Synthesis Z.-P. Chen, Y.-G. Zhou Short Review

Asymmetric Hydrogenation of Heteroarenes with Multiple Heteroatoms

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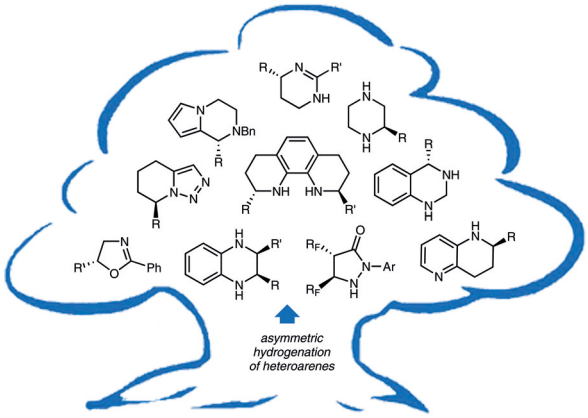

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Abstract Enantiopure heterocyclic architectures containing two or more heteroatoms in the ring system have attracted considerable attraction due to this motif playing a role of great importance in asymmetric synthesis and the pharmaceutical chemistry. This review focused on recent advances in the homogeneous asymmetric hydrogenation of heteroarenes with multiple heteroatoms, which provide an efficient and practical method to structural diverse chiral heterocyclic compounds.

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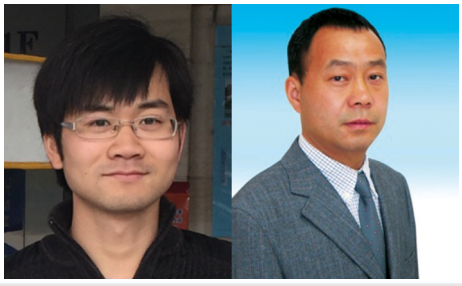
Key words hydrogenation, enantioselectivity, heteroarenes, heterocycles, asymmetric catalysis



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1 Introduction

Heterocyclic architectures containing N, O, or other heteroatoms in the cyclic rings are omnipresent in many bioactive natural products, synthetic drugs, and materials science.[1] Particularly, enantiopure heterocyclic compounds have a wide range of applications and resonate across numerous disciplines.[2] Accordingly, the preponderance of chiral heterocyclic compounds has expedited the exploration of efficient and environmentally benign synthetic methods for their preparation. Among the methods for their preparation, asymmetric hydrogenation reactions are the most attractive methodologies and the need for the development of practical, highly efficient, and enantioselective hydrogenation protocols for heteroaromatic substrates is evident.[3]

Compared with the elaborate exploitation of the catalytic asymmetric hydrogenation of olefins, ketones, and imines, the asymmetric hydrogenation of heteroarenes remains much less explored.[4] Several difficulties in this area are as follows: (i) the inherent stability resulting from aromaticity and the corresponding harsh conditions needed to destroy this stability which adversely affects the enantioselectivity and chemoselectivity; (ii) strong coordination effects of the heteroatoms can poison or deactivate the chiral catalysts; (iii) both lack of a secondary coordinating group and the strong coordination effects of the heteroatoms can result in lack of stereoselective control; (iv) in addition, the facile cleavage of bonds between heteroatoms makes chemoselectivity difficult to control. In general, the low activity and poor stereoselectivity and chemoselectivity constitute the major stumbling blocks for the asymmetric hydrogenation of heteroarenes.

Despite these difficulties, synthetic chemists continue to make progress in this field[5] and various strategies for overcoming these problems have been developed, including catalyst activation, substrate activation, and relay catalysis (Figure 1).

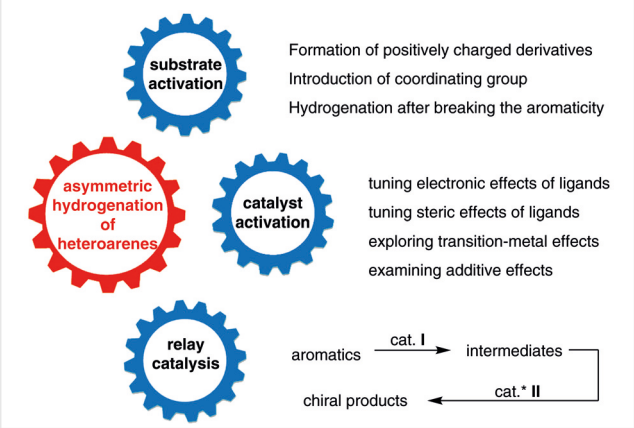


Figure 1 Strategies for asymmetric hydrogenation of heteroarenes

Catalyst activation includes the tuning of electronic and steric effects of ligands, the exploration of efficient transition-metal precursors, and the examination of additive effects. Since there is no 'universal' ligand that can be applied in every reaction, the development of efficient ligands is of great significance and highly desirable.[6] To date, many structurally diverse and electronically variant phosphine-containing and phosphine-free ligands have been designed and applied to the chemistry of this field. In addition, different types of transition-metal precursors have been explored, such as transition-metal complexes of Ru, Rh, Ir, or Pd. Furthermore, after the initial finding that iodine can facilitate the iridium-catalyzed asymmetric hydrogenation of quinolines,[7] the addition of halogen additives has gained in popularity and it has become a widely used activation strategy for the hydrogenation of heteroarenes. All in all, the core target of the catalyst activation strategy is to search for efficient catalytic systems for different types of heteroaromatics.

Substrate activation generally utilizes the partial destruction of the aromaticity of heteroarenes with the assistance of various activators that interacted with certain substrates. In summary, the following three methods are frequently utilized to effectuate the activation of different kinds of heteroarenes.[8] The first method is performed by decreasing aromaticity through the formation of a positively charged derivative of the aromatic heterocycle, such as the formation of salts with Brønsted acids. The second approach is to introduce a tethering auxiliary group to assist its coordination to the metal center and facilitate hydrogenation, such as the attachment of acyl motifs to the corresponding aromatic compounds. The last technique is achieved by partially breaking the aromaticity of heteroaromatic compounds with the aid of additives, and this is followed by asymmetric hydrogenation.

Currently, the hydrogenation or reduction of heteroarenes inevitability results in the sequential reduction of carbon–heteroatom or carbon–carbon double bonds, and thus an elegant strategy was established that has changed this field. This strategy is known as relay catalysis, which is composed of two hydrogenation catalysis procedures: catalyst **I** hydrogenates the aromatic substrates to afford partial hydrogenation intermediates, and chiral catalyst **II** enantioselectively reduces the corresponding intermediates to furnish chiral products.

Thanks to the indefatigable efforts of chemists, some important advances in the homogeneous asymmetric hydrogenation of heteroaromatic compounds have been achieved by employing both chiral organometallic catalysts and organocatalysts, and a few of excellent reviews on this topic have already been published. However, to the best of our knowledge, none of these reviews provided a comprehensive and timely overview of the asymmetric hydrogenation of more complicated heteroarenes with multiple heteroatoms. Considering the extensive utility of such scaffolds for the construction of building blocks in medicinal and synthetic chemistry, and combining this with highlighting the efforts that promote the development of asymmetric hydrogenation reactions, this short review summarizes progress in this field. Other related works on the asymmetric hydrogenation of heteroaromatics are not included.

