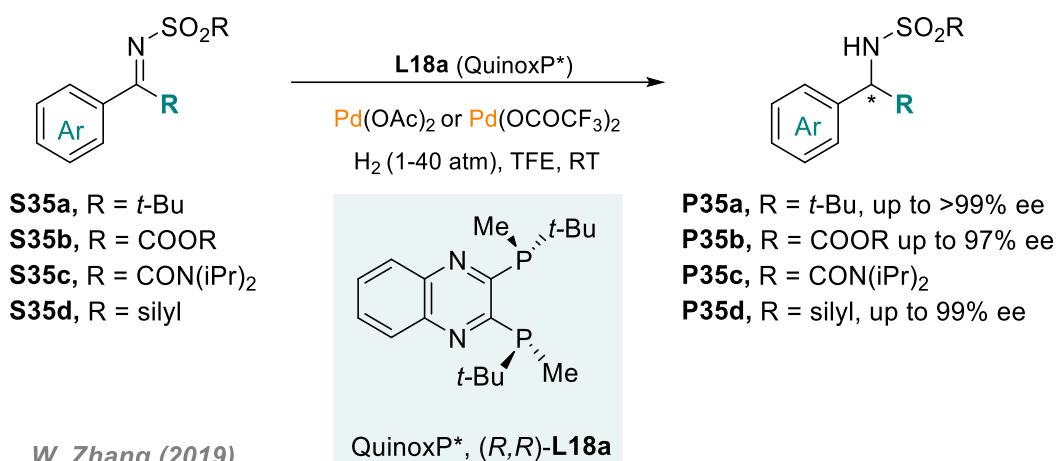
Scheme 24. Enantioselective palladium-catalyzed hydrogenation of cyclic *N*-sulfonyl amino alcohols.



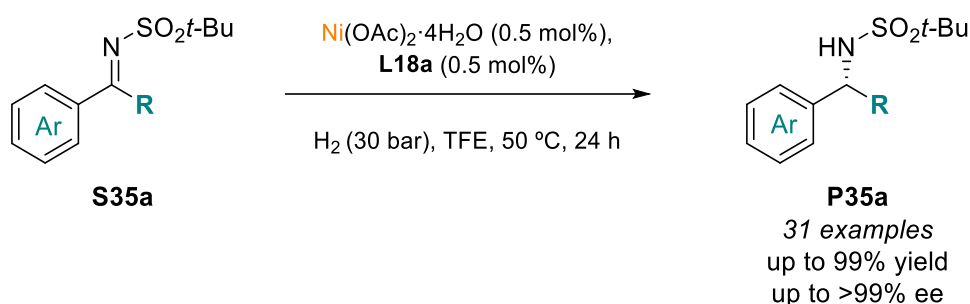
Imines bearing small substituents, such as methyl or ethyl groups connected to the carbon atom, have been widely used as substrates. In sharp contrast, the AH of sterically demanding imines (from ketones bearing bulky substituents) or other α -heteroatom-substituted imines are still rare. W. Zhang expanded the frontiers of the AH of *N*-sulfonyl imines by employing the P-stereogenic diphosphine Quinox-P* (**L18a**),¹⁶⁶ previously designed by Imamoto (Scheme 25). In 2018, the group reported the palladium-catalyzed AH of sterically hindered *N*-tosylimines under 1 bar of H_2 pressure with high catalytic activities (S/C up to 5000) and excellent enantioselectivities (up to 99% ee, Scheme 25, **P35a**).¹⁶⁷ This methodology was also applied to dialkyl *N*-tosyl imines and *N*-sulfonyl α -iminoesters¹⁶⁸ with the same level of enantiocontrol. W. Zhang and co-workers also described the AH of α -iminosilanes.¹⁶⁹ (up to 99% ee, Scheme 25), albeit using higher H_2 pressures. The low activity of earth-abundant transition metal catalysts has prevented their broad adoption in AH.¹⁷⁰ Undeterred by this challenge, W. Zhang's group recently demonstrated that the combination of nickel complexes with QuinoxP* **L18a** allows the AH of *N*-sulfonyl imines **S35** with high catalytic activity (S/C = 10500) and exquisite enantiocontrol (>99% ee in the best cases for **P35d**, Scheme 25).¹⁷¹

Scheme 25. Metal-catalyzed AH of different acyclic α -substituted *N*-sulfonyl imines.

W. Zhang (2018-19)

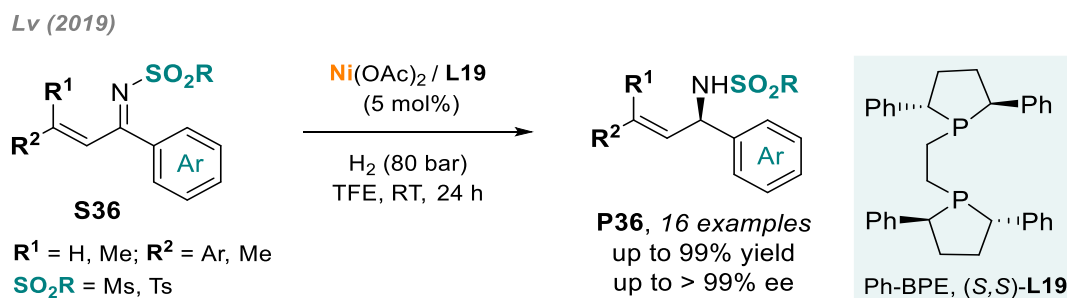


W. Zhang (2019)



A similar catalytic system using Ph-BPE (**L19**) as a ligand was recently reported by Lv and co-workers (Scheme 26).¹⁷² The nickel-catalyzed chemoselective AH of α,β -unsaturated ketoimines **S36** afforded chiral allylic amines **P36** in excellent yields and enantioselectivities. The last two examples confirm that nickel can be an effective transition-metal for AH—a concept also disclosed by Chirik¹⁷³ and Hamada.¹⁷⁴

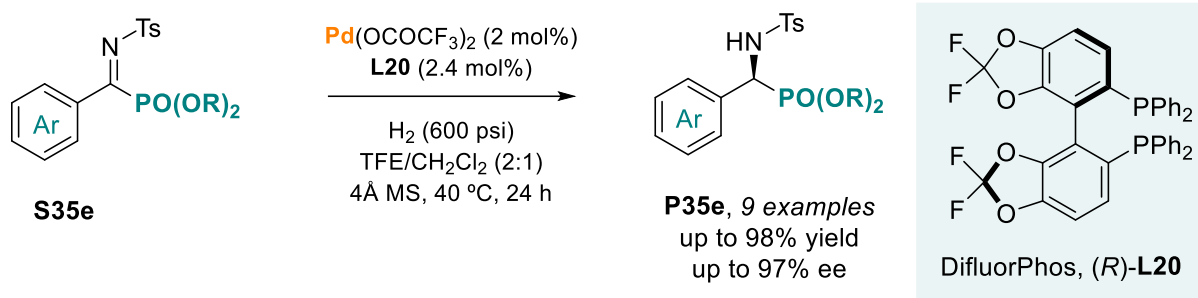
Scheme 26. Nickel-catalyzed chemoselective AH of α,β -unsaturated ketoimines.



Other α -heteroatom *N*-sulfonyl imines have been also explored. Zhou and co-workers disclosed the palladium-catalyzed AH of a series of linear and cyclic α -iminophosphonates.¹⁷⁵ The combination of Pd/(*R*)-DifluorPhos-**L20** as catalyst provided an efficient route to obtain optically active α -amino phosphonates **P11e** with up to 97% ee (Scheme 27).

Scheme 27. Metal-catalyzed AH of α -substituted *N*-sulfonyl imines.

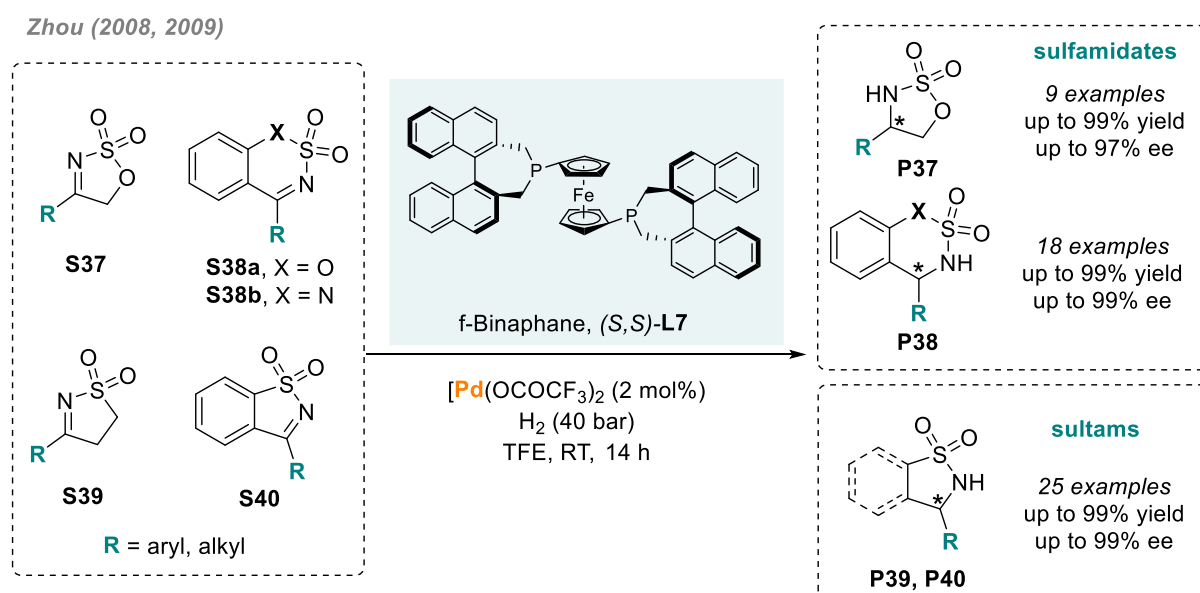
Zhou (2016)



2.5.2. Cyclic *N*-sulfonyl imines

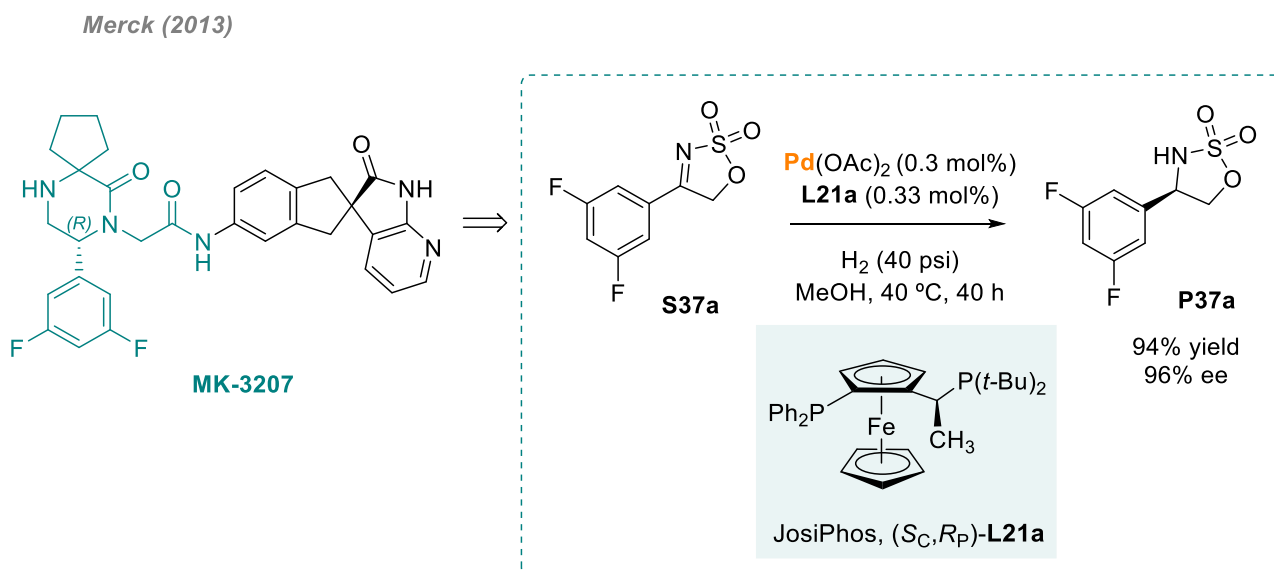
Sulfamidates (**P37** and **P38**) and sultams (**P39** and **P40**) are privileged building blocks in medicinal chemistry and useful chiral auxiliaries and ligands in asymmetric catalysis. They can be synthesized through the AH of the corresponding imines **S37-S40** (Scheme 28). Zhou and co-workers reported an efficient AH of cyclic *N*-sulfonyl imines using Pd(CF₃CO₂)₂/(*S,S*)-f-binaphane-**L7** as catalyst, to afford the corresponding chiral amines in high enantioselectivity (up to 99% ee).^{176,177} The catalytic system was valid for both sulfamidates and sultams, and it was further extended to the AH of benzofused imines **S38** and **S40**. Fan reported a previous version of this transformation using ruthenium catalysts, but with lower enantiomeric ratios.¹⁷⁸

Scheme 28. Palladium-catalyzed AH of sulfamidites and sultams using (*S,S*)-f-Binaphane as a chiral ligand.



An example of the importance of chiral sulfamidates as drug building blocks is the Merck's synthesis of MK-3207.¹⁷⁹ The chirality of the benzylic stereocenter was introduced *via* the palladium-catalyzed AH of the cyclic sulfamidate imine **S37a** using either **L7** or JosiPhos (**L21a**) as chiral ligands (Scheme 29).

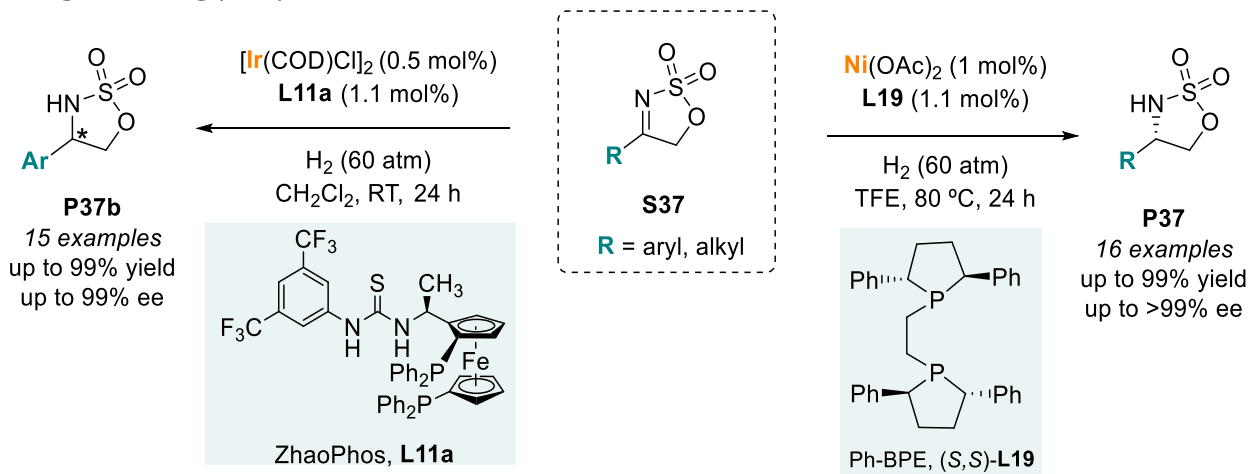
Scheme 29. Synthesis of MK-3207 via palladium-catalyzed AH of cyclic sulfamidate imine **S37a**.



More recently, in 2019, Dong, X. Zhang and co-workers performed the iridium-catalyzed AH of **S37** using ZhaoPhos (**L11a**) to attain sulfamidates **P37b** with excellent activities and enantioselectivities (Scheme 30).¹⁸⁰ ZhaoPhos is a family of chiral bifunctional diphosphine-thiourea ligands based on the synergistic cooperation between transition metal catalysis and organocatalysis.¹⁸¹ The substrate scope was limited to aryl or heteroaryl substituents. In contrast, the combination of Ni/**L19**, which gave excellent results for the AH of α,β -unsaturated ketoimines,¹⁷² is an alternative for the AH of **S37** bearing both aryl and alkyl substituents.¹⁸² Several chiral cyclic sulfamidates **P37** were prepared, even at gram scale, in high enantiomeric purity.

Scheme 30. Iridium- and nickel-catalyzed AH of sulfamidate imines **S37**.

Dong & X. Zhang (2019)

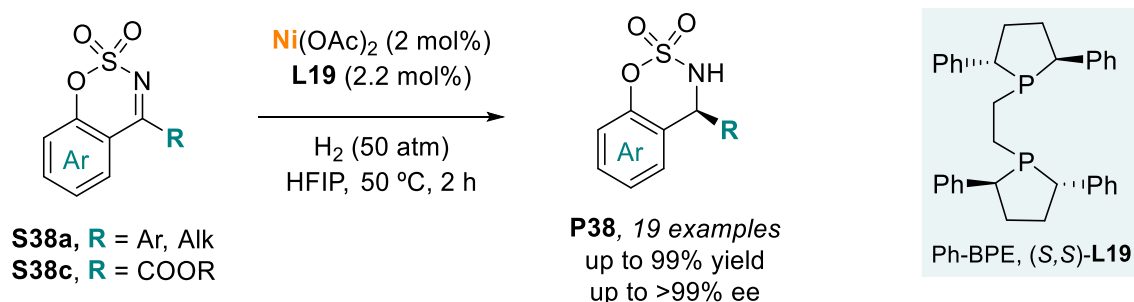


The same catalytic system was used in the highly efficient AH of cyclic *N*-sulfonyl ketimino esters **S38c**, among other **S38a**-type substrates, which had not been disclosed before (Scheme 31).¹⁸³ This transformation led to the facile synthesis of various chiral α -monosubstituted α -amino acid derivatives with excellent results.

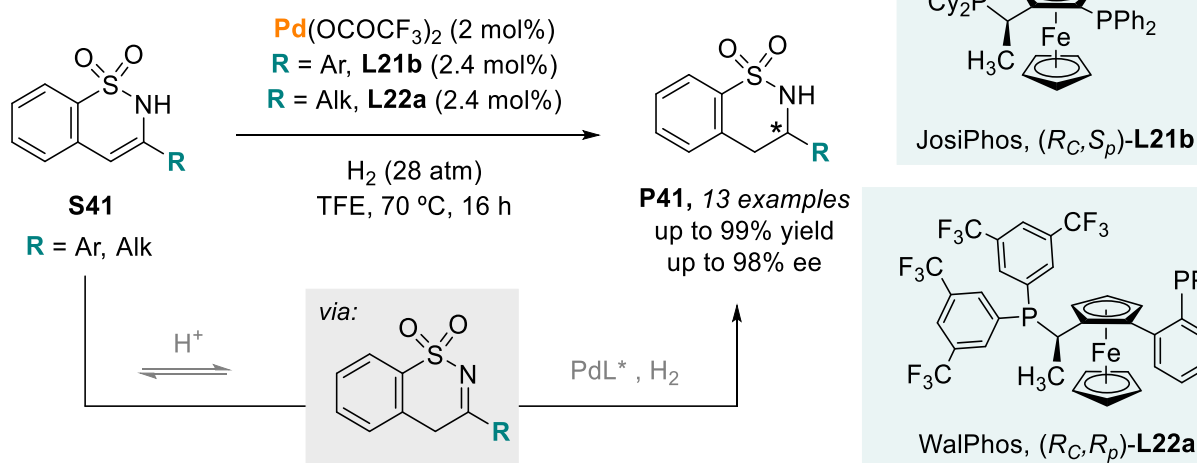
Another strategy for the synthesis of cyclic sultams is the AH of enesulfonamides **S41**. In 2011, Zhou's group reported an innovative transformation, using a catalytic system based on Pd/JosiPhos-type ligands.¹⁸⁴ JosiPhos-**L21b** and WalPhos-**L22a**, in particular, were excellent chiral ligands for enesulfonamides **S41** bearing aryl and alkyl substituents, respectively (Scheme 31). Interestingly, labeling experiments confirmed that the hydrogenation was conducted via *N*-sulfonylimine intermediates. Later, in 2015, the same group reported the enantioselective synthesis of sultams by a palladium-catalyzed formal hydrogenolysis of racemic *N*-sulfonyloxaziridines with up to 99% ee.¹⁸⁵

Scheme 31. AH of cyclic *N*-sulfonyl ketimino esters **S38** and enesulfonamides **S41**.

Dong & X. Zhang (2020)



Zhou (2011)



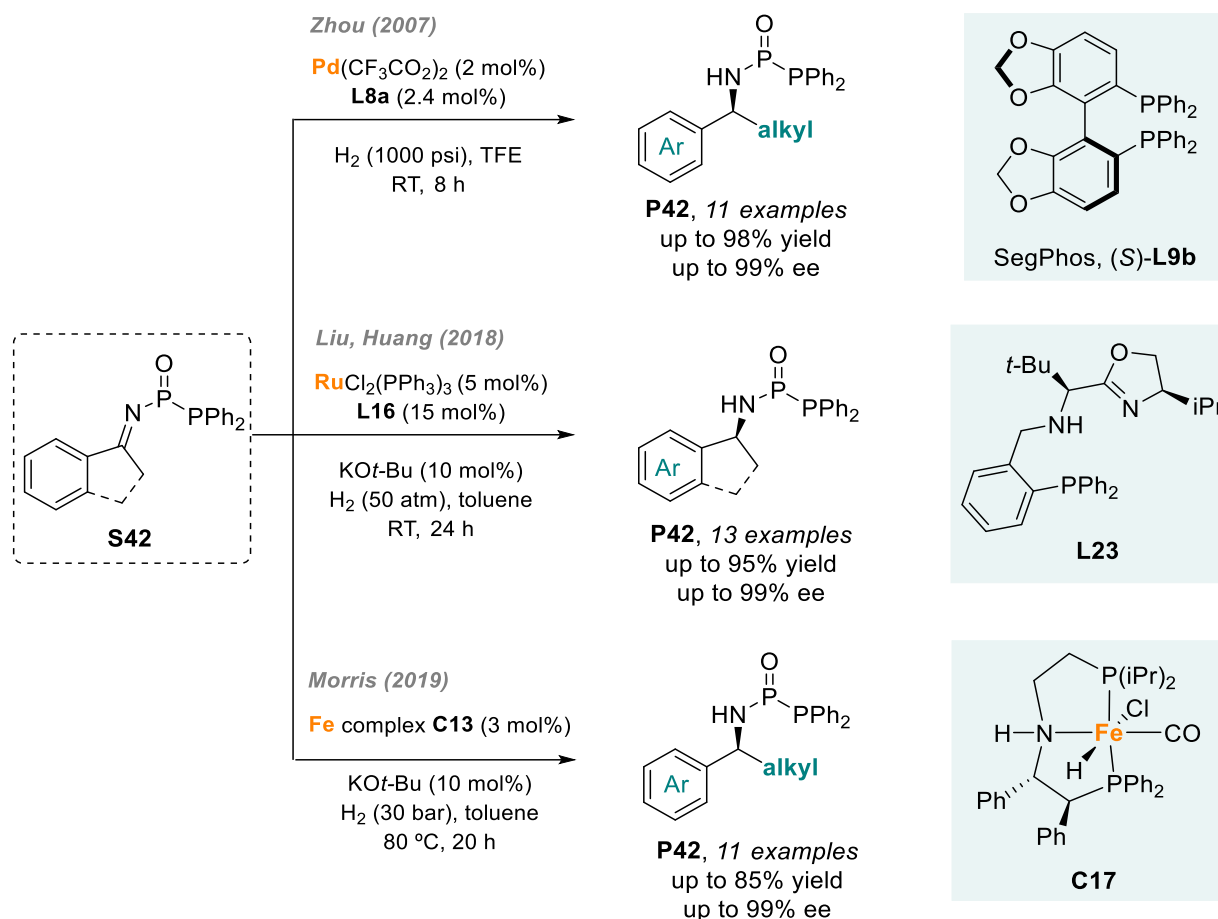
2.6. *N*-Phosphinyl imines

As described before, palladium complexes bearing diphosphine ligands are highly effective catalysts for the AH of *N*-sulfonyl imines in fluorinated solvents such as TFE (trifluoroethanol) or HFIP (hexafluoroisopropanol). Similarly, other activated imines, such as *N*-phosphinyl imines, are also suitable substrates for this catalytic system. After the pioneering work of Blaser,¹⁸⁶ Zhou described the highly efficient palladium-catalyzed AH of activated imines, including *N*-diphenylphosphinyl ketimines.¹⁸⁷ These ketimines (**S42**) were hydrogenated using **L9b** as a chiral ligand (Scheme 32) attaining excellent levels of enantioselectivity (up to 99% ee). The reaction showed a dramatic solvent effect, as only TFE led to high conversion towards **P42**.

Alternatively, Liu, Huang and co-workers designed a phosphino-oxazoline ligand (**L23**) for the ruthenium-catalyzed AH of **S42** (Scheme 32).¹⁸⁸ The catalytic system exhibited good activity and excellent enantioselectivity, providing an efficient and mild approach to optically active secondary amines **P42**. Using iron as earth-abundant transition metal, Morris and co-workers reported that an unsymmetrical iron P-NH-P' complex (**C17**, Scheme 32) gave excellent enantioselectivity for the AH

of prochiral *N*-phosphinyl imines **S42**, but with poorer activity than the previous catalytic systems.¹⁸⁹ The same group had previously foreseen that these iron-hydride catalytic species were highly active towards the AH of polar bonds.¹⁹⁰ Nonetheless, the system failed when using dialkyl-substituted or exocyclic *N*-phosphinyl imines, which remains as a current challenge in the field.

Scheme 32. Metal-catalyzed AH of *N*-phosphinyl imines.

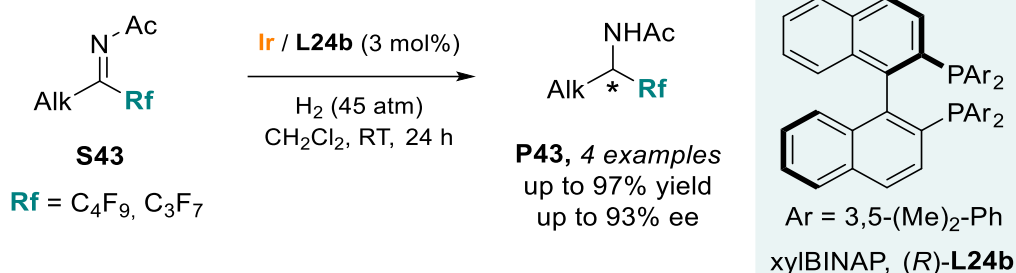


2.7. *N*-acyl imines

In 2010, Mikami and co-workers reported a catalytic AH of acyclic ketimines **S43** bearing a perfluoroalkyl chain as substituent (Scheme 33).¹⁹¹ The introduction of fluorine into molecules enhances their lipophilicity, metabolic stability and bioavailability, thus remarkably affecting the physicochemical properties.^{192,193,194} Using a Ir/**L24b** (a 3,5-dimethylphenyl analog of BINAP, **L24a**) as catalytic system, four examples of chiral perfluoroalkyl amines were obtained with excellent enantioselectivity. Moreover, this work established an important precedent in the field, as the direct AH of *N*-acyl imines is still rare.¹⁹⁵

Scheme 33. Iridium-catalyzed AH of *N*-acyl imines.

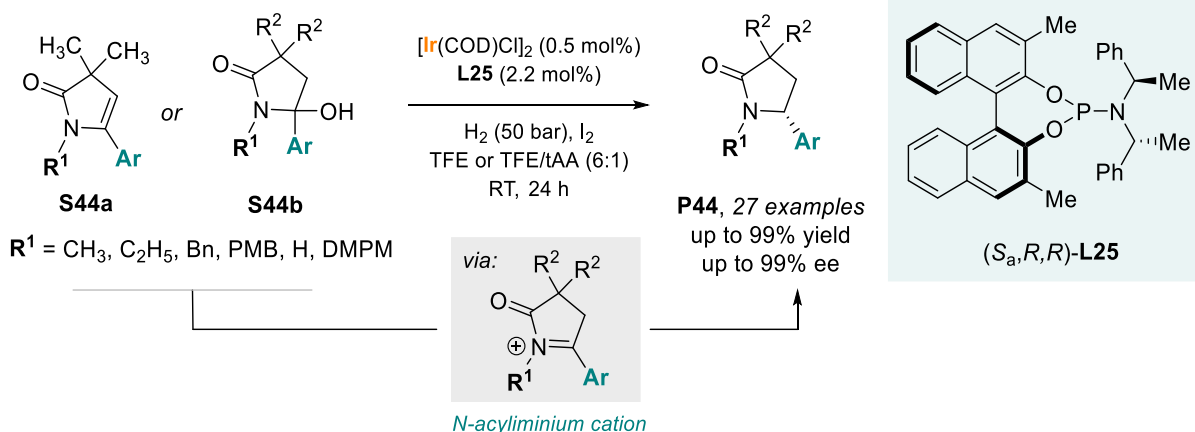
Mikami (2010)



A novel strategy for the AH of β,γ -unsaturated γ -lactams **S44a** was described by Liu, W. Zhang and co-workers using iridium catalysis in combination with a phosphoramidite ligand **L25** and I_2 (Scheme 34).¹⁹⁶ The chiral γ -lactams **P44** were obtained in excellent yields and enantioselectivities. Mechanistic studies detailed that the reduced products were obtained via the hydrogenation of *N*-acyliminium cations, rather than directly by the hydrogenation of **S44a**. Therefore, using the same catalytic system, these chiral γ -lactams were also prepared via *in situ* elimination/AH of racemic γ -hydroxy- γ -lactams **S44b**.¹⁹⁷

Scheme 34. Synthesis of chiral γ -lactams via iridium-catalyzed AH of *N*-acyliminium cations.

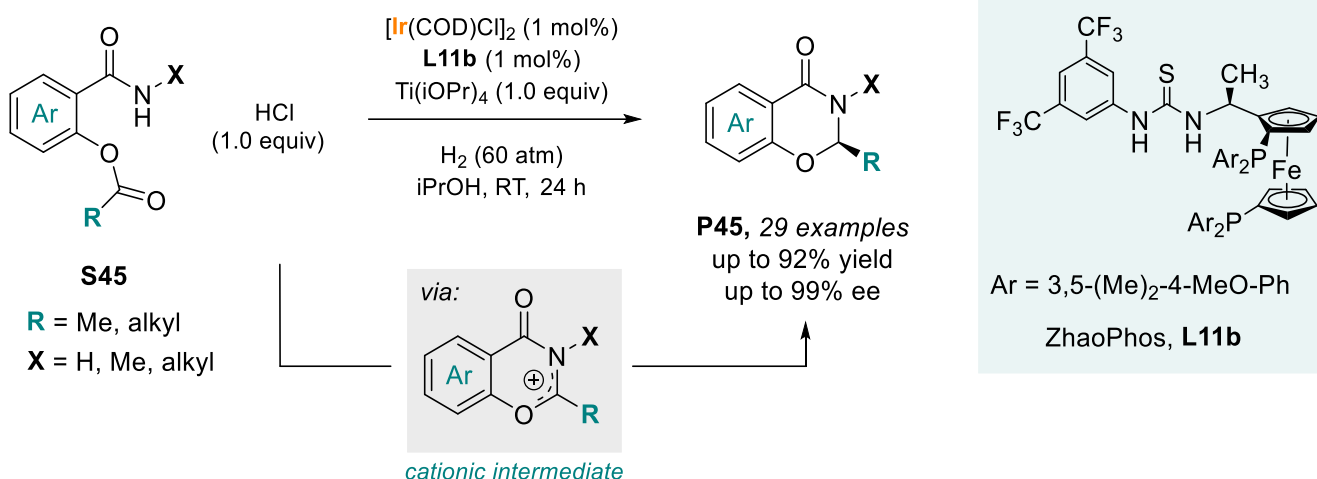
Liu, W. Zhang (2017)



A related iridium-catalyzed AH of cationic species was recently reported by Wen, X. Zhang and co-workers for the enantioselective synthesis of chiral *N,O*-acetals (Scheme 35).¹⁹⁸ Under acidic conditions, *O*-acetylsalicylamides **S45** underwent cyclization to generate cationic intermediates, which were subsequently hydrogenated by an iridium complex bearing a ZhaoPhos- ligand (**L11b**), thus obtaining **P45** in excellent yields and enantioselectivities.

Scheme 35. Synthesis of chiral *N,O*-acetals via iridium-catalyzed AH of cationic intermediates.

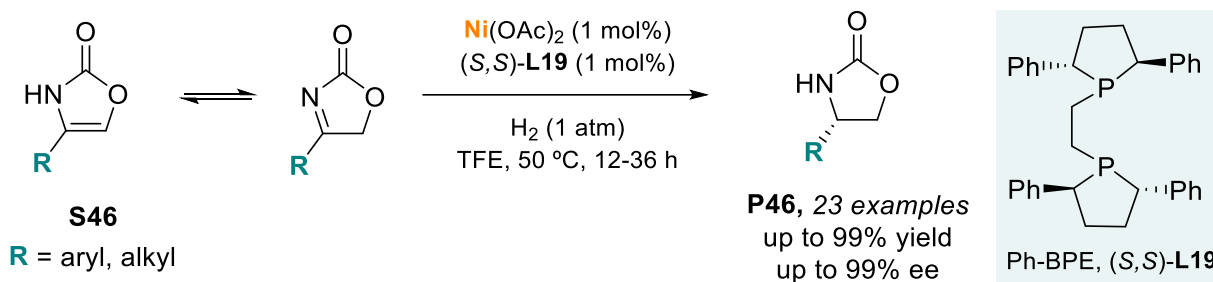
Wen & X. Zhang (2020)



The same group recently reported the nickel-catalyzed AH of 2-oxazolones (**S46**) to afford 2-oxazolidinones in excellent yields and enantioselectivities (Scheme 36).¹⁹⁹ Interestingly, deuterium labeling experiments and DFT calculations were conducted to reveal the catalytic mechanism for this hydrogenation, which indicated an equilibrium between the enamine and its imine isomer, the latter being the substrate of choice for the asymmetric 1,2-addition of Ni(II)-H.

Scheme 36. Nickel-catalyzed AH of 2-oxazolones.

