Asymmetric Catalysis

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Brønsted Acid Activation Strategy in Transition-Metal Catalyzed Asymmetric Hydrogenation of N-Unprotected Imines, Enamines, and N-Heteroaromatic Compounds

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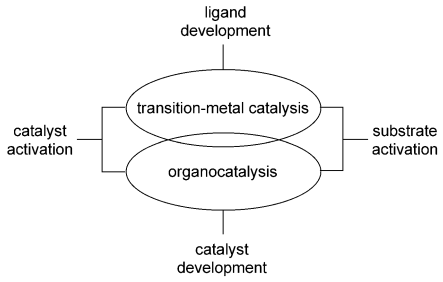
asymmetric catalysis · Brønsted acid · heterocycles · hydrogenation · transition metals

***A**symmetric hydrogenation plays an important role in organic synthesis, but that of the challenging substrates such as N-unprotected imines, enamines, and N-heteroaromatic compounds (1H-indoles, 1H-pyrroles, pyridines, quinolines, and quinoxalines) has only received increased attention in the past three years. Considering the interaction modes of a Brønsted acid with a Lewis base, Brønsted acids may be used as the ideal activators of C=N bonds. This Minireview summarizes the recent advances in transition-metal-catalyzed, Brønsted acid activated asymmetric hydrogenation of these challenging substrates, thus offering a promising substrate activation strategy for transformations involving C=N bonds.*

1. Introduction

Chiral amines are widespread structural units in many bioactive molecules such as pharmaceuticals and agrochemicals. Among the available synthetic approaches developed for the preparation of chiral amines, transition-metal-catalyzed asymmetric hydrogenation of prochiral imines, enamines, and N-heteroaromatic compounds has been shown as the most promising straightforward route,[1–5] and the asymmetric hydrogenation of N-protected imines, enamines, and enamides has been extensively investigated. Because chiral indolines are common structures present in alkaloids and other bioactive natural and synthetic products, asymmetric hydrogenation of N-protected indoles has received attention.[6,7] Some work has also been documented on the enantioselective hydrogenation of multisubstituted N-Boc pyrroles[7,8] and imidazoles,[9] and enantioselective hydrogenation of functionalized pyridines has been occasionally reported.[10,11] Compared to the relatively unexplored enantioselective hydrogenation of the five-membered N-heteroaromatic compounds and pyridines, considerable effort has been made towards the enantioselective hydrogenation of rather unreactive quinolines and quinoxalines.[12] However, enantioselective hydrogenation of N-unprotected imines, enamines, indoles, and simple pyrroles as well as unactivated pyridines, quinolines, and quinoxalines, which are usually classified as the challenging substrates for asymmetric hydrogenation, has been seldom documented until recently.

In general, two strategies can be applied for the enantioselective hydrogenation of prochiral substrates to make chiral amines (Scheme 1): a) catalyst activation, and b) substrate activation. In the former case, diverse transition-metal catalysts combined with organic ligands and additives,[1–5] or with organocatalysts[13,14] have been employed in the enantioselective hydrogenation of N-protected imines, enamines, and some N-heteroaromatic compounds. As an alternative method, transition-metal-catalyzed enantioselective transfer hydrogenation of imines in an azeotropic mixture of formic acid



Scheme 1. The general routes for establishing an efficient catalytic system.

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and triethylamine has also proved to be successful.[15] In the latter case, Brønsted acid catalyzed asymmetric transfer hydrogenation of N-protected imines and N-heteroaromatic compounds with Hantzsch esters and other reducing agents has been explored.[16–18]

Other methods to activate N-containing substrates are also known. Protected acyclic imines can be activated by organoboranes through forming imine–borane adducts[19] or by Lewis acids.[20–22] Cyclic imines were reduced in their activated forms, that is, iminiums[23] and azomethine imines,[24] trialkylsilyls were used to activate pyridines as pyridium salts,[25] and pyridine-N-aminides can also act as activated pyridines.[26] By using chloroformates as the activating agents, quinolines and isoquinolines were asymmetrically hydrogenated.[27] Through combination with organocatalysis,[28,29] breakthroughs have recently been achieved in the enantioselective hydrogenation of N-unprotected imines, enamines, indoles, simple pyrroles, and N-heteroaromatic compounds by using Brønsted acids to activate these challenging substrates.