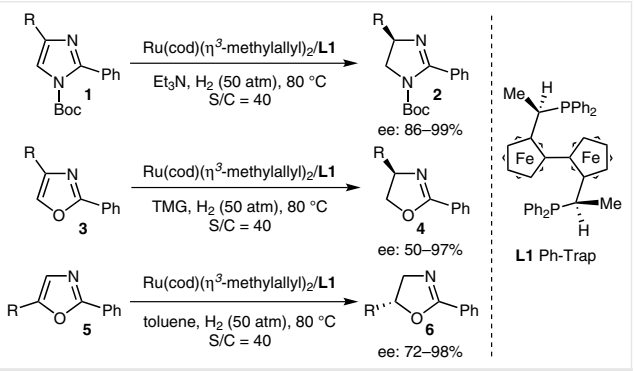
2 Asymmetric Hydrogenation of Five-Membered-Ring Heteroarenes

The asymmetric hydrogenation of 1,3- and 1,2-azoles has attracted a lot of attention in recent years. These compounds each contain one heteroatom in an environment analogous to that of the nitrogen in pyridine, an imine ni-

trogen, and another heteroatom like the nitrogen in pyrrole, a secondary amine nitrogen, or like the oxygen in furan. Consequently, asymmetric hydrogenation of these compounds is inescapably confronted with strong coordination effects and the facile cleavage of the heteroatom–heteroatom bond or carbon–heteroatom bond.

2.1 Imidazoles and Oxazoles

In line with the catalyst activation strategy, Kuwano and co-workers disclosed the first successful catalytic asymmetric hydrogenation of imidazole with a *trans*-chelating bisphosphine Ru–PhTRAP complex as the catalyst (Scheme 1).[9] In the presence of a catalytic amount of basic additive triethylamine to improve the reactivity, a series of 2-phenyl-4-alkyl-substituted *N*-Boc-imidazoles **1** were hydrogenated to the corresponding imidazolines with excellent enantioselectivities and yields. However, replacing the phenyl substituent at C2-position with ethyl or utilizing 2,4-diarylimidazoles as substrates resulted in a dramatic fall in the reaction activity and enantioselectivity.

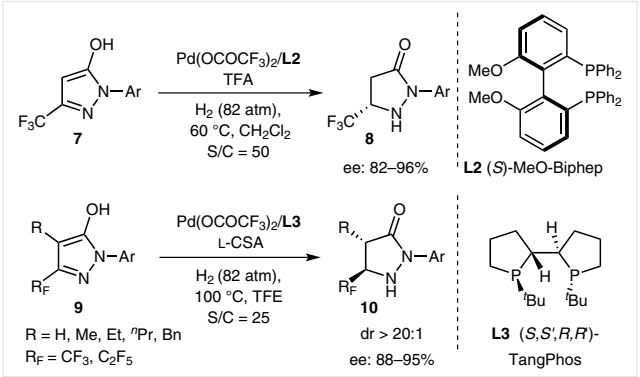


Scheme 1 Asymmetric hydrogenation of imidazoles and oxazoles

Oxazoles represent another type of 1,3-azole, and they were also hydrogenated by the effective Ru-PhTRAP complex catalytic system, affording oxazolines with high to excellent ee. Both 2,4- and 2,5-disubstituted oxazoles were hydrogenated smoothly. For 4-substituted 2-phenyloxazoles **3**, the basic additive was changed to *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) to accelerate the selective hydrogenation. In contrast, such additive was unnecessary for 5-substituted 2-phenyloxazoles **5** and toluene was found to be the best solvent in terms of enantioselectivity. In addition, the hydrogenolysis or acid-facilitated hydrolysis of the obtained chiral imidazolines and oxazolines could provide valuable acyclic chiral 1,2-diamine and β-amino alcohols, respectively, without loss of enantiopurity.

2.2 Pyrazole Derivatives

The asymmetric hydrogenation of pyrazole derivatives is undoubtedly a straightforward method for the synthesis of chiral five-membered heterocyclics with two contiguous nitrogen atoms that play a role of great importance in asymmetric synthesis and the pharmaceutical chemistry.[10] Unfortunately, this area of research, the direct asymmetric hydrogenation of pyrazole derivatives, has, for a long time, been in a developmental phase due to the electronically enriched nature and multitudinous reaction possibilities for these compounds. In 2015, Zhou and co-workers reported the first asymmetric hydrogenation of fluorinated pyrazol-5-ols by capturing one of the active tautomers with an equivalent amount of Brønsted acid as an activator (Scheme 2).[11] The enantioselective hydrogenation of fluorinated aromatic pyrazol-5-ols **7** was carried out using $Pd(OCOCF_3)_2$/**L2**/TFA in dichloromethane to provide a wide variety of 2,5-disubstituted pyrazolidinones **8** in high yields and enantioselectivities. The electronic properties of the substituents on phenyl ring had little effect on the activity and enantioselectivity, but the hydrogenation of a sterically hindered 2-*o*-tolyl-substituted pyrazol-5-ol had only moderate 82% enantioselectivity and low reactivity even with a higher catalyst loading.

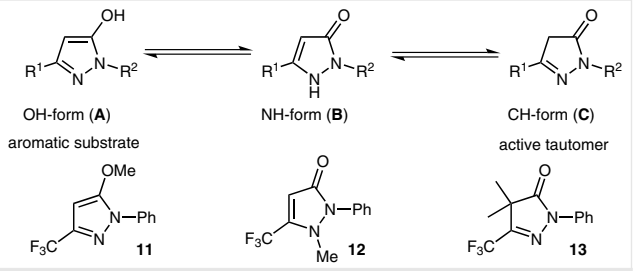


Scheme 2 Asymmetric hydrogenation of fluorinated pyrazol-5-ols

When the TangPhos **L3** was employed as the ligand and simultaneously elevating the temperature, a range of pyrazol-5-ol substrates bearing a 4-alkyl substituent could be hydrogenated smoothly with excellent enantioselectivities and diastereoselectivities. Moreover, pentafluoroethyl-substituted pyrazol-5-ols are also suitable substrates providing the corresponding pyrazolidinones with up to 95% ee.

In principle, pyrazol-5-ol compounds exist in three tautomeric forms, i.e. the OH-, NH- and CH-forms (Scheme 3). To verify the hypothesis that this hydrogenation was carried out by capture of the active tautomer, the hydrogenation of three substrates, form **A** type **11**, form **B** type **12**, and form **C** type **13**, was carried out under the optimized reaction conditions. No reaction was observed for substrate **11**;

and for substrate **12**, low 10% ee and 14% yield were obtained; in a sharp contrast, the CH-form substrate **13** gave excellent 91% ee with 89% yield. Based on these experimental results, it was proposed that the reaction experienced a Brønsted acid promoted tautomerization process of aromatic compound **A** to form CH-form tautomer **C**, followed by Pd-catalyzed asymmetric hydrogenation of the relatively active tautomer **C** to give enantioenriched pyrazolidinones. In addition, these results demonstrated the practicability of the substrate activation strategy in the asymmetric hydrogenation of intractable isomerizable heteroarenes.

