

Recent Advances in Homogeneous Catalysts for the Asymmetric Hydrogenation of Heteroarenes

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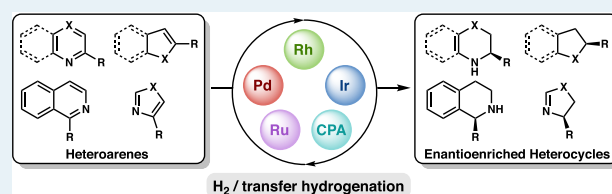
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ABSTRACT: The asymmetric hydrogenation of heteroarenes has recently emerged as an effective strategy for the direct access to enantioenriched, saturated heterocycles. Although several homogeneous catalyst systems have been extensively developed for the hydrogenation of heteroarenes with high levels of chemo- and stereoselectivity, the development of mild conditions that allow for efficient and stereoselective hydrogenation of a broad range of substrates remains a challenge. This Perspective highlights recent advances in homogeneous catalysis of heteroarene hydrogenation as inspiration for the further development of asymmetric hydrogenation catalysts, and addresses underdeveloped areas and limitations of the current technology.

KEYWORDS: hydrogenation, asymmetric catalysis, heterocycles, heteroarenes, homogeneous catalysts



1. INTRODUCTION

Heterocycles are important structural motifs found frequently in natural products¹ and industrial products such as pharmaceuticals² and agrochemicals.³ Nitrogen heterocycles constitute approximately 59% of recent FDA-approved small-molecule drugs, with an average of two to three nitrogen atoms per drug.^{2a} In the context of pharmaceutical development, a significant positive correlation exists between key structural elements of drug candidates, such as degree of saturation and number of stereogenic centers, with observed clinical success.^{2c,d} Thus, the ability to access stereochemically complex heterocyclic scaffolds has been of great interest in recent years. Considering the ubiquity of both aromatic and saturated heterocycles in pharmaceuticals, the direct access to enantiopure heterocycles via heteroarene hydrogenation continues to be an important research area in both academia and industry.²

While significant progress has been made in the area of asymmetric heteroarene hydrogenation, these transformations continue to pose a challenge for catalytic processes, ostensibly due to the high energetic cost of breaking aromaticity and the presence of heteroatoms that may poison and deactivate the catalyst.⁴ Nevertheless, the asymmetric hydrogenation of heteroarenes, including quinolines, isoquinolines, quinoxalines, pyridines, indoles, furans, and benzoxazines has been extensively explored, and several comprehensive reviews have been published on this subject (Figure 1).⁴ The hydrogenation of many common heteroarenes can be achieved using a variety of catalyst systems, including homogeneous and heterogeneous catalysts, such as metal nanoparticles.^{4d} Among these,

homogeneous catalyst systems have found widespread application for the asymmetric hydrogenation of heteroarenes, often providing access to different enantioenriched motifs with a simple adjustment of the chiral ligand.^{4,5} This Perspective is focused on highlighting homogeneous catalyst systems that have recently been developed for the asymmetric hydrogenation of heteroarenes, evaluating the general relationships between different catalyst complexes and their reactivity for various heterocycles. The following sections will feature reports that have been published since 2011, as previous reports have already been discussed comprehensively in prior review articles.⁴

2. GENERAL MECHANISTIC CONSIDERATIONS

Heteroarenes pose a significant challenge for asymmetric catalysis due to their inherent thermodynamic stability and the tendency of both reactants and products to deactivate catalysts. Three general strategies have been employed to overcome these difficulties: catalyst activation, substrate activation, and relay catalysis.^{4a} Catalyst activation involves either the preformation of the active catalyst or the addition of reagents to form a more active catalyst species in situ. For instance, the addition of halide sources to an iridium precatalyst was

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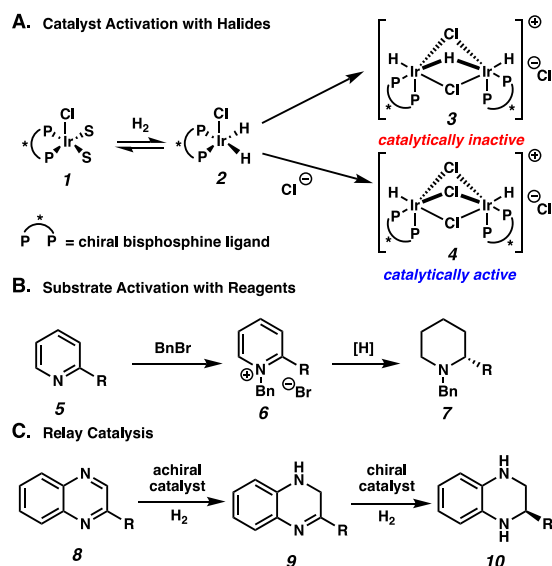


⁴⁴ Ru	14		2		5	1	1	1	1	2	1	
⁷⁷ Ir	28	7	5	5	3			1	3	4		
⁴⁵ Rh	3	1			4							
⁴⁶ Pd	1				8	1						
²⁶ Fe			1							1		
⁵ B	3		2									
OC	13		3	1	2					5	1	

Figure 1. Overview of the total number of published reports on the asymmetric hydrogenation of common heteroarenes ($\geq 90\%$ ee, minimum of three substrates).⁴

reported by Mashima and co-workers to prevent the irreversible formation of catalytically inactive dimeric iridium hydride species **3** (Scheme 1A).⁶ The substrate activation

Scheme 1. Examples for the Asymmetric Hydrogenation of Heteroarenes

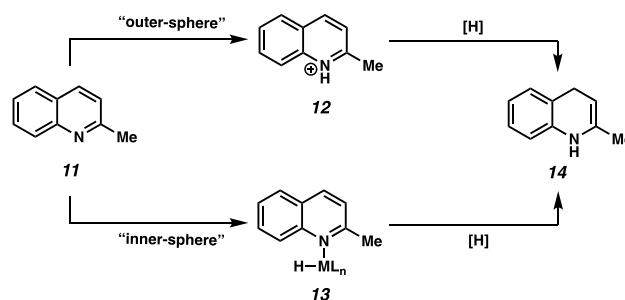


approach introduces reagents to overcome the inherent aromatic stability of heteroarenes through in situ generation or preformation of activated substrates, such as quinolinium or pyridinium salts (e.g., **6**, Scheme 1B).⁷ Finally, relay catalysis involves the use of two or more catalysts for the asymmetric hydrogenation of heteroarenes. For example, an achiral transition metal catalyst is often employed to induce initial partial hydrogenation of the substrate **8**, followed by an enantioselective hydrogenation of an intermediate such as imine **9** aided by a chiral Brønsted acid catalyst (Scheme 1C).⁸ Overall, these distinct strategies enable high stereoselectivity and functional group tolerance in the asymmetric hydrogenation of heteroarenes.

The general mechanism of the asymmetric hydrogenation of heteroarenes can be thought to involve the following steps

(depending on the degree of unsaturation): formation of the active catalyst species, hydride addition from the catalyst to the substrate, and regeneration of the catalyst from a hydrogen source.⁹ However, several questions regarding the mechanism of asymmetric hydrogenation that could be addressed include the order of hydride addition (1,2- vs 1,4-addition), substrate coordination to the catalyst (inner- vs outer-sphere), the rate-determining step, and the enantio-determining step.^{4a-d,9c} For instance, both inner-sphere and outer-sphere processes have been proposed to explain the mechanism for the iridium-catalyzed hydrogenation of 2-methylquinoline **11** (Scheme 2).^{9b} In an outer-sphere pathway, protonation of the substrate

Scheme 2. Possible Mechanistic Pathways for the Hydrogenation of 2-Methylquinoline **11**



occurs to form iminium intermediate **12**, followed by external hydride delivery to the activated substrate from the transition metal center. In contrast, an inner-sphere process involves a substrate that is bound to the metal hydride species (**13**) that undergoes a hydride transfer step. While other catalyst systems have been proposed to undergo an outer-sphere mechanism for the hydrogenation of various heterocycles (vide infra), other studies also support an inner-sphere coordination of the substrate to the catalyst.¹⁰ Thus, the coordinating ability of different heteroatom-containing substrates to the catalyst complex is not explicitly defined, and therefore it is difficult to predict how it would behave under different hydrogenation systems.

Although the asymmetric hydrogenation of heteroarenes is often difficult to monitor due to the use of high-pressure reactors, several mechanistic studies have been conducted

using empirical data and computational modeling to elucidate the mechanisms of transition metal-catalyzed and organic-catalyzed heteroarene hydrogenation reactions. The proposed catalytic cycles of these studies will be addressed in the following sections of this Perspective for each transition metal and organic catalyst system.