1.1. Catalyst Activation

Construction of an efficient catalytic system may be realized by combining transition-metal complexes, organic ligands, additives, and solvents. This strategy (designated as "catalyst activation") has received much more attention than other protocols in the enantioselective hydrogenation of specified C=N- and C=C–N-containing compounds, however chiral organophosphoric acid catalyzed asymmetric transfer hydrogenation (ATH) of N-protected imines and N-heteroaromatic compounds by Hantzsch esters has recently been explored. The development of chiral ligands has played an important role in the construction of efficient catalytic systems for asymmetric hydrogenation.[30–33]

Zhang and co-workers have established a large ligand toolbox including ligands with phosphocyclic motifs, or atropisomeric backbones, and bisphosphine ligands featuring the structure of 2,3-*O*-isopropylidene-2,3-dihydroxyl-1,4-bis-(diphenylphosphino)-butane (DIOP).[31,34] Zhou et al. developed a series of chiral spiro ligands for the same purpose,[4,35] and other types of ligands have also been employed in this area.[36–38] Additives usually play an important role in the enantioselective hydrogenation.[2] Variation of the parameters such as reaction media,[39] catalyst types,[40] and procedure manipulations[41] may lead to efficient catalytic systems.

The combination of transition-metal catalysis and Brønsted acid catalysis or organocatalysis has recently received more and more attention as a strategy to explore new reactions and overcome conventional synthetic limitations in organic chemistry.[42,43] Such a cooperative catalysis strategy has been successfully applied in the asymmetric hydrogenation of N-protected imines.[44–47]

1.2. Substrate Activation

In addition to the catalyst activation strategy, substrate activation can also be applied to establish an efficient catalytic system for difficult catalytic transformations in organic synthesis. In 1985 Darensbourg and co-workers,[48] and Gibson and El-Omrani[49] reported the hydrogenation of aldehydes by group 6 carbonyl hydrides and acetic acid. Vos et al. documented the hydrogenation of acetone by a hydride in an acidic aqueous solution,[50] and Bullock and Song performed the hydrogenation of substituted olefins with $[CpMoH(CO)_3]$ (Cp = cyclopentadienyl) and CF_3SO_3H.[51] These reactions resemble the "ionic hydrogenation" with silane as a hydride donor, and the procedure has been successfully extended to the hydrogenation of C=N bonds.[52,53] It seems that the reaction proceeds through rapid, reversible protonation of the substrate with subsequent hydride transfer from the metal (or Si of the silane). It can be reasonably expected that the reaction rates increase with acidity.[50,51] Although Lewis acid activation of C=N bonds has been envisioned (Scheme 2), the first catalytic enantioselective hydrogenation of C=N bonds

Lewis acid activation Brønsted acid activation

Scheme 2. Activation modes of C=N bonds.

through an ionic mechanism was not reported until 2001 by Norton and Magee [Eq. (1); Bn = benzyl].[54] With the iminium cation **1**, generated in situ from the corresponding N-benzyl arylimine and $HBF_4{\cdot}OMe_2$, as a substrate for hydrogenation, 90% conversion was achieved and the target

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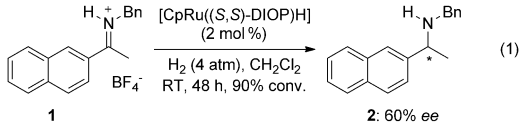
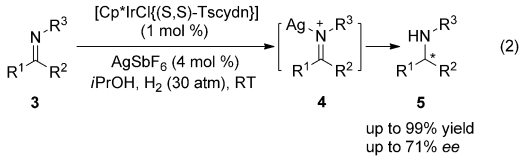
Weiwei Jin studied chemistry at Central China Normal University and received his BSc and MSc in 2006 and 2009, respectively. In September 2009, he began his PhD at Dalian Institute of Chemical Physics (DICP), Chinese Academy of Sciences (CAS) under the supervision of Prof. Dr. Zhengkun Yu. His current research is focused on transition-metal-catalyzed alkenylation.



(1)

amine product **2** was obtained with 60% *ee*, thus demonstrating a promising protocol to activate C=N-containing compounds.

During the last few decades, asymmetric hydrogenation of olefins and ketones has been extensively investigated,[55,56] but enantioselective hydrogenation of C=N-containing compounds remains a major challenge in organic synthesis. Continuous efforts have been made to explore activation methods of C=N for its catalytic hydrogenation. The Lewis acid $AgSbF_6$ was found to activate both the cyclic and acyclic imines **3** in rhodium- or iridium-catalyzed asymmetric hydrogenation to produce chiral amines **5** [Eq. (2); Cp* = C_5Me_5,