Wang, Dong, X. Zhang (2020)

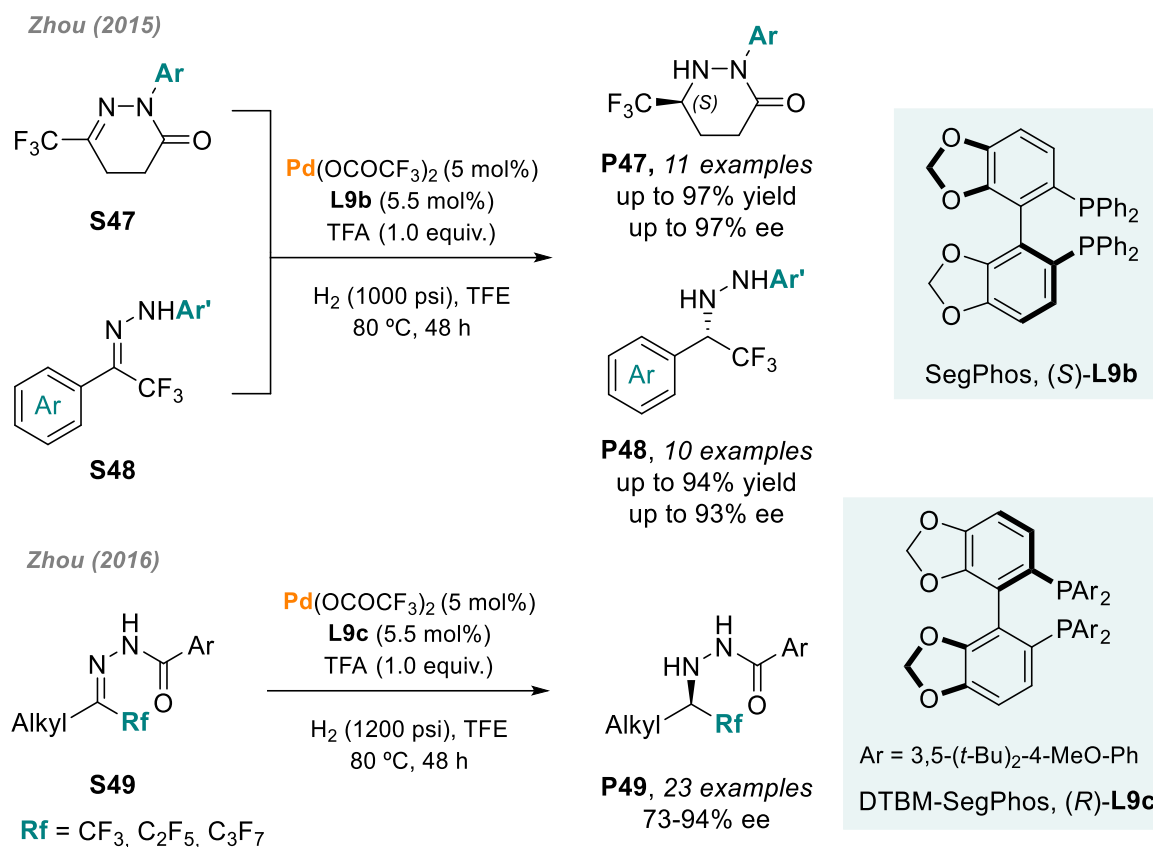


2.8. N-heteroatom-substituted imines

The hydrogenation of other *N*-heteroatom imines, such as hydrazones or oximes, remains a challenge. In 2015, Zhou and co-workers reported the enantioselective synthesis of cyclic and linear chiral trifluoromethyl-substituted hydrazines via the palladium-catalyzed AH of *N*-acyl and *N*-aryl hydrazones (**S47** and **S48**, Scheme 37).²⁰⁰ Currently, many compounds bearing a hydrazine moiety, such as atazanavir or azacastanospermine, show pharmacological activity. By using Pd/(*S*)-SegPhos **L9b** as a catalyst and TFA as an essential additive, chiral hydrazines **P47** and **P48** were obtained in

excellent yields and up to 97% ee. A year later, the same authors reported that, by using the bulkier DTBM-SegPhos (**L9c**) as a chiral ligand, the palladium-catalyzed AH of α -alkyl hydrazones **S49** proceeded smoothly, thus affording the corresponding fluorinated hydrazines **P49** in excellent enantioselectivities (Scheme 37).²⁰¹

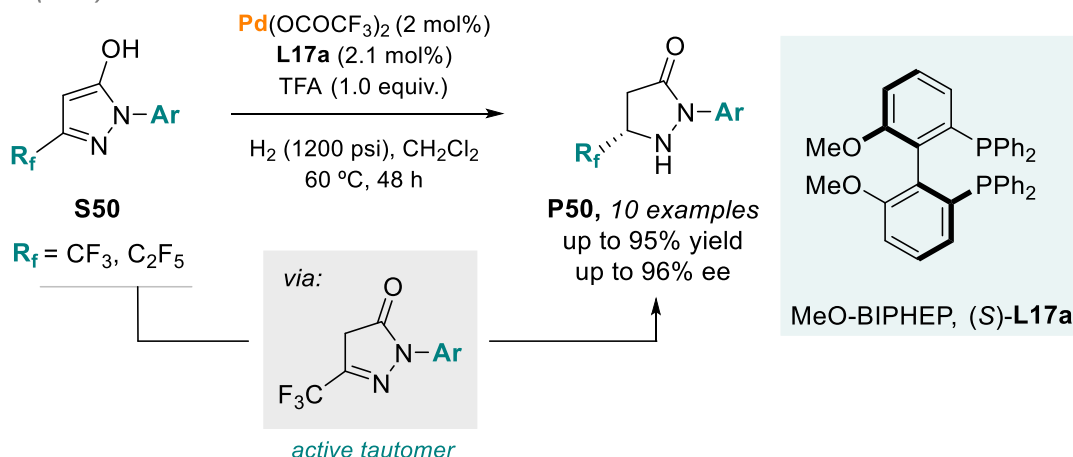
Scheme 37. Palladium-catalyzed AH of α -aryl hydrazones and α -alkyl hydrazones.



In addition, the same laboratory reported the palladium-catalyzed AH of fluorinated aromatic pyrazol-5-ols **S50** (Scheme 38).²⁰² The key for the success of this transformation is the Brønsted acid-promoted tautomerization, thus capturing the active form, followed by enantioselective hydrogenation. A wide variety of substituted pyrazolidinones **P50** were synthesized with up to 95-96% ee using (*S*)-MeO-Biphep (**L17a**) as the chiral ligand.

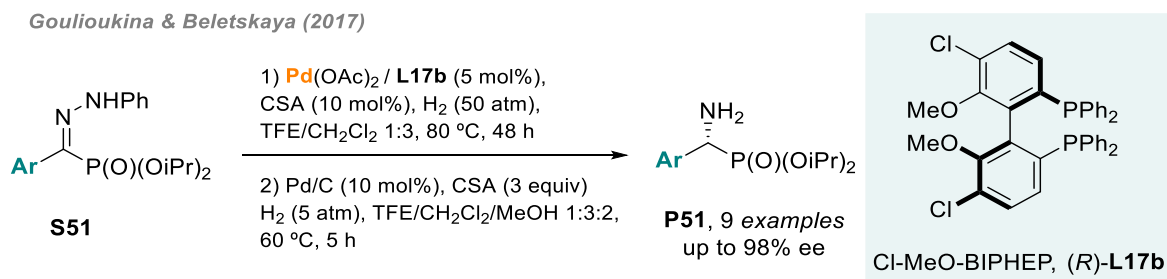
Scheme 38. Palladium-catalyzed AH of fluorinated aromatic pyrazol-5-ols via *CH*-tautomer.

Zhou (2015)



In 2017, Beletskaya and co-workers reported a convenient one-pot procedure for the asymmetric synthesis of α -amino phosphonates, which are also important structural motifs in many bioactive compounds. Using a combination of Pd and biaryl chiral ligand **L17b**, the AH of α -hydrazono phosphonates **S51** proceeded with high enantiocontrol.²⁰³ Subsequent cleavage of the N-N bond after the addition of Pd/C and methanol into the crude reaction mixture afforded the optically active **P51** (Scheme 39).

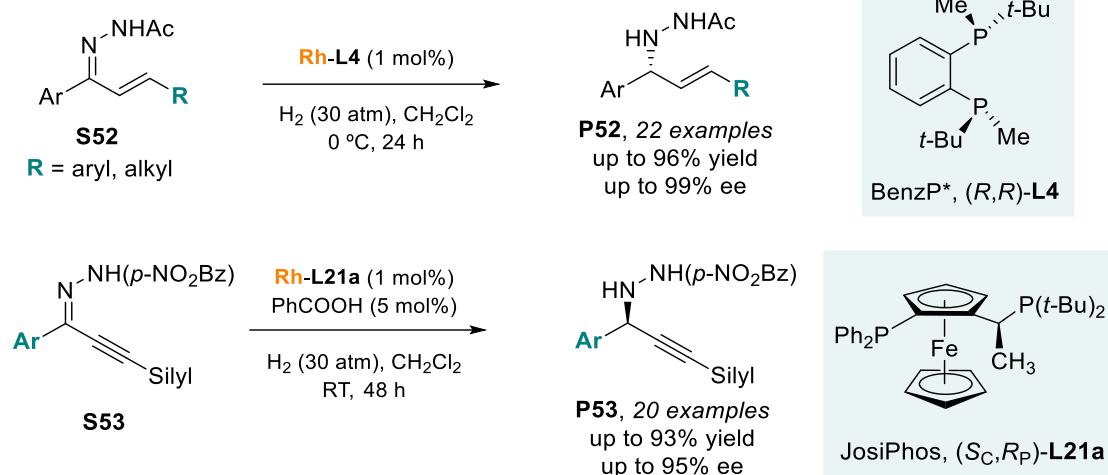
Scheme 39. Sequential palladium-catalyzed AH/Hydrogenolysis of α -hydrazono phosphonates.



The laboratory of W. Zhang developed highly efficient protocols for the chemo- and enantio-selective hydrogenation of allyl and alkynyl hydrazones using rhodium catalysts.^{204,205} When using BenzP* (**L4**) or JosiPhos (**L21a**) as a chiral ligand, allyl or alkynyl-aryl hydrazones (**S52-S53**) were hydrogenated with excellent results (Scheme 40).

Scheme 40. Rhodium-catalyzed AH of allyl and alkynyl-aryl hydrazones.

W. Zhang (2017, 2018)



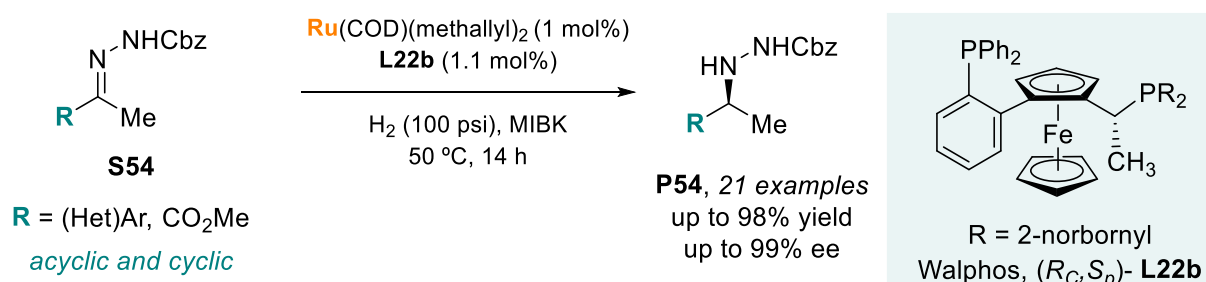
Alternatively, Schuster and co-workers described the ruthenium-catalyzed AH of hydrazones **S54** using a Walphos-type ligand **L22b** (Scheme 41).²⁰⁶ The method allowed access to versatile chiral hydrazine building blocks **P54** containing aryl, heteroaryl, cycloalkyl and ester substituents, and the protocol was demonstrated on >150 g scale. The use of Rh complexes in the AH of hydrazones had been described early this decade, but with lower ee values.^{207, 208}

The use of chiral Ir complexes in the AH of hydrazones was described by X. Zhang, using f-binaphane as the chiral ligand. Of note, they reported a direct catalytic asymmetric reductive amination of simple aromatic ketones with phenylhydrazide, thus offering an attractive route for the synthesis of chiral hydrazine-derived compounds.²⁰⁹

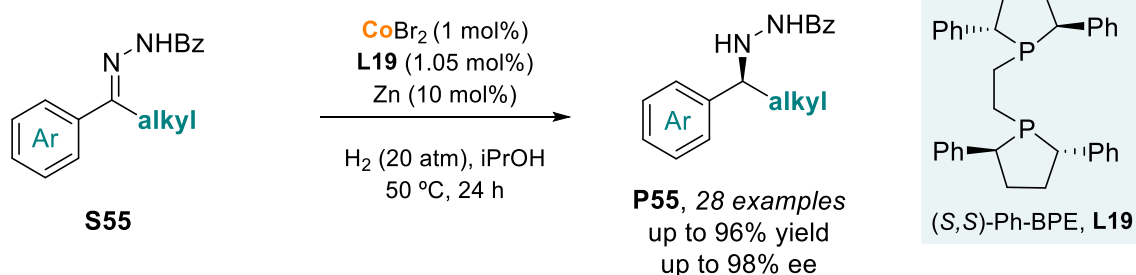
In 2019, W. Zhang and co-workers disclosed, for the first time, the efficient cobalt-catalyzed AH of C=N bonds.²¹⁰ Although the use of cobalt as an earth-abundant transition metal in AHs was first pioneered by Chirik, the scope was limited to C=C or C=O bonds.^{211,212,213} Interestingly, the success of this reaction relies on the presence of an NHBz group (**S55**, Scheme 41), which acts as a directing group. The reactivity and enantioselectivity were further enhanced by assisted coordination to the cobalt atom and π - π non-bonding interactions between the phenyl groups on the substrates and the chiral diphosphine (*S,S*)-Ph-BPE **L19**. The resulting chiral nitrogen-containing compounds **P55** were attained in high yields and excellent enantioselectivities (95-98% ee).

Scheme 41. AH of hydrazones with ruthenium and cobalt complexes.

Schuster (2020)



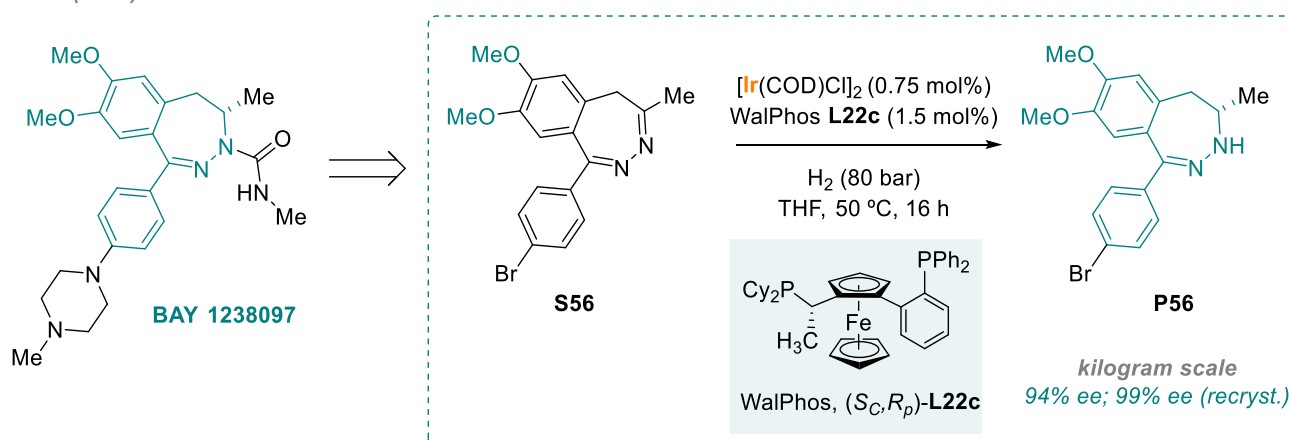
W. Zhang (2019)



In 2020, Lefort and co-workers reported the first example of a regio- and enantio-selective AH of a C=N-N=C motif.²¹⁴ As shown in Scheme 42, the prochiral benzodiazepine **S56** was efficiently hydrogenated using a chiral catalyst based on Ir and a Walphos bisphosphine **L22c**. No undesired hydrogenation of the C=N double bond in the 1,2-position was observed. Using the optimal conditions, the AH was performed on a kilogram scale leading to the production of **P56**, an intermediate of BET inhibitor BAY 1238097, in enantiopure form after crystallization.

Scheme 42. Enantioselective synthesis of an intermediate of BET inhibitor BAY 1238097 via iridium-catalyzed AH.

Lefort (2020)



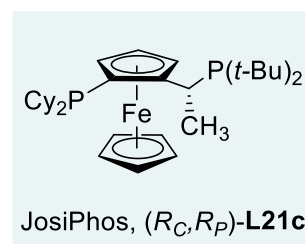
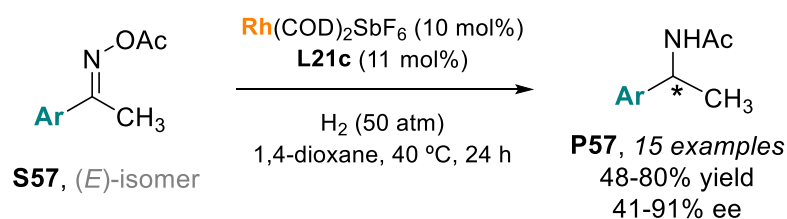
The AH of oximes and their derivatives remained a long-standing problem. To solve this gap in the field, X. Zhang and co-workers proposed the rhodium-catalyzed AH of oxime acetates **S57** (Scheme

43).²¹⁵ Unexpectedly, the reaction led to the formation of chiral acetamide **P57** as the major product, thus affording a new strategy for the straightforward synthesis of chiral acetamides from oxime derivatives. After an exhaustive screening of phosphine ligands, JosiPhos **L21c** was found to give the highest enantioselectivities (up to 91% ee). The main limitations of this approach are the moderate activity, as well as the low enantiocontrol, in the case of *ortho*-substituted groups on the aromatic ring.

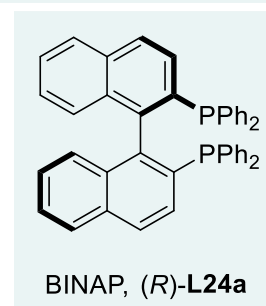
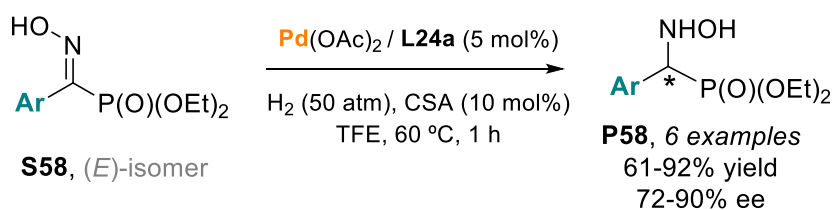
The AH of *N*-hydroxy- α -imino phosphonates **S58** was studied by Goulioukina *et al.*²¹⁶ using the Pd/BINAP (**L24a**) as catalytic system, first reported by Amii and co-workers.²¹⁷ The synthesis of chiral **P58** was achieved in up to 90% ee (Scheme 43). The catalytic reaction was performed using a Brønsted acid (CSA) as an activator and TFE as solvent. However, the scope was limited to phenyl and *para*-substituted aromatic rings.

Scheme 43. Metal-catalyzed AH of ketoximes.

X. Zhang (2013)



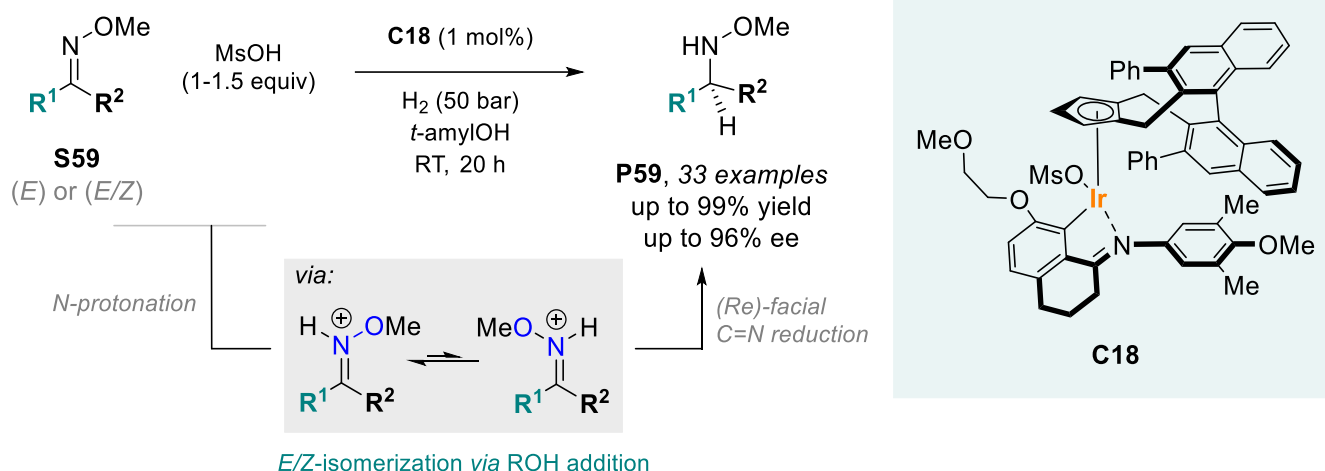
Beletskaya, Goulioukina (2012)



The selective reduction of an oxime to the corresponding chiral hydroxylamine derivative remains a challenge in this field because of undesired cleavage of the weak N-O bond. In this regard, in 2020, Cramer and co-workers described a methodology to overcome this limitation. He reported a robust cyclometalated Ir(III) complex **C18** bearing a chiral cyclopentadienyl ligand as an efficient catalyst for this transformation (Scheme 44).²¹⁸ Using MsOH as activator, this acid-assisted AH of oximes **S59** avoids overreduction of the N-O bond via C=N reduction after substrate protonation, thus accessing valuable chiral *N*-alkoxy amines **P59** in excellent yields and enantioselectivities.

Scheme 44. Iridium-catalyzed acid-assisted AH of oximes to hydroxylamines.

Cramer (2020)



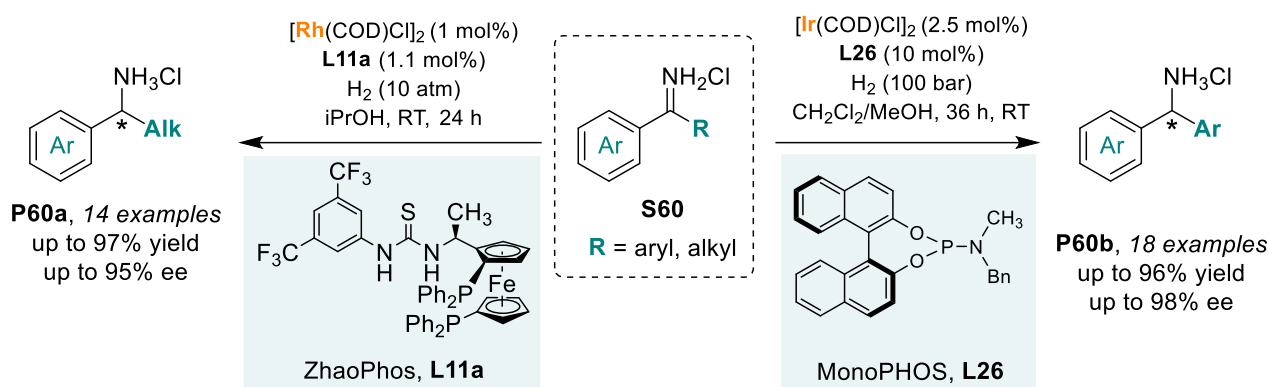
2.9. Unprotected imines

The transition metal-catalyzed AH of *N*-unprotected imines⁶⁴ has been widely pursued. X. Zhang's laboratory, in collaboration with Merck, developed the first efficient and atom-economic iridium-catalyzed AH of unprotected ketimines using HCl as Brønsted acid to activate the substrate.²¹⁹ Ketimine hydrochlorides **S60** were efficiently hydrogenated using Ir/(*S,S*)-f-Binaphane **L7**, although in high catalyst loading (5 mol%). Later, in 2014, Wang, Anslyn, X. Zhang and co-workers improved this transformation in terms of TON using Rh/ZhaoPhos (**L11a**) as catalyst. Taking advantage of the anion binding interaction between the thiourea and chloride counterion, chiral amines **P60a** were afforded in high yields and enantioselectivities (Scheme 45).²²⁰ The iridium-catalyzed AH of substituted benzophenone imines **S60** was also efficiently conducted in X. Zhang's group.²²¹ Enantioenriched diarylmethylamines **P60b** were obtained using a monodentate phosphoramidite **L26** and rather harsh reaction conditions (100 atm H₂, Scheme 45). Substitution at the 2-position on the aryl group in **S60** is essential to achieve good enantiocontrol.

Scheme 45. Metal-catalyzed AH of *N*-unprotected imines.

Wang, Anslyn & Zhang (2014)

Zhang / Merck
(2010)



It is worth mentioning that direct asymmetric reductive amination (ARA) has become an important branch of asymmetric hydrogenation. However, as stated in the introduction, this topic is not covered here since it has been comprehensively reviewed very recently.^{10,11,12}

3. Asymmetric hydrogenation of enamides

In 1972, Kagan, Dang and co-workers reported the first example of the AH of *N*-protected enamines, using the chiral ligand DIOP.⁵³ Although the enantioselectivity was only moderate, this work opened a door towards the enantioselective synthesis of chiral amines. Knowles,²²² Noyori,²²³ and Burk²²⁴ strongly contributed to the field by introducing DIPAMP, BINAP and DuPhos ligands, respectively. Since then, many highly efficient Rh catalysts bearing chiral diphosphine ligands have been developed. In addition, at the beginning of the century, Reetz, Feringa and Zhou's groups independently demonstrated that Rh complexes bearing monodentate phosphorus chiral ligands were also highly efficient catalysts.^{225,226,227} The direct catalytic AH of enamides is, arguably, the method of choice for the synthesis of amino acids and chiral amines bearing a stereogenic center in α or β position to the nitrogen atom.

3.1. Acyclic *N*-acyl enamines

3.1.1. Chiral Rh catalysts

The presence of a coordinating group adjacent to the C=C make *N*-acyl enamines ideal substrates for rhodium-catalyzed AH, which very often induces very high enantioselectivity.²²⁸ In contrast to imines, the use of iridium complexes in the AH of acyclic *N*-acyl enamines is uncommon.²²⁹ Nevertheless, the chiral ligand makes a critical contribution to the achievement of high activity and

selectivity. Consequently, the development of more efficient ligands for a range of catalytic processes is still a vital research topic. During the last decade, new families of chiral phosphines,²³⁰ including monodentate phosphines,^{231,232,233,234} bis(aminophosphine)-type ligands,^{235,236,237} phosphino-phosphite (P-OP),^{238,239,240,241,242,243,244} phosphino-phosphoramidite,^{245,246,247,248,249,250,251,252} spiroketal^{253,254} or supramolecular-type^{255,256,257,258,259} biphosphines, and others,^{260,261} have found widespread use in the rhodium-catalyzed AH of *N*-acyl enamines.²⁶² Among these, the last decade has witnessed the development of *P*-stereogenic electron-rich alkyl phosphines as highly proficient ligands.^{44,45,263,264,265} Figure 5 shows the most relevant *P*-stereogenic ligands used in the rhodium-catalyzed AH of benchmark enamides (Table 1). These chiral ligands have stood out from others in the AH of standard *N*-acylenamines such as methyl α -acetamidoacrylate (MAA, **S61**), (*Z*)-methyl α -acetamido-3-phenylacrylate (*Z*-MAC, **S62**), β -dehydroamino acids (**S63**)²⁶⁶ and *N*-(1-phenylvinyl)acetamide (PVA, **S64**).

In 2004, Hoge and co-workers established an important breakthrough in the field by preparing a *C*₁-diphosphine with three-hindered quadrants (trichickenfootphos -TCFP-, **L27**).^{267,268,269} This ligand showed very high enantioinduction for a wide variety of *N*-acyl enamines (**S61-S64**, Table 1). However, TCFP is difficult to handle in air, which explains why it has received little attention in asymmetric catalysis. To overcome this limitation, Imamoto recently prepared a crystalline, air-stable analog of TCFP by replacing the *tert*-butyl groups in the non-stereogenic phosphorus atom for the bulkier 1-adamantyl (**L28**).²⁷⁰ Its catalytic activity on the rhodium-catalyzed AH of enamides afforded excellent enantioselectivities for the substrates tested, including β -keto enamides (**S65**).²⁷¹ In 2010, Riera & Verdaguer's laboratory reported the first synthesis of optically pure, borane-protected primary and secondary aminophosphines.²⁷² These compounds were found to be valuable *P*-stereogenic building blocks for the preparation of new chiral aminodiphosphine ligands. The synthesis and catalytic evaluation of small-bite angle MaxPHOS ligand (**L30**) was first described.²⁷³ Indeed, MaxPHOS is a nitrogen-containing analog of TCFP (**L27**). However, and in contrast to **L27**, the presence of an -NH- bridge between the two phosphine moieties allows the NH/PH tautomerism to take place. The protonation of MaxPHOS led to the stable PH form of the ligand, which turned into air-stable compounds both in the solid state and in solution. The complex Rh/**L30** proved to be a highly enantioselective and robust system for the AH of a wide range of *N*-acyl enamines (Table 1). Later, a new class of *P*-stereogenic *C*₂-symmetric ligands with a hydrazine backbone was also disclosed by Riera & Verdaguer.²⁷⁴ **L31**, in particular, showed excellent catalytic performance in the rhodium-catalyzed AH of several benchmark substrates (Table 1).

C_2 -symmetric *P*-stereogenic ligands have been widely used in AH. Stephan's laboratory performed the rhodium-catalyzed AH of a wide spectrum of representative enamides using **L32** and **L33** (SMS-Phos) as chiral ligands.^{275,276} Both catalytic systems showed excellent enantioselectivities (>99% ee for several model substrates; Table 1). The catalytic activity of the ligand was markedly affected by the nature of its aryl substituents in terms of both bulkiness and electronic properties. Of note, *t*-Bu-SMS-Phos **L33** outperformed other reported ligands (Table 1), although the enantioselectivity dropped considerably when using tetrasubstituted vinyl acetamides.²⁷⁷

In 2010, Tang designed and synthesized a novel family of chiral bisdihydrobenzoxaphosphole ligands (BIBOP, **L34**).^{278,279} Their ease of preparation and excellent air stability make BIBOP a practical ligand. Moreover, it can also be highly modular by fine-tuning the substituents at the 4,4'-positions. The rhodium-catalyzed AH of various *N*-acyl enamines using BIBOP ligands was exploited, including in kilogram scale.²⁸⁰ When using Rh/**L34** in the AH of benchmark substrates, the corresponding chiral amines were attained in excellent enantioselectivities (Table 1). The same group later developed a similar ligand named WingPhos (**L35**) and the introduction of 9-anthracenyl substituents conferred a deeper chiral pocket.²⁸¹ Other ligands were efficiently applied to the rhodium-catalyzed AH of (*E*)- β -aryl enamides, which is a class of substrates that remained underdeveloped.^{282,283} More recently, a novel class of benzoxaphosphole ligands (BABIPhos, **L36**) has been reported.²⁸⁴ The high catalytic performance of these ligands was showcased in rhodium-catalyzed AH, although for **S63** the enantioselectivity achieved was lower than with BIBOP.

The use of *P*-stereogenic *N*-phosphine-phosphinite ligands is still rare. Recently, Dieguez's laboratory developed a family of these ligands (**L37**) that has been applied in rhodium-catalyzed AH.²⁸⁵ By choosing the appropriate ligand for each substrate family, benchmark enamides were hydrogenated, giving excellent results (Table 1).

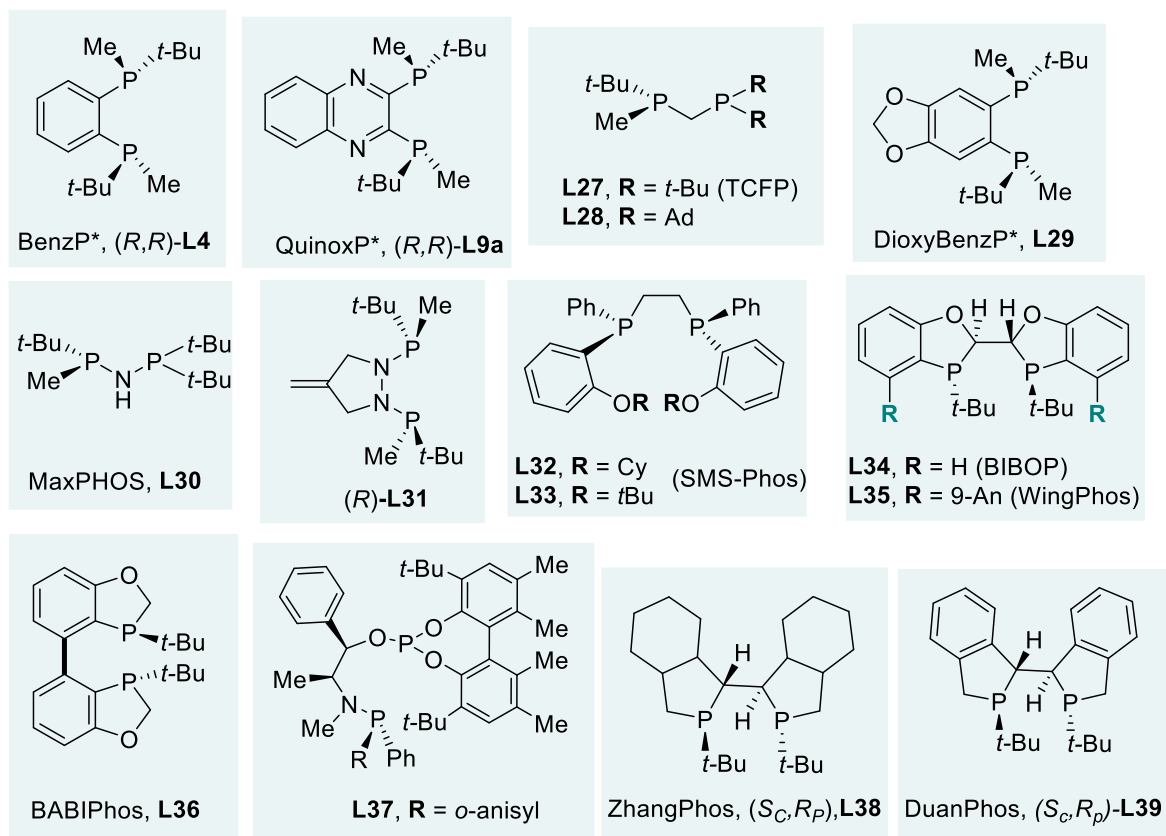
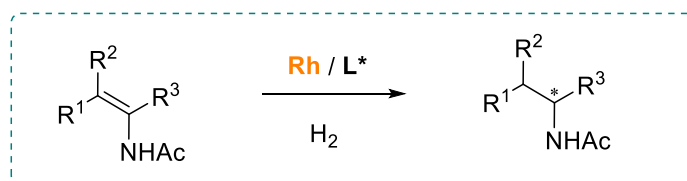


Figure 5. *P*-stereogenic chiral ligands used in the metal-catalyzed AH of *N*-acyl enamines.

Table 1. Enantiomeric excesses (%) in the rhodium-catalyzed AH of benchmark *N*-acyl enamines using the *P*-stereogenic ligands shown in Figure 5.



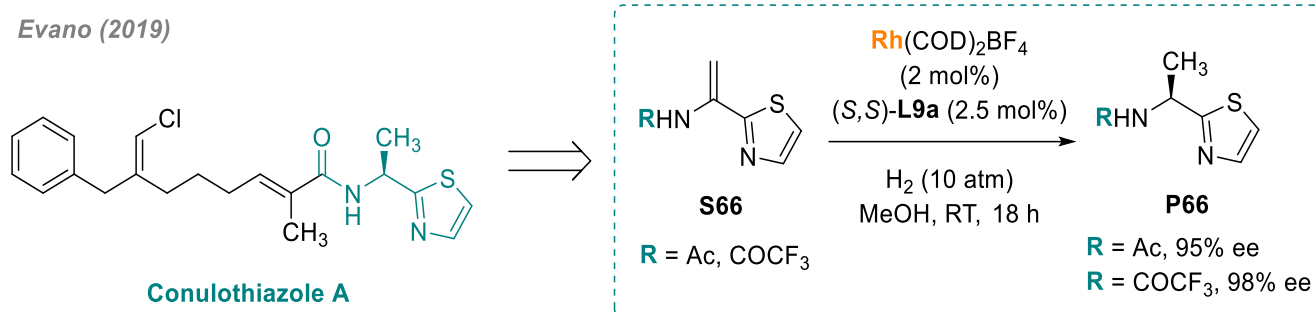
	S61	S62	(E)-S63	(Z)-S63	S64	S65
L27	>99	>99	99	96	98	-
L28	>99	>99	>99	96	97	97
L9a	>99	>99	>99	99	>99	97
L4	>99	>99	>99	98	93	99
L29	>99	>99	>99	99	90	99
L30	99	99	99	96	97	92
L31	98	99	-	-	97	-
L32	>99	>99	98	88	>99	-
L33	>99	>99	97	80	>99	-
L34	>99	97	99	99	99	-
L36	-	>99	-	90	96	-
L37	99	>99	-	-	96	-
L38	>99	>99	>99	97	>99	96
L39	>99	>99	>99	97	>99	96

Between 1998 and 1999, Imamoto pioneered the use of the *tert*-butylmethylphosphine synthon in C_2 chiral diphosphines with the development of BisP* and MiniPHOS.^{286,287,288} Afterwards, he improved the ligand design by introducing this *P*-stereogenic synthon into many other ligands such as QuinoxP* (**L18a**), BenzP* (**L4**) and DioxyBenzP* (**L29**).^{289,290,291} These conformationally rigid ligands are crystalline solids and, once coordinated to Rh, exhibited excellent enantioselectivities in the AH of a broad range of enamides and other functionalized alkenes (Table 1). **L18a** showed unbeatable enantioselectivities when acetamido acrylates and vinyl acetamides were used, but gave poor conversion for the AH of β -keto enamide **S65**. In contrast, **L4** and **L29** gave the best results reported to date with **S65**.