3. RUTHENIUM-CATALYZED ASYMMETRIC HYDROGENATION

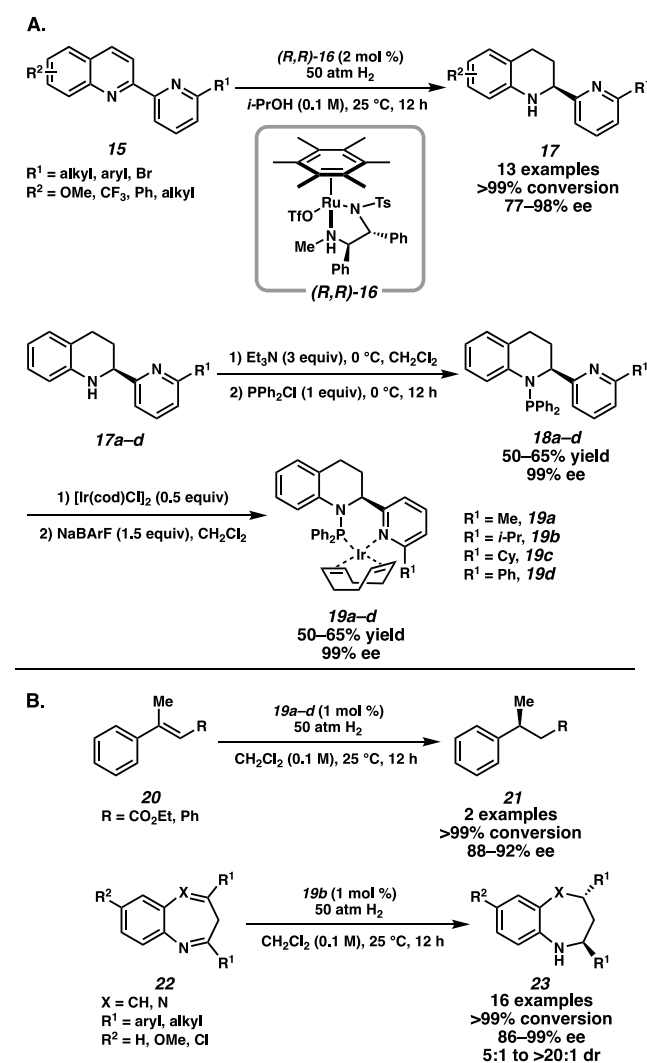
With regard to homogeneous catalysis, ruthenium was among the first transition metals explored in asymmetric hydrogenation reactions. In 1995, Noyori and co-workers introduced a Ru(II) catalyst with a chiral diamine ligand that promotes the highly stereoselective reduction of aromatic ketones through an asymmetric transfer hydrogenation process.¹¹ Shortly after, this catalyst system was applied to the asymmetric hydrogenation of imines with a formic acid–triethylamine mixture as the hydrogen source.¹² Since then, several established ruthenium catalyst systems with common ligand scaffolds were developed for the asymmetric hydrogenation of heteroarenes (Figure 2), as well as the hydrogenation of carbocyclic aromatic compounds.¹³

<div style="display: flex; align-items: center; justify-content: center;"> <div style="border: 1px solid black; padding: 2px; margin-right: 10px;">Heteroarenes</div> <div style="text-align: center; margin-right: 10px;"> Hydrogen Source: H₂ </div> <div style="border: 1px solid black; padding: 2px; margin-left: 10px;">Enantioenriched Heterocycles</div> </div>		
Catalyst System	Heteroarenes	References
Ru/DPEN R ¹ = Ts, Ms R ² = H, Me R ³ = <i>p</i> -cymene, hexamethylbenzene X = OTf, PF ₆ , BF ₄ , OPOPh ₂		14–17
		14c
		15d
		15c, 18
		19
Ru/PhTRAP, base (S,S)-(R,R)-PhTRAP (L1)		23a
		23b
		23c
		23d
Ru/NHC, KOt-Bu NHC-BF ₄ (L2)		25a
		25b–c

Figure 2. Common Ru-based catalyst systems for the asymmetric hydrogenation of heteroarenes ($\geq 90\%$ ee, minimum three substrates). Only one enantiomer of the ligand is shown for simplicity.

The air-stable Ru/TsDPEN catalyst (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine), initially developed by Fan and Chan for the hydrogenation of quinolines, has found widespread application in the asymmetric hydrogenation of *N*-heterocycles (Figure 2).^{14–19} In these reports, hydrogen gas is activated by the catalyst to reduce quinolines at ambient temperatures in ionic liquids and even under solvent-free conditions. Subsequent studies also utilize this system for sequential reductive amination and asymmetric hydrogenation cascade reactions of quinoline derivatives to access structurally diverse scaffolds.¹⁵ Since 2011, the Ru/TsDPEN catalyst system has evolved with important applications toward the development of novel chiral ligands. Fan and co-workers demonstrated that chiral Ru/TsDPEN catalysts can reduce 2,2'-bisquinoline and bisquinoline derivatives with high stereoselectivity.¹⁶ More recently, the system was applied to hydrogenate 2-(pyridine-2-yl)quinoline derivatives for the synthesis of novel *N,P*-ligands (Scheme 3).¹⁷ Using chiral catalyst complex **16** (Scheme 3A), selective hydrogenation of the quinoline ring was observed in a range of substrates (**15**) with high enantioselectivities. Although *ortho*-substituents on the pyridine ring are necessary to prevent catalyst deactivation, this requirement further

Scheme 3. Ru-Catalyzed Asymmetric Hydrogenation of Quinolines and Applications of Hydrogenated Products



enables the tuning of the steric effect of the chiral ligand generated.

The hydrogenated products **17a–17d** can then be transformed into a novel class of chiral *N,P*-ligands by treatment with PPh_2Cl in NEt_3 . After recrystallization, these ligands are then treated with $[\text{Ir}(\text{cod})\text{Cl}]_2$, followed by anion metathesis to yield chiral iridium complexes **19a–19d**.¹⁷ These catalysts are then successfully used for the asymmetric hydrogenation of olefins and seven-membered cyclic imines (Scheme 3B). Notably, replacement of the phenyl substituent on the pyridine ring of **19d** with an alkyl group (**19a–19c**) improves the enantioselectivity of the hydrogenation of trisubstituted olefin **20** to **21** in 88–92% ee. Catalyst **19b** is further utilized in the asymmetric hydrogenation of benzazepines and benzodiazepines, providing product **23** in up to 99% ee and 20:1 dr. The efficient synthesis of a novel class of chiral ligands through the asymmetric hydrogenation of heteroarenes is a promising application of this hydrogenation technology. The Ru/TsDPEN catalyst system is also effective for the asymmetric hydrogenation of unprotected indoles, which traditionally require protection of the indole nitrogen to prevent catalyst deactivation,¹⁸ C(3)-substituted benzoxazines,¹⁹ and a variety of polycyclic heteroarenes.²⁰

On the basis of experimental results and theoretical calculations, Fan and co-workers propose a catalytic cycle for the asymmetric hydrogenation of quinolines with Ru/TsDPEN catalysts (Figure 3). The Ru(II) catalyst activates molecular H_2 to form dihydrogen complex **24** and the activated substrate **26**, subsequent 1,4-hydride addition affords an enamine intermediate **29**.^{4e,15a} Tautomerization then occurs to form imine **30**, which is protonated by complex **24** to produce iminium **31**. Intermediate **31** undergoes an asymmetric 1,2-hydride transfer from complex **27** to deliver product **32** via **TS1**. The enantioselectivity is proposed to originate from the attractive CH/π interaction between the η^6 -arene ligand and the carbocyclic ring of the dihydroquinoline via a 10-membered transition state with participation of the triflate anion, as shown in **TS1**.^{15,21}

Although Ru/TsDPEN systems are efficient catalysts for the hydrogenation of bicyclic aromatic compounds, preformation of the active catalyst is required. Alternatively, other common chiral bisphosphine ligands that are explored in ruthenium-catalyzed asymmetric hydrogenations include PhTRAP (2,2''-bis[1-(diphenylphosphino)-ethyl]-1,1''-biferrocene), a C_2 symmetric biferrocene framework.²² Kuwano and co-workers demonstrate that ruthenium catalysts bearing PhTRAP ligand (**L1**) are productive in the hydrogenation of *N*-Boc-protected indoles (Scheme 4A), as well as substituted *N*-Boc-protected pyrroles and imidazoles (Scheme 4B,C).²³ Considering the high aromatic stability of single-ring aromatic compounds, the exhaustive hydrogenation of trisubstituted pyrroles to yield chiral pyrrolidines under this catalyst manifold is a significant advancement.^{4a,23c} The Ru/PhTRAP catalyst can also be applied to the hydrogenation of other five-membered heterocycles such as disubstituted imidazoles and oxazoles; however, only partial hydrogenation is observed in these cases.^{23d}

Finally, ruthenium *N*-heterocyclic carbene (NHC) complexes have found many applications in the transfer hydrogenation of ketones, nitriles, as well as the regioselective hydrogenation of heterocycles.²⁴ Glorius and co-workers first demonstrated the regioselective hydrogenation of the aromatic carbocyclic ring of quinoxalines, albeit with moderate