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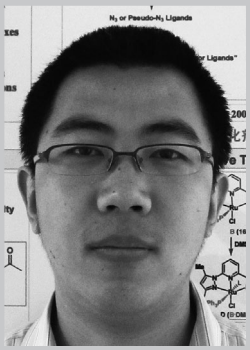
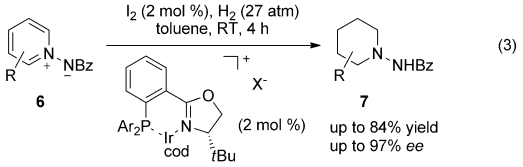
Tscydn = *N*-(p-toluenesulfonyl)-1,2-cyclohexanediamine].[20,21] The intermediate species **4**, formed in situ by coordination of silver cation to the imino nitrogen atom, was detected by NMR measurements in solution. Zinc(II) triflate was also effective for activating the imine intermediate in the reductive amination of aldehydes.[22]

Iridium-catalyzed hydrogenation has been known to be among the best methods to prepare chiral amines, but this protocol cannot exhibit considerable efficiency in the hydrogenation of pyridines. However, by means of the readily available N-iminopyridium ylides **6** as substrates, the chiral substituted piperidine derivatives **7** were efficiently synthesized [Eq. (3); Bz = benzoyl; cod = 1,5-cyclooctadiene].[57] Activated by chloroformates, quinolines **8** and isoquinolines were successfully hydrogenated to afford 3,4-dihydro-2*H*-quinolincarboxylic acid benzyl esters (**9**) and the partially hydrogenated products dihydroisoquinolines, respectively [Eq. (4); SegPhos = (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis-(diarylphosphine)].[27] The in situ formation of quinolinium



Quanbin Jiang studied materials chemistry at Harbin University of Science and Technology and obtained his BSc in 2007. In September 2008, he joined Prof. Dr. Zhengkun Yu's group at DICP, CAS to pursue a PhD. Since then, he has been working on transition-metal-catalyzed unactivated C–Cl bond activation and transformations.



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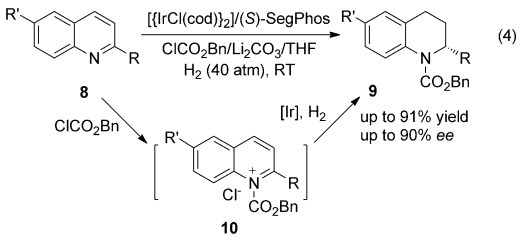
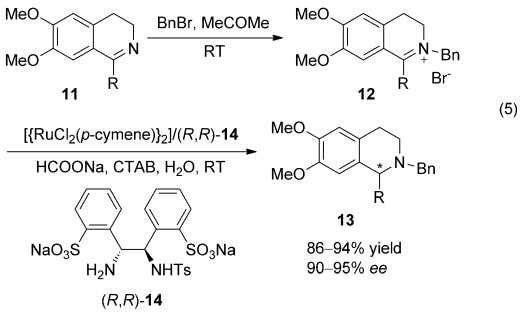


(4)

and isoquinolinium salts such as **10** results in partial destruction of the substrate aromaticity and thus increases the substrate reactivity. The relatively easy removal of Cbz-protecting groups (Cbz = carbobenzyloxy) makes the methodology a promising avenue for the hydrogenation of N-heteroaromatic compounds. Alternatively, the N-alkyliminiums **12** were utilized as the activated forms of the cyclic imines **11** in aqueous asymmetric transfer hydrogenation to give the cyclic amines **13** using HCOONa as the hydrogen source in the presence of the water-soluble ligand **14** [Eq. (5); CTAB = cetyltrimethylammonium bromide].[23]



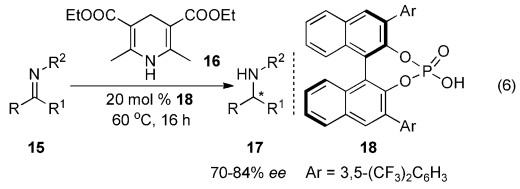
(5)

Although only limited work has been directed at functionalization of a C=N bond to increase its reactivity, undesired deprotection is always required to generate the target chiral amine product. In an applicable view of activating a C=N bond, Brønsted acid activation[28,29,58–60] seems to be the most direct, efficient, atom-economical, and environmentally benign approach because of the diverse availability of Brønsted acids and easy deprotection of the protonated products under basic work-up conditions.