As an example of a synthetic application, Evano's group recently developed a short and modular total synthesis of Conulothiazole A in 7 steps and 30% overall yield.²⁹² One of the key steps was an efficient rhodium-catalyzed AH of a 2-enamido-thiazole **S66** (Scheme 46) using (*S,S*)-QuinoxP* **L18a**. The catalytic system was extended to a variety of 2-enamido-heteroarenes with excellent results (up to 99% ee), thus providing efficient access to 2-aminoethyl-arenes, which are useful

building blocks in medicinal chemistry. Of note, the rhodium-catalyzed AH of acetamidoacrylates or vinylacetamides has been widely used as a powerful tool in total synthesis of natural products^{293,294} and for the preparation of drugs and pharmacologically active compounds.^{295,296,297,298,299,300,301,302}

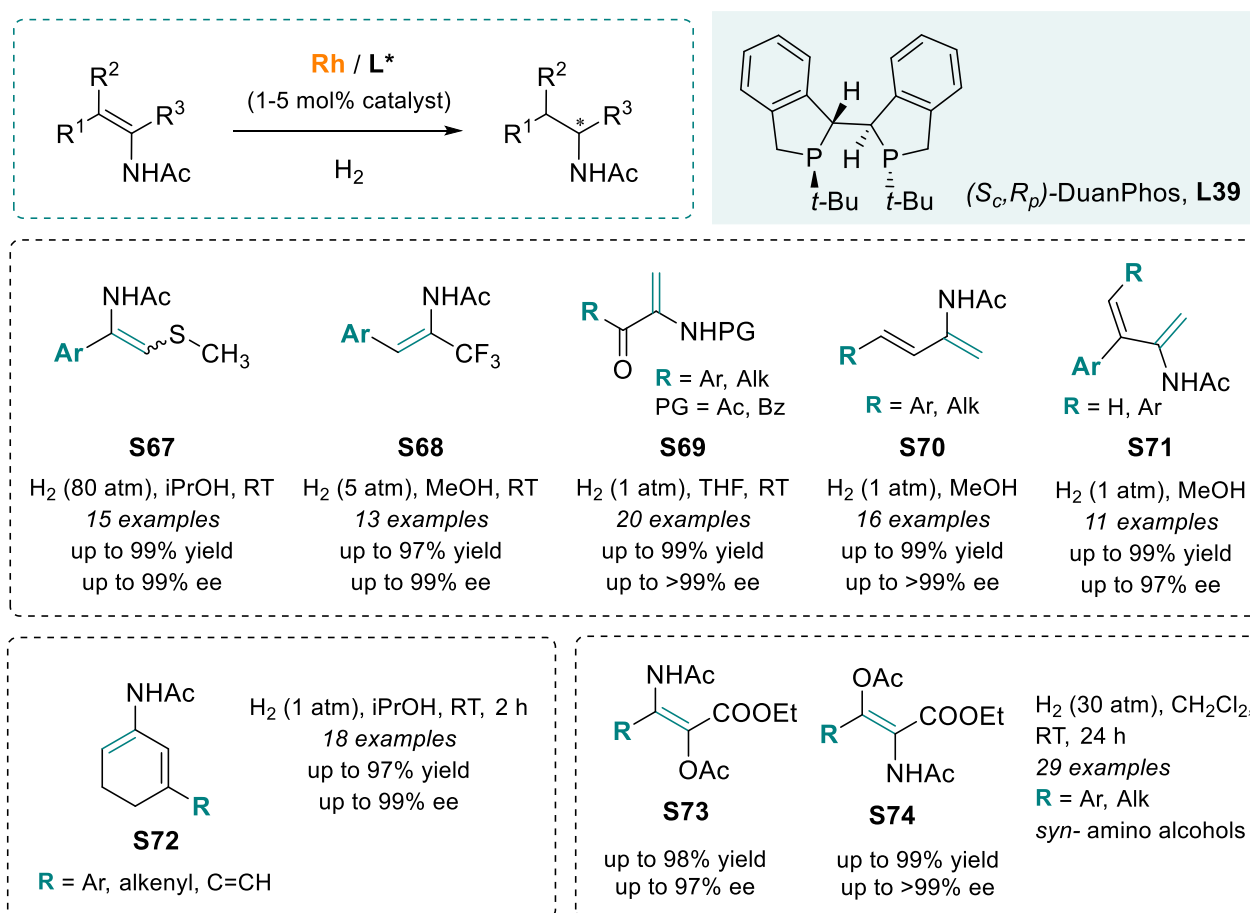
Scheme 46. Total synthesis of Conulothiazole A via rhodium-catalyzed AH.



At the beginning of the decade, X. Zhang and co-workers reported the preparation of an electron-donating *P*-stereogenic biphospholane ligand (ZhangPhos, **L38**) for the Rhodium-catalyzed AH.^{303,304} The group had also previously reported other *P*-stereogenic ligands with *C*₂-symmetry, such as TangPhos (**L2**)^{305,306} or DuanPhos (**L39**),^{307,308} among others.³⁰⁹ Compared to those, ZhangPhos is conformationally more rigid, and it achieved better or similar enantioselectivities (up to 99% ee, Table 1). Moreover, **L38** exhibited extremely high reactivity (up to 50 000 TON) in the rhodium-catalyzed AH of a wide range of *N*-acyl enamines and had the advantage that both enantiomers can be prepared by asymmetric synthesis.

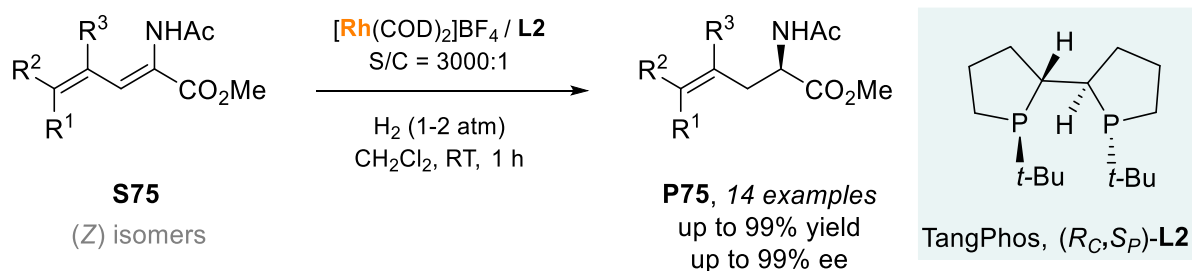
Nevertheless, Rh-DuanPhos is a highly versatile catalytic system that was used in many other functionalized substrates. Wiest, Dong and co-workers recently applied this chiral catalyst in the cascade hydrogenation of cyclic dehydropeptides controlled by catalyst-substrate recognition.³¹⁰ Previously, X. Zhang, Lv and co-workers used this catalyst for the efficient AH of β -acetylamino vinylsulfides **S67**,³¹¹ α -CF₃-enamides **S68**,³¹² α -dehydroamino ketones **S69**,^{313,314} aliphatic dienamides **S70**³¹⁵ and **S71**³¹⁶, and cyclic dienamides **S72** (Scheme 47).³¹⁷ The resulting chiral amines were afforded in excellent yields and enantioselectivities. Furthermore, other challenging functionalized substrates, such as tetrasubstituted enamides, were hydrogenated in a highly enantioselective manner. In particular, the AH of α -acetoxy β -enamido esters **S73**³¹⁸ and β -acetoxy α -enamido esters **S74**³¹⁹ for the preparation of *syn* amino alcohols was conducted using Rh/DuanPhos catalyst, achieving excellent results (Scheme 47). In 2015, the same group also reported the highly regio- and enantio-selective synthesis of γ,δ -unsaturated amido esters **P75** by AH of conjugated enamides using Rh/TangPhos-**L2** (Scheme 48).³²⁰

Scheme 47. Scope of substrates for rhodium-catalyzed AH using DuanPhos.



Scheme 48. Rhodium-catalyzed AH of conjugated enamides.

X. Zhang, Lv (2015)

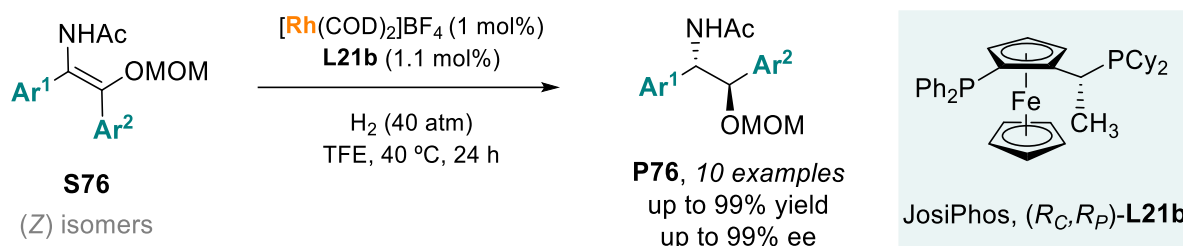


In addition, the AH of tetrasubstituted enamides in *Z* form was also accomplished by the same laboratory (Scheme 49).³²¹ However, in this case, Rh-DuanPhos-L39 gave poor conversion for **S76**. In contrast, JosiPhos ligand **L21b** afforded a set of *anti* β -amino alcohol derivatives **P76** in excellent yields and enantioselectivities. Simultaneously, scientists at Merck reported a concise, enantio- and diastereoselective route to novel non-symmetrically substituted *N*-protected β,β -diaryl- α -amino acids

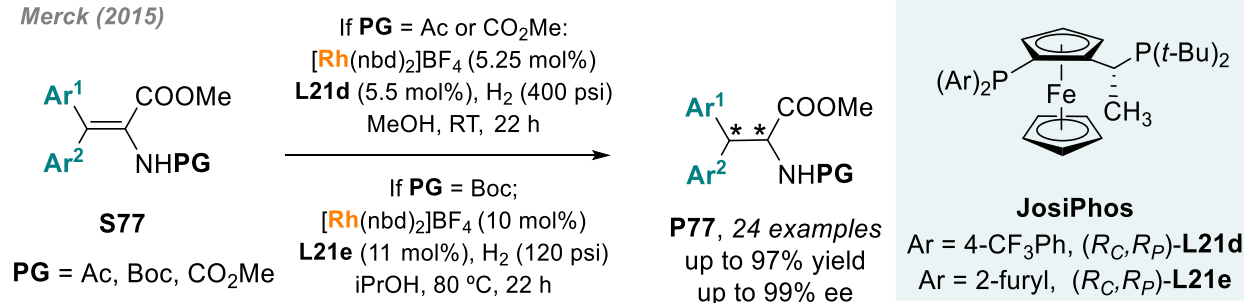
and esters through the AH of tetrasubstituted enamides **S77** (Scheme 49).³²² Again, JosiPhos ligands (**L21d** and **L21e**) allowed complete stereocontrol over the two vicinal stereogenic centers. Remarkably, an example of **S77** was previously hydrogenated by Ramsden and co-workers for the asymmetric synthesis of an intermediate of denagliptin.³²³ The rhodium-catalyzed AH of other tetrasubstituted enamides has also been investigated. A noteworthy example was the asymmetric synthesis of cannabinoid-1 receptor inverse agonist taranabant, reported by a Merck team in 2009.³²⁴

Scheme 49. Rhodium-catalyzed AH of (*Z*)- tetrasubstituted enamides.

X. Zhang (2015)



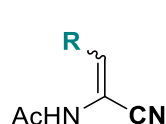
Merck (2015)



Another important transformation in this section is the rhodium-catalyzed AH of α -amino acrylonitriles **S78**, as it provides a concise route to the synthesis of chiral α -acylamino nitriles **P78** (Scheme 50). These compounds are versatile synthetic intermediates, and they can be direct precursors of valuable α -amino acids. X. Zhang and co-workers recently reported that Rh-Me-DuPhos (**L40a**) is an efficient catalyst for this transformation, thus furnishing **P78** in excellent yields and enantioselectivities.³²⁵ Previously, the same group described the highly enantioselective rhodium-catalyzed AH of β -acylamino acrylonitriles **S79** using TangPhos (**L2**) or QuinoxP* as chiral ligands (Scheme 50).^{326,327} Interestingly, in both cases, the hydrogenation of an *E/Z* mixture gave excellent enantioselectivities, thus making it unnecessary to isolate the substrate's isomers.

Scheme 50. Rhodium-catalyzed AH of α - and β -amino acrylonitriles.

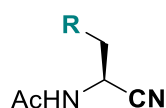
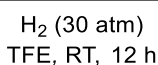
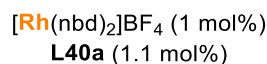
X. Zhang, Lv (2017)



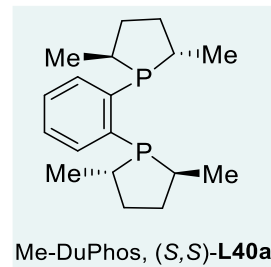
S78

(Z) or (E/Z)

R = aryl, alkenyl

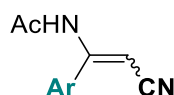


P78, 16 examples
up to 99% yield
up to >99% ee



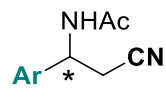
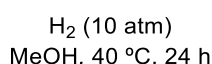
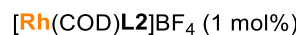
Me-DuPhos, (S,S)-L40a

X. Zhang, Wang (2010)

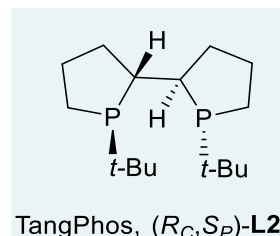


S79

(E) or (E/Z)



P79, 12 examples
up to >99% ee

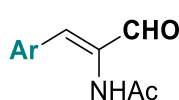


TangPhos, (R_C, S_P)-L2

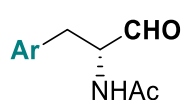
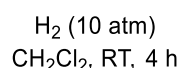
In 2019, W. Zhang and co-workers described a powerful strategy for the preparation of enantioenriched chiral α -amido aldehydes, which have many potential applications in organic synthesis and medicinal chemistry. Using a rhodium complex of a *P*-stereogenic biphosphine ligand ((*R,R*)-BenzP*, **L4**), α -formyl enamides **S80** were hydrogenated in a highly chemo- and enantioselective manner (up to >99.9% ee, Scheme 51).³²⁸ Under different hydrogen pressures, the preparation of highly enantioenriched β -amido alcohols is also plausible. The method can be carried out on a gram scale, thus demonstrating its high efficiency and practicability.

Scheme 51. Rhodium-catalyzed AH of α -formyl enamides.

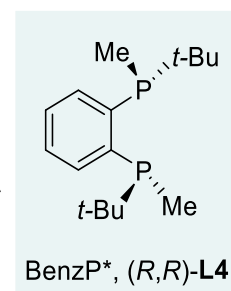
W. Zhang (2019)



S80



P80, 27 examples
up to 99% yield
up to 99% ee

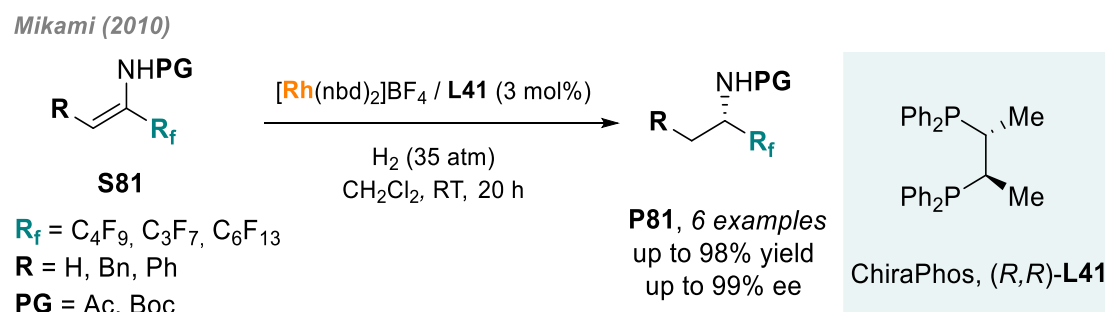


BenzP*, (R,R)-L4

Although the AH of enamido esters, vinyl acetamides or related compounds has received the most attention in the field, the AH of other α - and β -functionalized enamides constitutes a privileged methodology in the design of new pharmaceuticals and agrochemicals. In 2010, Mikami and co-workers described the enantioselective synthesis of α -(perfluoroalkyl)amines via the rhodium-catalyzed AH of enamides **S81**, which can be prepared by perfluoroalkylation of nitriles with Ti/Mg-reagents.³²⁹ By using ChiraPhos **L41**, acyclic perfluoroalkyl *sec*-amines were furnished with excellent

enantioselectivities (Scheme 52). Also in 2010, Benhaim *et al.* reported the first enantioselective synthesis of β -trifluoromethyl α -amino acids using rhodium-catalyzed AH with TCFP (**L27**).³³⁰

Scheme 52. Enantioselective synthesis of α -perfluoroalkylated chiral amines.

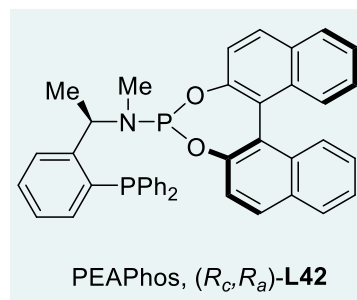
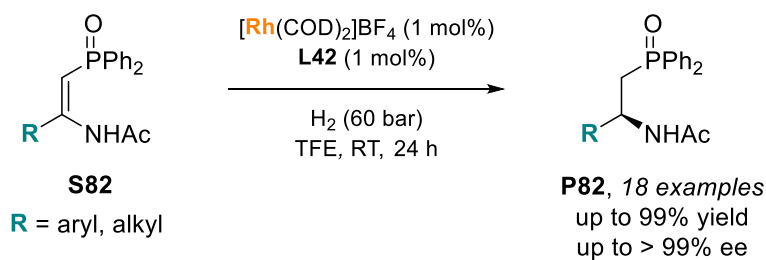


Another type of well-established chiral scaffolds are β -amino phosphine derivatives. Hu and co-workers recently reported an unprecedented, catalytic AH of β -phosphorylated enamides **S82** (Scheme 53).³³¹ The method used rhodium catalysis derived from an unsymmetrical hybrid chiral phosphine-phosphoramidite ligand (**L42**). A wide range of aromatic and alkylic enantioenriched β -acetamidophosphine oxides **P82** were efficiently prepared. These compounds could be readily hydrolyzed and reduced, thus providing an efficient route to important chiral β -aminophosphines.

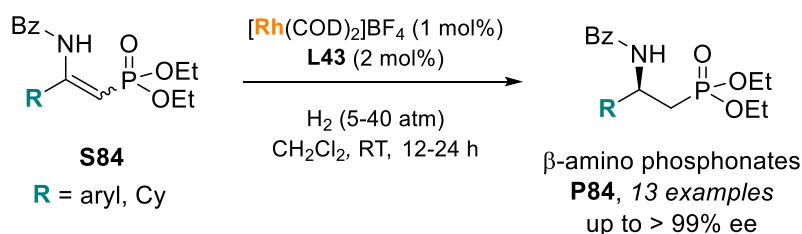
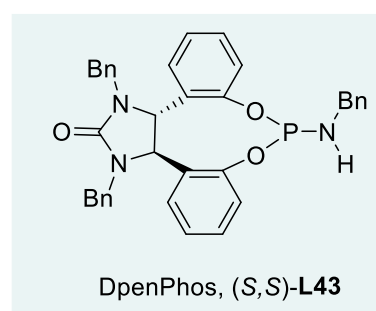
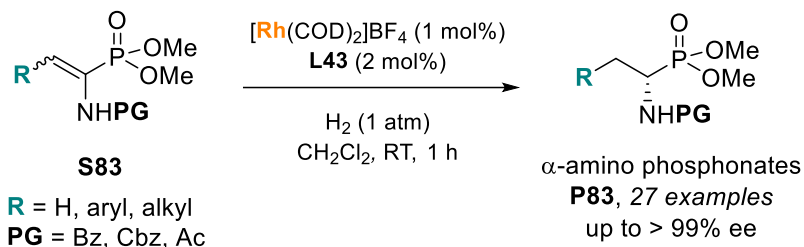
Optically active α - and β -amino phosphonic acid derivatives can also be prepared by means of AH. In fact, in 2011, Ding designed a family of chiral monodentate phosphoramidite (DpenPhos) ligands that were found to be highly efficient in the rhodium-catalyzed AH of enamides **S83** and **S84** (Scheme 53).³³² Of note, when **L43** was used, a set of chiral amino phosphonates **P83** and **P84** were prepared with excellent results. In several cases, the enantioselectivity values obtained were higher than those reported previously.^{333,334}

Scheme 53. Rhodium-catalyzed AH of enamido phosphonates and β -phosphorylated enamides.

Hu (2019)

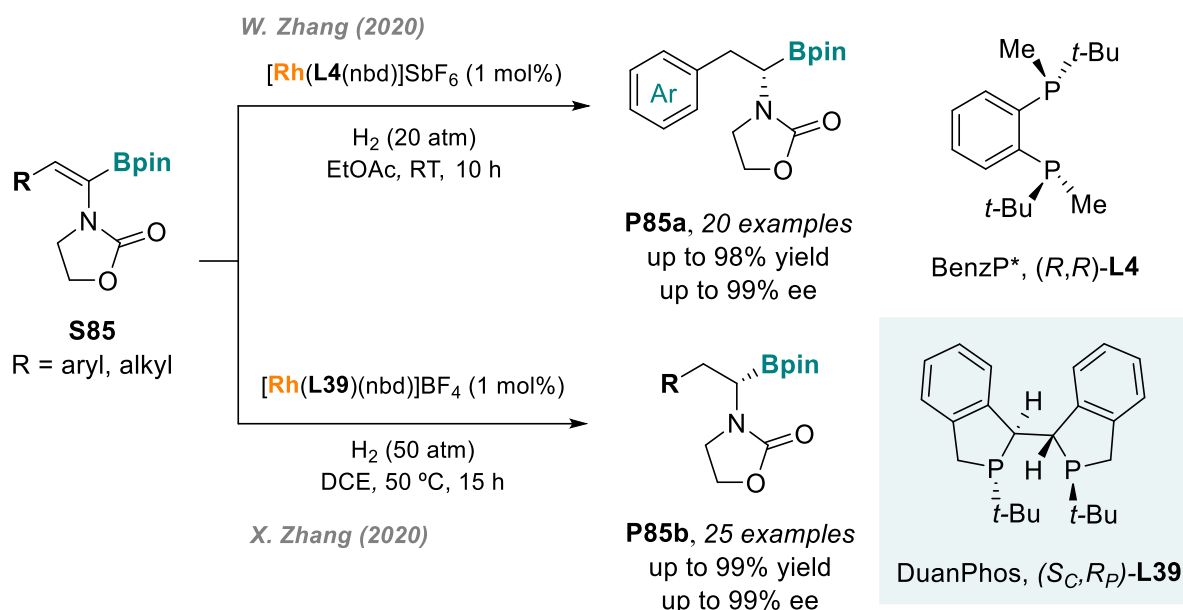


Ding (2011)



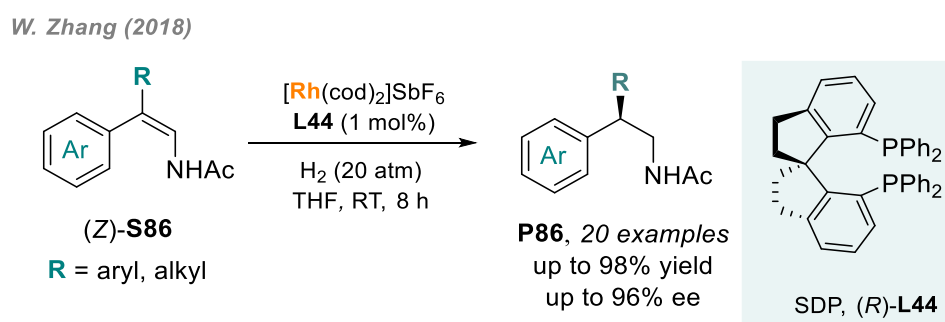
Organoboron compounds are also important due to their unique physical, chemical and biological properties. However, the preparation of chiral α -aminoboronic acids, as mimics of chiral amino acids, is not trivial. In 2020, W. Zhang and X. Zhang, independently pioneered this field describing the rhodium-catalyzed AH of α -boryl enamides (**S85**) using the *P*-stereogenic diphosphines **L4** and **L39**, respectively (Scheme 54).^{335,336} Critical to the success of this method was the chelate coordination of the amido group to rhodium and the nonbonding interactions between the substrate and the ligand. Whereas by using **L4** the method was limited to aryl substituents in β position, the use of **L39** allowed an expanded substrate scope, as alkyl substituents were also well tolerated. Chiral α -amidoboronic esters **P85** were furnished in quantitative conversion and excellent enantioselectivity. Exquisite chemoselectivity was observed as no protodeboronation was detected.

Scheme 54. Rhodium-catalyzed AH of α -boryl enamides.



While the hydrogenative synthesis of chiral α -substituted amines has been widely addressed, synthetic methodologies for the preparation of β -chiral amines are rare. Only few examples have been reported, mostly by AH of dehydroamino acids.^{337,338} The AH of β -branched simple enamines remained a long-standing challenge due to the difficulties related to the stereocontrol of the reaction. To overcome this issue, in 2018, W. Zhang and co-workers disclosed the first catalytic protocol using a Rh complex bearing a diphosphine ligand with a large bite angle (SDP, **L44**).³³⁹ β -Branched simple enamides with a (*Z*)-configuration (**S86**) were efficiently hydrogenated to optically pure β -chiral amines **P86** in quantitative yields and with excellent enantioselectivities (Scheme 55).

Scheme 55. Enantioselective synthesis of β -stereogenic amines via AH.



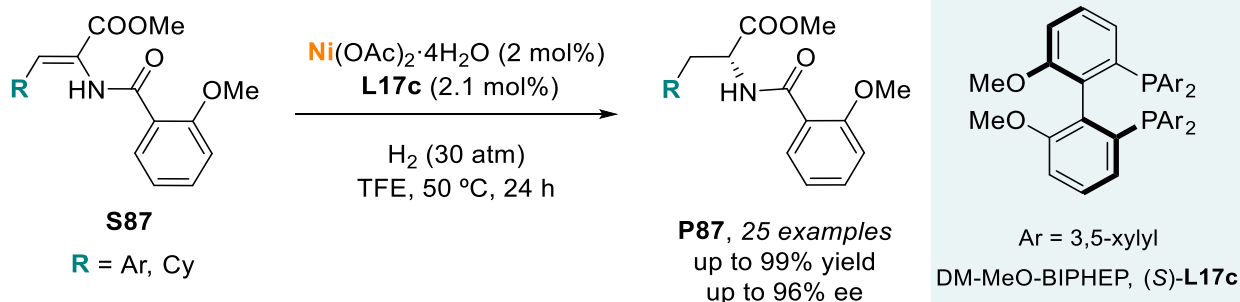
3.1.2. Ni and Co catalysts

The limited availability, high cost and toxicity of noble metals stimulated the research in their replacement with earth-abundant, inexpensive first-row transition metals. However, challenges such as different reaction mechanism and unexpected deactivation of the catalyst prevented their widespread use in asymmetric hydrogenation.^{340,341} While dozens of examples using Rh catalysis

have been reported during the last decade, the use of earth-abundant transition metals have just started showing practical efficiency in AH. In 2020, W. Zhang and co-workers reported a highly efficient nickel-catalyzed AH of 2-amidoacrylates (Scheme 56).³⁴² In contrast to the AH with Rh catalysts, where the amido-assisted activation strategy allowed to attain high activity and enantioselectivity, Ni catalysts cannot utilize this approach as they have their own coordination modes. However, W. Zhang envisioned that other interactions between the substrate and catalyst would lead to high catalytic activity. Interestingly, when using **S87** bearing an *ortho*-methoxy substituted benzoyl group and Ni/BIPHEP-type ligand (**L17c**), the AH occurred smoothly and the corresponding chiral α -amino acid esters **P87** were afforded in excellent enantioselectivities (up to 96% ee).

Scheme 56. Nickel-catalyzed AH of 2-amidoacrylates.

W. Zhang (2020)

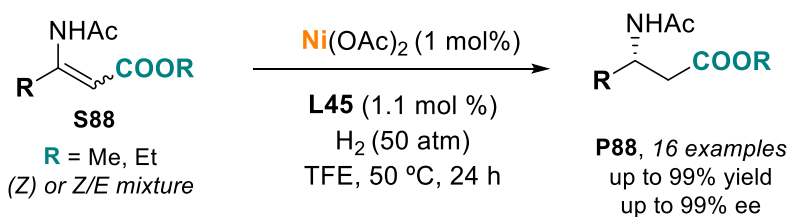


Nickel-catalyzed AH has been also used in the synthesis of chiral β -amino acid derivatives. Lv and X. Zhang and co-workers reported a highly enantioselective hydrogenation of (*Z*)- β -(acylamino)acrylates **S88** to provide enantiomerically pure β -amino acid derivatives **P88** using a commercially available binapine ligand (**L45**) (Scheme 57).³⁴³ High enantioselectivities were obtained even using *Z/E* isomeric mixtures. The same catalytic system proved to be fruitful for many other functionalized enamides, including benchmark substrates.³⁴⁴ In 2018, Lv and co-workers expanded its use for the Ni-catalyzed AH of β -acetylamino vinylsulfones **S89** (Scheme 57).³⁴⁵ The methodology showed good compatibility with substituted (*Z*)-isomers and of *Z/E* isomeric mixtures, thus being an alternative to the previously reported protocol using Rh/TangPHOS-**L2**.³⁴⁶ The resulting chiral sulfones **P89** were obtained in high yields and excellent enantioselectivities, in gram scale in the presence of only 0.2 mol % of catalyst. This catalyst also showed high activity towards the AH of β -acylamino nitroolefins **S90**. These are usually challenging substrates for AH due to the weak binding affinity of the olefins with the electron-withdrawing nitro group and, in fact, only a few examples have been reported involving precious transition metal catalysts.^{347, 348, 349} Despite this, Chung, X. Zhang and co-workers showed that Ni/Binapine could be used as catalyst to attain chiral

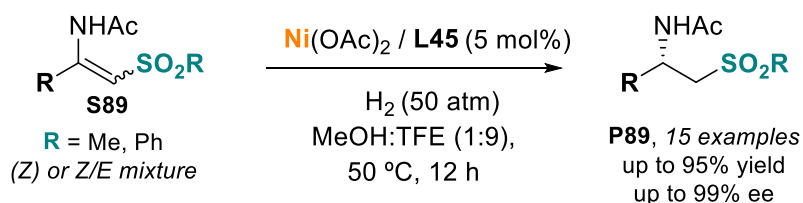
β -amino nitroalkanes **P90** with excellent enantioselectivity (>99% ee in the best cases) and high TONs using mild conditions (Scheme 57).³⁵⁰ Finally, Lv also reported the AH of tetrasubstituted β -enamino- α -fluoro esters **S91** in high yields and excellent diastereo- and enantioselectivities using Ni/**L45** (Scheme 57).³⁵¹ Interestingly, key experiments revealed the critical role of acidic solvent in modulating the reaction pathway, as well as for the control of diastereoselectivity. This method provides a highly straightforward and concise route to α -fluoro- β -amino esters **P91**.³⁵²

Scheme 57. AH of β -functionalized *N*-acyl enamines using the Ni/Binapine system.

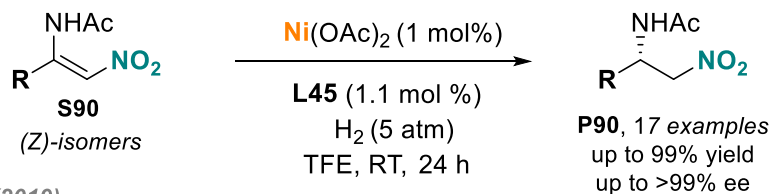
Lv / Zhang (2017)



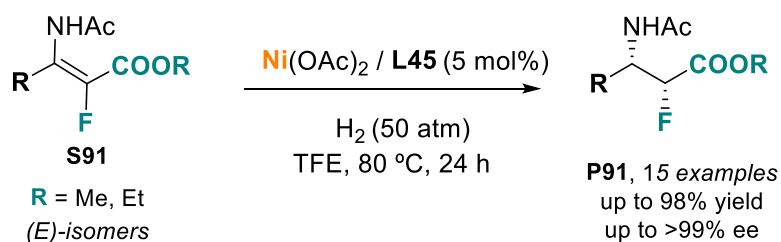
Lv (2018)



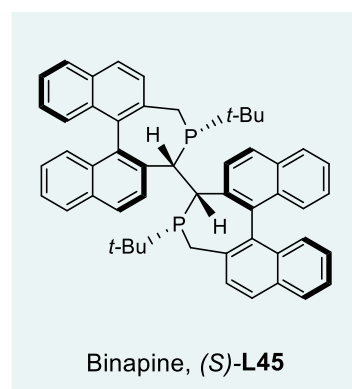
Chung / Zhang (2017)



Lv (2019)



R = aryl, alkyl

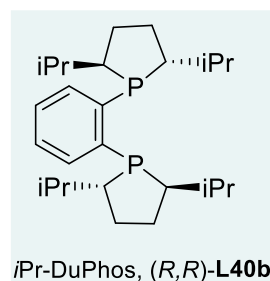
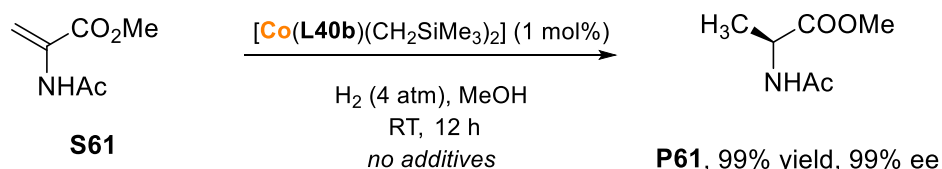


Cobalt has also gained great importance during the last decade in the field of AH. Chirik's laboratory has pioneered the use of cobalt complexes bearing chiral diphosphines to attain hydrogenative processes with extraordinary activity and enantioselectivity.^{353,354} In 2019, the group demonstrated that cobalt complexes bearing DuPhos-type ligand (**L40b**) efficiently hydrogenated MAA **S61** in excellent enantioselectivity (Scheme 58).³⁵⁵ More importantly, the reaction was carried out using MeOH, an industrially preferred green solvent which is often a poison for reduced earth-abundant metals, and without the use of additives. Other α,β -unsaturated carboxylic acids, including di-, tri-

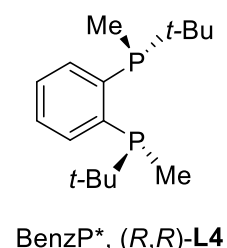
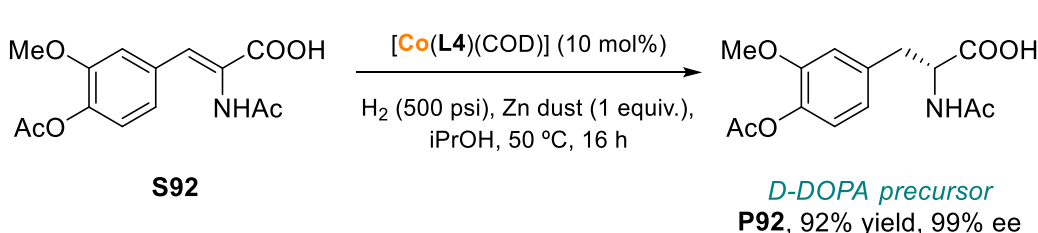
and tetra-substituted acrylic acid derivatives, as well as dehydro- α -amino acid derivatives, were hydrogenated using Co/BenzP*-**L4** (Scheme 58).³⁵⁶ Chiral carboxylic acids, including bioactive ones such as Naproxen, (*S*)-Flurbiprofen and a *D*-DOPA precursor **P92**, were attained in high yields and enantioselectivities. Again, protic solvents such as MeOH were identified as optimal, and Zn dust was used stoichiometrically. The group had previously described the Co-catalyzed AH of enamides using zinc-activation, which promoted straightforward single-electron reduction to enable the catalytic process (Scheme 58).³⁵⁷ The optimized protocol, using Co/**L19**, exhibited high activity and enantioselectivity and allowed the asymmetric synthesis of the epilepsy drug levetiracetam (**P93**) at 200-gram scale with only 0.08 mol % of catalyst loading.