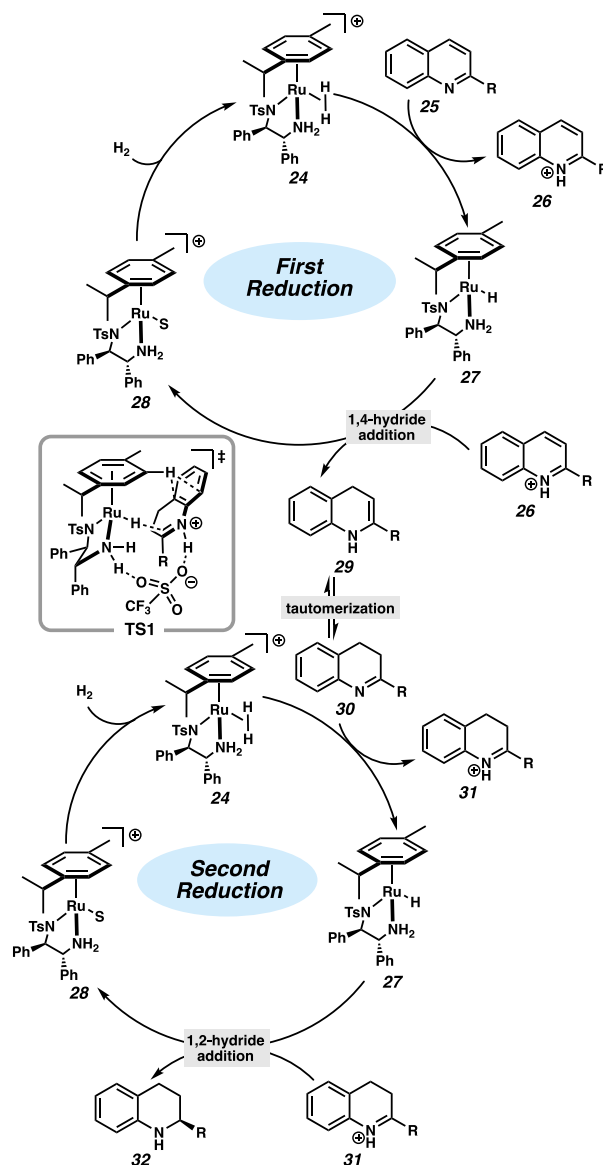
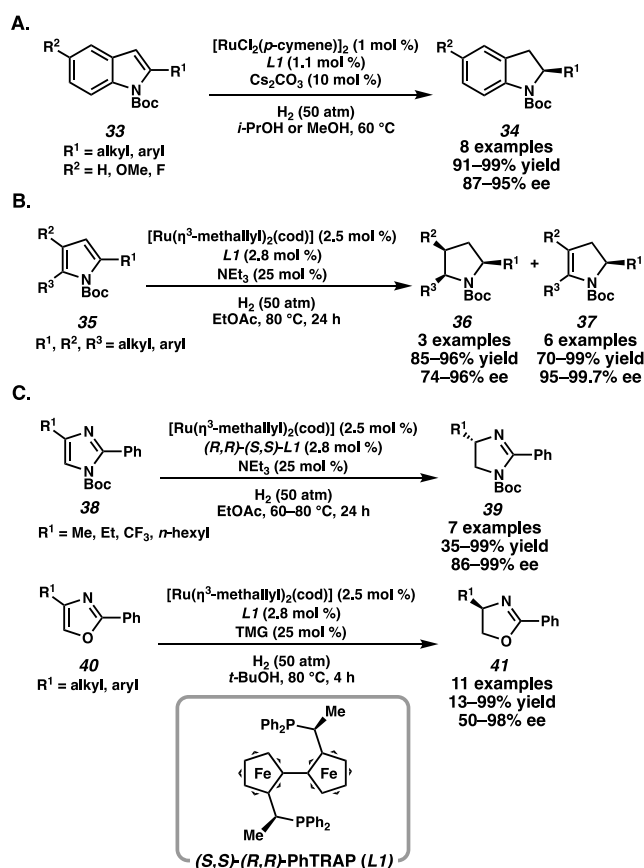


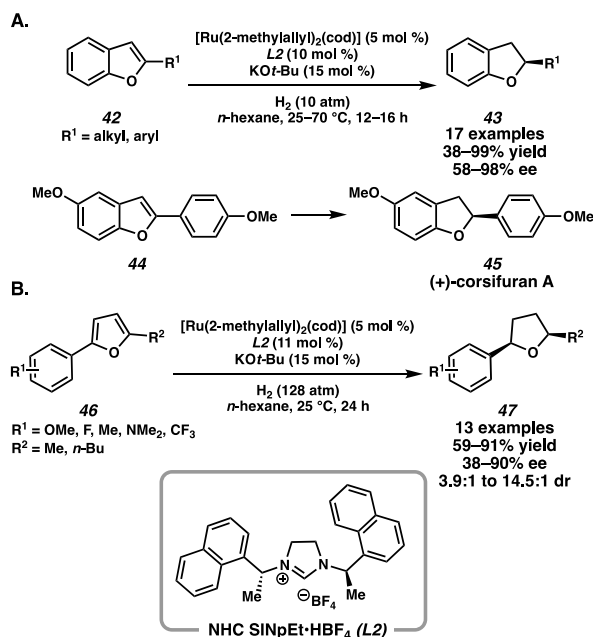
Figure 3. Proposed catalytic cycle for the asymmetric hydrogenation of quinolines with a Ru/TsDPEN catalyst.^{4e,15a}

enantioselectivity. They observed that the identity of NHC ligand was critical in determining the regioselectivity of hydrogenation, and found that these catalytic systems can also be applied toward the asymmetric hydrogenation of furans and benzofurans.²⁵ Using chiral NHC ligand SiNpEt-HBF_4 (**L2**), the asymmetric hydrogenation of disubstituted furans and 2-substituted benzofurans proceeded in high yields and enantioselectivities (Scheme 5). A wide range of substituted furans were hydrogenated with this catalyst system, demonstrating a significant correlation between strongly electron-withdrawing groups on the substrate and diminished enantioselectivity.^{25a} Overall, the Ru/NHC complex demonstrated its capability to hydrogenate a range of heteroarenes, particularly oxygen-containing heterocycles, allowing direct access to natural metabolites such as (+)-corsifuran A (Scheme 5A). Further studies of the Ru/**L2** catalyst system by Glorius and co-workers revealed that hydrogenation of the naphthyl substituents of the NHC ligand was a key step in accessing the active catalyst.²⁶

Scheme 4. Ru-Catalyzed Asymmetric Hydrogenation of Heteroarenes with PhTRAP Ligand L1



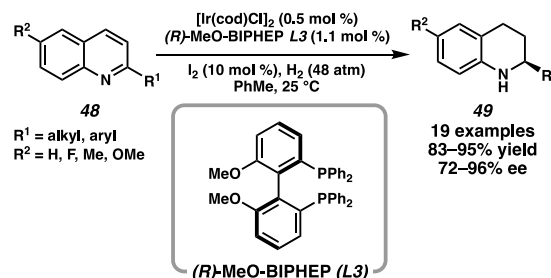
Scheme 5. Ru-Catalyzed Asymmetric Hydrogenation of Furans and Benzofurans with NHC Ligand L2



4. Iridium-CATALYZED ASYMMETRIC HYDROGENATION

Following the initial disclosure of the enantioselective hydrogenation of quinolines using [Ir(cod)Cl]₂ and bisphosphine ligand MeO-BIPHEP (L3) in 2003 (Scheme 6),²⁷ much attention has been devoted toward the develop-

Scheme 6. First Reported Ir-Catalyzed Asymmetric Hydrogenation of Quinolines



ment of the iridium-catalyzed hydrogenation of heteroarenes. Most studies have focused on the exploration of different types of activating agents to reduce substrate aromaticity, as well as to prevent the irreversible formation of catalytically inactive dimeric iridium hydride species 3.^{6,27} Common ligand scaffolds utilized in this transformation include atropisomeric biaryl bisphosphine ligands, as well as phosphine–phosphite ligands, *N,P*-ligands, and chiral diamine ligands that have been explored for the asymmetric hydrogenation of a range of heterocycles (Figure 4).

The biaryl bisphosphine ligand scaffold is most common in iridium-catalyzed asymmetric hydrogenation due to its excellent steric and electronic tunability. Structural variations of the ligand include alteration of *P*-substitution and modifications of the phenyl backbone, including the synthesis of supramolecular chiral ligands appended with crown ethers that induce strong complexation between the ligand and alkali cations.²⁸ Since 2011, the combination of iridium and biaryl bisphosphine ligands has been extensively studied by Zhou, Agbossou-Niedercorn, and Mashima in the asymmetric hydrogenation of heteroarenes, including quinolines,²⁹ isoquinolines,^{6,30} quinoxalines,^{29e,31} pyridines,^{30e} pyrazines,³² and benzoxazines.³³ Iodine, chloroformates, amines, and Brønsted acids are common activating reagents for enhancing catalytic activity of these heterocyclic substrates.

The mechanism and the role of iodine as an activator was initially proposed by Zhou and Li (Figure 5).^{27b} Starting from [Ir(cod)Cl]₂, the addition of I₂ oxidizes the Ir(I) precursor to an Ir(III) species 51. Subsequent heterolytic cleavage of H₂ with the release of HI forms catalytically active Ir(III) complex 53. The heteroarene then coordinates to generate octahedral complex 54, followed by a 1,4-hydride transfer to form intermediate 55. An additional molecule of H₂ regenerates the iridium hydride species 53 and protonates the enamine, which can isomerize to imine 30 and undergo a second reduction. The enantio-determining step is proposed to be a 1,2-hydride addition that establishes the stereogenic center, with the addition of H₂ releasing the product and regenerating Ir(III) species 53. It is unclear, however, whether substrate coordination to the metal center occurs, as other studies have proposed an outer-sphere pathway for the homogeneous iridium-catalyzed hydrogenation of quinolines and isoquinolines (vide supra).^{6,9b}

Recently, Zhou and co-workers employed trichloroisocyanuric acid (TCCA) as a traceless activating

Heteroarenes		Enantioenriched Heterocycles
Catalyst System	Heteroarenes	References
<p style="text-align: center;">Ir/P–P* biaryl bisphosphine ligands:</p> <div style="text-align: center;"> </div> <p style="text-align: center;">Ar = Ph, xyllyl X = CH, N R¹ = OMe, OCF₃, OTf, OC₁₂H₂₅, OPEG, O₂(C₆H₁₀) (TunePhos) R² = H, OMe, OPEG</p> <div style="text-align: center;"> <p>○ = SEGPHOS (<i>L</i>4), DIFLUORPHOS ○ = SYNPHOS, BINAP, H₈-BINAP</p> </div> <div style="text-align: center;"> <p>X = CH₂, O R¹ = H, Et</p> </div>	<div style="text-align: center;"> </div> <p style="text-align: right;">27–29, 35</p> <div style="text-align: center;"> </div> <p style="text-align: right;">6, 30</p> <div style="text-align: center;"> </div> <p style="text-align: right;">29e, 31</p> <div style="text-align: center;"> </div> <p style="text-align: right;">30e</p> <div style="text-align: center;"> </div> <p style="text-align: right;">32</p> <div style="text-align: center;"> </div> <p style="text-align: right;">33</p>	
<p style="text-align: center;">Ir/P–P* Josiphos ligands (<i>L</i>6/<i>L</i>7):</p> <div style="text-align: center;"> </div> <p style="text-align: center;">Ar = Ph, DMM (4-methoxy-3,5-dimethyl(phenyl)) R = xyllyl, <i>t</i>-Bu</p>	<div style="text-align: center;"> </div> <p style="text-align: right;">37</p> <div style="text-align: center;"> </div> <p style="text-align: right;">32a</p>	
<p style="text-align: center;">Ir/P–OP* P–OP* ligand (<i>L</i>8):</p> <div style="text-align: center;"> </div>	<div style="text-align: center;"> </div> <p style="text-align: right;">38b</p> <div style="text-align: center;"> </div> <p style="text-align: right;">38c</p> <div style="text-align: center;"> </div> <p style="text-align: right;">38c</p>	
<p style="text-align: center;">Ir/N–P* N–P* ligands:</p> <p>Select Examples:</p> <div style="text-align: center;"> </div> <div style="text-align: center;"> <p>(<i>L</i>9)</p> </div>	<div style="text-align: center;"> </div> <p style="text-align: right;">39a</p> <div style="text-align: center;"> </div> <p style="text-align: right;">39a,b</p> <div style="text-align: center;"> </div> <p style="text-align: right;">39b</p> <div style="text-align: center;"> </div> <p style="text-align: right;">39d</p>	
<p style="text-align: center;">Ir/N–N* TsDPEN ligands:</p> <div style="text-align: center;"> </div> <p style="text-align: center;">R¹ = H, Me R² = 4-CH₃C₆H₄, 4-CF₃C₆H₄</p>	<div style="text-align: center;"> </div> <p style="text-align: right;">16c, 40</p>	