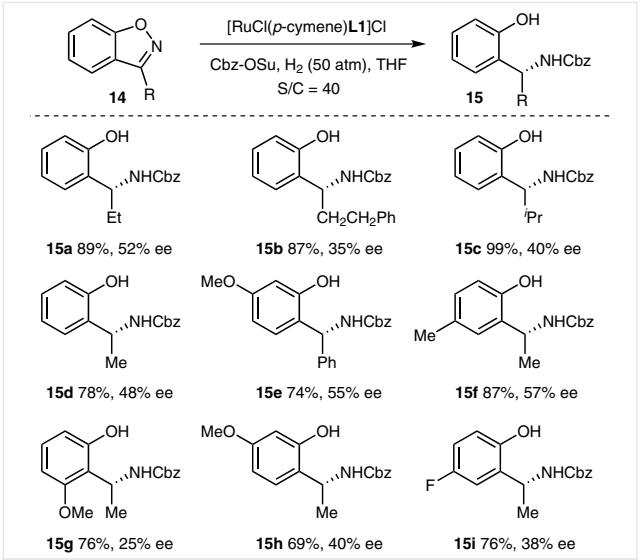


Scheme 3 Mechanism investigation

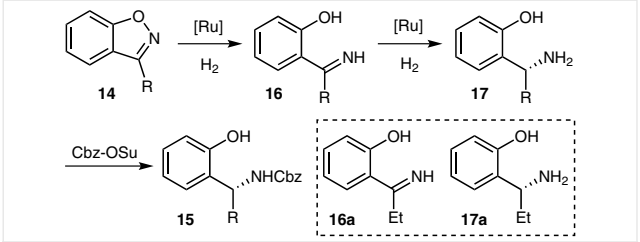
2.3 Benzisoxazoles

The hydrogenation of heteroarenes containing an N–O bond, such as isoxazoles and benzisoxazoles, is a challenging task. The major difficulty is that the N–O bond is facile to break down and the free amino group generated in situ would poison the catalyst under the hydrogenation conditions. The Kuwano group first reported the asymmetric hydrogenation of benzisoxazoles with [RuCl(*p*-cymene)**L1**]Cl as the catalyst.[12] In this transformation, the N–O bond of the benzisoxazole substrate was reductively cleaved by the ruthenium complex and the C–N double bond of the resulting imine was hydrogenated stereoselectively. As depicted in Scheme 4, a number of 3-substituted benzisoxazoles **14** were reduced with high yields in the presence of an acylating reagent, and afforded the corresponding α-substituted *o*-hydroxybenzylamines **15** with up to 57% ee.

To investigate the mechanism, a series of reactions using imine **16a** as the substrate were conducted (Scheme 5). First, no formation of *N*-Cbz-imine was observed when **16a** was treated with Cbz-OSu in the absence of Ru catalyst. Next, the hydrogenation of **16a** with Ru catalyst in the absence of Cbz-OSu produced only a small amount of the expected primary amine **17a**. At last, in the presence of Ru catalyst and Cbz-OSu, the reduction of imine **16a** conducted favorably to give **15a** in high yield with 56% ee. In light of these observations, they proposed that the hydrogenation of benzisoxazoles occurs through the pathway presented in Scheme 5. The ruthenium catalyst initially cleaved the N–O bond in benzisoxazole **14** to give imine **16**, and subsequently hydrogenation of the C–N double bond in **16** occurred prior to Cbz protection of the nitrogen atom. Although the resulting primary amine **17** strongly inhibits the catalysis of the PhTRAP–ruthenium complex, the generated amino group was rapidly captured by the coexistent Cbz-OSu under the hydrogenation conditions. Thus, the rapid acylation effectively avoids the inhibition of the ruthenium catalyst by the free amino group of **17**.



Scheme 4 Catalytic asymmetric hydrogenation of benzisoxazoles



Scheme 5 Possible pathway for the asymmetric hydrogenation of benzisoxazoles

3 Asymmetric Hydrogenation of Six-Membered-Ring Heteroarenes

3.1 Quinoxalines

The asymmetric hydrogenation of quinoxalines, which directly provides chiral tetrahydroquinoxalines, has already attracted much attention over the last decade.[13] Various transition-metal-catalyzed enantioselective hydrogenation and organocatalyzed asymmetric transfer hydrogenation reactions of quinoxalines have been developed. Very recently, an emerging reaction, the metal-free chiral frustrat-

ed Lewis pair (FLP) catalyzed asymmetric hydrogenation using molecular hydrogen gas as the hydrogen source, has also been introduced into this chemistry.

3.1.1 Transition-Metal-Catalyzed Asymmetric Hydrogenation

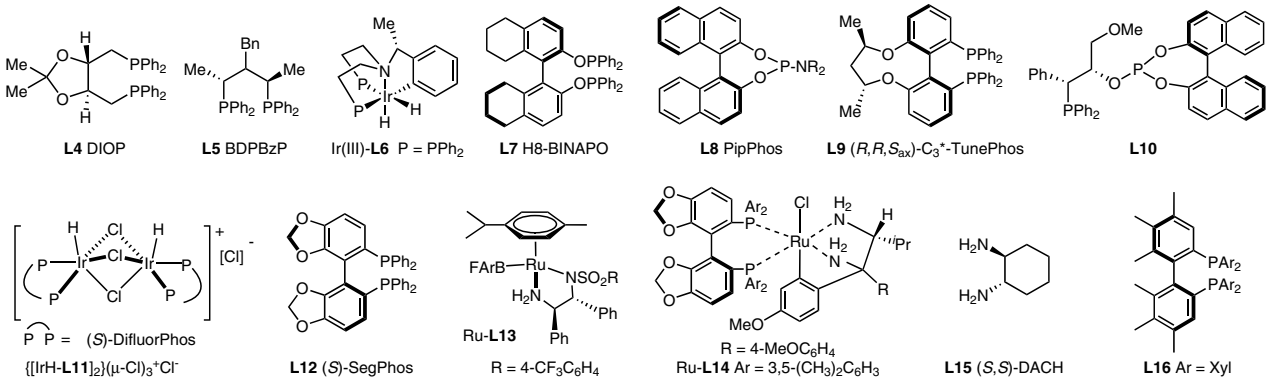
Since the first example of the asymmetric hydrogenation of quinoxalines catalyzed by chiral rhodium catalyst in 1987,[14] miscellaneous transition-metal catalysts including rhodium,[15] iridium,[16] and ruthenium complexes,[17] have been applied to this transformation. Early reported catalytic systems suffered from low enantioselectivities or limited substrate scope. On the basis of activation strategies discussed *vide supra*, significant progress has now been achieved by several research groups. In order to avoid the overlap with the contents of previous review articles,[5] we will provide a overview in this short review (Table 1).

3.1.2 Enantioselective Catalytic Reduction of Quinoxalines with Chiral Phosphoric Acid

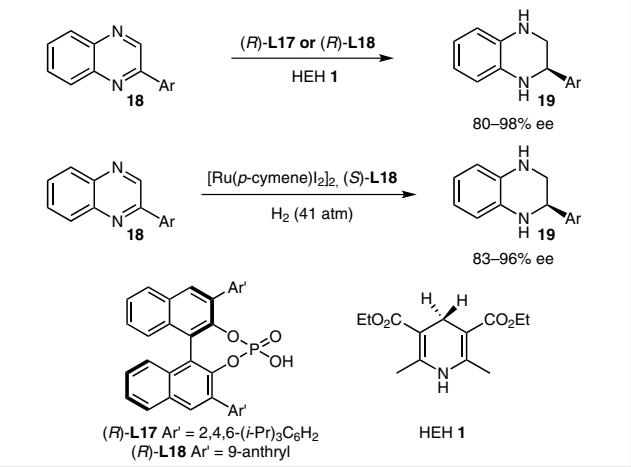
In 2010, Rueping and co-workers first disclosed the asymmetric transfer hydrogenation of aryl-substituted quinoxalines activated by a catalytic amount of chiral BINOL-derived phosphoric acid (*R*)-**L17** or (*R*)-**L18** with a Hantzsch ester as the hydrogen source (Scheme 6).[18] The mechanism involved transfer hydrogenation of the sterically less hindered C=N bond with Brønsted acid promoted protonation of the quinoxaline to generate the partial hydrogenated dihydroquinoxaline, and this was followed by asymmetric transfer hydrogenation of the sterically hindered C=N bond to give the desired chiral tetrahydroquinoxaline. Subsequently, Zhou and co-workers reported a relay catalysis to prepare chiral tetrahydroquinoxalines using a combination of achiral ruthenium complex $[Ru(p\text{-cymene})I_2]_2$ and phosphoric acid (*S*)-**L18**.[19] With this metal/Brønsted acid relay catalyst system, a variety of quinoxalines were hydrogenated to provide 1,2,3,4-tetrahydroquinoxalines in high yields