Scheme 58. Co-catalyzed AH of 2-functionalized *N*-acyl enamines.

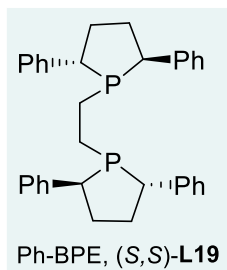
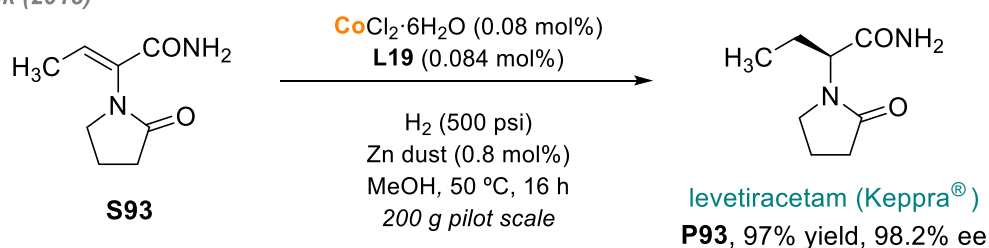
Chirik (2019)



Chirik (2020)



Chirik (2018)

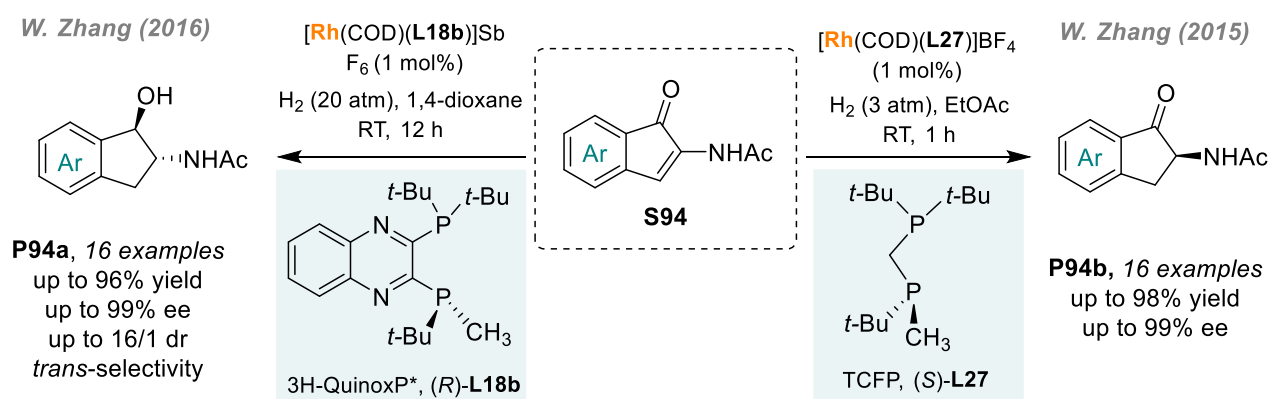


3.2. Endocyclic *N*-acyl enamides

In contrast to acyclic enamides, which have been extensively studied, the AH of cyclic enamides remained a challenge before the last decade. Despite that, the resulting chiral cyclic amines are very useful structural motifs that can be found in a range of bioactive molecules.³⁵⁸ An example of this class of substrates are cyclic α -dehydro amino ketones (**S94**, Scheme 59). In 2016, W. Zhang and co-workers reported that *P*-stereogenic chiral ligand **L18b**, using Rh catalysis, efficiently hydrogenated

S94 to chiral cyclic *trans*- β -amino alcohols **P94a** via a one-pot sequential AH with excellent enantioselectivities and diastereoselectivities.³⁵⁹ The same group achieved rhodium-catalyzed partial hydrogenation using small-bite angle ligand TFCP (**L27**) in a completely chemoselective manner (Scheme 59).³⁶⁰ Thus, chiral α -amino ketones **P94b** were exclusively obtained with excellent results, and both synthetic protocols were scaled up to gram scale. In contrast, the AH of cyclic β -keto enamides remains unexplored, with only one precedent in the literature and with very limited scope.³⁶¹

Scheme 59. Partial and total rhodium-catalyzed AH of cyclic α -dehydroamino ketones.



Another family of long-standing challenging substrates are cyclic enamides derived from tetralones and chromanones. The resulting chiral amines are highly desirable as they are precursors of therapeutic drugs. In this regard, the AH of cyclic enamides has typically relied on the use of Rh and Ru catalysts.^{362,363,364,365} Among the most successful examples, Ratovelomanana-Vidal and co-workers reported up to 96% ee in the reduction of **S95** (Scheme 60). The method employed Ru catalysis in combination with binap-type ligand SynPhos **L46**.^{366,367} Later, Tang and co-workers described the use of WingPHOS ligand (**L35**) in the rhodium-catalyzed AH of cyclic enamides **S95**, which yielded the corresponding chiral amines **P95** in up to 98% ee (Scheme 60).²⁸¹

However, these methods suffer from harsh reactions conditions such as high H₂ pressure or heating. In this regard, iridium catalysis, which has scarcely been used in the AH of *N*-acyl enamides and other alkenes bearing a metal-coordinating group, offered an excellent alternative. In 2016, Verdaguer, Riera and co-workers reported the highly enantioselective iridium-catalyzed AH of cyclic enamides **S95** and **S96**, derived from α - and β -tetralones (Scheme 60).⁷⁷ They optimized the iridium complexes bearing *P*-stereogenic phosphino-oxazoline ligands (**C6a** or **C6b**). These catalytic systems provided the highest selectivity reported to date for the reduction of these substrates. The resulting chiral amines **P95** and **P96** were obtained in 99% ee. Moreover, the process was carried out in

environmentally friendly solvents such as MeOH and EtOAc without loss of selectivity and under very mild conditions (3 bar of H₂). When the ligand was replaced with a *P*-stereogenic phosphino-imidazole ligand, the enantioselectivity decreased considerably.³⁶⁸ Diéguez and co-workers also reported the iridium-catalyzed AH of cyclic enamides **S95** and **S96** in excellent enantioselectivities employing a phosphite-oxazoline ligand (**L47**, Scheme 60).^{369,370} The same group further extended this methodology using other modular ligands.^{371,372,373,374} Overall, these protocols allowed an efficient route to the asymmetric synthesis of 2-aminotetralines and 3-aminochromanes, key structural units in many biologically active agents such as rotigotine, terutroban and nepicastat (Figure 6).^{375,376}

Scheme 60. Metal-catalyzed AH of cyclic enamides derived from α - and β -tetralones.

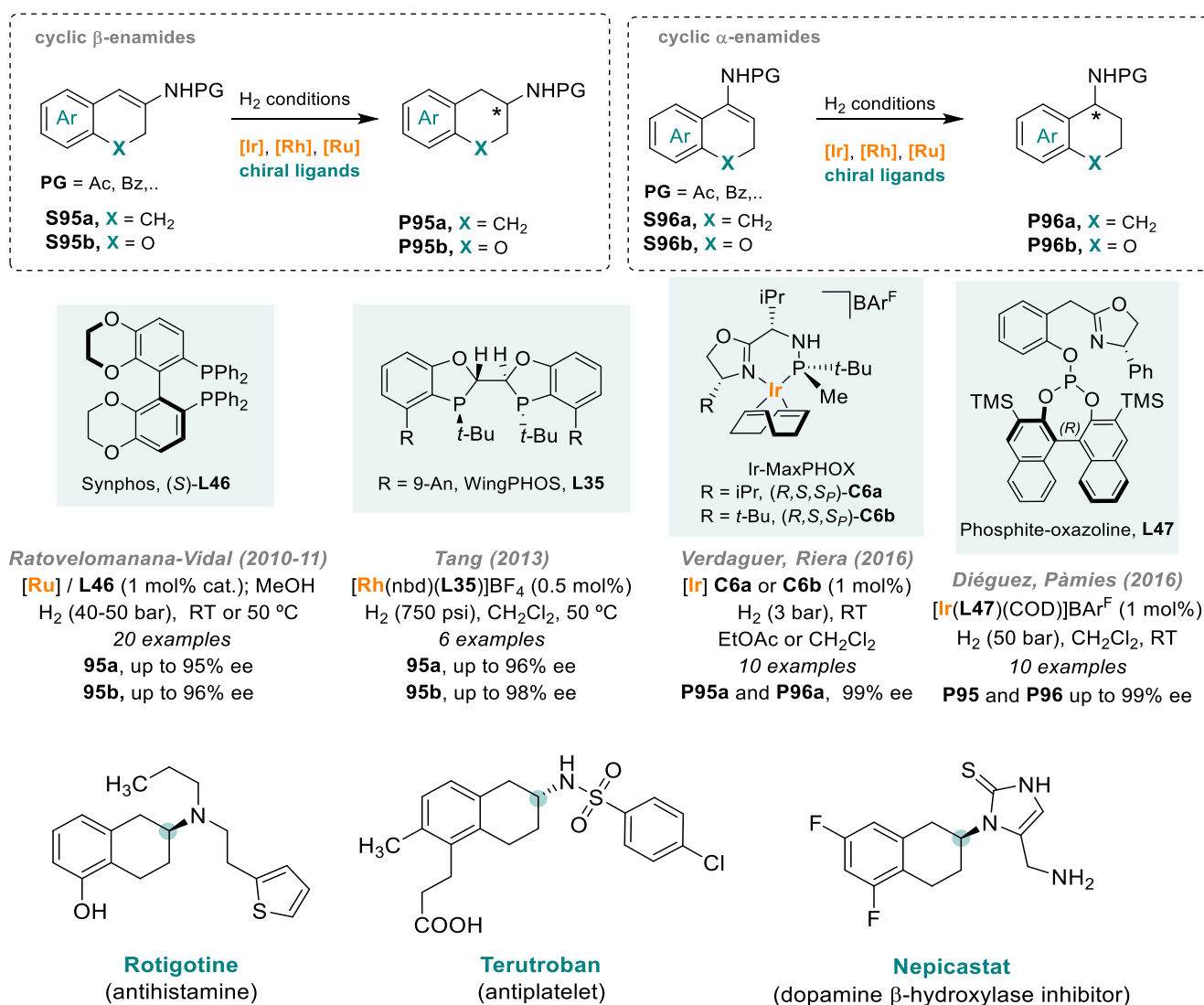


Figure 6. Pharmaceutical drugs containing the chiral 2-aminotetraline structure.

The AH of tetrasubstituted endocyclic enamides²⁹ has been a focus of great attention over the last years. The resulting chiral cyclic amines with a substitution at the 2-position are important motifs in many bioactive molecules and drugs (Figure 7).

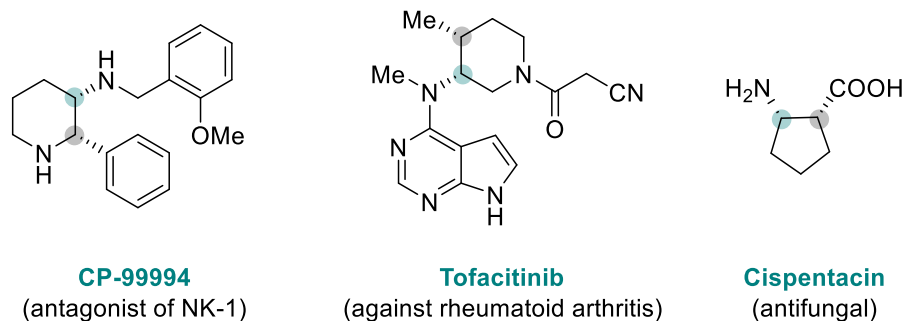
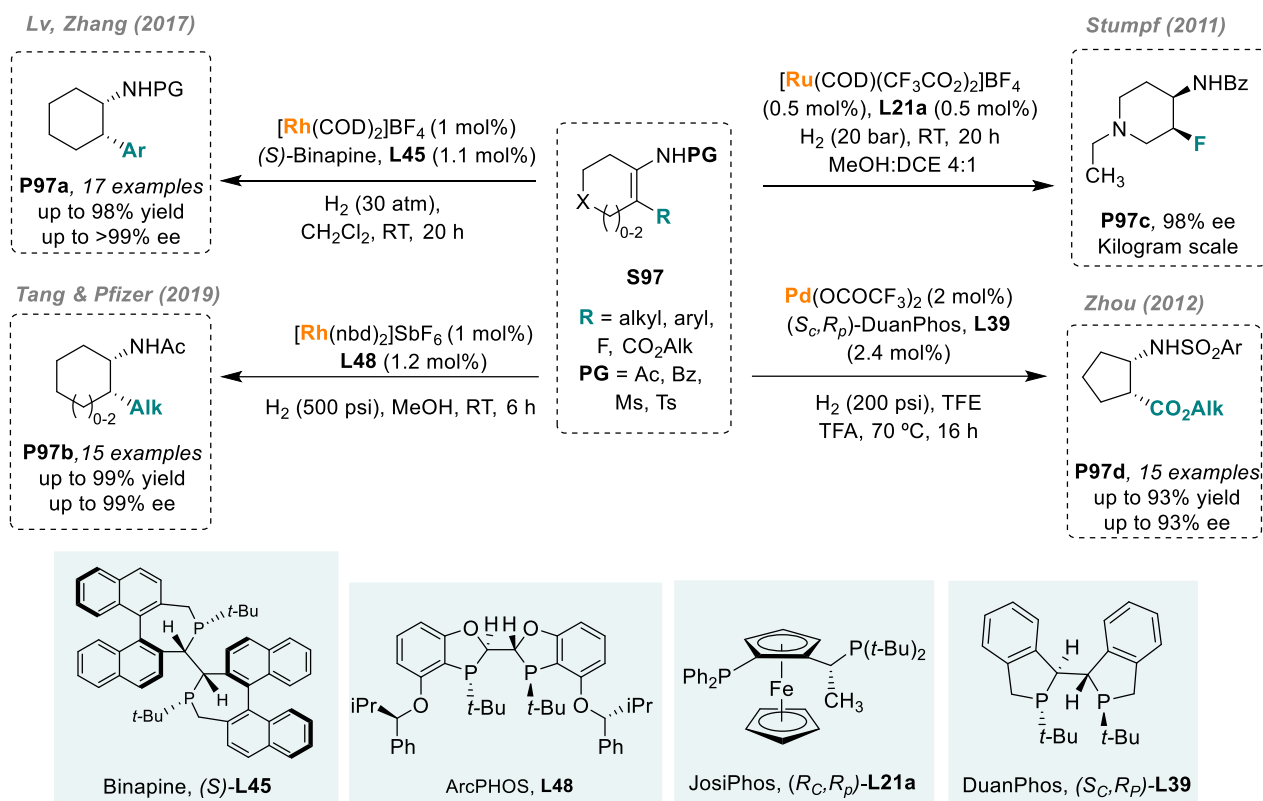


Figure 7. Pharmaceutical drugs containing amines with vicinal chiral centers.

In 2017, Lv, X. Zhang and co-workers developed a highly enantioselective hydrogenation of cyclic *N*-acyl enamines **S97** to provide optically pure cycloalkyl amides **P97a** using Rh-Binapine (**L45**) as catalyst (Scheme 61).³⁷⁷ The resulting chiral amides had an aryl substituent in the vicinal position. The methodology could be applied to prepare biologically active compounds. More recently, in 2019, Tang, in collaboration with a team from Pfizer, demonstrated that an electron-rich *P*-stereogenic bisphosphorus ligand with deep chiral pockets (ArcPHOS, **L48**) could be applied to the rhodium-catalyzed AH of **S97** bearing alkyl substituents at the 2-position (Scheme 61).³⁷⁸ Consequently, chiral amides **P97b** were attained in excellent yields and enantioselectivities. The methodology was showcased by a concise synthesis of Tofacitinib (Figure 7). Previously, Stumpf and co-workers reported a multi-kilogram scale asymmetric synthesis of the enantiomerically pure fluoropiperidine **P97c** via AH using a Ru/JosiPhos (**L21a**) catalyst with high enantiomeric excesses (Scheme 61).³⁷⁹ This fluorinated aminopiperidine is also present as a structural motif in the antibacterial clinical candidate AZD9742. In fact, researchers at AstraZeneca have recently reported its enantioselective synthesis by means of AH using $[(S)\text{-BINAP})\text{RuCl}_2](p\text{-cymene})$.³⁸⁰

Chiral cyclic β -amino acids,³⁸¹ such as cispentacin (Figure 7), are important in the synthesis of β -peptides. In 2003, X. Zhang and co-workers pioneered the AH of tetrasubstituted cyclic β -(acylamino)acrylates using the chiral biaryl ligand C₃-TunaPhos.³⁸² Following this path, Zhou's group hydrogenated tetrasubstituted cyclic β -(arylsulfonamido)acrylates. Using Pd/DuanPhos-**L39** as catalyst, a range of five-membered chiral β -amino acid derivatives **P97d** were obtained in excellent yields and enantiomeric excesses (Scheme 61).³⁸³ More recently, the same group described the asymmetric hydrogenation of carbocyclic aromatic amines using a ruthenium-DuPhos (**L40b**) complex as catalyst.³⁸⁴

Scheme 61. Metal-catalyzed AH of tetrasubstituted cyclic enamides.

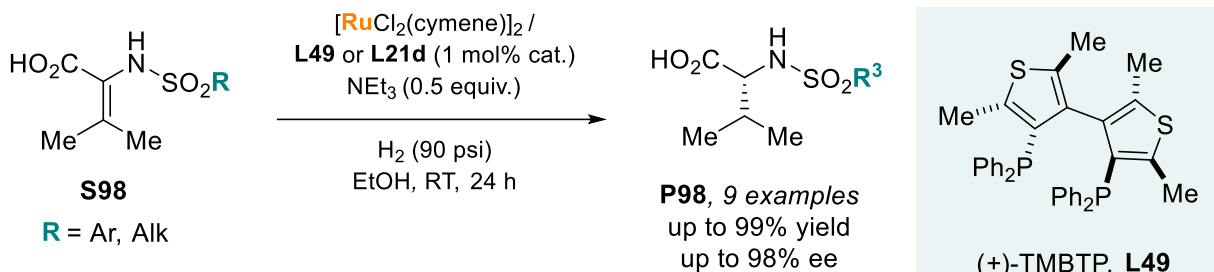


3.3. N-sulfonyl enamines

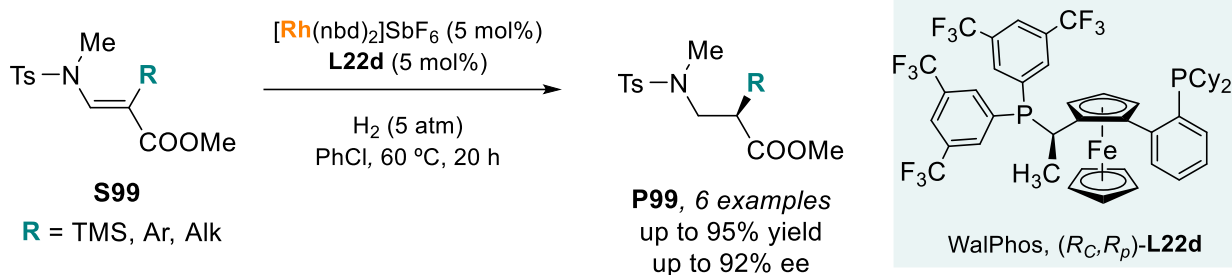
Little attention has been devoted to the AH of *N*-sulfonyl enamines, and only few examples can be found in the literature.^{385,386} Following the latter example (**P97d**, Scheme 61), the enantioselective synthesis of chiral amino acids via AH of non-cyclic α - and β -(arylsulfonamido)acrylates is of great importance. In 2005, a team from Merck published the synthesis of an anthrax lethal factor inhibitor via ruthenium-catalyzed AH of **S98** (Scheme 62).³⁸⁷ Catalyst screening identified that JosiPhos **L21d** and the bis-thiophene atropisomeric ligand **L49** gave excellent enantioselectivities. Later, in 2016, Sato, Saito and co-workers reported nickel-promoted regioselective carboxylation of internal enamides to afford a range of α -substituted β -aminoacrylates **S99**. These were then subjected to the rhodium-catalyzed AH using Walphos ligand **L22d**. Chiral amino acid derivatives **P99** were furnished in a highly enantioselective manner (Scheme 62).³⁸⁸ On the other hand, the AH of cyclic *N*-sulfonyl enamines is rare. To the best of our knowledge, there is only one example in the literature, reported by Andersson's group, using iridium complexes bearing chiral P,N ligands.³⁸⁹ However, the method was hampered by low conversions and moderate enantioselectivities with a very narrow scope.

Scheme 62. Metal-catalyzed AH of α - and β -(arylsulfonamido)acrylates.

Merck (2005)



Sato, Saito (2016)

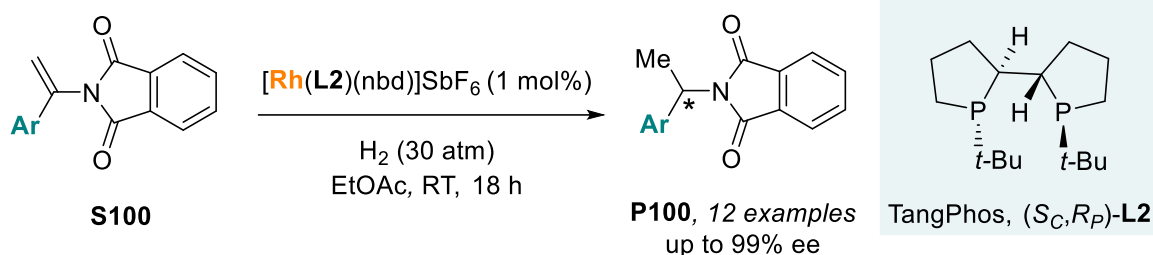


3.4. Other enamides

The AH of *N*-phthaloyl enamides is a promising method for the preparation of chiral amines. Apart from serving as a directing group, the phthalimido functionality can be easily removed under mild conditions. In 2006, X. Zhang and co-workers reported the highly enantioselective hydrogenation of α -aryl *N*-phthaloyl enamides using rhodium catalysts derived from TangPhos (**L2**) (Scheme 63).³⁹⁰ The resulting chiral α -methyl, aryl *N*-phthalimides **P100** were generally obtained in excellent enantioselectivities but these dramatically decreased for substrates bearing an *ortho*-substituent on the aromatic ring. In contrast, the preparation of enantioenriched α -methyl, alkyl *N*-phthalimides using AH has not yet been explored. Later, the authors reported the use of the same chiral ligand **L2** in the rhodium-catalyzed AH of *N*-phthaloyl dehydroamino acid esters, thus affording highly valuable chiral α - or β -amino acid derivatives with good to excellent enantioselectivities.³⁹¹

Scheme 63. Rhodium-catalyzed AH of *N*-phthaloyl enamides.

X. Zhang (2006)

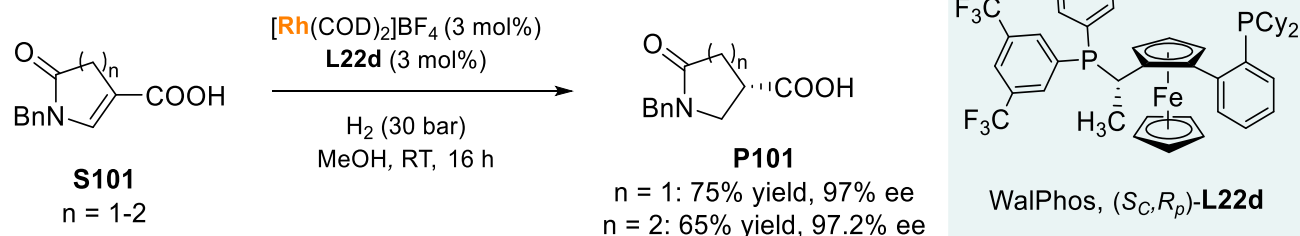


The rhodium-catalyzed AH of heterocyclic β -aminoacrylates **S101** was accomplished by Gallagher and co-workers in 2016 (Scheme 64).³⁹² By using WalPhos **L22d** as a chiral ligand, several pyrrolidine and piperidone variants were efficiently hydrogenated, providing chiral heterocyclic amino acids **P101** with high enantioselectivity. The use of the carboxylic acid was essential for the success of the reaction. Similarly, the AH of β, γ -unsaturated γ -lactams was described by Liu, W. Zhang and co-workers, although the hydrogenation proceeded via *N*-acyliminium cations.¹⁹⁶

On the other hand, Ding, Han and co-workers recently described the double asymmetric hydrogenation of 3,4-dialkylidene-2,5-diketopiperazines using an iridium-SpinPhox (**C4**) complex as catalyst.³⁹³

Scheme 64. Metal-catalyzed AH of lactams.

Gallagher (2016)

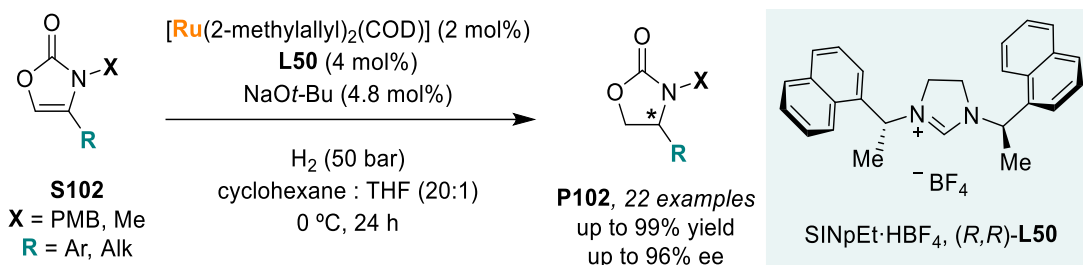


The enantioselective synthesis of chiral 2-oxazolidinones, widely used as Evans' chiral auxiliaries, has attracted considerable attention for the construction of new chiral building blocks and the development of new asymmetric transformations. An alternative to the conventional approach, limited to easily accessible chiral β -amino alcohols, is the direct AH of 2-oxazolones. In this regard, in 2018, Glorius and co-workers reported an innovative protocol for the ruthenium-catalyzed AH of **S102** using **L50** as precursor of the NHC ligand (Scheme 65).³⁹⁴ A variety of chiral 2-oxazolidinones **P102** were obtained in excellent enantioselectivities (up to 96% ee). The formal synthesis of (-)-aurantioclavine was demonstrated as a synthetic application. X. Zhang's group previously reported the rhodium-catalyzed AH version of this transformation using TangPhos **L2**, albeit with moderate

enantioselectivities and restricted mainly to substrates bearing electron-donating groups on the aryl ring.³⁹⁵

Scheme 65. Ruthenium-catalyzed AH of 2-oxazolones.

Glorius (2018)



4. Asymmetric Hydrogenation of Enamines

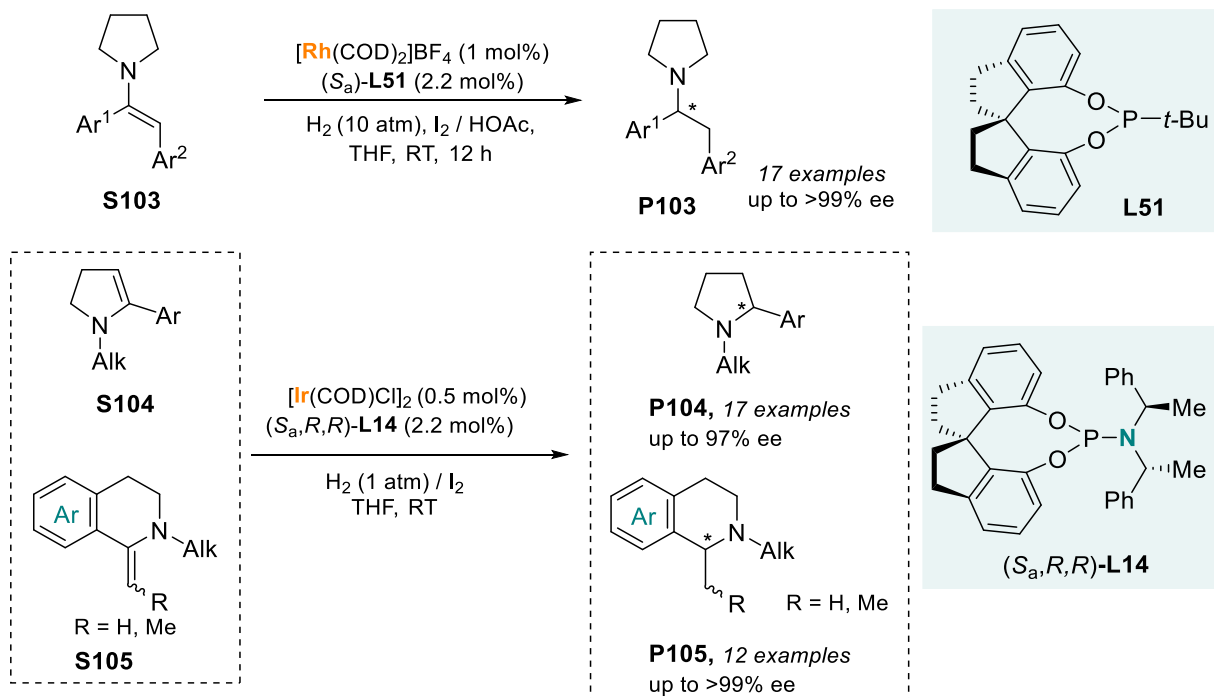
Although great progress has been made in the transition metal-catalyzed asymmetric hydrogenation of *N*-protected enamides, the introduction and removal of the protecting group reduce the overall efficiency of the method and limit its applications in the synthesis of optically active amines. To overcome this drawback, significant efforts have been devoted to the development of new chiral catalysts for the direct AH of enamines, including *N*-alkyl, *N*-aryl or unprotected amines.⁴⁰

4.1. *N*-alkyl enamines

In 2006, Zhou pioneered the AH of cyclic enamines using rhodium catalysts bearing monophosphorus ligands. In particular, spiro-phosphinite ligand **L51** showed excellent enantioselectivities for simple *N,N*-dialkyl enamines **S103** (Scheme 66).^{396,397} The reaction rates were enhanced using I₂/acetic acid as additives. Later, in 2009, the same group reported that other *N*-alkylated enamines could be efficiently hydrogenated using a similar catalytic system Ir/**L14**/I₂ (Scheme 66). This protocol allowed the hydrogenation of both endocyclic³⁹⁸ (**S104**) and exocyclic³⁹⁹ (**S105**) enamines in excellent enantioselectivities under very mild conditions (1 bar of H₂ and RT). Pfaltz also contributed to the field using phosphino-oxazoline ligands for the iridium-catalyzed AH of **S103**-type substrates, albeit with lower ee values.⁴⁰⁰

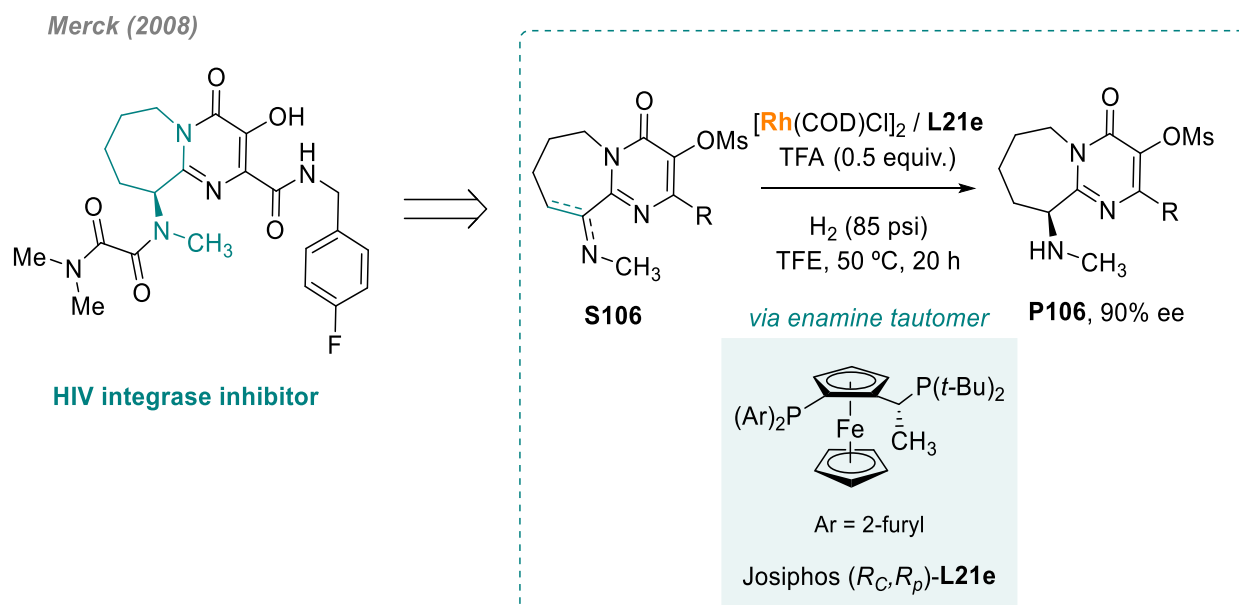
Scheme 66. Metal-catalyzed AH of endocyclic and exocyclic *N*-alkyl enamines.

Zhou (2006, 2009)



In 2009, a team from Merck applied the direct AH of alkylated enamines to the synthesis of an HIV integrase inhibitor (Scheme 67).⁴⁰¹ Using Rh and a JosiPhos ligand (**L21e**) a mixture of imine/enamine **S106** was efficiently hydrogenated, affording **P106**, a direct precursor of the target drug, in 90% ee. Interestingly, a deuterium labeling study suggested that the AH proceeds predominantly via the enamine tautomer.