Figure 4. Common Ir-based catalyst systems for the asymmetric hydrogenation of heteroarenes ($\geq 90\%$ ee, minimum three substrates). Only one enantiomer of the ligand is shown for simplicity.

reagent for the iridium-catalyzed hydrogenation of isoquinolines and pyridines (Scheme 7). This method circumvents the

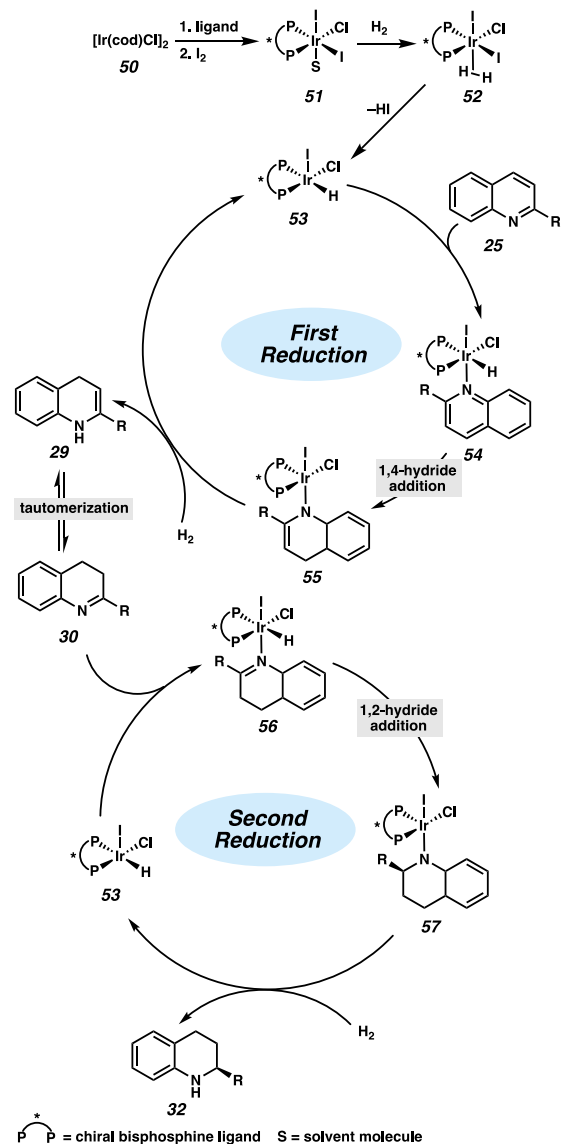
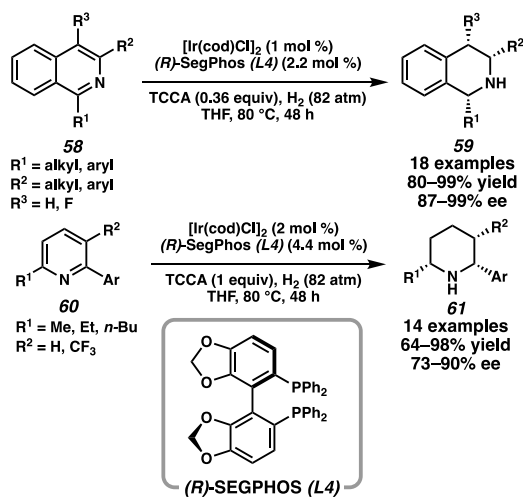


Figure 5. Proposed catalytic cycle for the Ir-catalyzed asymmetric hydrogenation of quinolines with I_2 as an additive.^{27b}

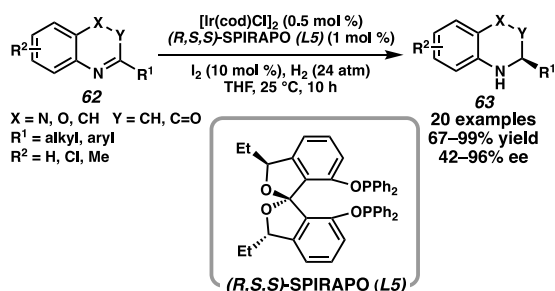
Scheme 7. Ir-Catalyzed Asymmetric Hydrogenation of Isoquinolines and Pyridines Using TCCA as the Activator



additional steps of installing and removing the *N*-acyl group to activate the substrates. Pairing [Ir(cod)Cl]₂ and bisphosphine ligand (*R*)-SEGPHOS (**L4**), a range of disubstituted isoquinolines and pyridines were hydrogenated in high yield and excellent enantioselectivity.^{30e} The use of TCCA as a halogen-bond activator gave the highest enantioselectivity compared to *N*-chlorosuccinimide or *N*-iodosuccinimide. Notably, 2,3,6-trisubstituted pyridines **60** were also converted to chiral piperidines **61** with higher enantioselectivity than previous methods, which often require more activated pyridinium salts as substrates.⁷

Extending BINAP-derived ligand scaffolds, biaryl spirocyclic ligands have emerged as powerful tools for asymmetric catalysis due to their higher rigidity.³⁴ Nagorny and co-workers reported that the chiral spiroketal-based bisphosphinite ligand (SPIRAPO; **L5**) is effective in the asymmetric hydrogenation of quinolines, quinoxalines, and benzoxazinones (Scheme 8).³⁵ Using 10 mol % I₂ and low catalyst loadings, the synthesis of a range of enantioenriched saturated heterocycles was achieved at 24 atm of H₂ and room temperature.

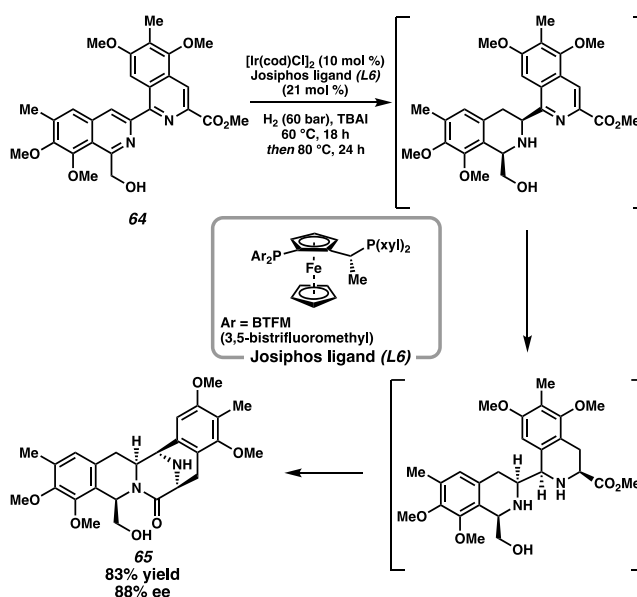
Scheme 8. Ir-Catalyzed Asymmetric Hydrogenation of Quinolines, Quinoxalines, and Benzoxazinones



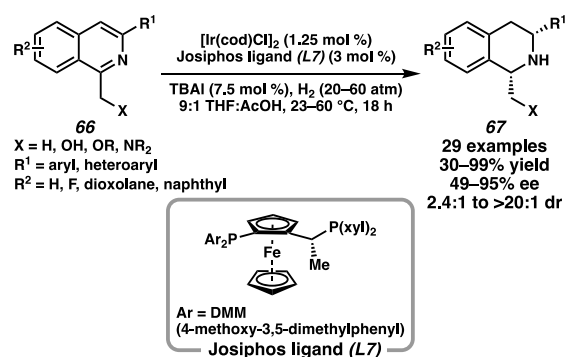
While there has been extensive development of biaryl bisphosphine (vide supra) and phosphoramidite³⁶ ligands for iridium-catalyzed hydrogenation, ferrocenyl-based Josiphos ligands are also efficacious ligand scaffolds for *N*-heterocycles, imparting excellent enantioselectivity and diastereoselectivity.³⁷ Inspired by the iridium catalyst system employed in the ether-directed asymmetric imine reduction en route to the herbicide metolachlor,¹⁰ Stoltz and co-workers explored the potential of directing groups as iridium catalyst chelating agents for the directed hydrogenation to a specific face of the substrate. Toward the total synthesis of the complex bis-tetrahydroisoquinoline alkaloid jorumycin, the hydroxymethyl functionality was utilized as a directing group for the iridium-catalyzed asymmetric hydrogenation of bis-isoquinoline **64** to generate pentacyclic intermediate **65** in one step as a single diastereomer in 88% ee (Scheme 9).³⁷

Utilizing directing groups is an underdeveloped activation strategy for the asymmetric hydrogenation of *N*-heterocycles, as Lewis basic functional groups are not as well tolerated with previous hydrogenation methods.³⁰ However, Stoltz and co-workers have extended this application of using a hydroxymethyl directing group toward the asymmetric hydrogenation of a range of 1,3-disubstituted isoquinolines. Using 1.25 mol % of [Ir(cod)Cl]₂ and 3 mol % of chiral Josiphos ligand (**L7**), a range of differentially substituted isoquinolines were hydrogenated in high yields and enantio- and diastereoselectivity (Scheme 10).^{37b} Heterocyclic substituents,