Table 1 Metal-Catalyzed Asymmetric Hydrogenation of Quinoxalines

Catalytic System		S/C	Hydrogen source	ee (%)	Ref.
Rh	Rh(I)-**L4**	50–100	H_2 (7 atm)	2–3	14
	Rh(I)-**L5**	50–100	H_2 (20 atm)	11–23	15
Ir	Ir(III)-**L6**	100	H_2 (5 atm)	90	16a
	$[IrCl(cod)]_2/I_2$/**L7**	100	H_2 (48 atm)	81–98	16b
	$[IrCl(cod)]_2$/**L8**	50	H_2 (25 atm)	75–96	16c,d
	$[IrCl(cod)]_2/I_2$/**L9**	100	H_2 (48 atm)	72	16e
	$[IrCl(cod)]_2$/**L10**	200	H_2 (80 atm)	70	16f
	{[IrH-**L11**]$_2$}$(\mu\text{-Cl})_3^+Cl^-$	100	H_2 (30 atm)	86–95	16g–i
	$[IrCl(cod)]_2/I_2$/**L12**	50	Et_3SiH/H_2O	58–78	16j
Ru	Ru-**L13**	100–9400	H_2 (20 atm)	96–99	17a
	Ru-**L14**	100	H_2 (80 atm)	95–99	17b
	$RuCl_2$[**L15**][**L16**]	1000	H_2 (29 atm)	73	17c,d

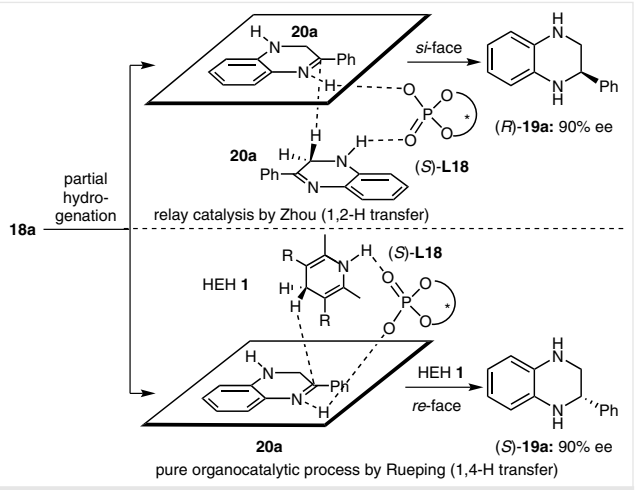


with good to excellent enantioselectivities (up to 96% ee). In contrast to the catalysis reported by Rueping, this reaction went by another mechanistic route. After partial hydrogenation of the 2-arylquinoxaline, the intermediate was enantioselectively reduced through convergent asymmetric disproportionation, in which a self-transfer hydrogenation process was involved.



Scheme 6 Asymmetric transfer hydrogenation of quinoxalines

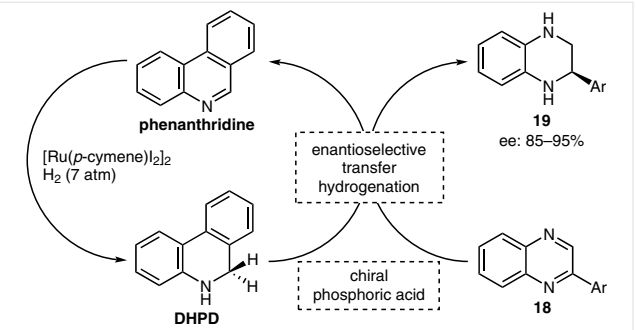
The same chiral phosphoric acid (*S*)-**L18** can provide products with the opposite absolute configuration under these two catalytic systems. The origin of enantioreversal can be explained by the stereochemical model as illustrated in Scheme 7. For the combination of metal complexes and organic molecules in the cooperative strategy developed by Zhou, the hydrogenation of **18a** firstly delivers intermediate 3,4-dihydroquinoxaline **20a** by using an achiral ruthenium(II) as the catalyst. Then **20a** interacts with chiral phosphoric acid (*S*)-**L18** through two hydrogen bonds. These hydrogen bonds with the phosphate and the effect of steric hindrance construct the 'three-point contact model' that determines the stereoselectivity in the disproportionation of 3,4-dihydroquinoxaline **20a**. Comparatively, in the pure organocatalytic process developed by Rueping's group, **20a**/(*S*)-**L18**/HEH **1** form another 'three-point contact model' leading to *Re*-face reduction. The reversal of enantioselectivity perhaps lies in the different steric demand between 1,2-hydride transfer pathway in the self-transfer hydrogenation of **20a** and 1,4-hydride transfer pathway using HEH **1**.



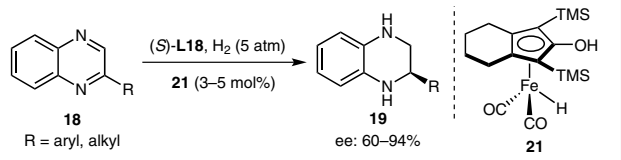
Scheme 7 Origin of enantioreversal in asymmetric transfer hydrogenation

In 2012, Zhou employed dihydrophenanthridine (DHPD) as a regenerable organic hydrogen source for the enantioselective transfer hydrogenation of 2-aryl-substituted quinoxalines affording the products in 96–99% yields and with 85–95% ee (Scheme 8).[20] Using a catalytic amount of hydride precursor phenanthridine, the demand for [Ru(*p*-cymene)I_2]$_2$ could be reduced to 0.5 mol% and hydrogen pressure could be decreased to 7 atm. Notably, the dihydrophenanthridine acts as an efficient hydride shuttle to bridge hydride transfer from the transition-metal center to the unsaturated substrates in this reaction.

Beller and co-workers demonstrated another catalytic strategy by the combination of an iron-based complex with chiral Brønsted acids (*S*)-**L18** to accelerate the enantioselective hydrogenation of quinoxalines without the use of a precious metal catalyst and chiral ligand (Scheme 9).[21] Employing achiral Fe complex **21** as a co-catalyst makes this transformation a benign and efficient process. Apart from 2-aryl-substituted quinoxalines, 2-alkyl-substituted substrates were also appropriate substrates providing the corresponding hydrogenated products in good yields and with moderate to excellent ee.