2. Activation of N-Protected Imines by Brønsted Acids

Because organocatalytic transfer hydrogenation of N-protected imines has recently been presented in reviews on organocatalysis,[13,14] only a brief overview will be given

herein. In 2005, Rueping, et al. reported the first enantioselective Brønsted acid catalyzed transfer hydrogenation of N-aryl ketimines **15** with the Hantzsch ester dihydropyridine **16** as the hydrogen source, thus providing a mild method to access chiral secondary amines **17**.[61,62] Chiral phosphoric acid **18** exhibited the best selectivity for the desired products, thereby suggesting that not only the steric but also electronic effect plays a role in the transformation [Eq. (6)]. The proposed mechanism (Scheme 3)[61] suggests that protonation



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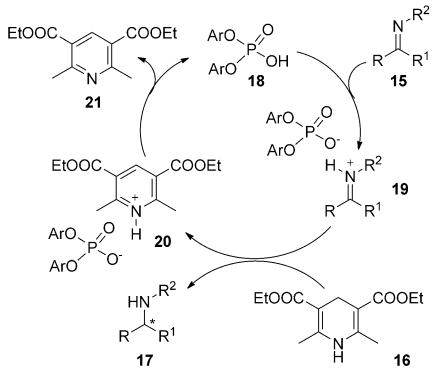


Scheme 3. Proposed mechanism for Brønsted acid catalyzed transfer hydrogenation of N-protected imines by Hantzsch esters.[61]

of ketimine **15** by Brønsted acid **18** generates the iminium intermediate **19**. Subsequent hydrogen transfer from dihydropyridine **16** yields the desired chiral amine **17** and pyridinium salt **20**, which undergoes proton transfer to regenerate **18** and produce the pyridine derivative **21**. In a similar fashion, List and co-wrokers reported a powerful Brønsted acid catalyst of type **18**, that is, **22a** (Ar = 2,4,6-tri(*iso*-propyl)phenyl) which has two bulkier aryl groups, for the organocatalytic asymmetric transfer hydrogenation of N-aryl ketimines.[63]

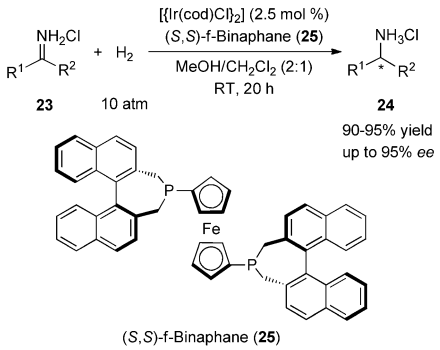
Intrigued by the pioneering work of Rueping et al. and Akiyama et al.,[61–64] chiral phosphoric acid catalyzed transfer hydrogenation of N-protected imines,[65–69] substituted pyridines,[70,71] quinolines,[72,73] quinoxalines, and quinoxalinones[74] using either Hantzsch ester dihydropyridines or benzothiazolines as hydrogen sources have been documented. In this review, no detailed discussion will be presented in this aspect.

3. Transition-Metal-Catalyzed, Brønsted Acid Activated Asymmetric Hydrogenation of Challenging Nitrogen-Containing Substrates

3.1. Asymmetric Hydrogenation of N-Unprotected Imines

The iminium salt of *N*-benzylimine can be reduced to the corresponding chiral amine by ruthenium(II)-catalyzed asymmetric hydrogenation,[54] whereas the N-unprotected imines do not show any reactivity under the same reaction conditions.[75] Thus, the currently available methods often require cumbersome protecting group manipulations to modify an imine substrate at the nitrogen atom to make it suitable for hydrogenation, with subsequent removal of the protecting group to afford the desired product. Moreover, N-unprotected ketimines are difficult to make and isolate, and often exist as complex mixtures of *E*/*Z* isomers and imine–enamine tautomers. The first enantioselective transfer hydrogenation of N-unprotected ketimines, that is, *ortho*-hydroxyaryl alkyl ketimines, was reported in 2010 by using 10 mol % of a chiral phosphoric acid of the type **18**, that is, **22b** (Ar = Ph_3Si), as the catalyst and Hantzsch *di*-tert-butyl ester as the reductant.[75] It was found that presence of the *ortho*-hydroxy group on the aryl moiety of the ketimine substrate is essential for the reaction to occur.