Scheme 9. Key Ir-Catalyzed Enantioselective Hydrogenation Step in the Total Synthesis of Jorumycin



Scheme 10. Ir-Catalyzed Asymmetric Hydrogenation of 1,3-Disubstituted Isoquinolines

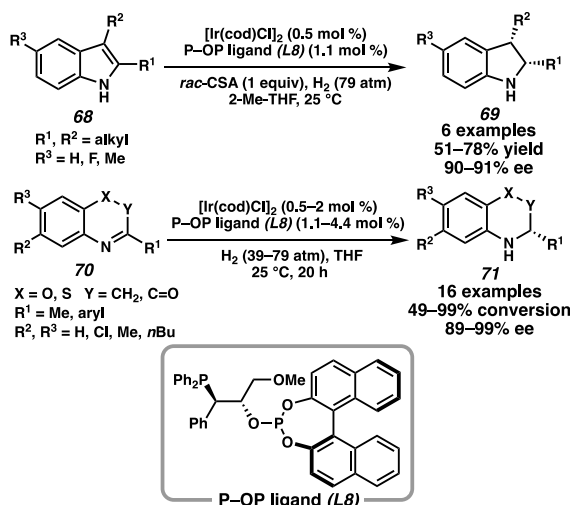


such as furan and thiophene, at the C(3) position were also tolerated in this transformation. Interestingly, altering the directing groups at the C(1) position of the isoquinoline lowered the levels of conversions but maintained similar levels of stereoselectivity.

Phosphine–phosphite (P–OP) ligands, an emerging class of chiral bisphosphine ligands, have been developed by Vidal-Ferran and co-workers for the iridium-catalyzed asymmetric hydrogenation of heterocycles.³⁸ This catalyst system is particularly reactive in the enantioselective synthesis of indolines from unprotected indoles,^{38b} as well as the asymmetric hydrogenation of benzoxazines and benzothiazinones.^{38c} Although stoichiometric amounts of sulfonic acids are needed to promote isomerization to the iminium intermediate, the transformation can be carried out using only 0.5 mol % of [Ir(cod)Cl]₂ (Scheme 11).³⁸

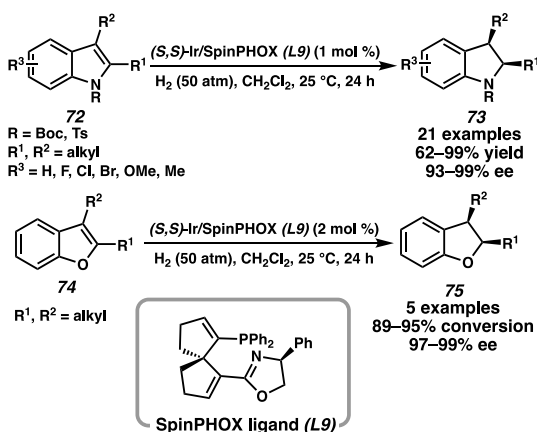
Although chiral bisphosphine ligands are most commonly employed for iridium-catalyzed asymmetric hydrogenation, chiral PHOX ligands with nitrogen and phosphorus chelating groups (*N,P*) have also been used to reduce a range of heteroarenes.³⁹ Most recently, Ding and co-workers reported the use of a SpinPHOX (spiro[4,4]-1,6-nonadiene-based phosphinooxazoline) ligand (**L9**) for the enantioselective

Scheme 11. Ir-Catalyzed Asymmetric Hydrogenation of Indoles, Benzoxazines, and Benzothiazinones with P–OP Ligand **L8**



hydrogenation of indole and benzofuran derivatives (Scheme 12). This iridium catalyst system is effective for the asymmetric

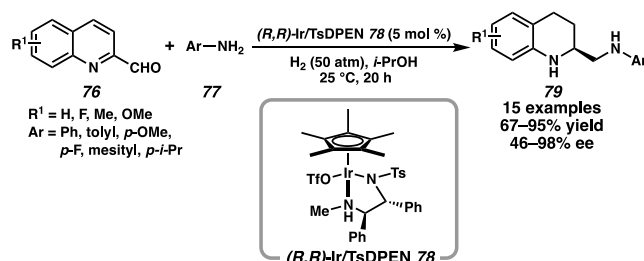
Scheme 12. Ir-Catalyzed Asymmetric Hydrogenation of Indoles and Benzofurans with SpinPHOX Ligand **L9**



hydrogenation of a diverse range of indoles with high functional group tolerance, using 1 mol % of catalyst loading and mild reaction conditions.^{39a} Although preformation of the Ir/SpinPHOX catalyst complex is necessary, up to 99% isolated yield and 99% enantiomeric excess are observed across differentially substituted indole and benzofuran substrates.

Unlike the ruthenium catalyst system, only a few reports employ the TsDPEN ligand for iridium-catalyzed asymmetric heteroarene hydrogenation.^{16c,40} In 2019, Fan and co-workers developed Ir/TsDPEN catalyst complex **78** for the enantioselective synthesis of vicinal chiral diamines. These products are synthesized through a relay sequence of intermolecular reductive amination followed by asymmetric hydrogenation of a range of 2-quinoline aldehydes and aromatic amines (Scheme 13).^{16c} For more sterically encumbered substrates, an addition of 10 mol % TfOH is required to generate chiral diamines in high levels of selectivity.

Scheme 13. Asymmetric Hydrogenation of Quinolines with Iridium Catalyst **78**



5. RHODIUM-CATALYZED ASYMMETRIC HYDROGENATION

Apart from iridium and ruthenium catalyst systems in the asymmetric hydrogenation of heteroarenes, rhodium catalysts have also been effective for the reduction of quinolines, isoquinolines, and indoles (Figure 6). The combination of a

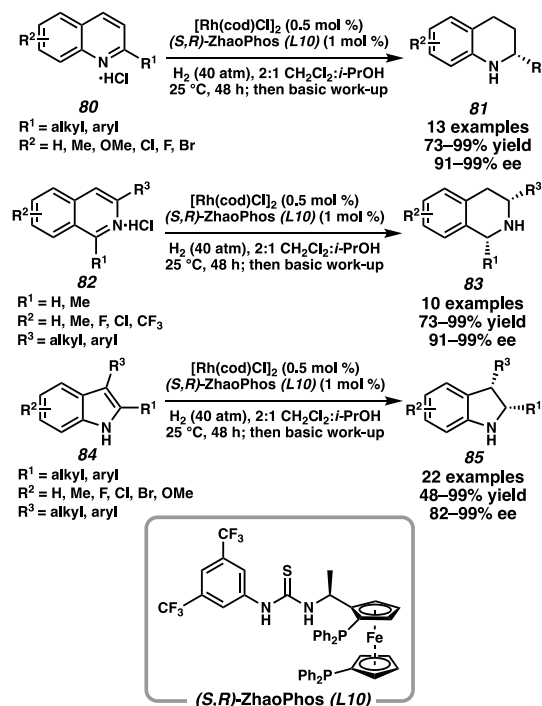
Catalyst System	Heteroarenes	References
Rh/P–P* biphosphine–thiourea ligand (L10): 	 	43b 43b 43c
Rh/PhTRAP, base (<i>S,S</i>)-(R,R)-PhTRAP (L1)	 R = Ac, Ts, Ms, Tf	41
Rh/N–N* TsDPEN ligands: R ¹ = H, CH ₂ C ₆ H ₄ (tethered) R ² = 4-CH ₃ C ₆ H ₄ , 4-C(CH ₃) ₃ C ₆ H ₄		42

Figure 6. Common Rh-based catalyst systems for the asymmetric hydrogenation of heteroarenes ($\geq 90\%$ ee, minimum three substrates). Only one enantiomer of the ligand is shown for simplicity.

rhodium(I) source and either a PhTRAP⁴¹ or TsDPEN⁴² ligand have been explored for the enantioselective hydrogenation of indoles and quinolines, respectively. More recently, Zhang and co-workers have developed a novel ferrocene-based biphosphine–thiourea ligand, ZhaoPhos (**L10**), for the cooperative catalysis of a transition metal center for hydrogenation and anion binding of the thiourea derivative.⁴³ This strategy allows a broader range of Brønsted acids to be

tolerated through hydrogen bonding interactions with the thiourea moiety, and simple tunability with the phosphine substituents to improve selectivity. Using ligand **L10** with 0.5 mol % rhodium catalyst loading, differentially substituted quinolines, isoquinolines, and unprotected indoles are hydrogenated with excellent yield and enantioselectivity (Scheme 14). The addition of HCl as a strong acid is well tolerated under this catalyst system due to the stabilizing interaction with the thiourea derivative.