Scheme 8 Asymmetric reduction of quinoxalines with DHPD



Scheme 9 Asymmetric reduction of quinoxalines with iron complex **21**

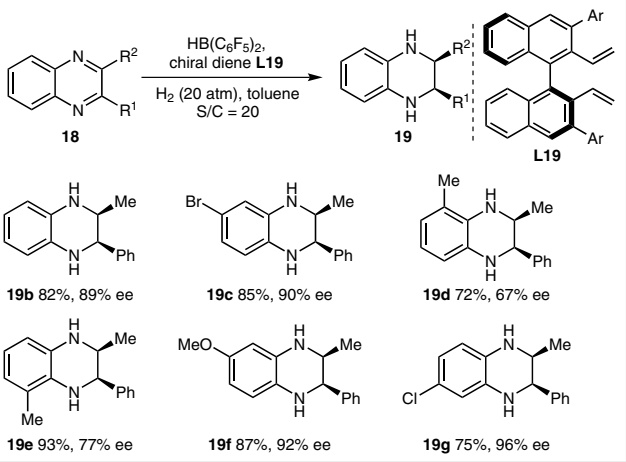
3.1.3 Chiral Frustrated Lewis Pair Catalyzed Asymmetric Hydrogenation

The recently emerging FLP chemistry provides a breakthrough approach for metal-free hydrogenation with molecular hydrogen since catalytic hydrogenation has long been dominated by transition-metal catalysis.[22] A wide range of unsaturated compounds proved to be effective substrates for FLP-catalyzed hydrogenation. In 2015, Du and co-workers developed a *cis*-selective hydrogenation of 2,3-disubstituted quinoxalines using chiral borane catalysts generated by the in situ hydroboration of the chiral diene **L19** with $HB(C_6F_5)_2$ under mild reaction conditions (Scheme 10).[23] A broad scope of 2-alkyl-3-aryl-substituted quinoxalines were successfully hydrogenated to furnish 1,2,3,4-tetrahydroquinoxalines with moderate to excellent ee and excellent diastereoselectivities. However, 2,3-dialkyl- and 2,3-diaryl-substituted quinoxalines were not suitable substrates. This asymmetric hydrogenation can be carried out on a relatively large scale.

3.2 Quinazolines

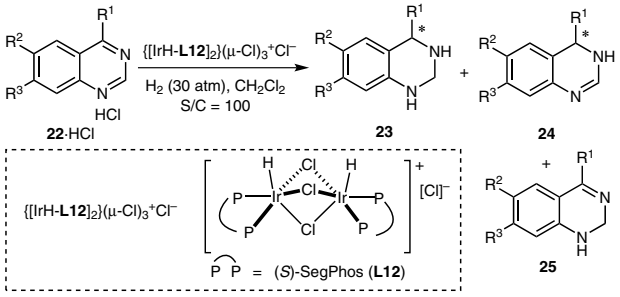
Over past decades, the synthesis of chiral dihydroquinazolines and tetrahydroquinazolines has drawn more and more attention due to the fact that they are present as potent T-type Ca^{2+} channel blockers and potential α-adrenergic blockers, respectively.[24] Under the guideline of decreasing aromaticity through the formation of a positively charged derivatives, the Mashima group reported the asymmetric hydrogenation of quinazolinium salts by utilizing halide-bridged dinuclear iridium complexes $\{[IrH\text{-}\mathbf{L12}]_2\}(\mu\text{-}Cl)_3^+Cl^-$ as the catalyst to afford the corresponding 1,2,3,4-tetrahydroquinazolines with high enantiomeric excess along with moderate to good yields (Table 2).[25]

Although it has excellent enantioselectivity, this method suffered from low chemoselectivity with the partially hydrogenated 3,4-dihydroquinazolines **24** and 1,2-dihydroquinazolines **25** as side products. According to time-course studies, the authors propose that this reaction proceeds preferentially through initial 1,2-reduction, followed by asymmetric hydrogenation of the imines to produce the chiral tetrahydroquinazolines. The partially hydrogenated products **24** and **25** remain intact as side products primarily due to the stability of this type of imine under these hydrogenation conditions.



Scheme 10 Chiral frustrated Lewis pair catalyzed asymmetric hydrogenation

Table 2 Asymmetric Hydrogenation of Quinazolines



Substrate	$R^1/R^2/R^3$	Yield (%) of **23**	ee (%) of **23**	Yield (%) of **24**	Yield (%) of **25**
22a·HCl	Ph/H/H	89	99	11	–[a]
22b·HCl	*p*-$F_3CC_6H_4$/H/H	82	99	6	10
22c·HCl	*p*-ClC_6H_4/H/H	87	>99	7	5
22d·HCl	*p*-MeC_6H_4/H/H	81	97	8	2
22e·HCl	*p*-$MeOC_6H_4$/H/H	66	98	14	20
22f·HCl	*m*-MeC_6H_4/H/H	trace	–	2	89
22g·HCl	*m*-$F_3CC_6H_4$/H/H	35	97	63	–[a]
22h·HCl	*o*-MeC_6H_4/H/H	trace	–	2	94
22i·HCl	Ph/Br/H	89	96	6	–[a]
22j·HCl	Ph/Cl/H	78	97	2	1
22k·HCl	Ph/OMe/OMe	–[a]	–	–a	36

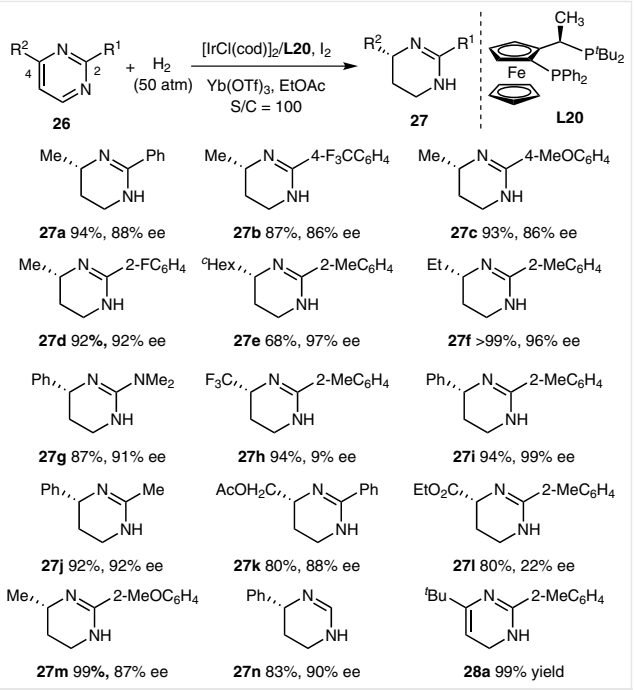
[a] Not determined.

3.3 Pyrimidines

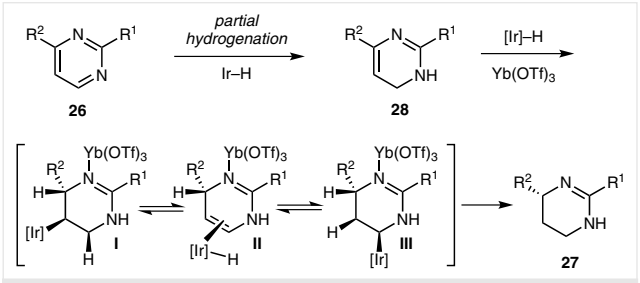
Despite the prevalence of the six-membered cyclic amidines products in natural products and potent pharmaceutical compounds,[26] the asymmetric hydrogenation of pyrimidines has remained unexplored in organic synthesis. This might be ascribed to both pyrimidines and amidine products binding strongly to the metal center in the catalyst and leading to the deterioration of the catalytic reactivity.

In 2015, Kuwano and co-workers developed a substrate activation strategy for the hydrogenation of pyrimidines with ligand **L20**, $[IrCl(cod)]_2$, iodine, and excess of Lewis acid (Scheme 11).[27] By employing $Yb(OTf)_3$ as an activator, a variety of 2,4-disubstituted pyrimidines **26** were converted into cyclic amidines **27** efficiently with high enantiomeric excesses and yields. However, the pyrimidines with an electron-withdrawing group at the C4 position produced amidines **27h** and **27l** with low enantiomeric excesses albeit with high yields. Notably, a pyrimidine bearing no substituent at C2 was also hydrogenated to **27n** with a high ee. When introducing the bulky *tert*-butyl substituent at C4, the substrate underwent hydrogenation at its N1–C6 bond, but the C4–C5 double bond remained intact to give partially hydrogenated product **28a** as the sole product.