Transition-metal-catalyzed hydrogenation of N-unprotected imines has been strongly desired in organic synthesis, but such a process was not realized until recently. In 2009, Zhang, et al. developed the first efficient and atom-economical iridium-catalyzed asymmetric hydrogenation of N-unprotected ketimines by means of their hydrochlorides **23** as substrates and H_2 gas as the hydrogen source, thus affording the corresponding chiral amine hydrochloride salts **24** as single isomers [Eq. (7)].[76] Both the (*S*,*S*)-f-Binaphane ligand

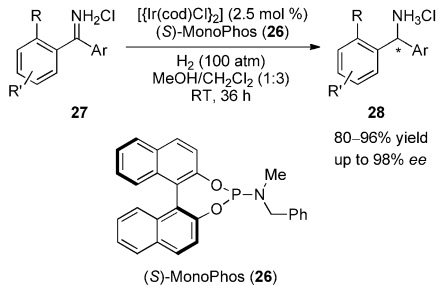


(7)

(**25**) and the solvent mixture MeOH/CH_2Cl_2 are crucial for the transformation. The bulkiness of the R^2 group in the substrates had an obvious influence on the enantioselectivity of the chiral amine products. As the R^2 group was changed from Me to *t*Bu, the enantioselectivity gradually decreased from 93 % to 80 % *ee*. To obtain good to excellent enantioselectivity, the R^1 group is preferably an aryl moiety, while the R^2 is usually an alkyl. Multigram amounts of **23** can be readily prepared by organometallic addition of Grignard or organolithium reagents to nitriles and subsequent quenching with anhydrous MeOH. The corresponding hydrochloride prod-

ucts **24** were single isomers isolated as free-flowing and bench-stable solids. Such a method is operationally simple and allows enantioselective synthesis of chiral amines without the use of N-protecting groups.

By using the same protection-free substrate activation strategy involving the Brønsted acid HCl, iridium(I)/**26**-catalyzed asymmetric hydrogenation of substituted benzophenone imines (**27**) was also efficiently conducted in Zhang's lab and the corresponding chiral diarylmethylamines **28** were obtained [Eq. (8)].[77] The ability of the catalyst system to



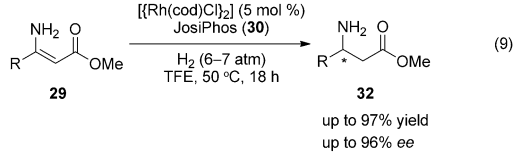
(8)

perform under acidic reaction conditions and its tolerance to excess chloride ions is remarkable. The reactions efficiently proceeded in the presence of chloride ions although halide ions usually poison the transition-metal catalysts.[78] Substitution at the 2-position on the aryl group in **27** is essential for the reactions to achieve good to excellent enantioselectivity for the desired products **28**. Substitution at the 3- or 4-position of the aryl group resulted in a decrease in the enantioselectivity of the desired product. In addition, the steric and electronic nature of the substituent at the *ortho* position of the aromatic ring also plays an important role in the enantiopurity of the products. The highly modular and inexpensive nature of the commercially available chiral phosphoramidite ligands and easy preparation of the N-unprotected imine substrates may offer a practical route to chiral diarylmethylamines. It is noteworthy that as compared to the asymmetric hydrogenation of ketimines **23**,[76] asymmetric hydrogenation of **27** is carried out under rather harsh reaction conditions (100 atm H_2).

3.2. Asymmetric Hydrogenation of N-Unprotected Enamines

Chiral β-amino acids are very important chemicals, and enantioselective hydrogenation seems to be a promising route to manufacturing them in industry. Unfortunately, their production on large scale through asymmetric hydrogenation has been limited by the indispensable N-acyl protection requirement, because formation of a chelate complex of the N-protecting group with the metal of the catalyst plays a crucial role in achieving high reactivity and enantioselectivity.[79] To overcome this limitation, Zhou et al. employed a combination of acetic acid and iodine as the additives to facilitate rhodium(I)-catalyzed asymmetric hydrogenation of N-protected enamines, that is, N,N-dialkylenamines, in the presence of spiro phosphonite ligands.[80] It has been known that acids can accelerate the reaction rate of iridium(I)-catalyzed asymmetric hydrogenation of imines by preventing deactivation of the catalyst caused by the amine products.[81] However, the use of acetic acid alone in this rhodium(I)-catalyzed hydrogenation of enamines strongly lowered conversion of the substrate. When acetic acid was applied together with 2 mol% iodine, the reaction rate was clearly increased, thus revealing that HOAc activated the enamine substrate at the same time. To avoid introduction and removal of the acyl protecting group, development of a highly efficient catalyst system for direct hydrogenation of N-unprotected enamine esters seems to be an ideal solution.