Scheme 14. Rh-Catalyzed Asymmetric Hydrogenation of *N*-Heteroarenes with ZhaoPhos Ligand **L10**



Zhang and co-workers performed DFT calculations to gain insight into the mechanism of the Rh-catalyzed transformation (Figure 7).^{43c} Rh(I) catalyst **86** undergoes oxidative addition with H₂ to generate the active Rh(III) species **88**. Protonation of the indole substrate with HCl allows anion binding with the thiourea moiety to form intermediate **90**, allowing hydrogen bonding interactions between the chloride ion and the indole N–H group. Hydride transfer then proceeds through an outer-sphere pathway to release the chiral indoline product **91** and complex **92**. The addition of another molecule of H₂ facilitates heterolytic cleavage of dihydrogen in complex **93** to generate Rh(III) catalyst **94** and HCl, in what was computed to be the rate-determining step. Overall, the thiourea–chloride anion binding proved to be crucial for inducing high enantioselectivity and reactivity in this system.^{43c}

6. PALLADIUM-CATALYZED ASYMMETRIC HYDROGENATION

Compared to ruthenium, iridium, and rhodium catalysts, homogeneous palladium catalysts for the asymmetric hydrogenation of heteroarenes remain relatively unexplored.⁴ In 2010, Zhou and co-workers reported the first Pd-catalyzed asymmetric hydrogenation of *N*–H indoles using Pd-(OCOCF₃)₂, a chiral H₈–BINAP ligand, and (–)-camphor-

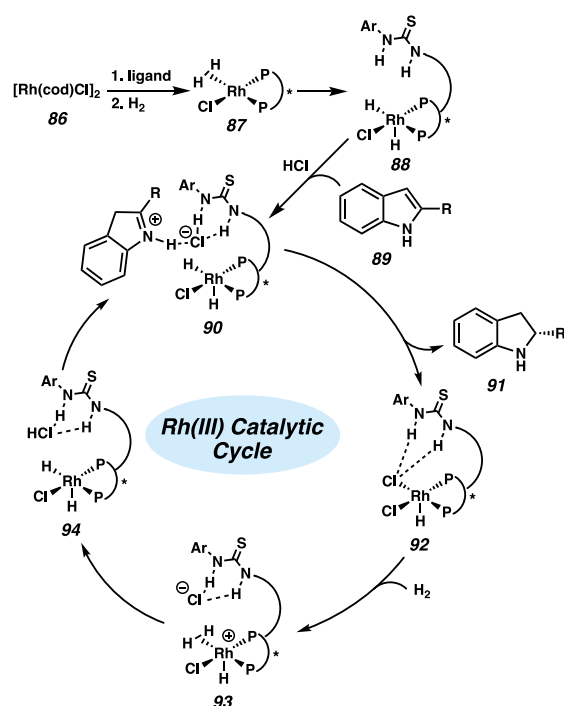


Figure 7. Proposed catalytic cycle for the Rh-catalyzed asymmetric hydrogenation of indoles with ZhaoPhos **L10.**^{43c}

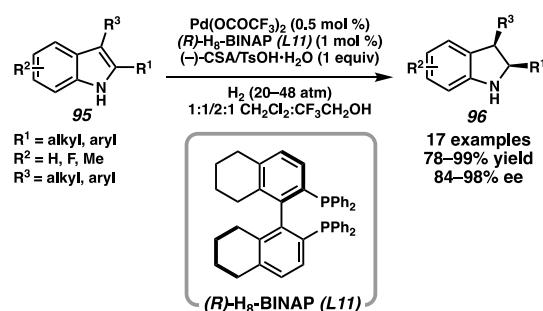
sulfonic acid.⁴⁴ Since their seminal report, the homogeneous palladium catalyst system has been extended to accommodate a range of *N*-heteroarenes, including quinolines,⁴⁵ indoles,⁴⁶ quinoxalinones,⁴⁷ and the partial hydrogenation of pyrroles (Figure 8).⁴⁸ Common among all these catalytic systems is the use of chiral biaryl bisphosphine ligands with different steric environments of the naphthyl ring.

<div style="display: flex; align-items: center; justify-content: center;"> <div style="border: 1px solid black; padding: 2px 5px; margin-right: 10px;">Heteroarenes</div> <div style="text-align: center; margin-right: 10px;"> </div> <div style="border: 1px solid black; padding: 2px 5px; margin-right: 10px;">Enantioenriched Heterocycles</div> </div> <div style="text-align: center; margin-bottom: 5px;">Hydrogen Source: H₂</div>		
Catalyst System	Heteroarenes	References
Pd/P–P* biaryl bisphosphine ligands: <div style="display: flex; align-items: center; margin-top: 5px;"> = </div>	 	45 47 48 46

Figure 8. Common Pd-based catalyst systems for the asymmetric hydrogenation of heteroarenes (≥90% ee, minimum three substrates). Only one enantiomer of the ligand is shown for simplicity.

Zhou and co-workers have extensively developed palladium catalyst systems for the hydrogenation of *N*-heteroarenes, as palladium complexes demonstrate a higher tolerance for strong Brønsted acids. When chiral ligand (*R*)-H₈-BINAP (**L11**), palladium(II) trifluoroacetate, and 1 equiv of (–)-camphor-sulfonic acid or TsOH·H₂O are used, the asymmetric hydrogenation of 2-substituted and 2,3-disubstituted indoles is achieved to synthesize enantioenriched indolines in up to 99% yield and 98% ee (Scheme 15).^{46c} Isotope-labeling studies demonstrate that the acid is necessary for formation of the iminium salt, which then undergoes hydrogenation by a Pd–H species.

Scheme 15. Pd-Catalyzed Asymmetric Hydrogenation of *N*-H Indoles



Using both experimental and theoretical methods, Zhou and co-workers analyzed several possible mechanisms and propose a stepwise outer-sphere pathway (Figure 9).^{46c} The indole is

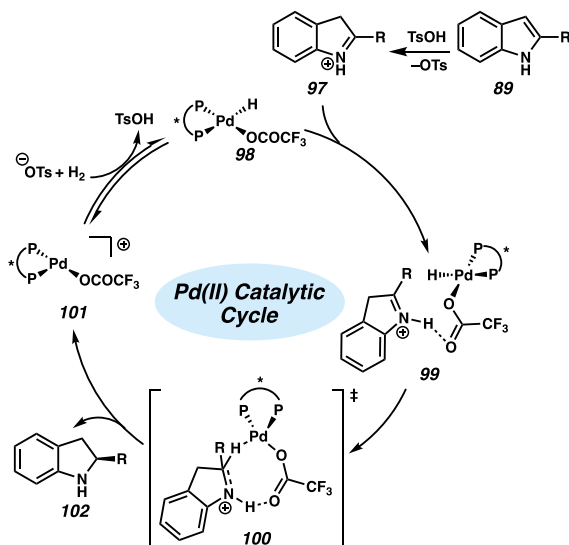


Figure 9. Proposed catalytic cycle for the Pd-catalyzed asymmetric hydrogenation of indoles.^{46c}

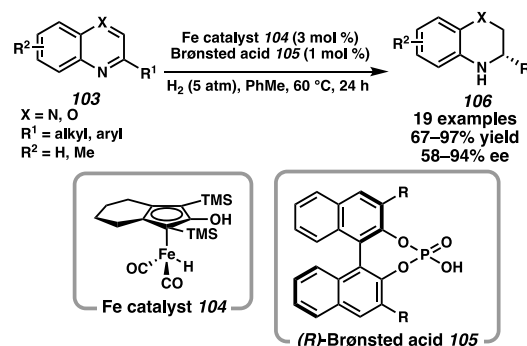
initially protonated by TsOH to give the iminium **97**, subsequently inducing hydrogen-bonding interactions with the trifluoroacetate ligand to generate intermediate **99**. A hydride transfer from the Pd(II) center to the hydrogen-bound iminium group of complex **100** is proposed to be the enantio-determining step. The addition is postulated to occur through an eight-membered transition state, in which differentiation of the enantiotopic face is achieved through steric interactions with the chiral bisphosphine ligand. After dissociation of the

chiral indoline product **102**, palladium hydride species **98** is regenerated with the release of TsOH from the activation of H₂. Additional mechanistic studies of palladium-catalyzed asymmetric hydrogenation of *N*-heteroarenes may provide key insights for further chiral catalyst design to improve the substrate scope of this transformation.

7. IRON-CATALYZED ASYMMETRIC HYDROGENATION

Despite the development of many efficient transition metal catalysts for the asymmetric hydrogenation of heteroarenes, the application of earth-abundant metals such as iron as hydrogenation catalysts is a promising avenue of further development. The first report of the homogeneous asymmetric hydrogenation of imines using first-row transition metals was only recently published in 2011.⁴⁹ Beller and co-workers developed a novel cooperative catalytic system combining an achiral iron hydrogenation catalyst with a chiral Brønsted acid that facilitates the enantioselective reduction of quinoxalines and benzoxazines.⁵⁰ Using chiral phosphoric acid **105** to activate the substrate and control the enantioselectivity, an iron complex (**104**) reacts with the activated intermediate to deliver enantioenriched tetrahydroquinoxalines and dihydrobenzoxazines in high yields and selectivity (Scheme 16).^{50a} Notably, both electron-donating and electron-with-

Scheme 16. Fe-Catalyzed Asymmetric Hydrogenation of Quinoxalines and Benzoxazines with Chiral Phosphoric Acid **105**



drawing substituents on the C2-substituted phenyl ring, as well as *meta*- and *para*-substituted substrates, had little impact on the reactivity and enantioselectivity of the hydrogenation reaction. The levels of selectivity observed with the iron catalyst system rival those of late transition metal-based catalysts for the hydrogenation of the same heteroarenes.