According to control and labeled experiments, the authors suggest that the hydrogenation proceeds through the following pathway (Scheme 12). First, partially hydrogenation of pyrimidine **26** gives dihydropyrimidine **28**, compound **28** could be activated by coordination to $Yb(OTf)_3$ and [Ir]–H is inserted into the C–C double bond of **28** to form intermediate **I**. The transformation of **I** into **27** proceeds through the migration of the iridium atom. Furthermore, the addition of $Yb(OTf)_3$ is crucial for the stereoselectivity and reactivity because its facilitates the hydrogenation of intermediate **28** as well as promoting the initial reduction of the N1–C6 double bond in pyrimidine **26**.



Scheme 11 Asymmetric hydrogenation of pyrimidines

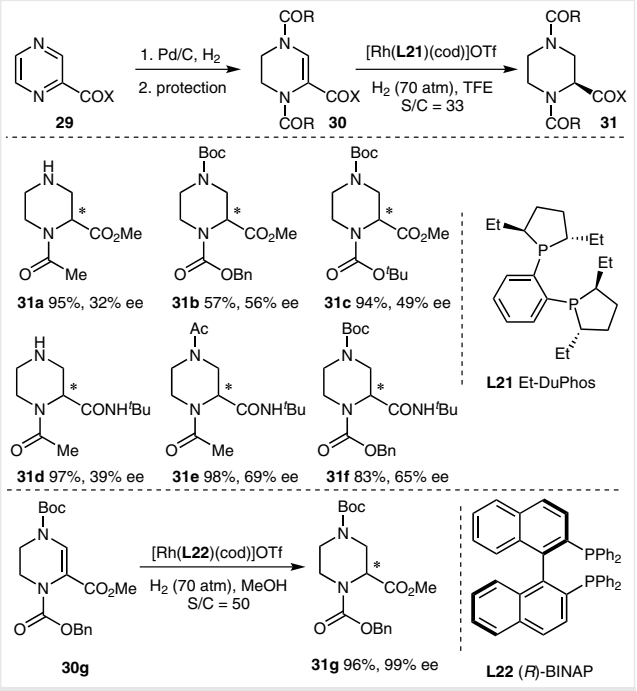


Scheme 12 Proposed pathway for the hydrogenation of pyrimidines

3.4 Pyrazines

Optically active chiral piperazines are ubiquitous substructures in natural alkaloids and many biologically relevant molecules.[28] Among the many synthetic approaches, the asymmetric hydrogenation of readily available pyrazines is undoubtedly the most direct and effective approach to these optically active compounds. However, until now, there are only limited reports of the transition-metal-catalyzed asymmetric hydrogenation of pyrazines or partially reduced pyrazines. From the reported methods, two main hydrogenation approaches are used to afford the chiral piperazines: (i) the indirect enantioselective hydrogenation of a partial hydrogenated intermediate that is generated by the Pd/C-catalyzed hydrogenation of pyrazines; (ii) the direct enantioselective hydrogenation of pyrazinecarboxylic acid derivatives with a chiral catalyst.

Rossen and co-workers found that the tetrahydropyrazine **30**, which was readily obtained by partial hydrogenation of the corresponding pyrazines **29** with Pd/C and protected with commonly used protecting groups, could be enantioselectively hydrogenated to give the chiral piperazines **31** with moderate 69% ee (Scheme 13).[29] Further investigation demonstrated that the Rh–BINAP complex was an efficient catalyst for the hydrogenation of **30g** to furnish piperazine **31g** with 99% ee. There are also a few reports of the asymmetric hydrogenation of other types of tetrahydropyrazines and dihydropyrazines, but they are not discussed here.[30]



Scheme 13 Indirectly asymmetric hydrogenation of pyrazines

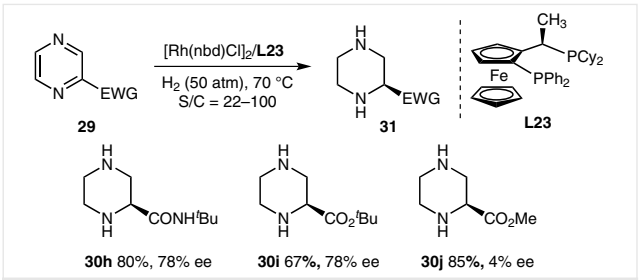
In 1997, Fuchs reported the first asymmetric hydrogenation of pyrazinecarboxylic acid derivatives by using homogeneous $[Rh(nbd)Cl]_2$/diphosphine with up to 78% ee (Scheme 14).[31] However, only limited substrates scope was published and other kinds of pyrazines still remain untested.

4 Asymmetric Hydrogenation of Fused Nitrogen Heteroarenes

4.1 Heteroarenes Containing a Ring-Junction Nitrogen

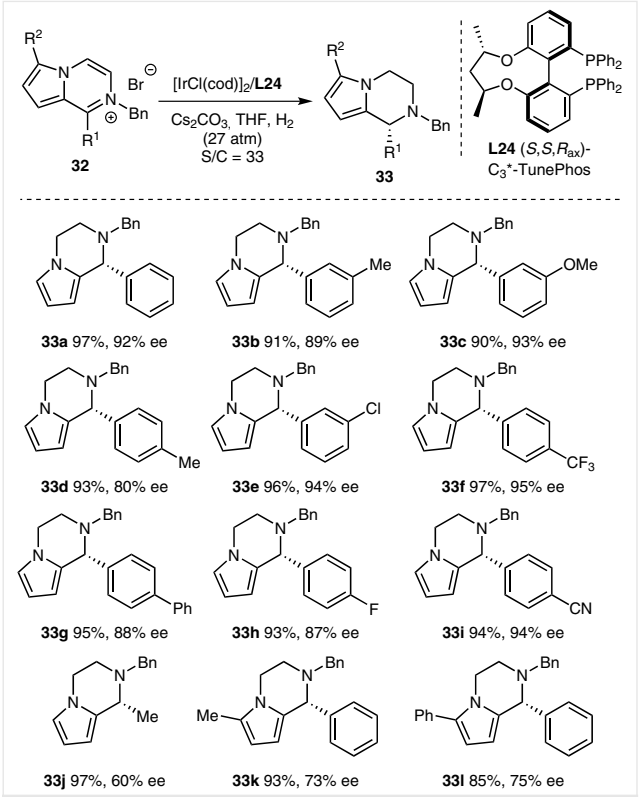
4.1.1 Pyrrolo[1,2-*a*]pyrazine Derivatives

The asymmetric hydrogenation of pyrrolo[1,2-*a*]pyrazines has emerged as one of the most attractive synthetic protocols for the construction of chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines which are a very important class of heterocycles for their potential biological activities.[32] Recently, Zhou and co-workers reported a substrate activation strategy to facilitate the iridium-catalyzed enantioselective hydrogenation of *N*-benzylated pyrrolo[1,2-*a*]pyrazinium salts (Scheme 15).[33] This transformation employed $[IrCl(cod)]_2$ as the iridium precursor and **L24** as ligand with an equivalent amount of cesium carbonate. Substrates with aryl substituents in the pyrazinium ring (R^1 = aryl groups) provided the hydrogenated products with 80 to 95% ee.