Merck and Solvias groups reported the first example of catalytic asymmetric hydrogenation of N-unprotected β-enamine esters **29** and amides **33** by means of rhodium(I)/JosiPhos catalysts with excellent enantioselectivity [Eqs. (9) and (10)].[82] With 5 mol% [{Rh(cod)Cl}$_2$] and the commercially available JosiPhos-type ligands **30** or **31** as the catalyst,



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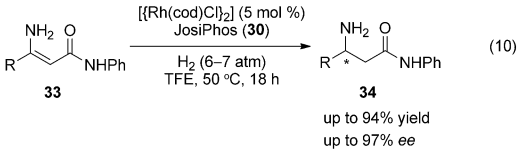

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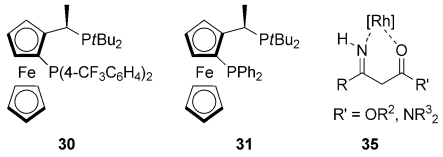
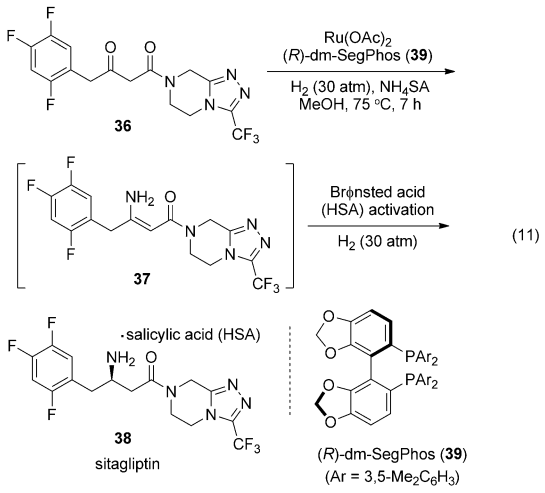
hydrogenation of **29** and **33** was efficiently performed in 1,1,1-trifluoroethanol (TFE) under mild reaction conditions, thus



affording the corresponding derivatives of β-amino acids, that is, **32** and **34**, in up to 94–97% yields and 97% *ee*. This synthetic method gives high enantioselectivity, high reactivity, and has wide applicability, and has demonstrated that the N-acyl protecting group is not a prerequisite for such transformations to be effected. The preliminary results from the deuterium experiments suggest that the reaction proceeds via the imine tautomer **35**, and is mechanistically analogous to β-ketoester and β-amide hydrogenation.[83] One drawback of this protocol is the low turnovers (< 1000) resulting from the product inhibition.

In 2009, Hansen et al. reported a highly efficient and rather green synthesis of sitagliptin (**38**), a potent and selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus (T2DM), through rhodium(I)/*t*Bu JosiPhos-catalyzed

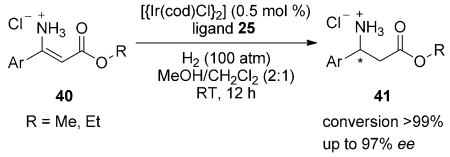
asymmetric hydrogenation of dehydrositagliptin, that is, the N-unprotected β-enamine amide **37**.[84] Steinhuebel et al., from the same laboratories, found that Brønsted acids remarkably accelerated ruthenium(II)-catalyzed asymmetric hydrogenation of **37**, the key intermediate in the reductive amination of β-keto amide **36**, to deliver N-unprotected β-amino amide **38** [Eq. (11)].[85] A combination of $Ru(OAc)_2$/



(11)

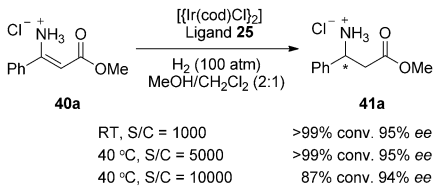
(*R*)-dm-SegPhos (**39**) was optimized as the catalyst by using ammonium salicylate (NH_4SA) as the amination reagent and H_2 as the reductant. Thus, the reductive amination of **36** afforded sitagliptin (**38**) as its salicylate in up to 91% yield and 99.5% *ee*. For the separate $Ru(OAc)_2$/**39**-catalyzed hydrogenation of **37** to **38** with H_2 gas, Brønsted acids such as acetic acid, benzoic acid, chloroacetic acid, salicyclic acid (HSA), and HSA/NH_4SA were effective, thus suggesting that during the reductive amination of **36**, NH_4SA not only behaved as an aminating agent but also released HSA as the Brønsted acid to improve the hydrogenation of the intermediate **37**.