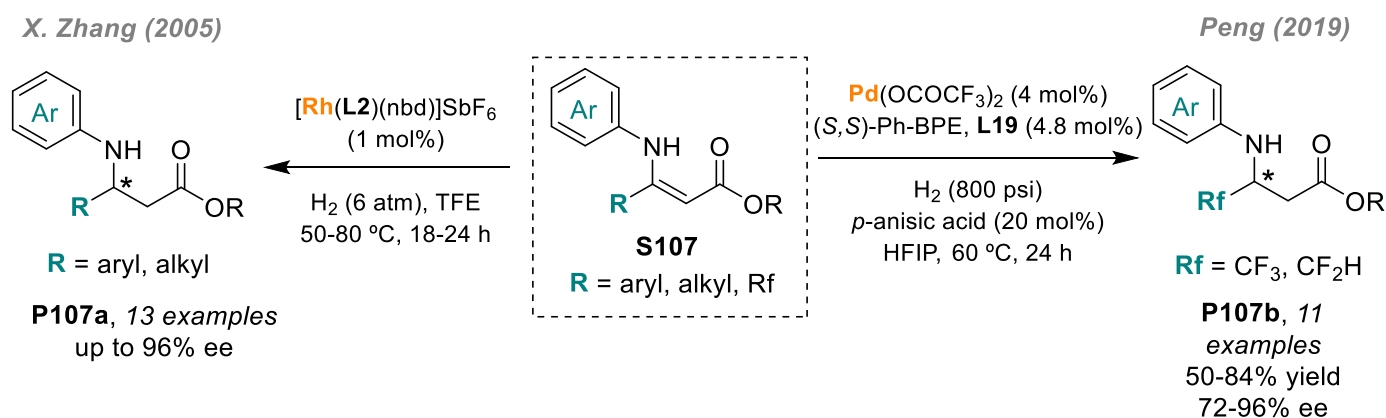
Scheme 67. Catalytic synthesis of an HIV integrase inhibitor.



4.2. *N*-aryl enamines

The enantioselective synthesis of *N*-aryl β -enamino esters was first studied in 2005, when X. Zhang and co-workers developed an enantioselective strategy based on the rhodium-catalyzed AH of *N*-aryl enamines **S107** (Scheme 68).⁴⁰² Chiral *N*-aryl substituted β -amino acid derivatives **P107a** were obtained in moderate to excellent enantioselectivities (79-96% ee) using a P-stereogenic ligand (TangPhos, **L2**). However, the reaction was highly substrate-dependent and **S107** bearing a CF₃ as high electron-withdrawing group showed poor conversion. To overcome this limitation, Peng recently reported an alternative approach using Pd/**L19** as catalyst.⁴⁰³ Chiral β -fluoroalkyl β -amino acid derivatives **P107b** were obtained in good yields and excellent enantioselectivities (Scheme 68). The use of *p*-anisic acid, which can promote the tautomeric transformation between imines and enamines, enhanced both the activity and enantioselectivity. The authors speculated that the hydrogenation could occur through an asymmetric reduction of the iminium ion rather than the enamine form of the substrate.

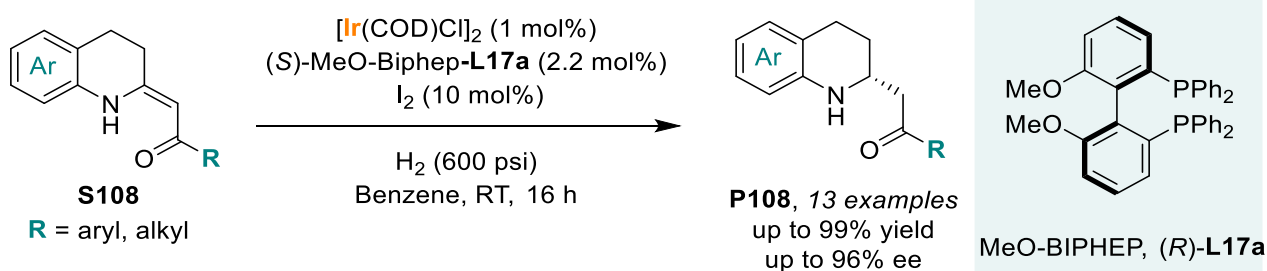
Scheme 68. Metal-catalyzed AH of *N*-aryl enamines.



In 2009, Zhou and co-workers described the first highly enantioselective AH of exocyclic unprotected enamines **S108** by using Ir/(*S*)-**L17a**/I₂ as catalytic system (Scheme 69).⁴⁰⁴ The resulting chiral amines **P108** were afforded in excellent yields and up to 96% ee.

Scheme 69. Iridium-catalyzed AH of exocyclic *N*-aryl enamines.

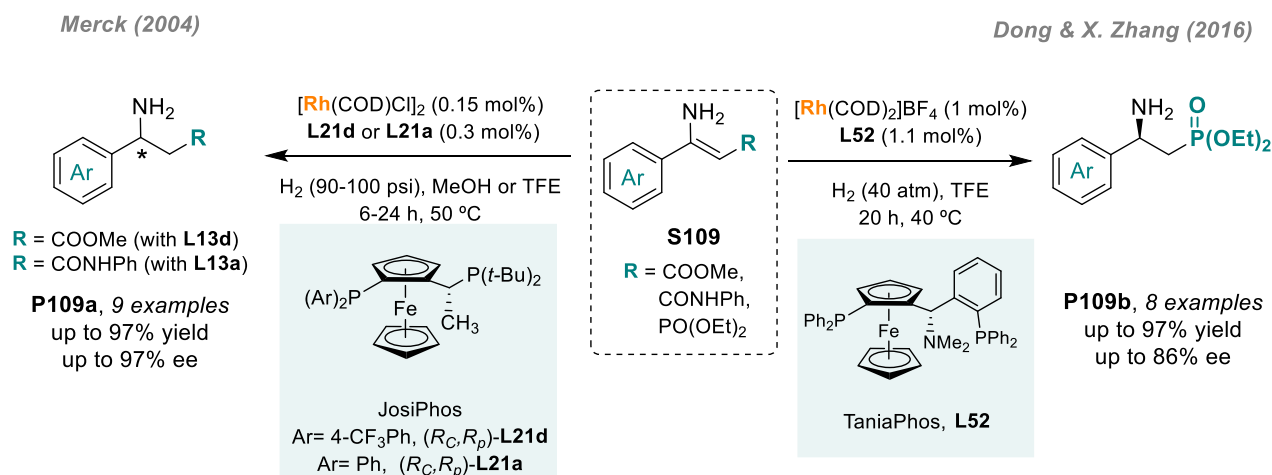
Zhou (2009)



4.3. Unprotected enamines

The AH of unprotected enamines has scarcely been studied because the transition metal catalyst is usually poisoned by the nucleophilic amino group. However, the direct AH of these substrates is highly desirable to avoid redundant introduction and subsequent removal of protecting groups, and also for the preparation of pharmacologically relevant compounds. In 2004, a team from Merck reported the first example of catalytic AH of unprotected β -enamine esters and amides (**S109**), using Rh-JosiPhos complexes as catalysts (Scheme 70).⁴⁰⁵ Ligand **L21d** gave the best results in the AH of enamine esters, while **L21a** gave the highest rates and enantioselectivities for the AH of enamine amides. β -Amino acids derivatives **P109a** were attained in excellent yields and enantioselectivities, thus proving that the *N*-acyl group is not always a prerequisite for such transformations.

Scheme 70. Rhodium-catalyzed AH of β -functionalized enamines.

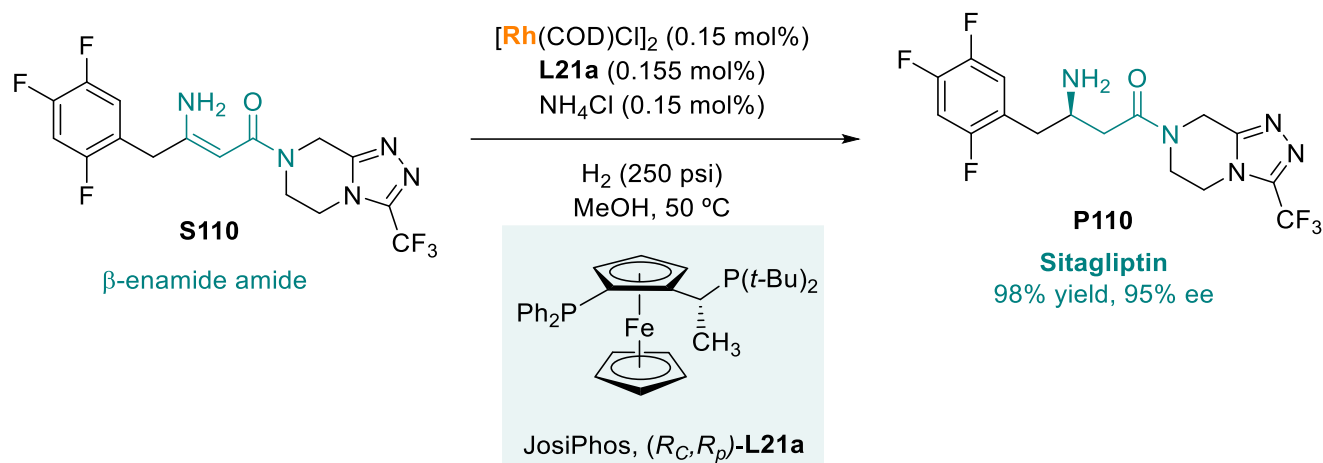


The applicability of this protocol in late-stage functionalization was showcased by the asymmetric synthesis of Sitagliptin (**P110**, Scheme 71), which was implemented on a manufacturing scale.⁵⁸ **P110** was obtained in 98% yield and 95% ee (improved to >99% ee by recrystallization) using (*R*_C,*R*_P)-**L21a**. More recently, Chikkali and co-workers reported that Rh complexes bearing chiral FerroLANE ligands also catalyze the AH of **S110** to yield sitagliptin with excellent enantioselectivity (98% ee).⁴⁰⁶

The asymmetric synthesis of **P110** was also accomplished via direct asymmetric reductive amination (ARA) with unprecedented levels of asymmetric induction.⁴⁰⁷ In addition, Ru catalysis has been successfully applied in both ARA or direct AH of unprotected enamines for the preparation of other pharmacologically relevant compounds.^{408, 409}

Scheme 71. Asymmetric synthesis of Sitagliptin via rhodium-catalyzed AH.

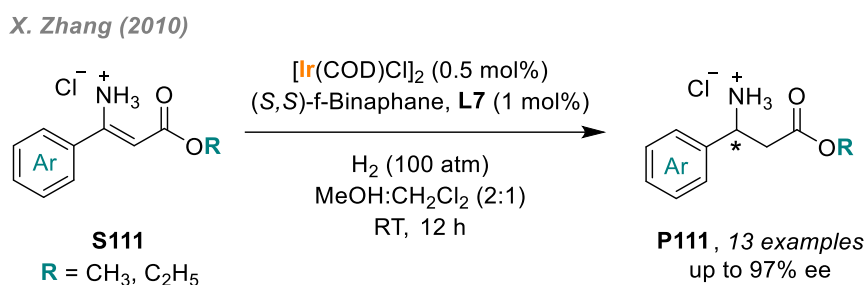
Merck (2009)



The rhodium-catalyzed AH of unprotected β-enamine phosphonates was described by Dong, X. Zhang and co-workers (Scheme 70).⁴¹⁰ By using Rh/TaniaPhos-**L52**, the method provided an efficient route to free β-amino phosphonates **P109b**, which are important intermediates in biochemistry and pharmaceuticals. This work provided an alternative to the protocol previously reported by Ding, in which the amine was necessarily protected by acyl groups (Scheme 53).³³² Also, Ruchelman *et al.* reported the enantioselective hydrogenation of unprotected β-aminosulfones using Rh catalysis, which afforded a key intermediate of the phosphodiesterase 4 (PDE4) inhibitor Apremilast.⁴¹¹

Iridium catalysis has also been applied in the AH of unprotected enamines. X. Zhang demonstrated that β-enamine hydrochloride esters **S111** can be suitable substrates for AH, despite primary amines might have a strong inhibitory effect on the iridium catalyst.⁴¹² The combination of Ir/f-binaphane (**L7**) and the use of hydrochlorides provided direct access to a range of enantiomerically enriched β-amino acids without use of an amino protecting group (Scheme 72).

Scheme 72. Iridium-catalyzed AH of β-enamine hydrochloride esters.



5. AH of allyl amines

The AH of allyl amines remained relatively underdeveloped before the last decade. Allyl amines are usually considered minimally functionalized olefins as the unsaturated bond lacks close coordinating groups. For this reason, the AH of allyl amines is more challenging if compared to imines or enamines. Early last decade, a range of new strategies were described for the metal-catalyzed AH of allyl amines, exhibiting high reactivity and enantiocontrol. Thus, the preparation of highly valuable β - and γ -substituted chiral amines is now more accessible. In this section, the most important precedents in the field will be described, along with pharmaceuticals and drugs that can be attained by means of the AH of allyl amines (Figure 8).

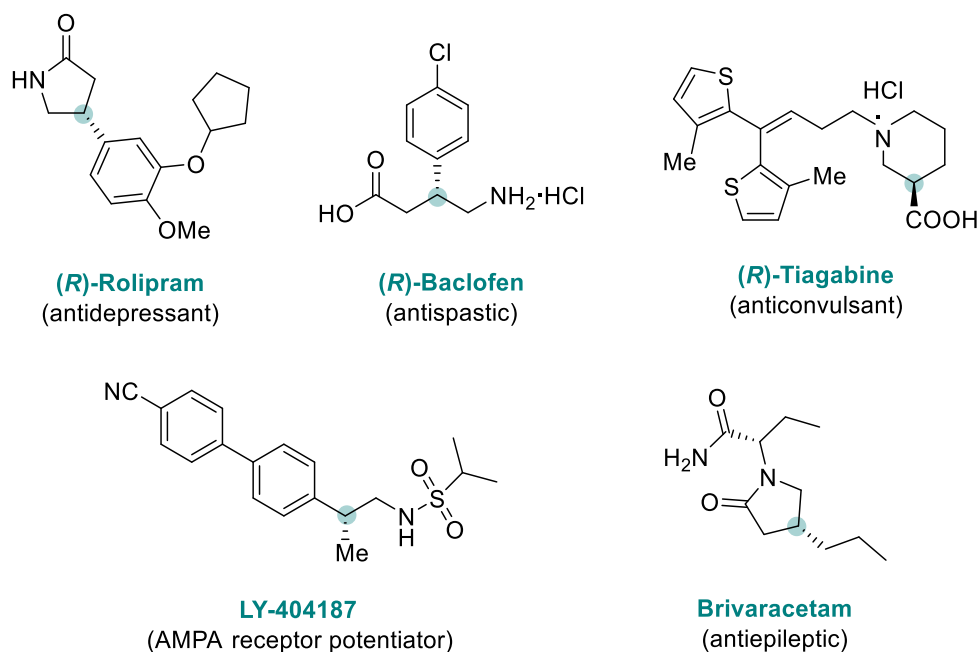


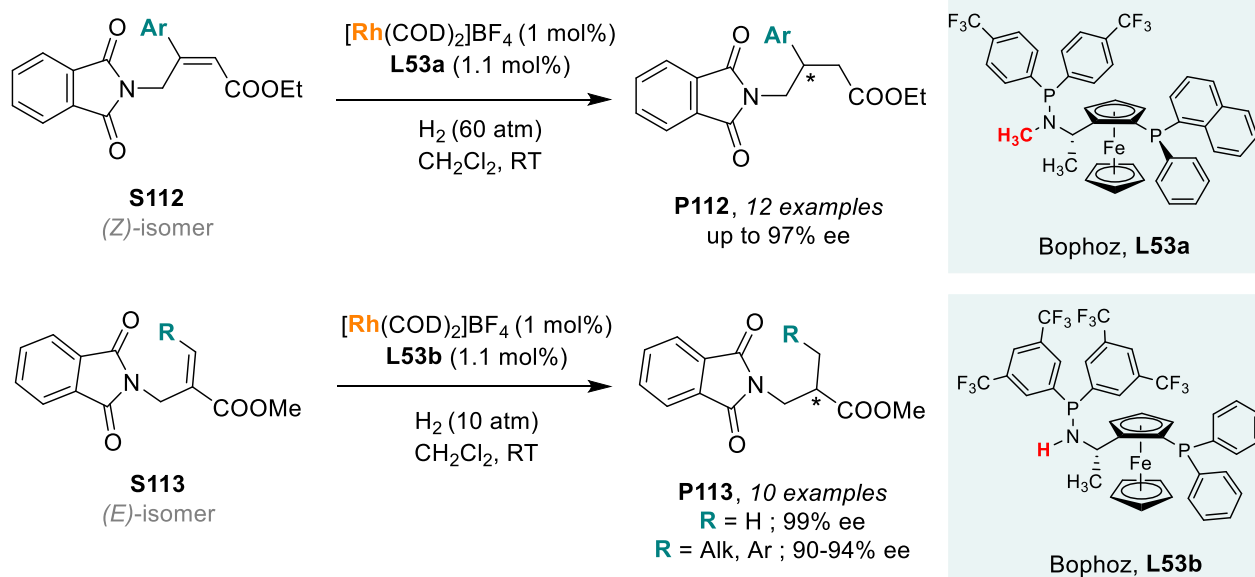
Figure 8. Representative drugs that can be prepared via the AH of allyl amines.

5.1. *N*-phthaloyl allyl amines

As previously stated, chiral β - and γ -amino acids and their derivatives are important building blocks in the synthesis of pharmaceuticals and other bioactive compounds. Zheng and co-workers reported the first highly enantioselective synthesis of chiral β -aryl- γ -amino acid ester derivatives **P112** via rhodium-catalyzed AH of γ -phthalimido-substituted acrylates⁴¹³ using the BoPhoz-type ligand^{414, 415} **L53a** (Scheme 73). The method showed high reactivity and enantioselectivity (up to 97% ee) for a range of (*Z*)-substrates **S112**. The method was successfully applied to the synthesis of several chiral pharmaceuticals including (*R*)-rolipram and (*R*)-baclofen (Figure 8) with high enantioselectivities. The same group later expanded the applicability of this approach to the asymmetric synthesis of β^2 -amino acids **P113** via rhodium-catalyzed AH using another ligand of the BoPhoz family: **L53b** (Scheme 73).⁴¹⁶ Interestingly, the presence of an N-H proton in the ligand significantly improved the enantioselectivity, whereas the introduction of a *P*-stereogenic center in the phosphino moiety proved unfruitful and displayed low conversion. The same catalytic system also exhibited excellent ee values for β -unsubstituted substrates **S113** (99% ee). Other protocols for the stereoselective synthesis of chiral β^2 -amino acids include the Rhodium-catalyzed AH of β -substituted α -aminomethylacrylates that Börner and co-workers^{417, 418} and Qiu and co-workers^{419, 420} independently reported earlier last decade.

Scheme 73. Rhodium-catalyzed AH of β - and γ -phthalimido substituted unsaturated esters.

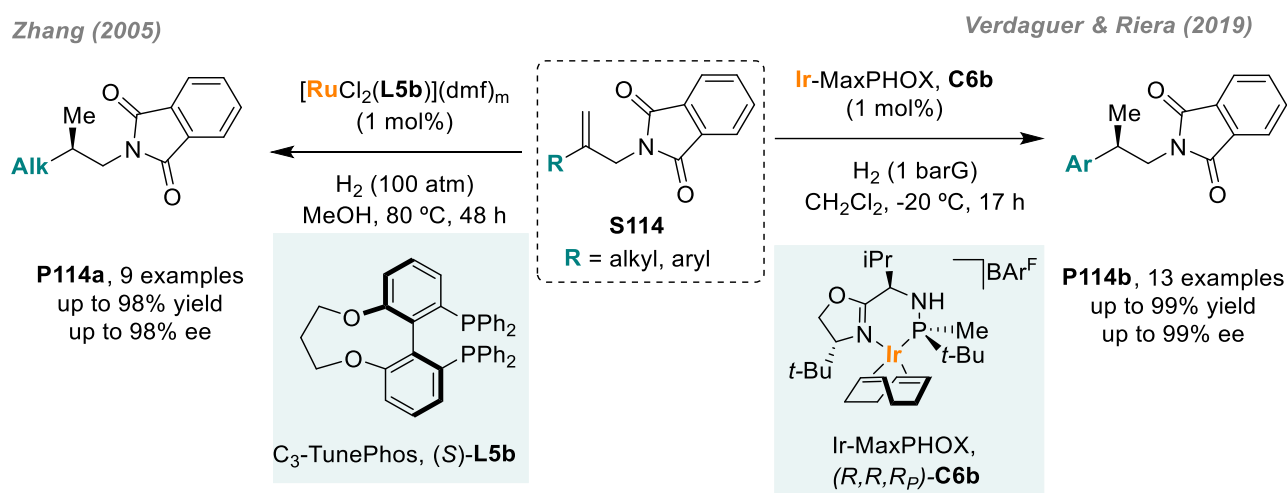
Zheng (2007, 2008)



Chiral amines bearing a β -methyl stereogenic center are extremely interesting as they are present in numerous drugs and pharmaceuticals. The AH of 2-substituted allyl phthalimides is an efficient route

towards their preparation. X. Zhang pioneered the field with the ruthenium-catalyzed AH of terminal disubstituted allylphthalimides **S114** using C_3 -TunePhos ligand **L5b** (Scheme 74).⁴²¹ Chiral β -alkyl- β -methyl amines **P114a** were attained in excellent yields and enantioselectivities. However, the scope of this reaction was limited to alkyl substituents, as the hydrogenation of an aromatic substrate gave moderate enantioselectivity. To overcome this limitation, Verdaguer & Riera's laboratory recently reported the highly enantioselective hydrogenation of 2-aryl allyl phthalimides using iridium catalysis (Scheme 74).⁴²² Ir-MaxPHOX **C6b** bearing a bulky substituent on the oxazoline ring gave the best enantioselectivities (>99% ee in the best cases for **P114b**), showing an exquisite functional group tolerance for a range of substrates. Several direct synthetic applications of this catalytic method were disclosed, such as the formal synthesis of (*R*)-Lorcaserin (Figure 1), which is a marketed anorectic drug, and also a novel approach to enantiomerically enriched 3-methyl indolines.

Scheme 74. Metal-catalyzed AH of *N*-allyl phthalimides.



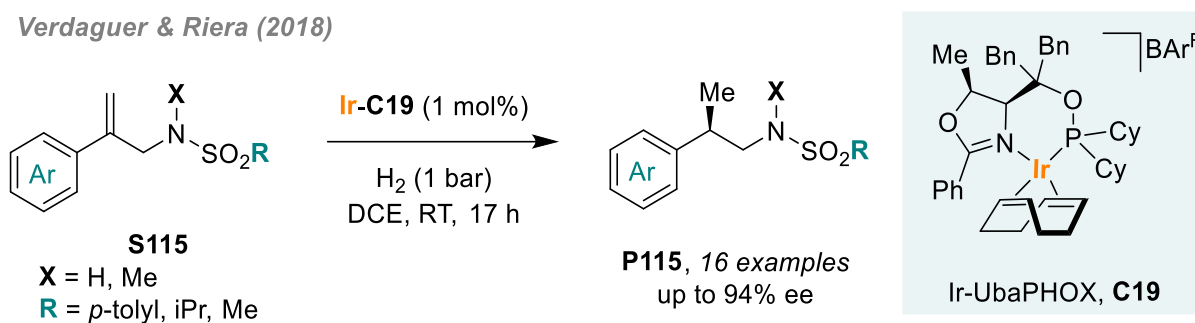
5.2. *N*-sulfonyl allyl amines

Verdaguer & Riera's group also reported the iridium-catalyzed AH of *N*-sulfonyl allyl amines **S115**,⁴²³ which can be easily prepared by the iridium-catalyzed isomerization of *N*-tosylaziridines.⁴²⁴ By using the commercially available iridium catalyst UbaPHOX (**C19**), first reported by Pfaltz,^{425,426} a wide range of chiral β -methyl amines were afforded with good to excellent enantioselectivities (Scheme 75). These compounds are also key intermediates for the preparation of allosteric modulators of AMPA receptor such as LY-404187 (Figure 8).⁴²⁷

Iridium complexes bearing chiral *P,N* ligands were also applied to the catalytic hydrogenation of cyclic *N*-sulfonyl allyl amines **S116**, as reported by Andersson and co-workers.^{428,389} The reaction

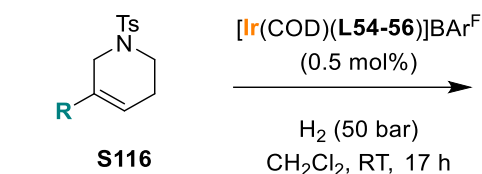
was highly substrate-dependent and an appropriate chiral ligand was used for each case. Substrates **S116** bearing aliphatic substituents were efficiently hydrogenated using a phosphino-oxazoline ligand **L54** whereas phosphino-imidazole **L55** and phosphino-thiazole **L56** gave excellent activities and selectivities for aromatic substrates, depending on their electronic properties (Scheme 76). In addition, the methodology was further expanded to the iridium-catalyzed AH of five- and seven-membered *N*-heterocyclic olefins. The chiral pyrrolidines, piperidines and azepanes, which are highly valuable motifs for the synthesis of medicinal compounds and natural products, were attained in excellent enantioselectivities. Similarly, W. Zhang and co-workers recently reported the catalytic AH of 3-substituted 2,5-dihydropyrroles (**S117**) using an Ir-catalyst with an axially flexible chiral phosphine-oxazoline ligand named BiphPhox (**L57**).⁴²⁹ Chiral *N*-tosyl pyrrolidines **P117** were efficiently prepared in good to excellent enantioselectivities (Scheme 76).

Scheme 75. Iridium-catalyzed AH of 2-aryl *N*-sulfonyl allyl amines.



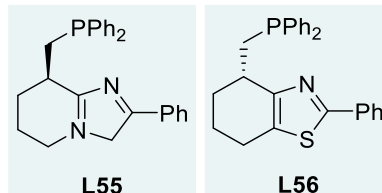
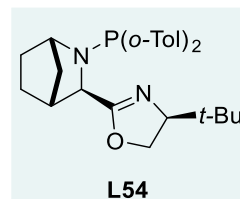
Scheme 76. Iridium-catalyzed AH of cyclic *N*-sulfonyl allyl amines.

Andersson (2010)

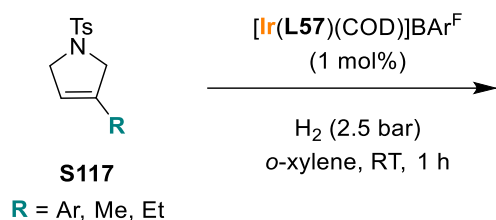


R = alkyl with **L54**
R = aryl (EDG) with **L55**
R = aryl (EWG) with **L56**

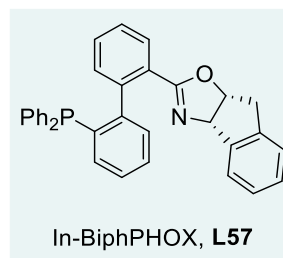
P116, 15 examples
up to >99% ee



Zhang, Yang (2017)



P117, 17 examples
R = Ar, up to 98% ee
R = Alk, up to 83% ee

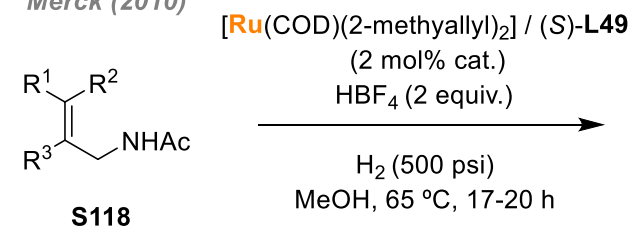


5.3. Other allyl amines

During the last decade, other remarkable examples have also been reported for the highly enantioselective hydrogenation of protected allyl amines. In 2010, a team from Merck described a general method for the ruthenium-catalyzed AH of trisubstituted *N*-acyl allyl amines **S118** using the axially chiral ligand **L49**, affording chiral β -substituted amines **P118** with excellent enantioselectivities (Scheme 77).⁴³⁰

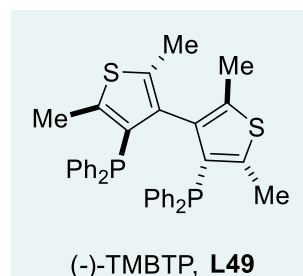
Scheme 77. Ruthenium-catalyzed AH of *N*-acyl allyl amines.

Merck (2010)



R¹ = H, Ph, alkyl; **R**² = H, alkyl;
R³ = aryl, Me, Bn

P118, 9 examples
up to 98% ee

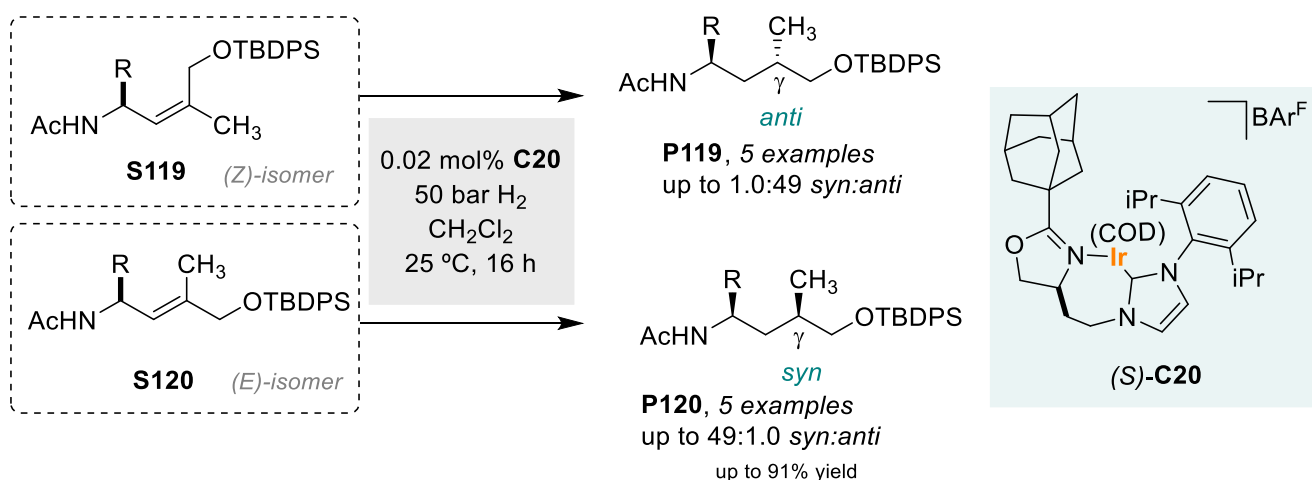


Optically active amines with remote stereocenters, such as γ -substituted chiral amines, are often key contributors to the potent biological activity of many natural products and pharmaceuticals. Important

examples of this class of compounds are dexbrompheniramine, which is an antihistaminic, and tolterodine, an anticholinergic (Figure 1). γ -Amino acids such as γ -aminobutyric acid (GABA) are also important in medicinal chemistry. Consequently, asymmetric synthesis of chiral derivatives of GABA with appropriate sidechains are potentially important for the design of new drug-like molecules with enhanced pharmacological properties. Nevertheless, the direct preparation of γ -substituted chiral amines remains underdeveloped compared to the well-established methods for constructing of α - and β -substituted chiral amines. In addition, most of the enantioselective syntheses of these compounds are indirect and often require multiple steps. Buchwald's group first reported a direct approach to γ -chiral amines by enantioselective CuH-catalyzed reductive relay hydroamination.⁴³¹ Hull and co-workers developed efficient conditions for the highly enantioselective synthesis of γ -branched amines via rhodium-catalyzed reductive amination.⁴³² Alternatively, the redox neutral asymmetric isomerization of allylic amines is a method of choice with an excellent atom economy, although current methods are hampered by very limited substrate scope.^{17,433} In this scenario, the development of new transition metal-catalyzed AH processes to afford enantioenriched γ -substituted amines is extremely desirable. In 2011, Burgess and co-workers reported the asymmetric synthesis of α -methyl- γ -amino acid derivatives via catalytic AH using a carbene-oxazoline iridium complex **C20** (Scheme 78).⁴³⁴ The method of optimization was based on varying peripheral aspects of the substrate rather than optimizing the catalyst via ligand modifications. Following this approach, *O*-TBDPS-protected allylic substrates gave the best results. Once hydrogenated under mild conditions, chiral γ -methyl amines were afforded in high stereocontrol. *Anti*-products **P119** were formed from the *Z*-alkenes **S119**, while the *E*-isomers **S120** gave *syn*-target compounds **P120**.

Scheme 78. Iridium-catalyzed AH of *N*-acyl allyl amines.

Burgess (2011)

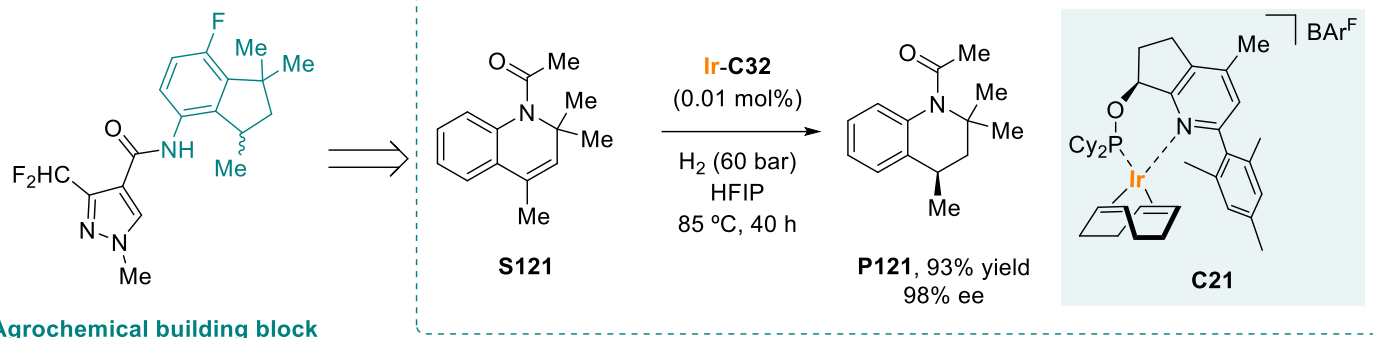


Similarly, Beller and co-workers recently used **C21**, an iridium-*P,N*-ligand complex, for the AH of *N*-acyl endocyclic allyl amines **S121** (Scheme 79).⁴³⁵ Using HFIP as reaction solvent, the reaction proceeded efficiently to afford chiral γ -methyl amide **P121**, which is a key intermediate for the preparation of a common agrochemical building block.

Another type of endocyclic allyl amines, amino acids **S122**, were hydrogenated by Zhou and co-workers using iridium complexes of *P,N*-ligands with a spiro backbone (**C3c** and **C3d**) (Scheme 80).⁴³⁶ In particular, **C3c** was chosen as the best catalyst for *N*-Boc allyl amines, while **C3d** was used for *N*-Me and unprotected allyl amines. The resulting chiral heterocyclic acids **P122** were afforded in excellent enantioselectivities, and the potential utility was demonstrated by the concise asymmetric synthesis of (*R*)-nipecotic acid and (*R*)-tiagabine (Figure 8). In fact, chiral cyclic amines with a β -carboxylic acid or derivatives are common structural motifs in many bioactive compounds. For example, the key intermediate for the preparation of a histone deacetylase inhibitor (HDAC, Scheme 81) was obtained via the ruthenium-catalyzed AH of **S123** using **L17d**.⁴³⁷ This achievement was reported by a team from Roche in 2014. They disclosed that the presence of a carboxylic acid was crucial for the rapid hydrogenation of the unsaturated bond.