Scheme 14 Asymmetric hydrogenation of pyrazines

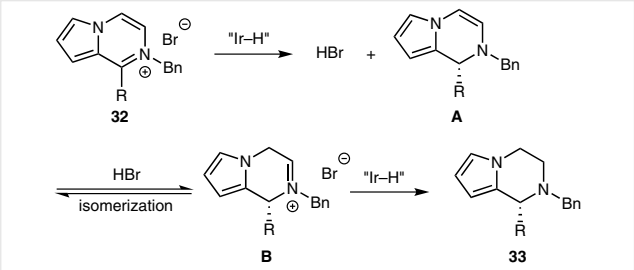
However, replacement of the aryl groups by alkyl substituents at the same position or utilizing the diaryl-substituted **32l** as the substrate led to a slight drop in the enantioselectivity.



Scheme 15 Asymmetric hydrogenation of pyrrolo[1,2-*a*]pyraziniums

A possible reaction pathway is shown in Scheme 16, the aromatic substrate first undergoes a 1,2-hydride addition to give 1,2-dihydropyrrolo[1,2-*a*]pyrazine intermediate **A**, which isomerizes to an iminium salt **B** in the presence of in situ generated HBr. Subsequent hydrogenation of the iminium salt provides the product. The in situ generated HBr is important for this reaction to proceed, but it also causes partial racemization of **33** through enamine/iminium isomerization involving the pyrrole ring. The addition of cesium

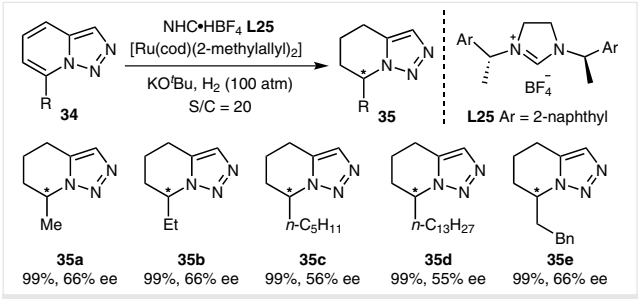
carbonate increases the conversion and prohibits the racemization of the products dramatically by gradually trapping the excess generated Brønsted acid.



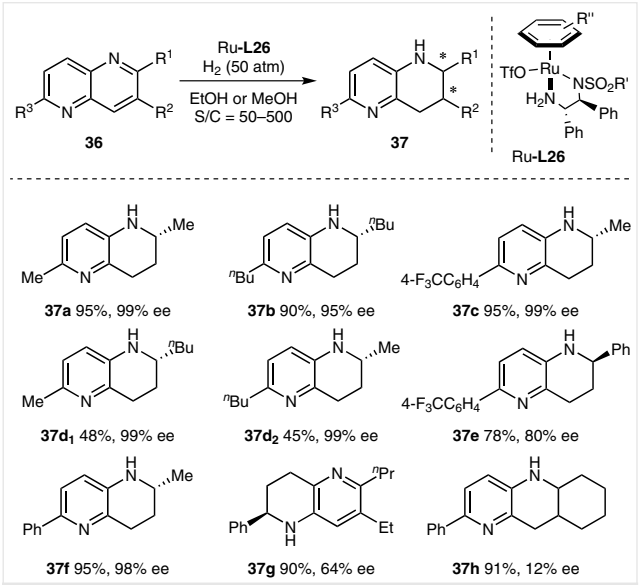
Scheme 16 A proposed hydrogenation mechanism

4.1.2 [1,2,3]Triazolo[1,5-*a*]pyridines

The enantioselective reduction of [1,2,3]triazolo[1,5-*a*]pyridines is a straightforward way to access novel and structural diverse chiral heterocyclic derivatives, and therefore is highly interesting for medicinal chemistry research.[34] Glorius and co-workers have successfully applied a chiral ruthenium–NHC complex as the catalyst for the high-yielding and completely regioselective asymmetric hydrogenation of substituted [1,2,3]triazolo[1,5-*a*]pyridines (Scheme 17).[35] The hydrogenation of different kinds of alkyl-substituted substrates proceeded with perfect conversion and moderate enantioselectivities. It is noteworthy that the enantiomeric ratio decreased slightly when the length of the alkyl chains was increased, while perfect conversions to the desired products were maintained. The reaction of 7-phenethyl-[1,2,3]triazolo[1,5-*a*]pyridine (**34e**) also gave the product **35e** with 66% ee.



Scheme 17 Scope of the [1,2,3]triazolo[1,5-*a*]pyridines



Scheme 18 Asymmetric hydrogenation of 1,5-naphthyridines

4.2 Asymmetric Hydrogenation of Heteroarenes Containing Fused Pyridine Rings

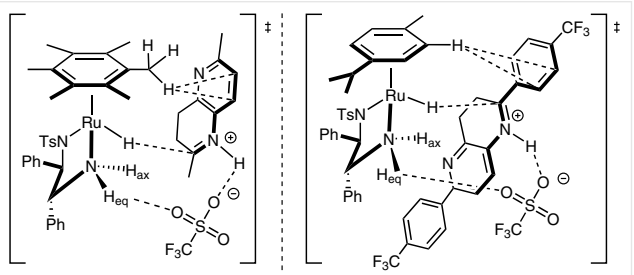
4.2.1 1,5-Naphthyridines

Chiral tetrahydronaphthyridine and diazadecalin ring systems are important structural units that have shown great potential for pharmaceutical development.[36] Fan and co-workers recently reported the first asymmetric hydrogenation of 2,6-disubstituted and 2,3,6-trisubstituted 1,5-naphthyridines to produce optically pure tetrahydronaphthyridines with chiral cationic ruthenium diamine complexes as the catalyst (Scheme 18).[37]

A wide scope of 1,5-naphthyridine derivatives were successfully hydrogenated to give 1,2,3,4-tetrahydro-1,5-naphthyridines with up to 99% ee. Substrates bearing symmetrical 2,6-dialkyl substituents gave excellent enantioselectivities and yields. However, the hydrogenation of unsymmetrical 2,6-dialkyl-substituted substrates gave low regioselectivities albeit with high ee. Interestingly, only the pyridyl ring bearing an alkyl group was hydrogenated when 2-aryl-6-alkyl substrates were subjected to this conversion. In addition, in the unsymmetrical 2,6-diaryl-substituted substrates, the pyridyl rings bearing the more electron-rich substituents were more easily hydrogenated under these conditions. Significantly, by using a heterogeneous PtO_2 catalyst, the remaining pyridine ring could also be hydrogenated to give the chiral 2,6-disubstituted 1,5-diaza-*cis*-decalins with identical enantioselectivity.

To further understand the mechanism and the origins of enantioselectivity, theoretical calculations were carried out. The computational results indicated that the final 1,2-hydride addition should proceed through an ionic pathway involving the transition states depicted in Scheme 19. In the case of substrates bearing at least one alkyl group at the C2-position, the enantioselectivity originates from the CH/π attraction between the η^6-arene ligand in the Ru complex and the fused pyridine ring of the dinaphthyridine via a 10-membered-ring transition state with the participation of the TfO^- anion. In contrast, for 2,6-diaryl-substituted 1,5-

naphthyridines, the enantioselectivity originates from the CH/π attraction between the η^6-arene ligand in the ruthenium complex and the substituted phenyl ring, instead of the fused pyridine ring. Finally, the metal–hydride intermediate attacks the *Si* face of the imine moiety to give the *R*-configured product.