Although the mechanism for this transformation has been previously investigated computationally using acyclic imines,⁵¹ Hopmann has proposed an alternative mechanism with benzoxazine as the substrate (Figure 10).⁵² Calculations indicate that hydrogenation may likely occur through a stepwise mechanism, in which initially the resting state **107** involves an adduct between the deprotonated acid and the iron complex. A molecule of H₂ generates dihydrogen complex **108**, subsequently splitting H₂ through proton abstraction by the phosphate to yield iron hydride species **109**. Benzoxazine **110** then coordinates to the chiral acid through hydrogen-bonding interactions, allowing hydride transfer to occur to form catalyst species **112**. Finally, product **113** is released with regeneration

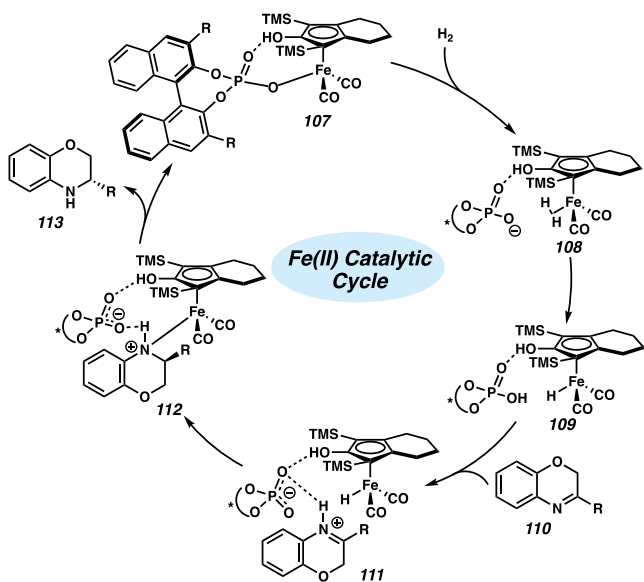


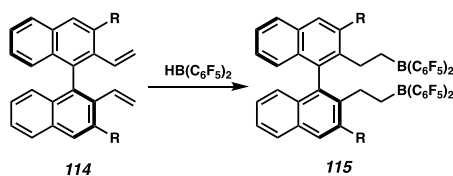
Figure 10. Proposed cooperative catalytic cycle for the Fe-catalyzed asymmetric hydrogenation of benzoxazines in the presence of a chiral phosphoric acid.⁵²

of the catalyst complex **107**.⁵² Computationally predicted enantioselectivities are in excellent agreement with experimental values, and the proposed mechanism is consistent with experimental observations by Beller and co-workers on possible reaction intermediates.⁵⁰

8. BORANE-CATALYZED ASYMMETRIC HYDROGENATION

Avoiding the use of transition metals for catalysis, the metal-free asymmetric hydrogenation of heteroarenes is an emerging research field for further development. Recently, frustrated Lewis pair (FLP) catalysis has been explored for the hydrogenation of heteroarenes with hydrogen gas or NH_3 , BH_3 as the hydrogen source.⁵³ Du and co-workers reported a novel FLP catalyst system using a chiral borane catalyst (**115**), generated in situ from the direct hydroboration of chiral dienes **114** with $\text{HB}(\text{C}_6\text{F}_5)_2$ (Scheme 17).⁵⁴ The binaphthyl

Scheme 17. In Situ Formation of Chiral Borane Catalyst **115** from Chiral Dienes

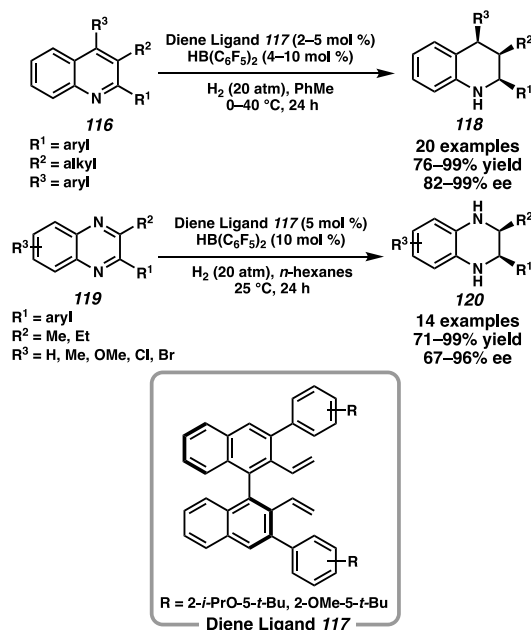


substituent presumably serves to control the stereoselectivity of the transformation, often requiring bulky aryl groups to achieve high selectivity. Although the mechanism for the asymmetric hydrogenation of heteroarenes using chiral borane catalysts has not been investigated thoroughly, FLP catalysts are well-known to activate H_2 splitting and undergo hydride transfer.⁵⁵

Chiral borane catalysts such as **115** are effective for the asymmetric hydrogenation of trisubstituted quinolines and disubstituted quinoxalines.⁵³ Du and others optimized the

catalyst system to generate the borane catalyst in situ with 2 to 5 mol % of the chiral diene ligand **117** and $\text{HB}(\text{C}_6\text{F}_5)_2$ in the presence of molecular H_2 gas (Scheme 18). Under mild

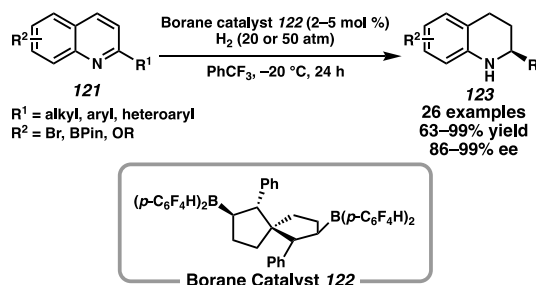
Scheme 18. Metal-Free Hydrogenation of Heteroarenes through in Situ Formation of a Chiral Borane Catalyst



reaction conditions, a range of chiral tetrahydroquinolines and tetrahydroquinoxalines were synthesized in high yield and enantioselectivity.^{53a-d} Overall, this catalyst system is a promising step toward the in situ generation of a library of chiral borane catalysts, and their application to the asymmetric hydrogenation of other heteroarenes could be explored.

In 2019, Wang and co-workers developed a similar catalytic system, employing chiral spiro-bicyclic bisborane catalysts for the asymmetric hydrogenation of C(2)-substituted quinolines.^{53e} The novel spiro-bicyclic bisborane catalyst **122** exhibited excellent activity and selectivity for alkyl-substituted quinolines at the C(2) position, which previously have not been well tolerated (Scheme 19). A range of quinolines bearing alkenes,

Scheme 19. Metal-Free Hydrogenation of Quinolines Using Spiro-Bicyclic Bisborane Catalyst **122**

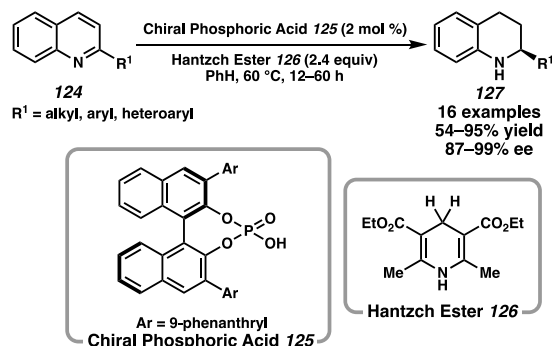


alkynes, and heterocycles were hydrogenated in excellent yield, enantioselectivity, and chemoselectivity, demonstrating the catalyst's broad functional group tolerance.

9. CHIRAL PHOSPHORIC ACID-CATALYZED ASYMMETRIC HYDROGENATION

Since Rueping's first report of an organic-catalyzed asymmetric reduction of heteroarenes in 2006, various chiral Brønsted acid catalysts have emerged as powerful agents for asymmetric arene hydrogenation (Scheme 20).^{4,56} Asymmetric

Scheme 20. First Reported Chiral Phosphoric Acid-Catalyzed Asymmetric Hydrogenation of Quinolines



transfer hydrogenation (ATH) reactions are promising alternatives to the use of transition metals or high pressure reactors, instead employing hydrogen sources like Hantzsch esters (HEH), dihydrophenanthridine (DHPD), and 4,5-dihydropyrrolo[1,2-*a*]quinoxalines.⁵⁷ In most cases, however, an unrecyclable excess of reductant is required for hydrogenation.

Over the past decade, several effective organic catalyst systems have been developed with chiral phosphoric acids (CPA) for the asymmetric reduction of quinolines,⁵⁸ indoles,^{58b,59} quinoxalines,^{58c} benzoxazines,^{57,58b,c,f,60} benzothiazines,⁶⁰ and the partial hydrogenation of pyridines (Figure 11).⁶¹ Rueping and others have reported the use of BINOL-based phosphoric acid catalysts for the asymmetric hydrogenation of heteroarenes, with similar catalyst systems as shown in Scheme 20.⁵⁶ More recently, Shi and co-workers have developed a new class of CPA catalysts with a 1,1'-spirobiindane-7,7'-diol (SPINOL) backbone for the enantioselective hydrogenation of a range of quinolines and benzoxazines.^{58f} Using 1 mol % of CPA 135 and 1.25 to 2.5 equiv of HEH (126), electron-withdrawing and electron-donating substituents at the C(2)-position are all well tolerated and afforded excellent enantioselectivities (Scheme 21).^{58f} The metal-free and mild reaction conditions of this transformation are an appealing alternative to transition metal catalyst systems.

The general mechanism of the asymmetric transfer hydrogenation of quinolines by Hantzsch esters has been explored computationally by Frison and co-workers.⁶² It is well-precedented that two subsequent reduction cycles occur, each with one equivalent of the hydride source and a chiral phosphoric acid. Quinoline 25 is first activated through a proton transfer from the phosphoric acid to the substrate, followed by a 1,4-hydride addition using HEH. The resulting dihydroquinoline can then isomerize to the imine, entering a second reduction cycle involving a similar stepwise process (Figure 12). Although previous studies have proposed the hydride transfer from 146 to 147 to be the rate- and enantio-determining step,⁶³ Frison revisited these calculations and proposed that the stereocontrol is determined from the steric