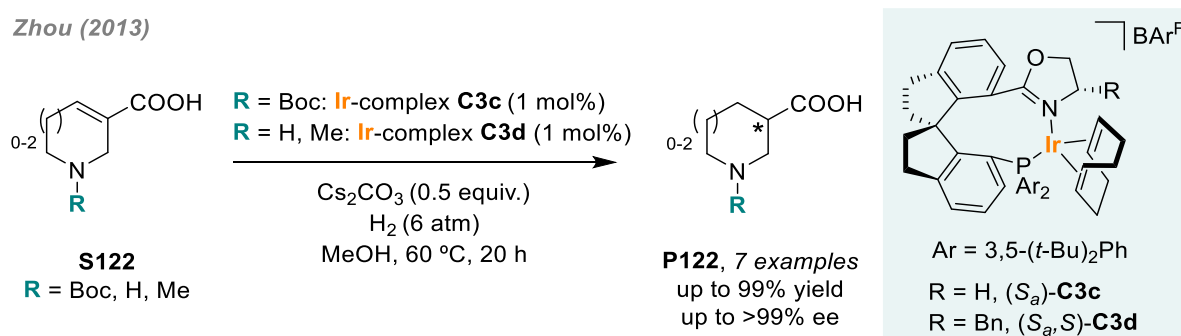
Scheme 79. Synthesis of an agrochemical building block via AH.

Beller (2020)



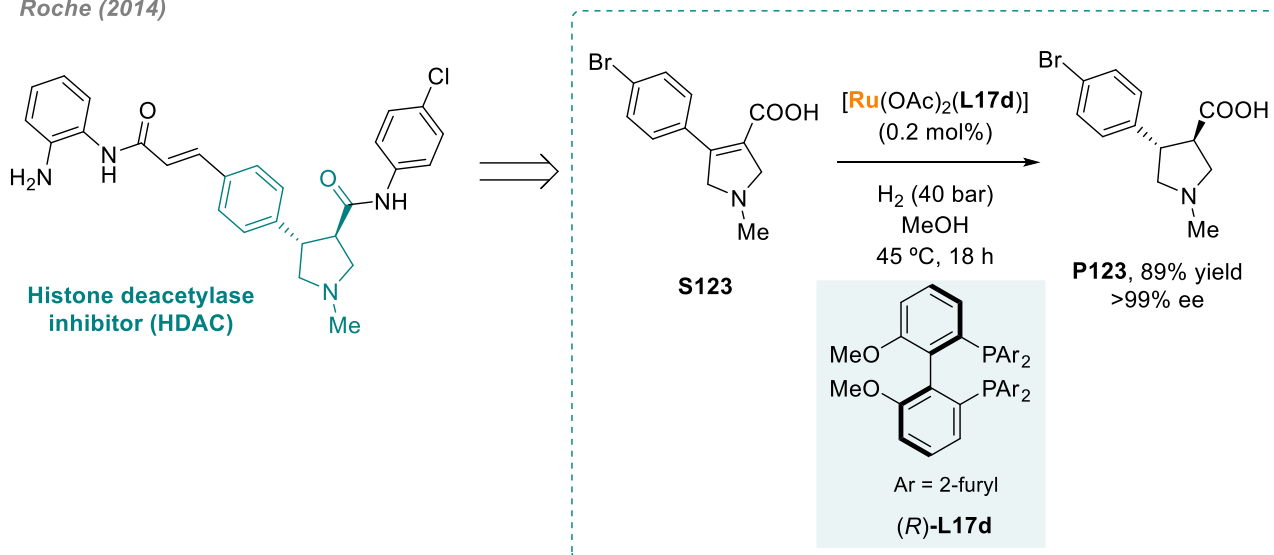
Scheme 80. Iridium-catalyzed AH of endocyclic *N*-allyl amines.

Zhou (2013)



Scheme 81. Asymmetric synthesis of a HDAC inhibitor via AH.

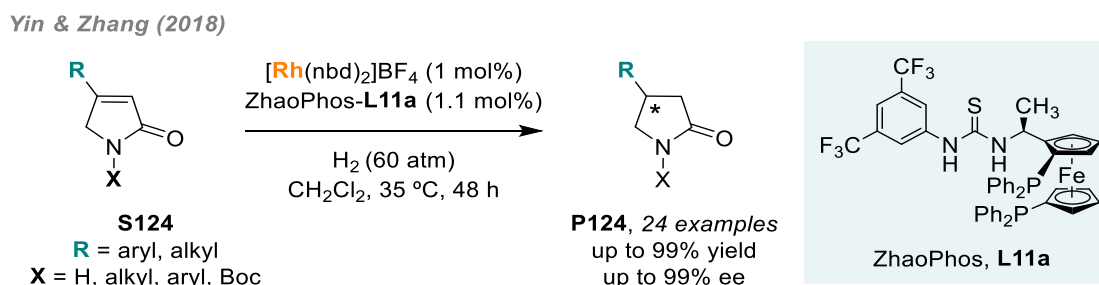
Roche (2014)



Chiral γ -lactams are ubiquitous in biological compounds. The antiepilepsy drug Brivaracetam or the PDE-4 inhibitor Rolipram® are examples of γ -lactam clinical drugs (Figure 8). These lactams are key building blocks in medicinal chemistry as masked γ -amino acids. In their efforts to prepare γ -lactams in optically pure form, Yin, X. Zhang and co-workers recently developed the AH of **S124** using Rh/ZhaoPhos-**L11a** (Scheme 82).⁴³⁸ A wide range of enantioenriched γ -lactams **P124** were

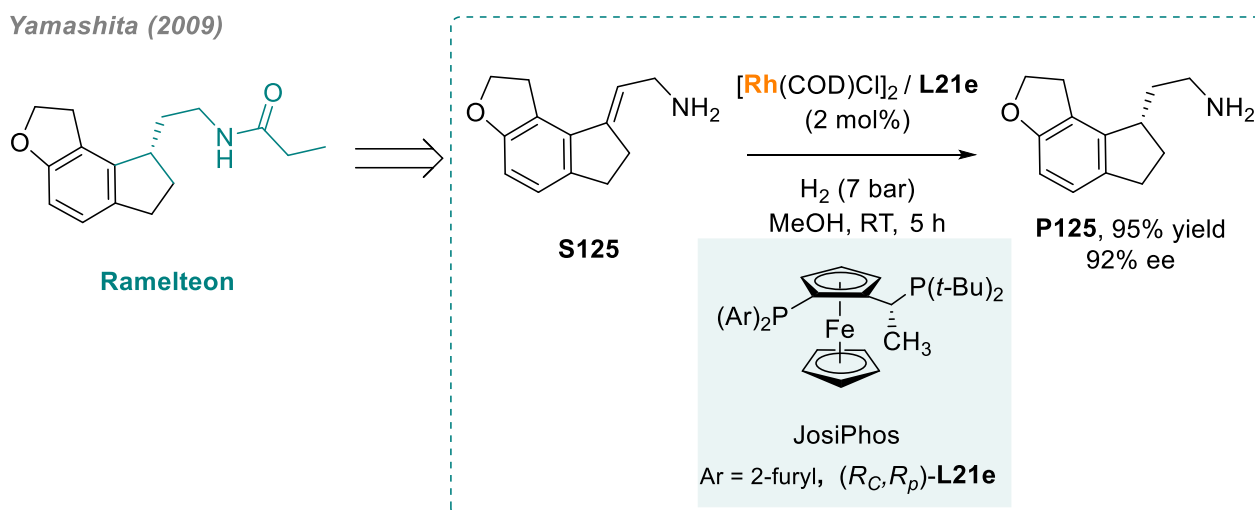
furnished in excellent yields and enantioselectivities. Interestingly, the catalytic system successfully tolerated free NH amide group which actually played a positive effect by hydrogen bonding with the thiourea motif of **L11a**.

Scheme 82. Rhodium-catalyzed AH of β -aryl-substituted α,β -unsaturated lactams.



Another important drug with a chiral center in γ -position of the amino group is ramelteon, a selective melatonin MT1/MT2 receptor agonist. Yamashita's laboratory reported that Rh/JosiPhos-**L21e** was a highly effective catalyst for the AH of a key precursor, the unprotected allyl amine **S125** (Scheme 83).⁴³⁹ Interestingly, the primary amino group might act as an anchoring group to the rhodium atom. Chiral amine **P125** was smoothly prepared in 92% ee using very mild conditions.

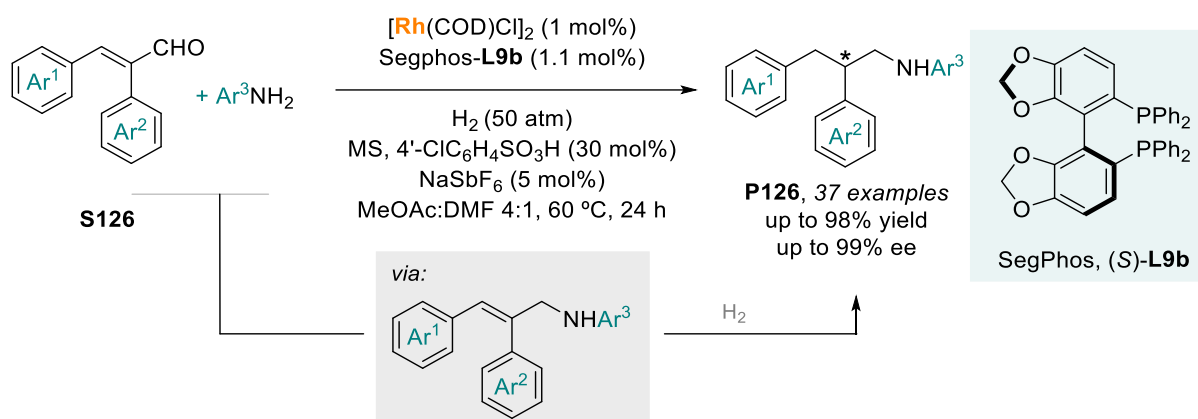
Scheme 83. Rhodium-catalyzed AH of unprotected primary allyl amine.



Finally, Huang, Geng, Chang and co-workers recently reported a practical combination of AH and reductive amination in the enantioselective synthesis of the chiral β -aryl amines **P126** (Scheme 84). Starting from readily available anilines and α,β -unsaturated aldehydes **S126**, they described a one-pot hydrogenation that involved DRA and AH, using Rh/**L9b** complex as catalyst.⁴⁴⁰ Control experiments revealed that the construction of the C-N bond beforehand helped to pave the way for the subsequent AH of the corresponding *N*-allyl amine.

Scheme 84. The combination of AH and reductive amination.

Huang, Geng & Chang (2020)



6. Asymmetric hydrogenation of heteroaromatic compounds

The direct AH of heteroaromatic compounds provides straightforward access to the corresponding chiral saturated *N*-cyclic skeletons. This is a less explored area than the AH of prochiral unsaturated amines such as imines or enamides.^{30,31,32,441} This may be ascribed to several reasons: a) the possible deactivation of the chiral catalysts due to the basicity of the nitrogen atom of the aromatic ring; b) the lack of a coordinating group in simple aromatic compounds; and c) the increased stability due to the aromaticity of these compounds, which might require harsher conditions. Despite all these issues, remarkable advances have been disclosed during the last decade. In this section, we will review these advances along with the pioneering works and research milestones in this field, focusing mainly on heteroarenes such as quinolines, pyridines, quinoxalines and indoles.

6.1. Quinolines and derivatives

Optically pure tetrahydroquinolines (THQs) and their derivatives are of great importance due to their pharmaceutical and agrochemical applications,⁴⁴² as they are basic units in many natural products. Among the different strategies for their preparation, the AH of quinolines is the most effective.⁴⁴³

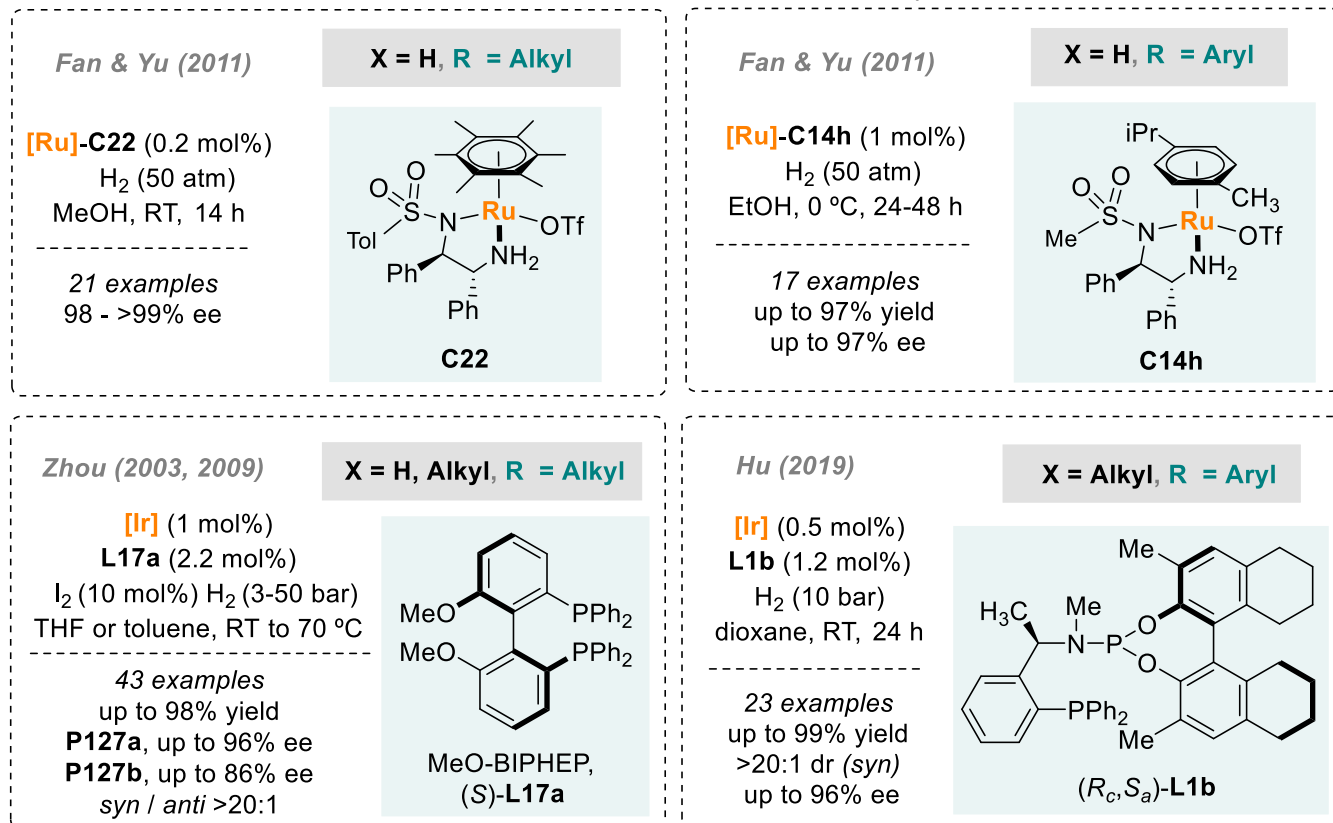
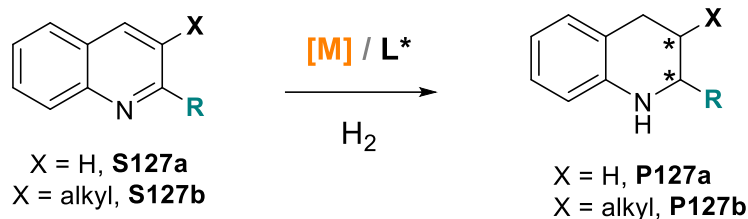
In 2011, Fan, Yu, Chan and co-workers reported the AH of a wide range of quinoline derivatives (**S127**) catalyzed by chiral cationic η^6 -arene Ru(II)-diamine complexes (Scheme 85).⁴⁴⁴ Interestingly, for 2-alkylquinolines, **C22** exhibited outstanding enantioselectivity as **P127a** (R = alkyl) were attained in excellent enantioselectivities (99% ee for most of the cases). To the best of our knowledge, this is the protocol with the highest level of enantioselectivity for 2-alkyl substituted quinolines

S127a. In contrast, the AH of 2,3-dialkyl quinolines **S127b** provided a very low ratio of diastereoselectivity. The same authors reported that similar Ru-diamine complexes were capable to efficiently hydrogenate **S127a** in solvent-free conditions,⁴⁴⁵ in neat water,⁴⁴⁶ in ionic liquids^{447,448} and in oligo(ethylene glycol)s through host-guest interactions.⁴⁴⁹ On the other hand, the AH of 2-aryl substituted quinolines resulted more challenging, and only few examples have been reported. The same group extended the use of these Ru(II)-diamine complexes and found that **C14h** was a highly active catalyst for the AH of 2-aryl quinolines, affording the corresponding **P127a** (R = aryl) in excellent yields and enantioselectivities (Scheme 85).⁴⁴⁴ Previously, Fan, Xu and co-workers had already disclosed that air-stable and phosphine-free iridium complexes were also efficient catalysts for the highly enantioselective hydrogenation of quinoline derivatives.⁴⁵⁰

Y.-G. Zhou's laboratory reported other important achievements in the field. In 2003, they pioneered the use of iridium complexes bearing axially chiral phosphines that, in combination with I₂, were found to be highly active in the AH of 2-alkyl quinolines (Scheme 85).⁴⁵¹ In particular, and when using **L17a**, **P127** were obtained in excellent yields and enantioselectivities (up to 96% ee). Using the same catalytic system, the substrate scope was further expanded to a wide range of 2-functionalized quinoline derivatives.^{452,453,454,455,456,457} More importantly, 2,3-dialkylquinolines were also efficiently hydrogenated using the same catalyst, although **P127b** were furnished from moderate to good enantioselectivities (up to 86% ee). Zhou's group later reported the iridium-catalyzed AH of quinolines activated by Brønsted acids, thus avoiding catalyst activation using I₂.⁴⁵⁸

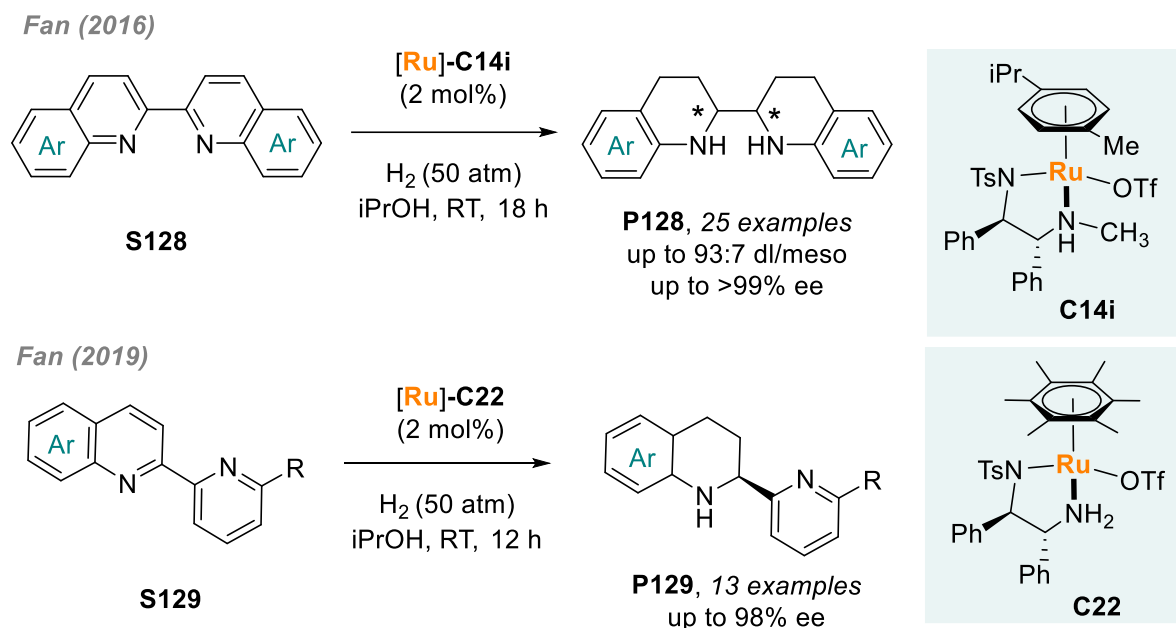
The highly enantioselective and catalytic hydrogenation of 3-alkyl-2-arylquinolines remained a challenging task until 2019, when Hu and co-workers examined the use of structurally fine-tuned phosphine-phosphoramidite **L1**-type ligands (Scheme 85).⁴⁵⁹ Using **L1b** as a chiral ligand, a highly diastereo- and enantioselective iridium-catalyzed AH of unfunctionalized 3-alkyl-2-arylquinolines was disclosed. The transformation displayed broad functional group tolerance, thus furnishing a wide range of 2,3-disubstituted tetrahydroquinolines **P127b** in up to 96% ee and with perfect *cis*-diastereoselectivity. In contrast, the AH of 2,3-diaryl quinolines remains unsolved. In general, the AH of 2,3-disubstituted quinolines represents a more difficult task due to the requirement of diastereocontrol in the construction of two vicinal stereogenic centers. Nevertheless, the AH of functionalized 2,3-disubstituted quinolines with a phthaloyl^{460,461} or an ester⁴⁶² group at the 3-position and an alkyl group at the 2-position of quinoline has been accomplished.

Scheme 85. Metal-catalyzed AH of unfunctionalized 2-quinolines and 2,3-disubstituted quinolines.



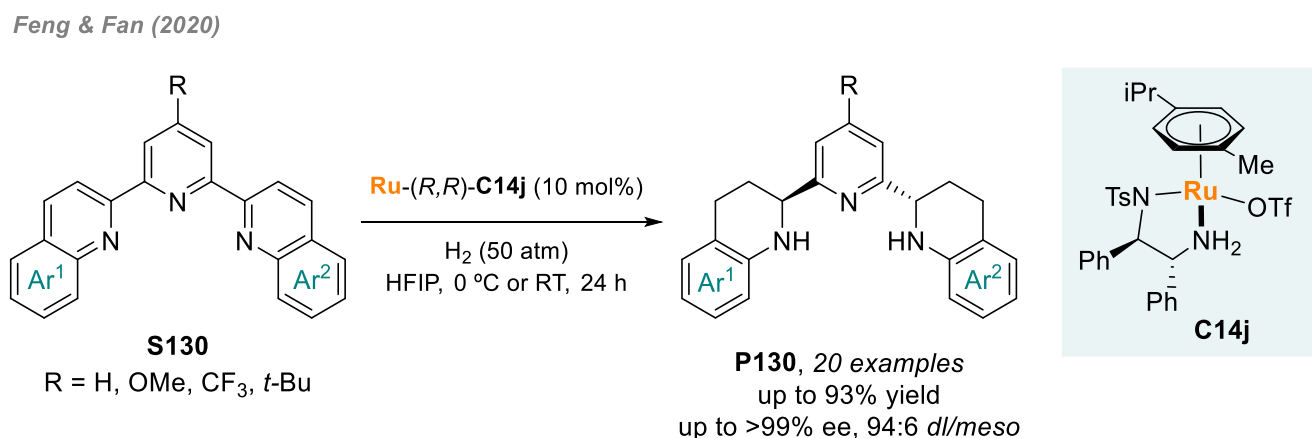
The chemistry of chiral vicinal diamines and their derivatives has attracted a great deal of interest because they are key substructures in many biologically active compounds. In 2016, Fan and co-workers reported the highly enantioselective synthesis of vicinal diamines by direct AH of 2,2'-bisquinolines **S128** (Scheme 86).⁴⁶³ Using the Ru/diamine complex **C14i**, the reaction proceeded with very good diastereoselectivity while reaching an unprecedented level of enantioselectivity (>99% ee in the best cases). The resulting chiral vicinal diamines **P128** can be used as new chiral ligands. Similarly, the same group later described the use of Ru-complex **C22** for the AH of 2-(pyridine-2-yl)quinoline derivatives **S129** (Scheme 86).¹¹⁸ Based on the resulting chiral scaffolds **P129**, a small library of tunable chiral pyridine-aminophosphine ligands were readily prepared.

Scheme 86. Ruthenium-catalyzed AH of 2,2'-bisquinoline derivatives.



In addition, the enantioselective hydrogenation of 2,6-bis(quinolinyl) pyridines (PyBQs) or terpyridine-type *N*-heteroarenes **S130** was successfully developed in 2020 by Fan's group using Ru(diamine) complex **C14j** as catalyst (Scheme 87).⁴⁶⁴ The method provided partially reduced chiral pyridine-amine-type products **P130** in high yields with excellent diastereo- and enantio-selectivity, which can serve as a new class of chiral nitrogen-donor ligands.

Scheme 87. Ruthenium-catalyzed AH of 2,6-bis(quinolinyl) pyridines (PyBQs).

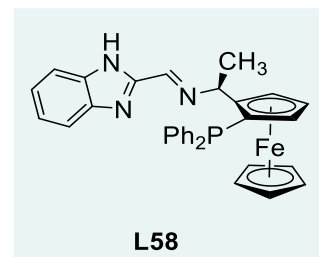
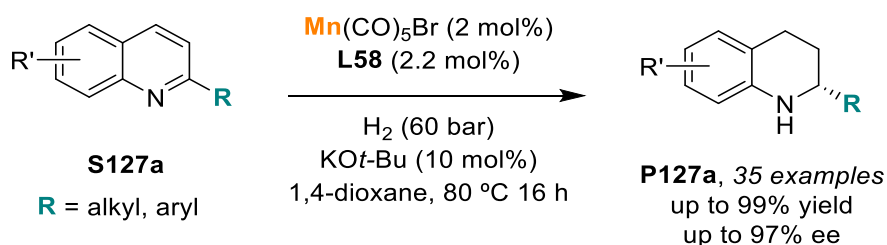


The AH of quinolines using a non-noble metal was also accomplished by Lan, Liu and co-workers in 2020. Using a chiral pincer manganese catalyst, the AH of quinolines **S127a** was achieved in high yields and enantioselectivities (up to 97% ee, Scheme 88).⁴⁶⁵ Interestingly, an effective π - π interaction between C=N double bond and the imidazole ring of the ligand **L58** ensured precise regulation of the

enantioselectivity. Undoubtedly, this represents an important precedent for the efficient AH of *N*-heteroaromatics without the need for precious metals.

Scheme 88. Mn-catalyzed AH of quinolines enabled by π - π interaction.

Lan & Liu (2020)

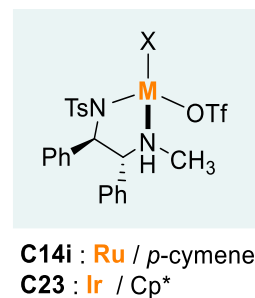
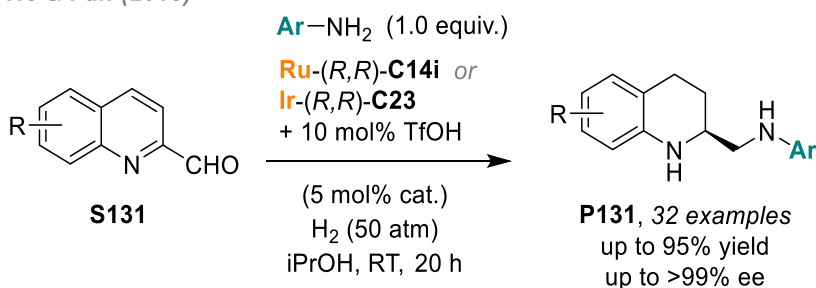


Although the catalytic AH of quinolines is the most direct and reliable approach, Mashima, Ratovelomanana-Vidal, Ohsima and co-workers reported the AH of quinolinium salts using cationic Ir(III) halide complexes with difluorophos (**L20**).⁴⁶⁶ This catalyst system successfully converted both 2-aryl- and 2-alkyl-quinolinium salts to the corresponding THQs with excellent enantioselectivities (up to 95% ee). The AH of quinolinium salts has been also applied as the key step for the synthesis of vabicaserin.⁴⁶⁷

The asymmetric synthesis of THQs using tandem processes involving hydrogenation has been thoroughly explored in recent years. In 2019, Fan, He and co-workers reported a novel strategy for the synthesis of chiral vicinal diamines based on a consecutive Ir- or Ru-catalyzed tandem intermolecular reductive amination/asymmetric hydrogenation.⁴⁶⁸ Using the appropriate catalyst (**C14i** or **C23**), 2-quinoline aldehydes (**S131**) and feedstock anilines were transformed into a broad range of sterically tunable chiral diamines **P131**, which were afforded in high yields with excellent enantioselectivity (Scheme 89). The usefulness and practicality of the method was exemplified by the transformation of **P131** into sterically hindered chiral *N*-heterocyclic carbene precursors.

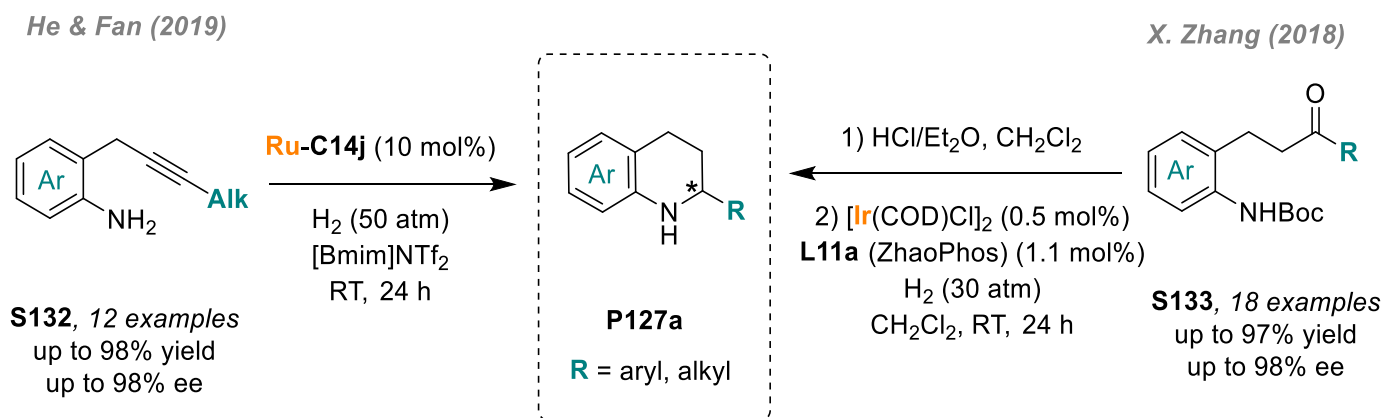
Scheme 89. Consecutive intermolecular reductive amination/AH.

He & Fan (2019)



The same group developed a synthetic route to chiral THQs via sequential intramolecular hydroamination and ruthenium-catalyzed AH of anilino-alkynes **S132** (Scheme 90).⁴⁶⁹ Alternatively, X. Zhang and co-workers reported a one-pot process involving *N*-Boc deprotection/intramolecular asymmetric reductive amination using **S133** (Scheme 90).⁴⁷⁰ This latter methodology was also applied to the synthesis of tetrahydroisoquinolines⁴⁷¹ as well as enantioenriched dibenz[*c,e*]azepines.⁴⁷²

Scheme 90. Asymmetric synthesis of THQs through sequential processes.



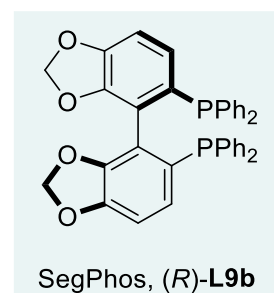
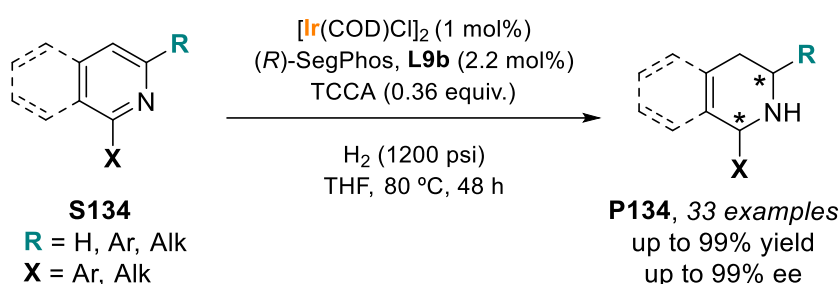
6.2. Isoquinolines, pyridines and pyridinium salts

In contrast to quinolines, the transition metal-catalyzed AH of isoquinolines has remained significantly underdeveloped. The resulting products (1,2,3,4-tetrahydroisoquinolines, THIQs) have a stronger basicity and coordination ability, which can lead to a more facile catalyst deactivation. Typically, the strategy most widely used for the AH of substituted isoquinolines was substrate activation via isoquinolinium salts.^{473, 474, 475, 476, 477} However, the requirement of prior formation of the salt for activation was a considerable limitation. Furthermore, *in situ* and transient activation using chloroformates⁴⁷⁸ or halogenides^{479, 480} have also been reported. An example of this approach was provided by Zhou's group in 2017 (Scheme 91).⁴⁸⁰ By using Ir/(*R*)-**L9b** as catalyst, a variety of both isoquinolines and pyridines (**S134**) were hydrogenated in excellent yields and enantioselectivities. The reaction was promoted using halogenide trichloroisocyanuric acid (TCCA) as traceless activation reagent. Mechanistic studies indicated that hydrogen halide generated *in situ* acted as the substrate activator. Nevertheless, and although this method avoided the tedious steps of the introduction and removal the activation groups, the reaction conditions were harsh as high temperatures and H₂ pressure were required. To overcome these limitations, Stoltz and co-workers recently reported a highly straightforward method for the iridium-catalyzed AH of 1,3-disubstituted isoquinolines **S135** under very mild conditions (Scheme 91).⁴⁸¹ The reaction, which involves a commercially available ligand (**L21f**), proceeded in good yields with high levels of enantio- and diastereoselectivity. The key

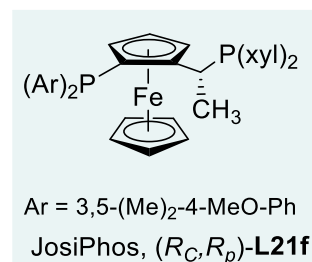
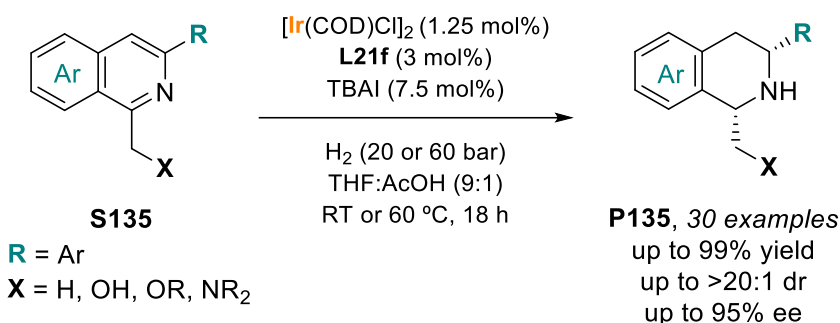
to the success of this approach was the introduction of a directing group at the C1 position that enabled hydrogenation to occur under mild reaction conditions. As result, a wide variety of chiral THIQs **P135** were prepared in optically pure form, in a broad scope and with a very high tolerance of Lewis basic functionalities. Using a similar catalytic system, the same authors applied this hydrogenation reaction as the key step to the concise total synthesis of (-)-jorunnamycin A and (-)-jorumycin (Scheme 92), which were attained with high efficiency after 15 and 16 steps, respectively.⁴⁸²

Scheme 91. Iridium-catalyzed AH of isoquinolines and pyridines.