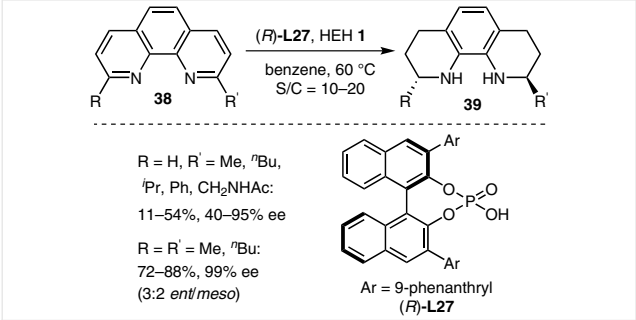
Scheme 19 Proposed transition states

4.2.2 1,10-Phenanthrolines

Due to its high stability and strong coordination ability, 1,10-phenanthroline and its derivatives containing two segregated pyridyl rings are good bidentate ligands for catalytic reactions, and, therefore, the direct asymmetric hydrogenation of these compounds is difficult. After continuous trial and error by organic chemists, the enantioselective hydrogenation of 1,10-phenanthrolines has been completed through two different pathways by employing, respectively, organocatalysis and transition-metal catalysis.

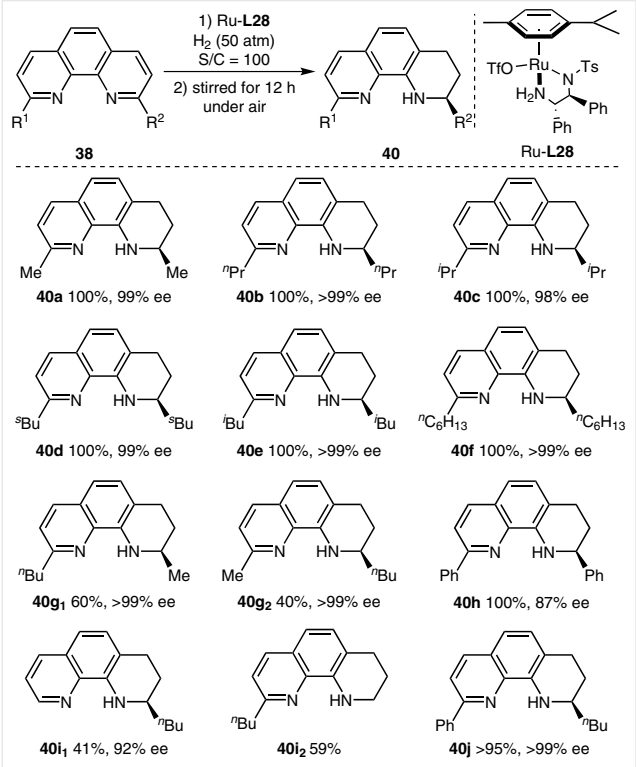
In 2008, the Metallinos group documented the enantioselective transfer hydrogenation of 2-substituted and 2,9-disubstituted 1,10-phenanthrolines by utilizing Brønsted acid **L27** as catalyst and HEH **1** as the hydrogen source (Scheme 20).[38] For the monosubstituted compounds, poor to moderate yields and moderate to high enantioselectivities were obtained for the desired products (11–54% yield, 40–95% ee). Significant improvement in yields was obtained with symmetrical 2,9-dialkyl-1,10-phenanthrolines (72–88% yield), although the diastereoselectivities still remained at a low level (3:2 *ent*/*meso*).

The enantioselective and diastereoselective hydrogenation of substituted 1,10-phenanthrolines using phosphine-free chiral cationic ruthenium diamine catalyst Ru–**L28** (Scheme 21) was developed by the Fan group.[39] With different catalytic protocols, selective or full reduction of the two pyridyl rings were achieved providing an efficient and practical approach for the synthesis of chiral 1,2,3,4-tetrahydro-1,10-phenanthroline and octahydro-1,10-phenanthroline derivatives with excellent enantioselectivities and diastereoselectivities. In combination with dehydrogenation under an air atmosphere, a variety of 2- and 2,9-substituted 1,10-phenanthroline derivatives were smoothly reduced to chiral 1,2,3,4-tetrahydro-1,10-phenanthrolines with excellent ee (87 to 99% ee). However, for the unsymmetrical 2-alkyl- and 2,9-dialkyl-substituted 1,10-phenanthroline substrates only moderate regioselectivities were obtained and the tetrahydrophenanthrolines **40** were obtained with high enantioselectivities.



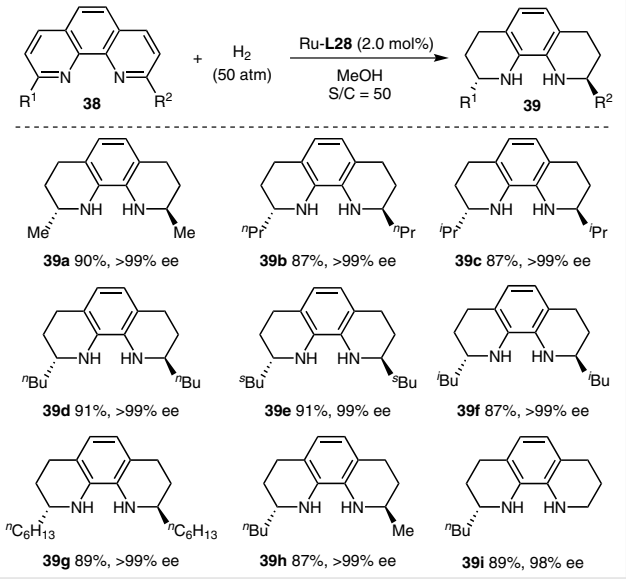
Scheme 20 Organocatalyzed asymmetric transfer hydrogenation

By elevating the catalyst loading and after completion of the hydrogenation directly decomposing the ruthenium catalyst to avoid the dehydrogenation of the products, a wide range of 2-alkyl-substituted and 2,9-dialkyl-substituted octahydro-1,10-phenanthrolines were isolated in good yields with up to 99% ee and greater than 20:1 d.r. (Scheme



Scheme 21 Asymmetric hydrogenation of 1,10-phenanthrolines to afford 1,2,3,4-tetrahydro-1,10-phenanthrolines

22). Unfortunately, 2,9-diaryl-substituted 1,10-phenanthrolines did not give the corresponding 2,9-diaryl-substituted octahydro-1,10-phenanthrolines under these conditions.



Scheme 22 Asymmetric hydrogenation of 1,10-phenanthrolines to afford octahydro-1,10-phenanthrolines

5 Conclusions and Outlook

This review has documented recent advances in the homogeneous asymmetric hydrogenation of heteroarenes with multiple heteroatoms. Three different strategies for the hydrogenation of heteroarenes including catalyst activation, substrate activation, and relay catalysis have been systematically summarized. Despite much progress, there remains great opportunities for progress and developments in this field of research. As there is a great diversity of heteroarenes, a vast number of heteroarenes with multiple heteroatoms are still unexplored and the asymmetric hydrogenation of such compounds is full of challenge. Future efforts may focus on the substrates as follows, heteroarenes containing free hydroxyl, amido, or other electron-enriched functional groups, such as amino-pyrimidine, oxy- and amino-1,2-azoles; five-membered-ring heteroarenes, such as isothiazoles, thiazoles, benzannulated azoles, thieno[2,3-*d*]imidazoles, oxadiazoles, and thiadiazoles; bicyclic heteroaromatic compounds containing a fused pyridine, pyrimidine, triazine, or pyrazine motif, such as aza-indoles, purines, aza-indolizines; other tricyclic fused molecules, such as cyclazines. In view the development of catalysts and novel strategies, together with the exciting reports on the application of substrate activation to improve the efficiency of asymmetric hydrogenation, we believe that there will be more breakthroughs in the research in this field.

Acknowledgment

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