In 2010, Zhang et al. reported the first example of a highly efficient and enantioselective hydrogenation of N-unprotected β-enamine esters catalyzed by an iridium(I)/(*S*,*S*)-f-Binaphane (**25**) complex [Eq. (12)].[86] Because the β-amino ester products in this transformation usually have a strong inhib-



(12)

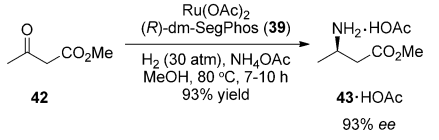
itory effect on the catalyst,[87] and are unstable with ester substrates in some solvents,[88] β-enamine hydrochloride esters **40** were employed as the substrates to be hydrogenated, thus forming β-amino esters **41** with up to 97% *ee* and high reactivity (TON > 5000; TON = turnover number). The solvent played a key role in this catalyst system and a mixture of $MeOH/CH_2Cl_2$ provided the best *ee* values and high reactivity. This catalyst system was further explored in the asymmetric hydrogenation of the β-enamine hydrochloride ester **40a** to demonstrate its potential applicability [Eq. (13)]. The reaction was completed with 0.1 mol% catalyst (TON =



(13)

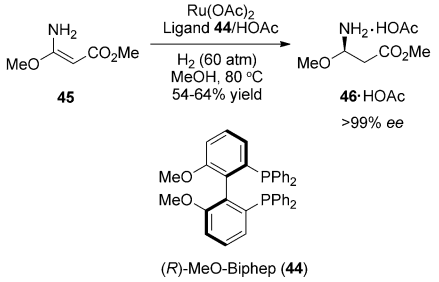
1000) at room temperature and with 0.02 mol% catalyst (TON = 5000) at 40 °C. With 0.01 mol% catalyst at 40 °C, the *ee* value decreased only slightly and the excellent enantioselectivity (94% *ee*) was still obtained. This is the highest turnover for asymmetric hydrogenation of N-unprotected β-enamine esters to date. The present method provides an efficient access to enantiomerically enriched β-amino acids without use of a protecting group, and may be potentially applicable for the preparation of chiral drug intermediates.

By using the $Ru(OAc)_2$/(*R*)-dm-SegPhos (**39**) catalyst in the presence of ammonium acetate, direct reductive amination of the structurally simple β-ketoester **42** via its N-unprotected intermediate methyl-3-aminocrotonate afforded the corresponding β-amino ester **43**·HOAc in both high yield (93%) and enantioselectivity (93% *ee*) [Eq. (14)].[89] This process was demonstrated on a greater than 100 kg scale, thus



(14)

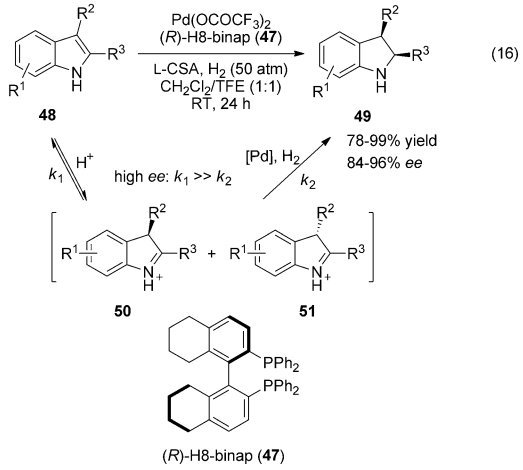
exhibiting its potential applicability. In a similar fashion, a $Ru(OAc)_2$/(*R*)-MeOBiphep (**44**)/HOAc catalyst system was applied in the key step for the synthesis of (*S*)-3-amino-4-methoxy-butan-1-ol, that is, asymmetric hydrogenation of the N-unprotected enamine **45** of the commercially available *β*-ketoester methyl 4-methoxy-3-oxy-butanoate, thus producing the target product **46** in moderate yields and excellent enantioselectivity [Eq. (15)].[90]



(15)

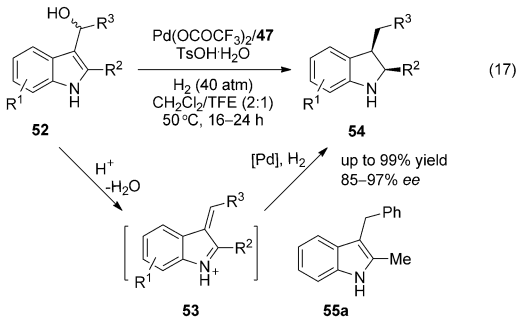
3.3. Asymmetric Hydrogenation of N-Unprotected Indoles