Zhou (2017)

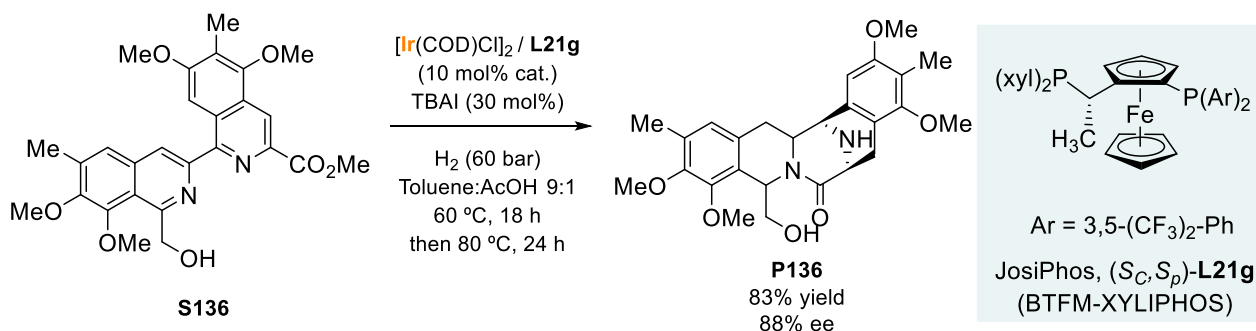


Stoltz (2020)



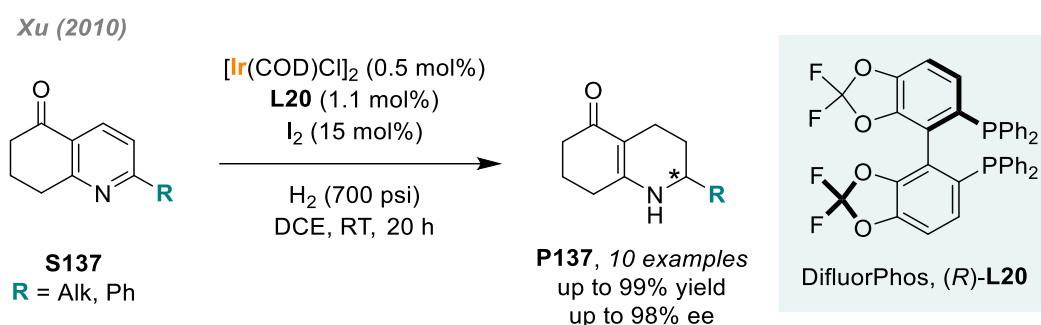
Scheme 92. Enantioselective hydrogenation as the key step for the total synthesis of (-)-jorunnamycin A and (-)-jorumycin.

Stoltz (2019)



Pyridines are also challenging substrates. Xu and co-workers reported the iridium-catalyzed AH of trisubstituted pyridine derivatives. They described that the iridium complex generated *in situ* from $[\text{Ir}(\text{COD})\text{Cl}]_2$, difluorophos-**L20** and I_2 was an excellent catalyst for the AH of **S137**, affording the corresponding chiral amines **P137** in excellent yields and enantioselectivities (Scheme 93).⁴⁸³ The same group reported that P-Phos (**L16**) could also be used as a chiral ligand without diminishing the reactivity or enantioselectivity.⁴⁸⁴ These protocols, which could also be applied to the AH of quinolines, were more efficient than the previous one reported by Zhou's group.⁴⁸⁵

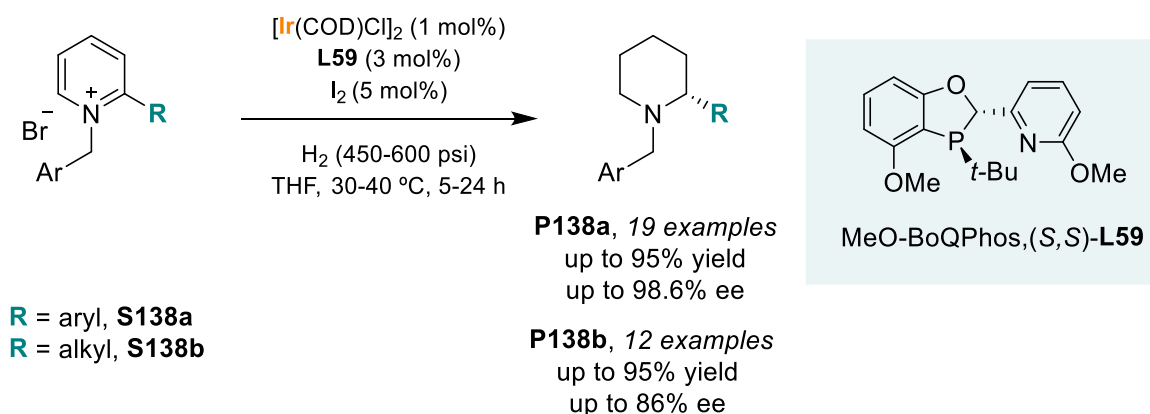
Scheme 93. Iridium-catalyzed AH of trisubstituted pyridines.



To facilitate the AH of pyridines, the activation of pyridine derivatives was first studied. In 2005, Legault & Charette demonstrated that chiral piperidine derivatives could be attained with high enantioselectivities (up to 90% ee) via the AH of *N*-acyliminopyridinium ylides using a Ir/P,N catalyst.⁴⁸⁶ Later, Andersson further developed this methodology with a screening of iridium catalysts with chiral *P,N*-ligands.⁴⁸⁷ In the search for an operationally simple protocol for large-scale synthesis, the *N*-benzylpyridinium salts emerged as the best method for pyridine activation. First described by Y.-G. Zhou's group⁴⁸⁸ and applied by X. Zhang's⁴⁸⁹ and Lefort's laboratories,⁴⁹⁰ this method provided a better approach in terms of safety and applicability. Using their catalytic systems, the subsequent iridium-catalyzed AH of these *N*-benzylpyridinium salts furnished a wide variety of 2-aryl pyridines in both high yields and enantioselectivities, but with limited application to 2-alkylpyridines. Qu *et al.* then reported the use of a new rigid P-stereogenic *P,N*-ligand **L59** for the iridium-catalyzed AH of **S138** (Scheme 94).⁴⁹¹ Chiral α -(hetero)aryl piperidines **P138a** were afforded in high levels of enantioselectivity. Using the same ligand, chiral α -alkyl piperidines **P138b** were also prepared but with lower enantiocontrol.⁴⁹² This catalytic system was also applied in the asymmetric construction of the indenopiperidine core of an 11 β -HSD-1 inhibitor.⁴⁹³

Scheme 94. Iridium-catalyzed AH of pyridinium salts.

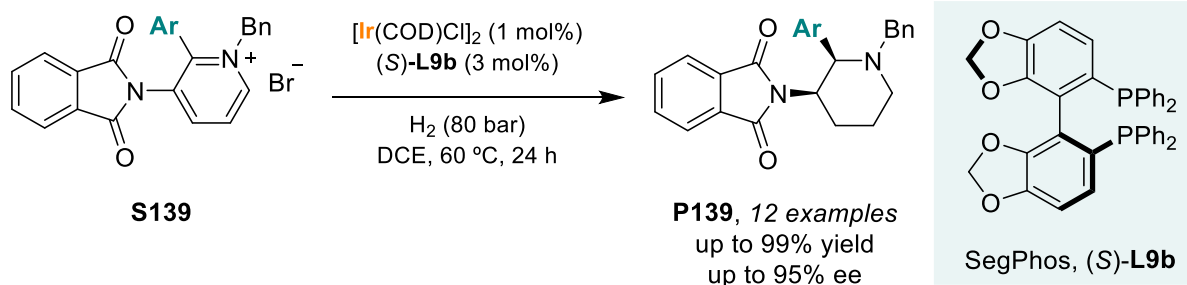
Qu (2016, 2018)



In addition, Mashima and Zhou's laboratories independently reported another strategy for the AH of Brønsted acid-activated multisubstituted pyridines using enantiopure binuclear iridium complexes, thus affording the corresponding chiral piperidines in high diastereo- and enantioselectivities (up to 90% ee).^{494,495} Later, Mashima expanded this methodology to the AH of 2-aryl-3-amidopyridinium salts, delivering the corresponding chiral piperidines with high diastereoselectivities and good enantioselectivities (up to 86% ee).⁴⁹⁶ These piperidines containing two contiguous centers as structural moieties are present in many neurokinin-1 (NK1) receptor antagonist derivatives, such as (+)-CP-99994 and Vofopitant. Due to the importance of these structural units, X. Zhang and co-workers recently described the AH of 2-aryl-3-phthalimidopyridinium salts **S139** driven by the Ir/SegPhos (S)-**L9b** catalytic system (Scheme 95).⁴⁹⁷

Scheme 95. Iridium-catalyzed AH of 2-aryl-3-phthalimidopyridinium salts.

X. Zhang, Chen (2020)



Furthermore, the AH of 3-substituted pyridinium salts was developed by Lefort and co-workers using a Rh-JosiPhos catalyst with ee values up to 90%.⁴⁹⁸ Working with similar substrates, Y.-G. Zhou's laboratory recently reported a highly enantioselective hydrogenation of 3-hydroxypyridinium salts using Ir/f-binaphane (**L7**) followed by sequential Swern oxidation, thus furnishing chiral 6-

substituted piperidin-3-ones in excellent enantioselectivities (up to 95% ee).⁴⁹⁹ On the other hand, in 2018, Peters and co-workers, reported an alternative synthesis of piperidines from isoxazolinones by Pd/Ir relay catalytic hydrogenation of the initially formed 3,4-dihydropyridines.⁵⁰⁰

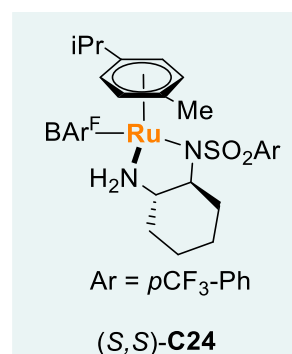
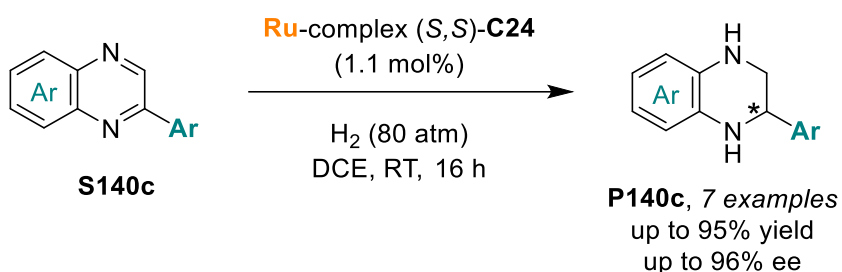
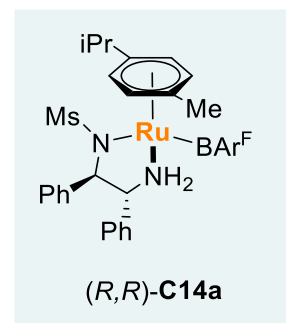
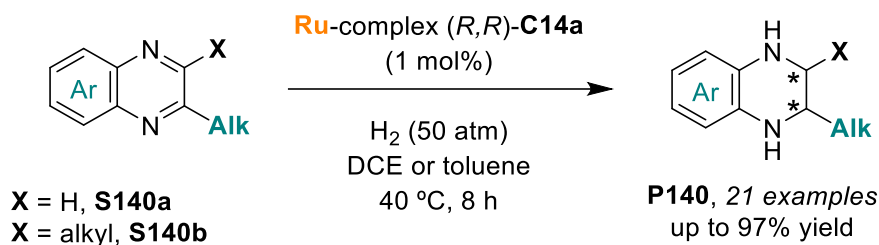
6.3. Quinoxalines and pyrazines

The 1,2,3,4-tetrahydroquinoxaline ring system is of great interest as a key structural unit in many therapeutically active compounds. In 2011, Fan's group described that the family of half-sandwich Ru-diamine complexes, which had already been used for the AH of quinolines, were excellent catalysts for the AH of other heteroaromatic compounds such quinoxalines. In particular, catalyst **C14a** was used for the enantioselective hydrogenation of 2-alkyl and 2,3-dialkyl quinoxalines **S140** with up to 99% ee (Scheme 96).⁵⁰¹ Of note, the bulky and weakly coordinating counteranion (BArF) was found to be critical for the high enantioselectivity and/or diastereoselectivity. On the other hand, and using **C24**, 2-aryl quinoxalines **S140c** were also hydrogenated in excellent ee values (up to 96% ee, Scheme 96). Later, in 2013, Ohkuma and co-workers reported an alternative protocol for the enantioselective hydrogenation of 2-alkyl quinoxalines using chiral ruthenabicyclic complexes.¹²⁹

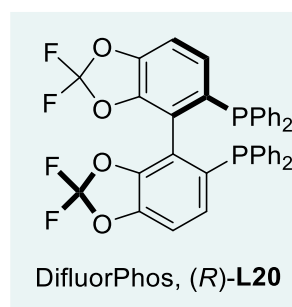
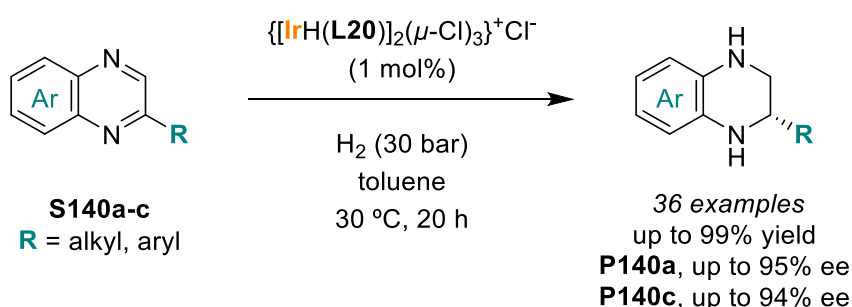
Although this work is the most successful precedent in the field, iridium catalysts had also found use in the AH of quinoxalines. In this regard, Chan, Xu, Fan and co-workers described a highly efficient AH of quinoxalines using Ir/H₈-binapo at low catalyst loading.⁵⁰² Later, Ratovelamana-Vidal and co-workers described a general AH of a wide range of 2-alkyl- and 2-aryl-substituted quinoxaline derivatives using a cationic dinuclear triply chloride-bridged Ir(III) complex bearing **L20** as a chiral ligand.^{503, 504} Of note, the efficiency of the catalytic system was demonstrated through a broad scope with excellent enantioselectivities (up to 95% ee, Scheme 96).

Scheme 96. Ruthenium-catalyzed AH of quinoxalines.

Fan (2011)



Ratovelomanana-Vidal (2012)



Mashima and co-workers showed that the use of amines as additives had a positive effect for the iridium-catalyzed AH of quinoxalines.⁵⁰⁵ In particular, they found that *N*-methyl-*p*-anisidine (MPA) was the best amine additive for achieving high enantioselectivity. More recently, Nagorny applied new chiral SPIROL-based phosphinite ligands for the iridium-catalyzed AH of heterocycles, including quinoxalines, in good to excellent enantioselectivities.⁵⁰⁶

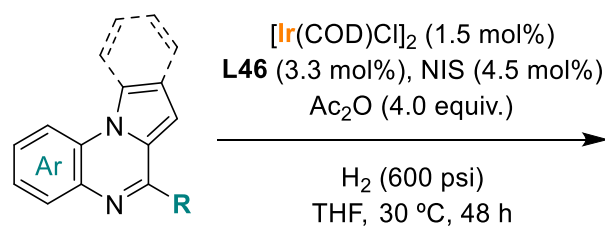
While 2-alkyl and 2-aryl substituted quinoxalines have been hydrogenated at useful levels of enantioselectivity, the AH of other derivatives such as quinoxaline-2-carboxylates is still underdeveloped, although the resulting chiral cyclic amino acids are highly valuable. To the best of

our knowledge, there is only one example in the literature, affording the corresponding chiral amino acid in moderate enantioselectivity (74% ee).⁵⁰⁷

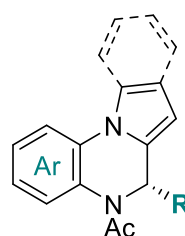
Iridium catalysis was also applied to the AH of pyrrolo/indolo[1,2-*a*]quinoxalines (Scheme 97). In 2018, Zhou's laboratory described the highly enantioselective hydrogenation of **S141** with Ir/Synphos-**L46**, providing facile access to chiral **P141** with up to 97% ee.⁵⁰⁸ However, the addition of acetic anhydride was pivotal for suppressing the rearomatization of hydrogenation products. The system was also applied to the AH of phenanthridines (see Section 6.5). The same laboratory studied the iridium-catalyzed AH of pyrrolo[1,2-*a*]pyrazines **S142** (Scheme 97).⁵⁰⁹ In this case, the preparation of the corresponding salt or the addition of a *N*-protecting group was not required. The reaction was performed under very mild conditions, and it exhibited excellent activity and enantioselectivity when using **L17e** as a chiral ligand. The group previously reported the enantioselective synthesis of **P142** via the iridium-catalyzed AH of pyrrolo[1,2-*a*]pyrazinium salts, which were prepared after substrate activation using alkyl halides.⁵¹⁰

Scheme 97. Iridium-catalyzed AH of pyrrolo/indolo[1,2-*a*]quinoxalines and of pyrrolo[1,2-*a*]pyrazines.

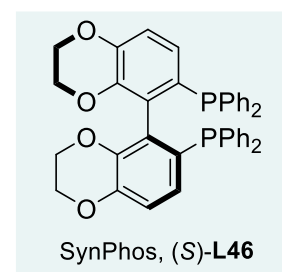
Zhou (2018)



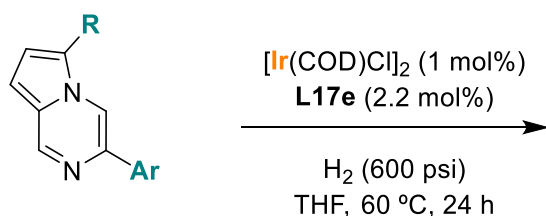
S141
R = Ar, Alk



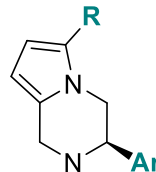
P141, 20 examples
up to 99% yield
R = Ar, 95-97% ee
R = Alk, 37-86% ee



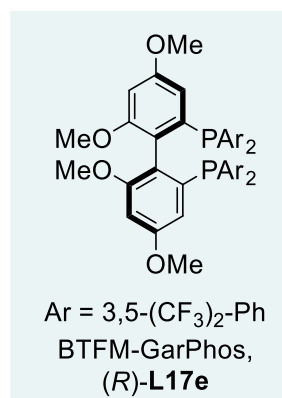
Zhou (2017)



S142
R = H, Me, Ar



P142, 17 examples
up to 98% yield
up to 96% ee

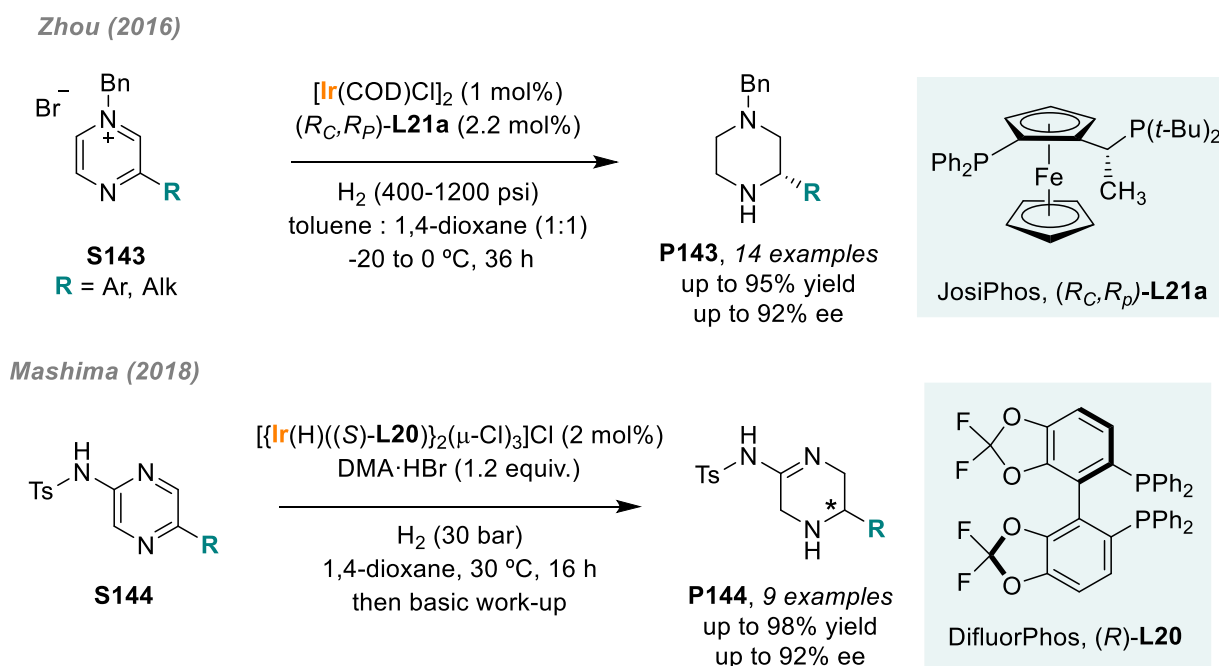


In 2016, Zhou's laboratory reported a facile method for the synthesis of chiral piperazines **P143** through iridium-catalyzed AH of 3-substituted pyrazinium salts **S143** using JosiPhos-type ligand

L21a (Scheme 98).⁵¹¹ The system showed broad substrate scope with good to excellent selectivity (up to 92% ee). Furthermore, 2,3- and 3,5-disubstituted pyrazinium salts were also hydrogenated with high yields and enantioselectivities when using the appropriate chiral ligand. To demonstrate the applicability of the methodology, Vestipitant, a potent and selective NK1 receptor antagonist, was prepared in just two steps.

In a similar approach, Mashima and co-workers reported the iridium-catalyzed enantioselective hydrogenation of tosylamido-substituted pyrazines **S144**. The addition of *N,N*-dimethylanilinium bromide (DMA·HBr) enhanced the catalytic activity of the iridium complexes, as well as the enantioselectivity (Scheme 98).⁵¹² Chiral tetrahydropyrazines with an amidine skeleton (**P144**) were obtained with good to excellent enantioselectivities (up to 92% ee) using dinuclear triply chloro-bridge Ir(III) complexes bearing chiral difluorophos (**L20**). The resulting tetrahydropyrazines **P144** are versatile precursors for the preparation of chiral piperazine derivatives without loss of enantioselectivity.

Scheme 98. Iridium-catalyzed AH of pyrazinium salts.



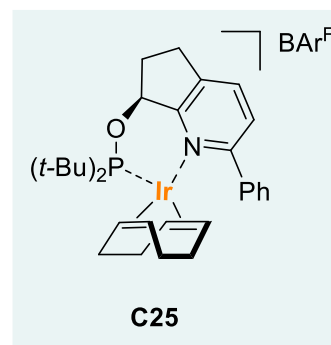
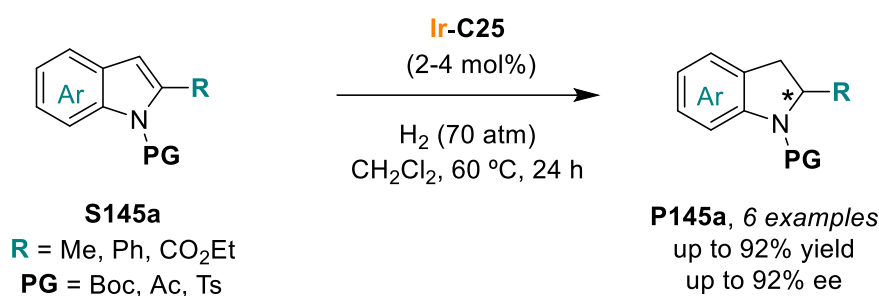
6.4. Indoles

Iridium chiral complexes were also applied to the AH of *N*-protected indoles to obtain chiral indolines, which are common structures occurring in alkaloids and other natural or synthetic products

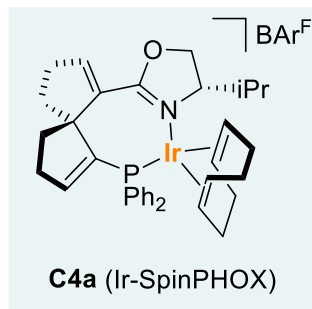
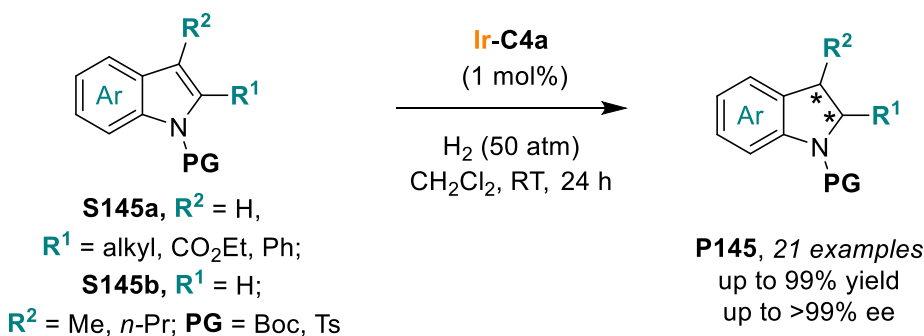
with biological activity.⁵¹³ Pfaltz pioneered the use of cationic Ir complexes derived from PHOX or other chiral *P,N*-ligands in the AH of 2-substituted *N*-protected indoles **S145a** (Scheme 99).⁵¹⁴ In particular, **C25** gave the highest enantioselectivities, and the results obtained demonstrate that the protecting group (*N*-Boc, *N*-acetyl or *N*-tosyl) influences both reactivity and enantiomeric excess. Moreover, various examples of 3-substituted indoles were also hydrogenated, using the right combination of catalyst and protecting group. On the other hand, Han, Ding and co-workers recently reported that Ir/SpinPHOX **C4a** is an efficient catalyst for the AH of both 2- and 3-substituted *N*-protected indoles (Scheme 99).⁵¹⁵ The corresponding chiral indolines were afforded in excellent yields and enantioselectivities (>99% ee in most cases).

Scheme 99. Iridium-catalyzed AH of *N*-protected indoles.

Pfaltz (2010)



Han, Ding (2020)

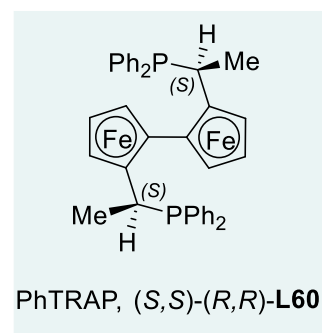
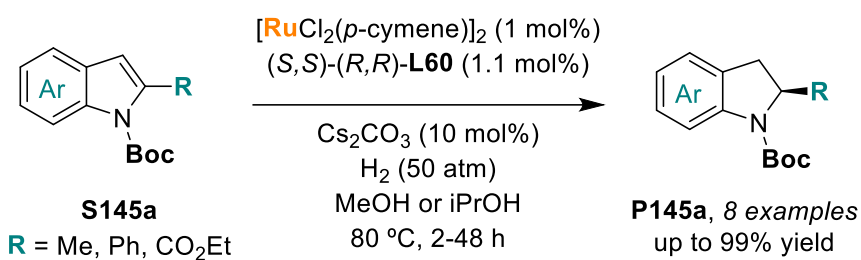


Prior to these iridium complexes, the only suitable catalytic systems known for the AH of *N*-protected indoles were Ru and Rh complexes bearing the *trans*-chelating chiral diphosphine (*S,S*)-(*R,R*)-PhTRAP ligand (**L60**), first reported by Kuwano's group.⁵¹⁶ In their work, a wide range of *N*-protected indoles were hydrogenated with high efficiency, thus providing the corresponding chiral indolines in excellent yields and enantioselectivities.⁵¹⁷ For example, the ruthenium-catalyzed AH of *N*-Boc 2-substituted (**S145a**) and *N*-tosyl 3-substituted indoles (**S145b**) furnished the corresponding indolines (**P145**) in excellent yields using **L60** (Scheme 100).^{518,519} 2-Substituted indole esters were

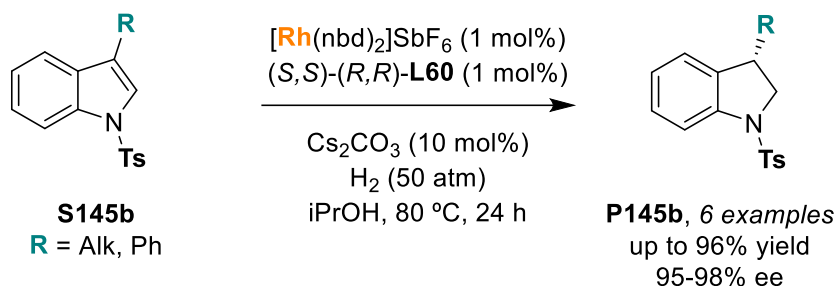
also hydrogenated by the groups of Minaard⁵²⁰ and Agbossou-Niedercorn⁵²¹ using Rh complexes bearing PinPhos or WalPhos as catalysts, although only moderate enantioselectivities were achieved.

Scheme 100. Metal-catalyzed AH of *N*-protected indoles using PhTRAP.

Kuwano (2006)



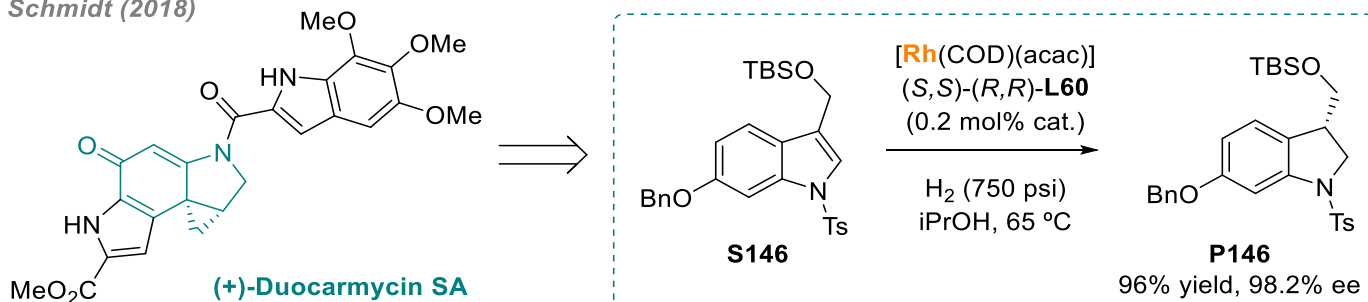
Kuwano (2004)



The methodology developed by Kuwano and co-workers allows the preparation of a wide range of optically active indolines with a chiral center at the 3-position. A team at Bristol-Myers Squibb recently used it in the enantioselective total synthesis of (+)-Duocarmycin SA, which is a potent antitumor antibiotic (Scheme 101).⁵²² The key tricyclic core was constructed through a highly enantioselective hydrogenation of indole **S146** using **L60**.

Scheme 101. Synthesis of (+)-Duocarmycin SA via rhodium-catalyzed AH.

Schmidt (2018)

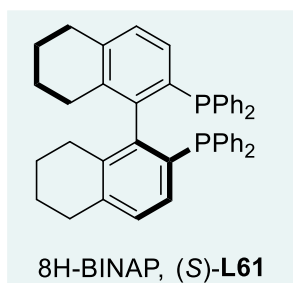


The progress achieved in the AH of *N*-protected indoles was in sharp contrast to the AH of simple unprotected indoles, which remain a challenge in organic synthesis. However, significant advances were made in this field in the last ten years.

In 2010, Y.-G. Zhou, X. Zhang and co-workers developed the first highly enantioselective hydrogenation of simple indoles using Pd/(*R*)-H₈-BINAP (**L61**) with a Brønsted acid (*L*-camphorsulfonic acid, *L*-CSA) as an activator and TFE as solvent (Scheme 102).⁵²³ This methodology provided an efficient route to make chiral indolines from unprotected indoles in excellent enantioselectivities (up to 96% ee). In 2014, Zhou's laboratory reported an extensive substrate scope, including 2-substituted and 2,3-disubstituted indoles (**S147**).⁵²⁴ Using the same reaction conditions as the previous work, chiral indolines were prepared in up to 98% ee (Scheme 102). The main drawback of this approach was the low activity and/or enantioselectivity of the 2-aryl substituted indoles. Interestingly, a mechanistic study using DFT calculations revealed that the hydrogenation occurs through a stepwise, ionic, and outer-sphere mechanism. As an alternative approach, W. Zhang reported that Pd/(*S*)-C₁₀-BridgePhos is a highly efficient catalyst for the AH of 2-, 3- and 2,3-substituted unprotected indoles.⁵²⁵

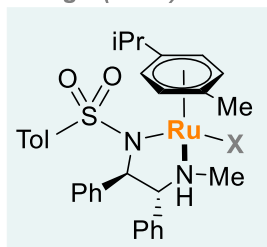
Scheme 102. Catalytic strategies towards the AH of unprotected indoles.

Zhou (2010, 2014)

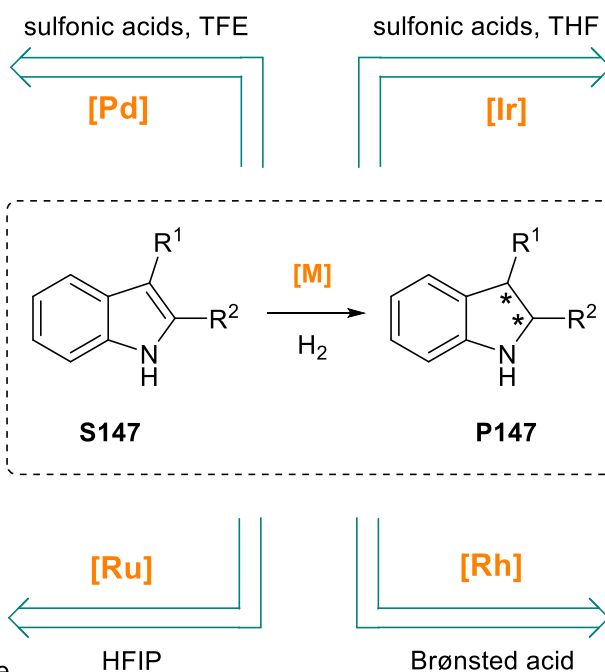


17 examples
up to 98% ee

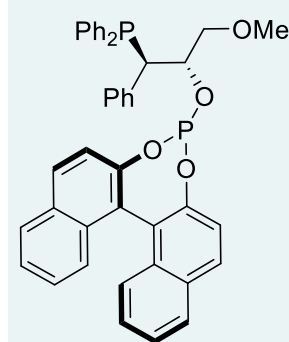
Fan (2016) and
Touge (2016)



X = OTf, **C14i**, up to 96% ee
X = BF₄, **C14k**, up to 99% ee



Vidal-Ferran (2014)



6 examples
up to 91% ee

Chung & Zhang (2018)

ZhaoPhos (**L11a**)
via cooperative
catalysis-anion binding

22 examples
up to 99% ee

Sulfonic acids were also used as Brønsted acids in the iridium-catalyzed AH of **S147**, reported by Vidal-Ferran and co-workers, using a P-OP ligand **L12** and TFE as solvent (Scheme 102).⁵²⁶ Enantiomerically enriched indolines **P147** were attained in up to 91% ee. The Brønsted acid (*rac*-CSA), which could be re-used by addition of heterogeneous additives, activates the indole ring by breaking its aromaticity. Interestingly, the reaction proceeded by a stepwise process: Brønsted acid-mediated C=C isomerization, thus generating the corresponding iminium ion, followed by asymmetric hydrogenation.