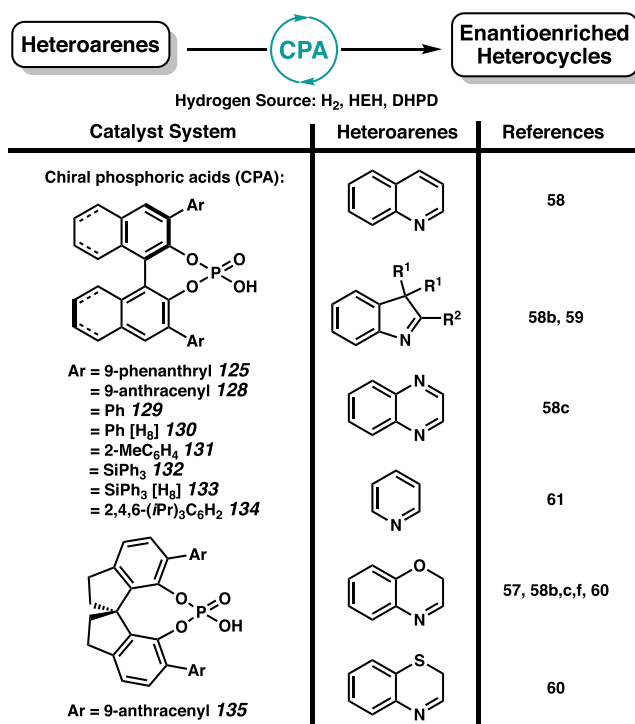
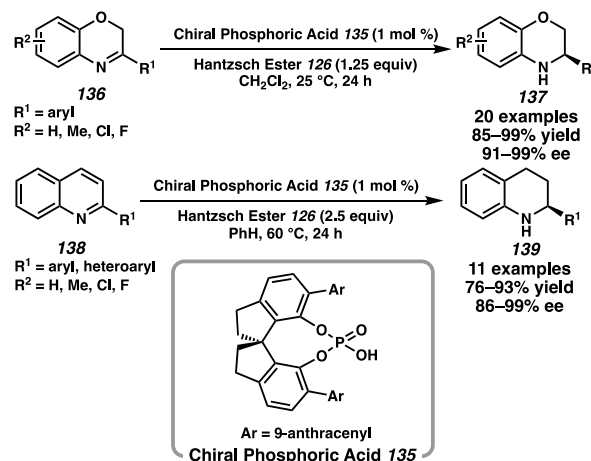


Figure 11. Common chiral phosphoric acid catalyst systems for the asymmetric hydrogenation of heteroarenes ($\geq 90\%$ ee, minimum three substrates). Only one enantiomer of the catalyst is shown for simplicity.

Scheme 21. Asymmetric Transfer Hydrogenation of Quinolines with SPINOL-Derived Phosphoric Acid 135



constraints by the aryl substituent of the CPA with HEH instead. Thus, the enantio-determining step would not be the hydride transfer but rather the coordination of HEH to complex 145 to generate intermediate 146, hindering access of the HEH to the catalytic site and controlling the facial approach of the hydride addition.⁶²

Using relay catalysis, Zhou and co-workers took inspiration from NAD(P)H models that enable the biomimetic asymmetric hydrogenation of heteroarenes, harnessing the in situ generation of dihydrophenanthridine (DHPD) from catalytic amounts of ruthenium, phenanthridine, and H₂ as the terminal reductant.^{58c,64} Using 0.5 mol % of [Ru(*p*-cymene)I₂]₂, 10 mol % of DHPD, and 1 mol % of CPA 130 or

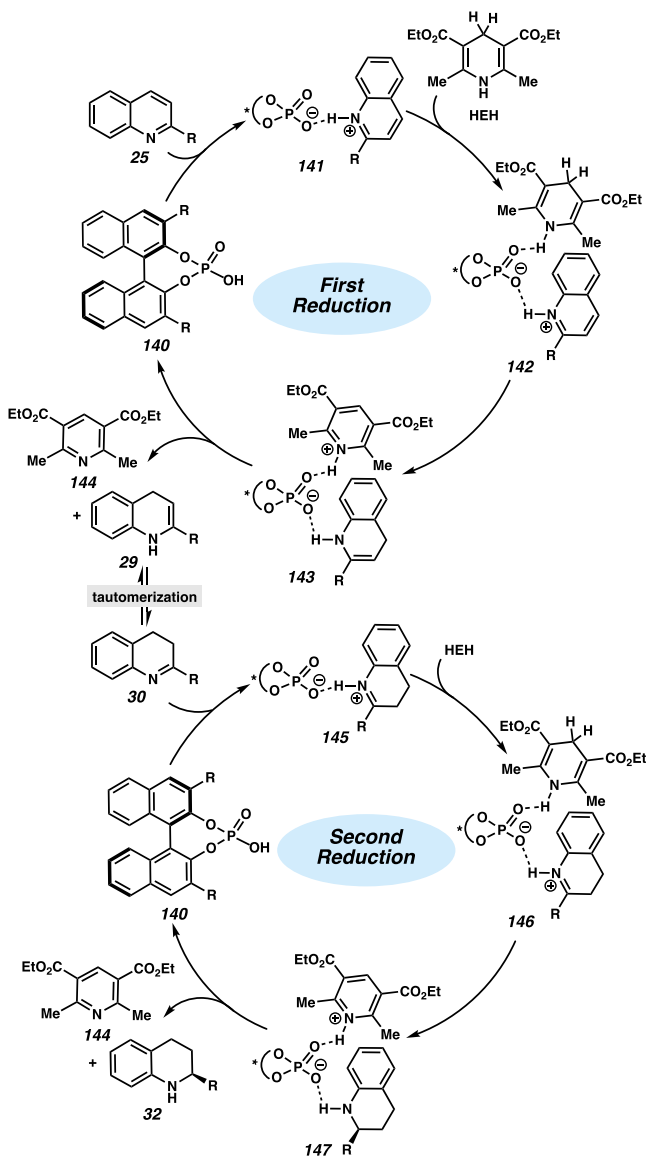
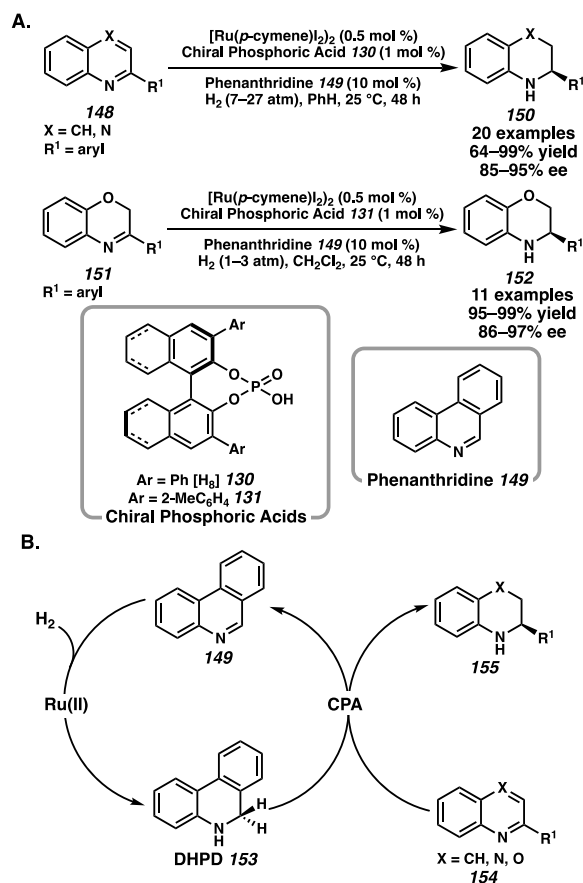


Figure 12. Proposed general catalytic cycle for the asymmetric transfer hydrogenation of quinolines in the presence of a chiral phosphoric acid and Hantzsch ester.⁶²

131, the asymmetric hydrogenation of 2-substituted quinolines, quinoxalines, and benzoxazines proceeded in up to 99% yield and 97% ee (Scheme 22A).

The mechanism of the biomimetic asymmetric hydrogenation reaction is proposed to involve two catalytic cycles, initially with Ru-catalyzed hydrogenation of phenanthridine 149 to generate DHPD 153. DHPD then coordinates to the chiral phosphoric acid to enantioselectively reduce the substrate 154, which is then regenerated to DHPD by the ruthenium hydride species (Scheme 22B). Interestingly, using a Hantzsch ester as the hydride source reverses the stereoselectivity due to the different steric demands of the coordination of the substrate and CPA, favoring the *Re*-face reduction instead.^{58c} Although a transition metal is employed to recycle the hydride source, the biomimetic cascade hydrogenation can be performed under mild conditions with excellent activities and enantioselectivities.

Scheme 22. Biomimetic Asymmetric Transfer Hydrogenation of Heteroarenes



10. CONCLUDING REMARKS

Over the past decade, many effective catalyst systems have been developed for the asymmetric hydrogenation or asymmetric transfer hydrogenation of heteroarenes. Although transition metal catalysts are most commonly employed for stereoselective hydrogenation with molecular hydrogen gas, a number of organic catalysts and dual catalytic systems have also been successfully applied for the synthesis of enantioenriched saturated heterocycles.

Despite the recent advances made in the field of asymmetric hydrogenation, as well as reports that have been discussed in prior reviews,⁴ significant challenges in this field remain. The discovery of a catalyst system with a broad substrate scope of more than four different heteroarenes has still not been achieved. Moreover, many asymmetric hydrogenation systems rely on acid activation of the substrates, which can be a limitation for more basic products. Development of novel ligand scaffolds and homogeneous catalyst systems will continue to be explored to design hydrogenation catalysts with improved selectivities. Creative activation strategies for these transformations should also be considered to extend the substrate scope, whether it be through pendant directing groups or recyclable activating reagents. Exploring these strategies will also provide insight into the challenge of developing a technology for the exhaustive asymmetric hydrogenation of simple five- or six-membered heteroarenes and benzene derivatives. Finally, a thorough mechanistic understanding of these asymmetric transformations is

necessary to advance this field. Although experimental mechanistic studies are often limited by high pressure reactors and catalyst deactivation pathways, further investigation is needed to guide the development of the next generation of hydrogenation catalyst systems.

The asymmetric hydrogenation of heteroarenes using homogeneous catalysts continues to be a valuable technology for the direct synthesis of enantioenriched, saturated heterocycles. These small molecules are critical structural motifs in natural products,¹ as well as pharmaceuticals,² and other molecules of industrial importance.³ Thus, the development of efficient catalyst systems for the enantioselective hydrogenation of a broad range of heteroarenes in good yields, stereoselectivity, and chemoselectivity remains highly desirable. We anticipate further advances in asymmetric hydrogenation technology that will revolutionize this field of research.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, this paper was published on the Web on November 12, 2020, with Figure 11 being double column width. The corrected version was reposted on November 16, 2020.