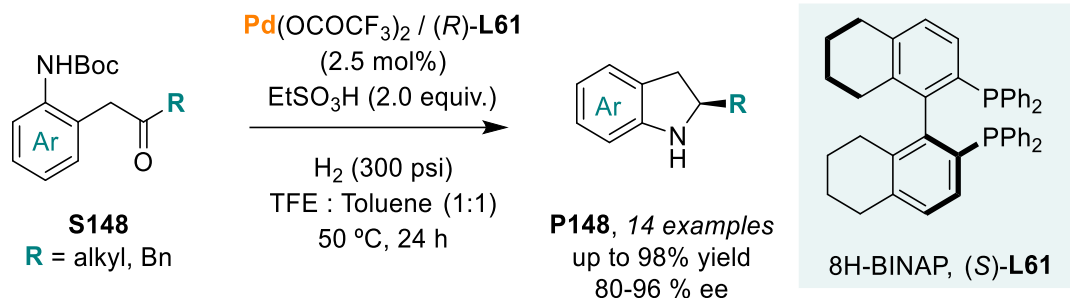
Chung & X. Zhang also envisioned a similar strategy. They developed an efficient method to obtain optically pure indolines using a Rh/ZhaoPhos-**L11a** complex (Scheme 102).⁵²⁷ Various 2-substituted and 2,3-disubstituted indoles **S147** were hydrogenated with high enantioselectivities. By employing HCl as Brønsted acid, an active iminium ion intermediate was formed and reduced. The thiourea anion binding of **L11a** proved crucial to achieve high enantioselectivity and reactivity.

Fan and co-workers also studied the AH of unprotected indoles using half-sandwich Ru-diamine complexes. In particular, when using **C14i** with a triflate as counteranion, indolines **P147** were afforded in up to 96% ee (Scheme 102).¹¹⁴ Of note, the reaction was performed under very mild conditions at room temperature and using HFIP as solvent, which significantly influenced catalytic performance. Excellent enantio- and diastereoselectivities were obtained for a wide range of indole derivatives. Simultaneously, Touge and Arai and co-workers described that a similar Ru-complex with a tetrafluoroborate as counteranion (**C14k**) also gave excellent yields and enantioselectivities in very mild conditions (Scheme 102).⁵²⁸

Subsequently, other related transformations using Pd catalysis emerged, including dehydration-triggered AH⁵²⁹ and consecutive Brønsted acid/Pd-complex-promoted tandem reactions.⁵³⁰ Moreover, 3-(toluenesulfonamidoalkyl)-indoles were synthesized and hydrogenated to form chiral indolines.⁵³¹ Of note, Y.-G. Zhou's group recently reported a facile synthesis of chiral indolines through the AH of *in situ* generated indoles.⁵³² The reaction was developed through an intramolecular condensation, deprotection, and palladium-catalyzed AH using **L61** in a one-pot process (Scheme 103). Chiral 2-alkyl substituted indolines **P148** were furnished in excellent yields and enantioselectivities (up to 96% ee).

Scheme 103. One-pot synthesis of chiral indolines via palladium-catalyzed AH.

Zhou (2018)

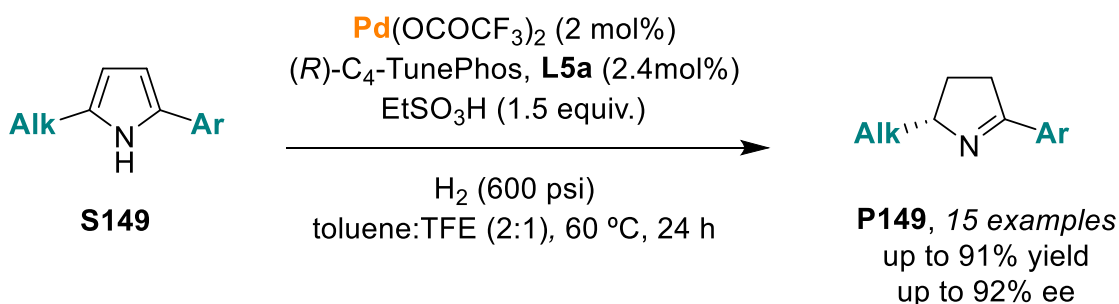


6.5. Other heteroaromatic compounds

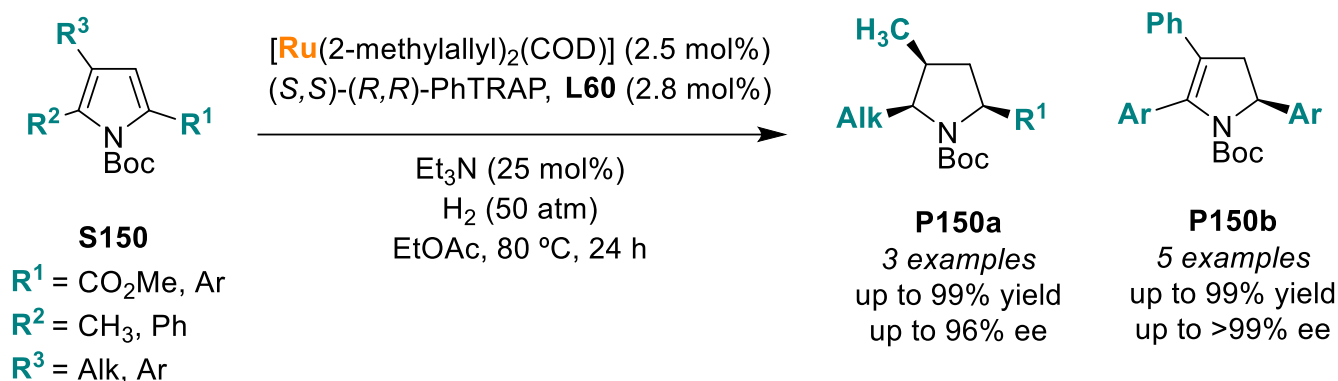
In 2011, Zhou, Fan and co-workers disclosed the first AH of simple unprotected pyrroles. In their work, the Brønsted acid-activation mode was applied to the partial AH of pyrroles **S149** (Scheme 104).⁵³³ Using sulfonic acid as activator, a highly enantioselective palladium-catalyzed partial hydrogenation using **L5a** was reported, providing chiral 2,5-disubstituted 1-pyrrolines **P149** with up to 92% ee. Previously, Kuwano's group applied the PhTRAP ligand **L60** to the ruthenium-catalyzed AH of *N*-Boc protected pyrroles (Scheme 104).⁵³⁴ Using this catalytic system, pyrroles **S150** were hydrogenated with high ees to give chiral pyrrolidines **P150a** or 4,5-dihydropyrroles **P150b**.

Scheme 104. Metal-catalyzed AH of pyrroles.

Zhou, Fan (2011)

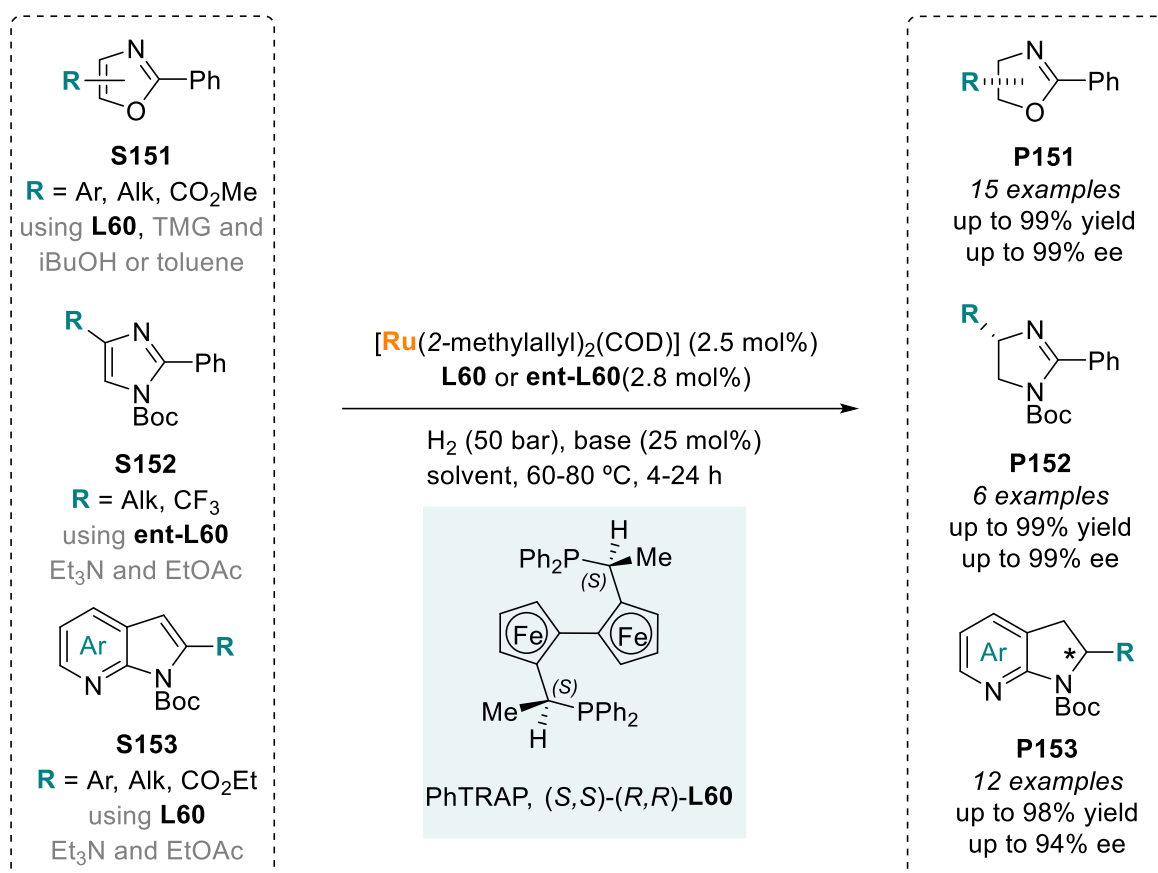


Kuwano (2008)



The Ru/**L60** system was further exploited by Kuwano's group for the AH of other single-ring heteroarenes. Using this catalytic system, oxazoles **S151** and N -Boc imidazoles **S152** were hydrogenated into the corresponding chiral oxazolines **P151** and imidazolines **P152**, respectively (up to 99% ee, Scheme 105).⁵³⁵ These hydrogenation products are highly valuable synthetic intermediates, as they can be easily converted to 1,2-diamines or β -amido alcohols without loss of enantiopurity. On the other hand, fused aromatic rings consisting of two (or more) heteroarenes are challenging substrates due to the need to control chemoselectivity. Pyrindo-fused pyrroles, namely azaindoles, are an important class of this type of substrate. In 2016, Kuwano and co-workers reported the chemo- and enantio-selective reduction of 7-azaindoles **S153** using Ru/**L60** as catalyst (Scheme 105).⁵³⁶ The reaction occurred exclusively on the five-membered ring, thus furnishing the corresponding azaindolines **P153** with up to 94% ee. Furthermore, the catalyst was also highly active for the AH of 6-, 5- and 4-azaindoles.

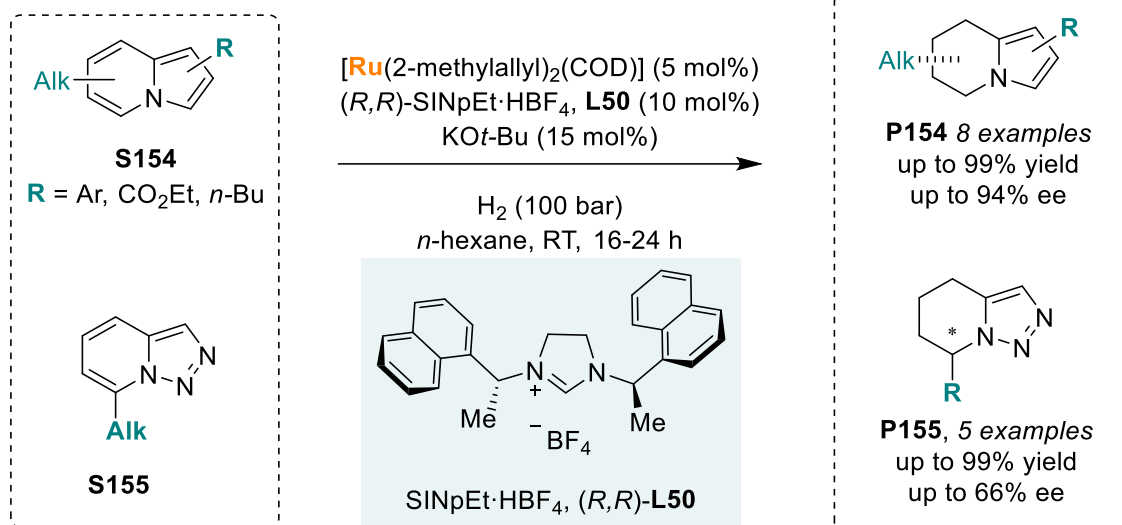
Scheme 105. Ruthenium-catalyzed AH of oxazoles, imidazoles and azaindoles using PhTRAP.



Indolizines are another class of ring-fused heteroaromatic compounds. However, their selective reduction is a difficult task due to the nitrogen atom of the bridgehead position. In fact, the efficient AH of indolizines had not been accomplished until 2013, when Glorius and co-workers described the Ru-catalyzed AH of indolizines **S154** using the chiral NHC-ligand **L50** (Scheme 106).⁵³⁷ The corresponding hydrogenated products, indolizidines **P154**, were afforded in high yields and enantioselectivities, the applicability of such methodology was exemplified by the synthesis of unnatural (-)-monomorine in only two steps. In addition, the catalyst was also used for the high-yielding and completely regioselective AH of 1,2,3-triazolo-pyridines **S155**, albeit in low to moderate enantioselectivity (Scheme 106). Later, the same group used this catalytic system for the enantioselective hydrogenation of imidazo[1,2-*a*]pyridines, with enantiomeric ratios of up to 98:2.⁵³⁸ Very recently, Fan and co-workers have also reported the synthesis of benzo fused indolizidines and quinolizidines via tandem AH/reductive amination using a Ru-DPEN catalyst (**C14j**).⁵³⁹

Scheme 106. Ruthenium-catalyzed AH of indolizines and 1,2,3-triazolo-pyridines.

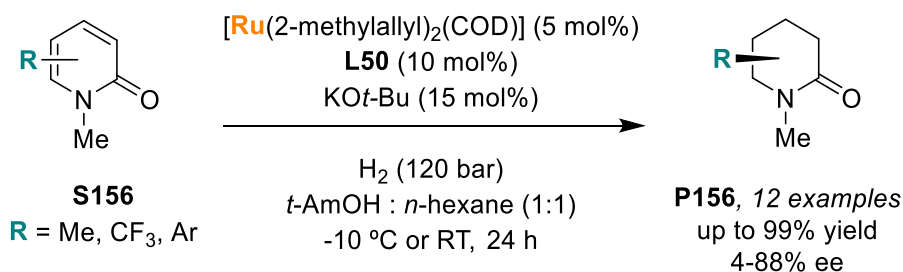
Glorius (2013)



In 2015, Glorius and co-workers applied the same catalyst Ru/**L50** for the AH of 2-pyridones **S156** into the corresponding enantioenriched 2-piperidones **P156** (Scheme 107).⁵⁴⁰ However, and even though this was the first related example using a homogeneous catalytic system, the method suffered from low enantioselectivities and therefore there is still plenty of room for improvement.

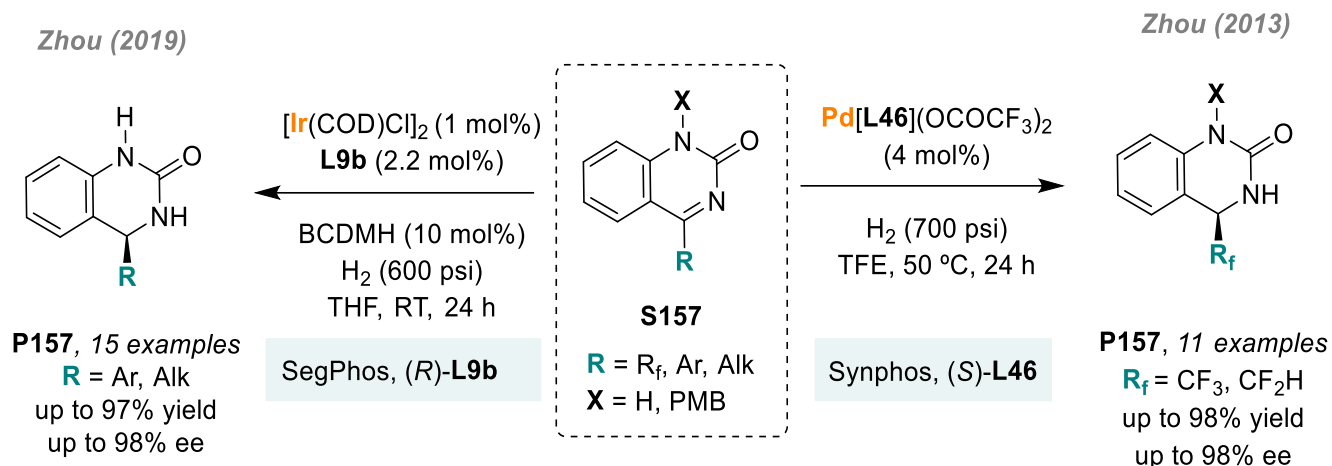
Scheme 107. Ruthenium-catalyzed AH of 2-pyridones.

Glorius (2015)



The enantioselective hydrogenation of quinazolinones was achieved by Zhou's laboratory, using Pd or Ir catalysis (Scheme 108). First, the group disclosed that Pd/SynPhos [(*S*)-**L46**] was an excellent catalyst for the AH of fluorinated quinazolinones (94-98% ee).⁵⁴¹ Later, the substrate scope was expanded to other substituted quinazolinones using iridium catalysis (with **L9b**), thus allowing the preparation of chiral dihydroquinazolinones **P157** in excellent yields and enantioselectivities (Scheme 108).⁵⁴²

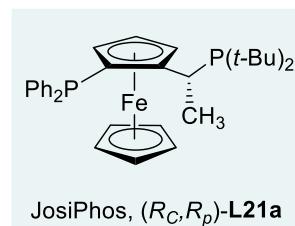
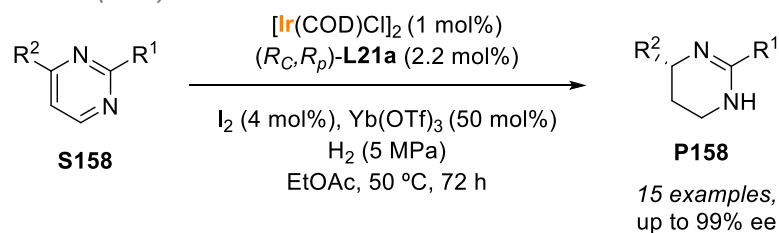
Scheme 108. Enantioselective hydrogenation of quinazolinones using Pd or Ir catalysts.



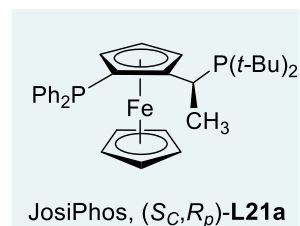
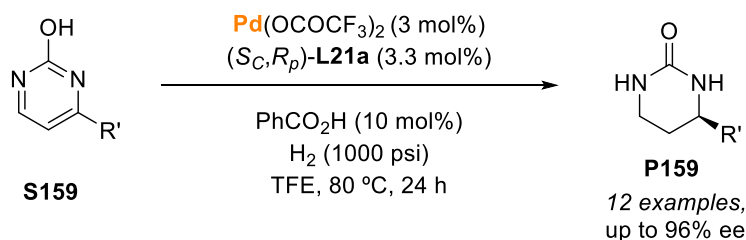
The AH of pyrimidines was first reported by Kuwano and co-workers in 2015.⁵⁴³ Using an Ir/**L21a** as catalyst, various 2,4-disubstituted pyrimidines **S158** were converted into chiral 1,4,5,6-tetrahydropyrimidines **P158** in high yield (Scheme 109). Interestingly, lanthanide triflate was used as additive for achieving high enantiocontrol, as well as for activating the heteroarene substrate. Similarly, the AH of 2-hydroxypyrimidines **S159** was reported by Zhou's group (Scheme 109).⁵⁴⁴ Taking advantage of the lactame-lactime tautomerism of the 2-hydroxypyrimidine, the authors developed two distinct catalytic systems for the efficient preparation of cyclic ureas **P159**, which are highly valuable structural motifs in many pharmacophores and other biologically active compounds. In particular, they reported an efficient Brønsted acid-activated palladium-catalyzed AH using chiral ligand **L21a**. By slightly modifying the catalytic system, di- and trisubstituted 2-hydroxypyrimidines were also hydrogenated in good yields. Alternatively, the same laboratory developed the same transformation using iridium catalysis with **L7**, in which the Brønsted acid was generated *in situ*.⁵⁴⁵ On the other hand, the AH of quinazolinium salts **S160** was reported by Mashima and co-workers (Scheme 109).⁵⁴⁶ By using halide-bridged dinuclear iridium complexes bearing SegPhos ((*S*)-**L9b**) as ligand, the corresponding 1,2,3,4-tetrahydroquinazolines **P160** were achieved in high enantiomeric excess along with some dihydroquinazolines.

Scheme 109. AH of pyrimidines.

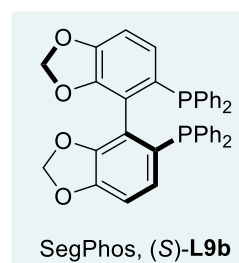
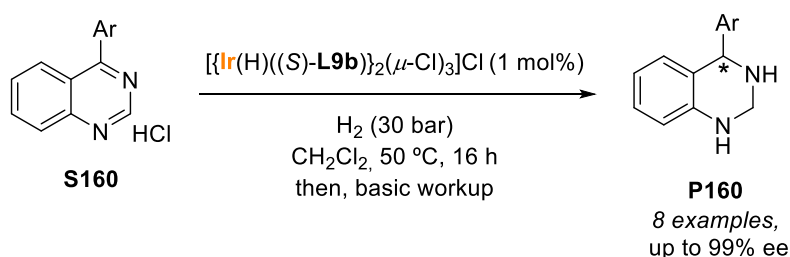
Kuwano (2015)



Zhou (2018)



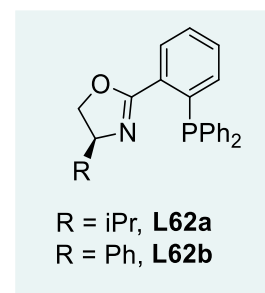
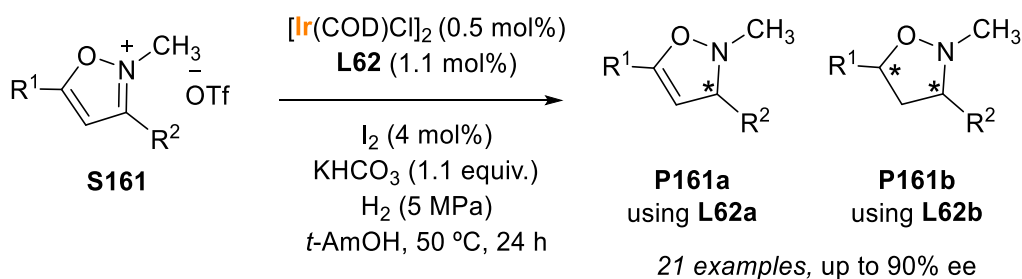
Mashima (2015)



Iridium catalysis was also used for the efficient AH of isoxazolium salts (Scheme 110). Kuwano's laboratory reported that iridium complexes bearing phosphino-oxazoline **L62**-type ligands were highly active catalysts for the AH of isoxazolium triflates **S161**.⁵⁴⁷ Interestingly, by fine-tuning the oxazoline substituent, isoxazolines **P161a** or isoxazolidines **P161b** were selectively obtained in good to high enantioselectivity.

Scheme 110. AH of isoxazolium salts

Kuwano (2016)

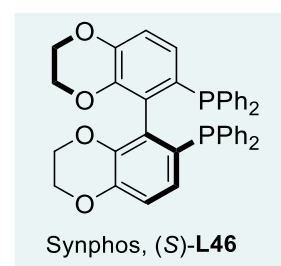
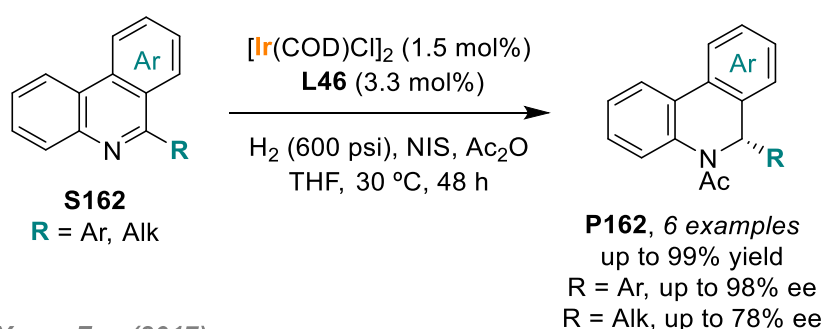


Dihydrophenanthridines (DHPDs, **P162**) are important structural units in natural products and biologically active molecules. In addition, 9,10-dihydrophenanthridine proved to be a regenerable biomimetic hydrogen source, as it was designed as a NAD(P)H analog by Zhou.⁵⁴⁸

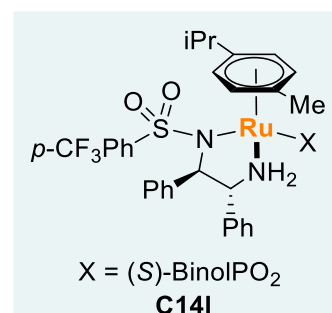
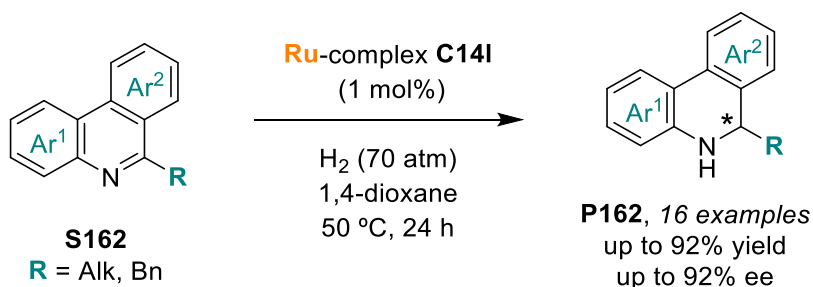
However, until 2017, the AH of substituted phenanthridines had not been documented. Phenanthridines are heteroarenes formed by three fused aromatic rings. Their hydrogenation is difficult due to the possible dehydrogenative aromatization of the reduced products. Moreover, the strong coordinative nitrogen atom can easily poison the metal catalyst. At that point, Zhou's laboratory reported a highly enantioselective iridium-catalyzed AH of phenanthridines **S162** through *in situ* protection of the reduced products with acetic anhydride to inhibit rearomatization (Scheme 111).⁵⁰⁸ This approach was also used for pyrrolo/indolo[1,2-a]quinoxalines, as previously stated (see Scheme 97). Aryl substituents were well-tolerated and the corresponding DHPDs **P162** were attained with excellent yields and enantioselectivities. For alkyl substituents, the level of enantioselectivity was only moderate. Nevertheless, alkyl-substituted phenanthridines **S162** had previously been hydrogenated by Yang, Fan and co-workers in a highly efficient manner (Scheme 111).⁵⁴⁹ By using a chiral cationic Ru-diamine complex **C141**, the corresponding enantioenriched **P162** were obtained. Interestingly, the counteranion was found to be critical for attaining high enantioselectivities (up to 92% ee).

Scheme 111. Metal-catalyzed AH of phenanthridines.

Zhou (2018)



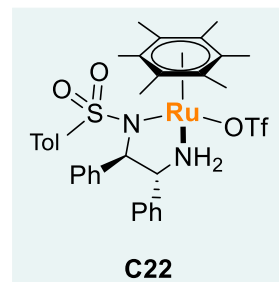
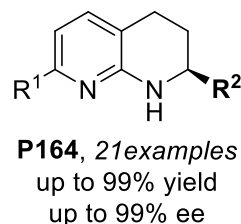
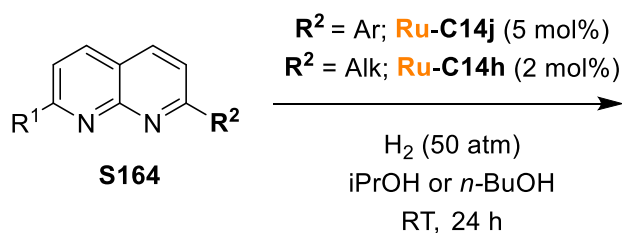
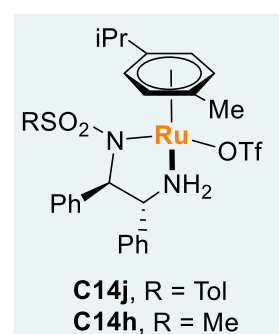
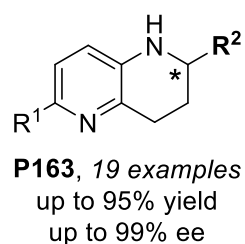
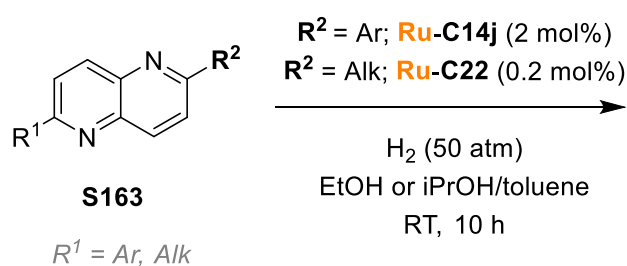
Yang, Fan (2017)



Fan and co-workers further exploited the use of chiral cationic Ru-diamine complexes to the AH of 1,5- and 1,8-naphthyridines (Scheme 112).^{550,551} By using the appropriate Ru catalyst, chiral amines containing the 1,2,3,4-tetrahydronaphthyridine ring were afforded in excellent yields and enantioselectivities. In fact, these chiral heterocycles have been used as rigid chelating diamine ligands for asymmetric synthesis and can be found in many biologically active compounds. Previously, in 2013, the same authors reported the highly enantioselective ruthenium-catalyzed AH of 1,10-phenanthroline and its derivatives using Ru-C14j.⁵⁵²

Scheme 112. Ruthenium-catalyzed AH of 1,5- and 1,8-naphthyridines.

Fan (2015, 2016)



7. Conclusions and outlook

The metal-catalyzed asymmetric hydrogenation of prochiral unsaturated amines has been intensively studied in the last ten years, and it continues to be a growing field and a fundamental tool in synthetic organic chemistry. More than four hundred articles have been published since 2010. Although a huge number of catalysts have been described to date, there are some privileged ligands, such as DuanPhos, SegPhos and ZhaoPhos, able to provide excellent results in a large variety of substrates. Moreover, some modular catalytic systems such as JosiPhos, WalPhos and the ruthenium DPEN have also proved highly versatile, through fine tuning the substituents and counter ions. In the last ten years we have witnessed incredible advances and may conclude that asymmetric hydrogenation is, arguably, the cleanest and most convenient methodology for the synthesis of chiral amines. Nevertheless, to overcome the fierce competition of biocatalytic and resolution methodologies further improvement is needed. In the years to come we might expect further development on the use of non-precious

metals to allow for greener and cheaper processes. On the other hand, catalytic systems that are active and resistant to basic and/or acidic conditions, catalyst deactivation or poisoning by amines are much needed. These advances and others which we may not foresee now will for sure keep the metal-catalyzed synthesis of chiral amines as thriving field in the next decade.

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Biographies.

Antoni Riera was born in Balsareny (Catalonia). He studied chemistry at the University of Barcelona, where he did his Doctoral thesis under the supervision of Profs. Fèlix Serratosa and Miquel A. Pericàs. After a post-doctoral stage at the University of Pennsylvania (Philadelphia, USA) under the supervision of Prof. Amos B. Smith III, in 1988 he returned to the Department of Organic Chemistry of the University of Barcelona as associate professor. In June 2003 he was promoted to full professor at the same university.

Since 2005 he has served as group leader of the Asymmetric Synthesis Group of the Institute for Research in Biomedicine (IRB Barcelona).

His main research area is organic synthesis. He works on synthetic methodology (Pauson-Khand reactions, asymmetric hydrogenation, new chiral ligands etc.) and on the synthesis of biologically active compounds (amino acids, aza-sugars, peptides, protein inhibitors, PROTACs, tetrazines).

Xavier Verdaguer is full professor at the Inorganic and Organic Chemistry Department at the University of Barcelona. In 1994 he earned his PhD degree from the University of Barcelona under

the supervision of Professors Miquel A. Pericàs and Antoni Riera. He carried out a 2 year postdoctoral stay in the laboratories of Prof. Stephen Buchwald at the Massachusetts Institute of Technology (MIT) where he worked on the titanocene-catalyzed asymmetric hydrosilylation of imines. In 2005 he was appointed research associate at the Asymmetric Synthesis Group of the Institute for Research in Biomedicine (IRB Barcelona). He's research interests focus on the field of asymmetric synthesis and asymmetric catalysis. He is interested in the synthesis and application of P-stereogenic phosphine ligands and on the use of iridium cyclometallated catalysts for asymmetric hydrogenation and rearrangement processes.

Albert Cabré studied chemistry at the Universitat Rovira i Virgili in Tarragona. In 2020, he received his Ph.D. from the Universitat de Barcelona under the supervision of Prof. Antoni Riera. His doctoral studies focused on the development of new catalytic methods for Pauson-Khand reactions, isomerizations and asymmetric hydrogenation processes. He performed a research stay in Prof. David W. MacMillan's laboratory at Princeton University (United States), where he worked on metallaphotoredox catalysis. He is the recipient of the 2020 Josep Castells Award for the best Doctoral Thesis from the Catalan section of the Spanish Royal Society of Chemistry. In 2020 he received a fellowship from the Fundación Ramon Areces to perform his postdoctoral studies at the Massachusetts Institute of Technology (United States), where he currently works under the guidance of Prof. Stephen L. Buchwald.

Abbreviations

AH: asymmetric hydrogenation

Alk: alkyl

ARA: asymmetric reductive amination

BAr^F: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

BCDMH: 1-bromo-3-chloro-5,5-dimethylhydantoin

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Boc: *tert*-butoxycarbonyl

Cbz: benzyloxycarbonyl

COD: cyclooctadiene

Cp*: pentamethylcyclopentadienyl

CSA: camphor-10-sulfonic acid

Cy: cyclohexyl

D-DTTA: D-Di-*p*-toluoyl-D-tartaric acid

DCE: dichloroethane

DHIQs: dihydroisoquinolines

DHPDs: dihydrophenanthridines

DFT: density functional theory
DMF: dimethylformamide
DPEN: *trans*-1,2-diphenylethylene diamine
dr: diastereomeric ratio
EDG: electron-donating group
ee: enantiomeric excess
EWG: electron-withdrawing group
HA: chiral phosphoric acid
HFIP: hexafluoroisopropanol
MIBK: methyl isobutyl ketone
MOM: methoxymethyl ether
MS: molecular sieves
Ms: methanesulfonyl (mesyl)
nbd: norbornadiene
NHC: *N*-heterocyclic carbene
NIS: *N*-Iodosuccinimide
PG: protecting group
PMB: *p*-methoxybenzyl
PMP: *p*-methoxyphenyl
Rf: perfluoroalkyl
RT: room temperature
S/C: substrate/catalyst ratio
tAA: *tert*-amyl alcohol
TBAI: tetrabutylammonium iodide
TBDPS: *tert*-butyldiphenylsilyl
TBS: *tert*-butyldimethylsilyl
TCCA: trichloroisocyanuric acid
TCFP: trichickenfootphos
Tf: trifluoromethanesulfonyl (triflate)
TFA: trifluoroacetic acid
TFE: trifluoroethanol
THF: tetrahydrofuran
THIQs: tetrahydroisoquinolines
THQs: tetrahydroquinolines
TMS: trimethylsilyl
TON: turnover number
Ts: *p*-toluenesulfonyl (tosyl)
Xyl: xylyl (dimethylphenyl)

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Graphical abstracts