Despite the progress achieved in the enantioselective hydrogenation of N-protected indoles,[91–97] efficient hydrogenation of N-unprotected indoles remains a challenge in organic synthesis. Recently, Zhou et al. reported the first transition-metal-catalyzed, Brønsted acid activated asymmetric hydrogenation of simple indoles [Eq. (16); TFE = trifluoroethanol].[98] With a $Pd(OCOCF_3)_2$/(*R*)-H8-binap (**47**) complex as the catalyst and L-camphorsulfonic acid (L-CSA) as an activator, a highly enantioselective hydrogenation of the simple unprotected indoles **48** was performed to give the chiral indolines **49**. In the absence of a Brønsted acid, the reaction did not occur. The solvent played an important role in this transformation and the reaction gave the best result in a solvent mixture of CH_2Cl_2/TFE (v/v, 1:1). Variation of temperature and H_2 pressure had no obvious effect on the enantioselectivity. The isotope-labeling experiments of 2-methylindole using D_2 and [D_3]TFE has confirmed that the N-unprotected indole can be activated by a Brønsted acid, thus forming in situ the iminium salts **50** and **51**, which are then hydrogenated under palladium catalysis. Hydrogenation of the intermediate iminium salts of 2-substituted indoles is the enantioselectivity-controlling step, while the enantioselectivity-controlling step for 2,3-disubstituted indoles is the protonation of the carbon–carbon double bond and hydrogenation of the iminium salts; this process is in fact a dynamic kinetic resolution process with $k_1 \gg k_2$.



(16)

In a similar fashion, Brønsted acid mediated dehydration-triggered asymmetric hydrogenation of N-unprotected 3-(α-hydroxyalkyl)indoles (**52**) was conducted [Eq. (17); Ts = 4-toluenesulfonyl].[99] The readily available indoles **52** were easily dehydrated to form the vinylogous iminium intermediates **53** in situ in the presence of *p*-toluenesulfonic acid hydrate, thus resulting in partial destruction of the substrate aromaticity. Such intermediates were then hydrogenated with the $Pd(OCOCF_3)_2$/**47** catalyst. This methodology provides an efficient and rapid access to chiral 2,3-disubstituted indolines **54**. A control experiment on the hydrogenation of (2-methyl-1*H*-indol-3-yl)phenylmethanol at various temperatures suggests that the enantioselective hydrogenation of **52** may proceed via the intermediates of type 3-benzyl-2-methyl-1*H*-indole (**55a**). By means of the same catalyst system, **54** was also synthesized through palladium/Brønsted acid catalyzed tandem reactions of 2-substituted N-unprotected indoles **56** with aldehydes by using H_2 as the reductant (Scheme 4).[100] The synthesis of the 2,3-disubstituted indolines **54** can be



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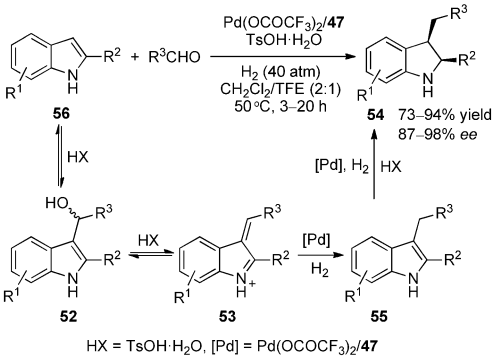
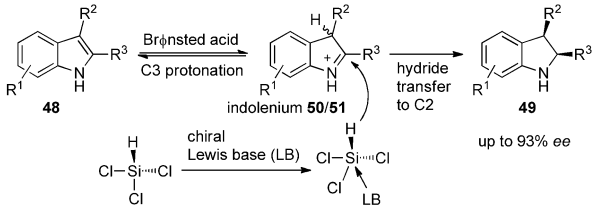


Scheme 4. Synthesis of 2,3-disubstituted indolines.[100]

considered a Brønsted acid (HX)-promoted three-step reaction and palladium-catalyzed two-step reaction. It should be noted that Chen, Sun, and co-workers recently developed the first organocatalytic direct asymmetric reduction of unprotected 1H-indoles into chiral indolines (Scheme 5).[101] The reaction proceeds through the generation of electrophilic indolenium ions **50**/**51** by C3 protonation with the in situ formed HCl acid, and subsequent chiral Lewis base mediated enantioselective hydrosilylation with $HSiCl_3$.

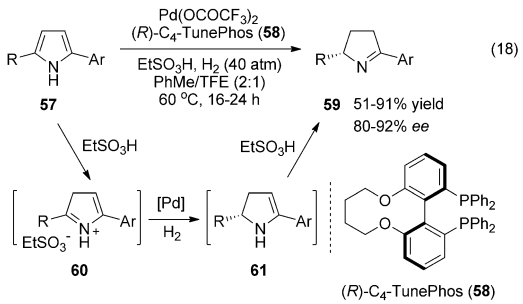


Scheme 5. Organocatalytic asymmetric reduction of 1*H*-indoles.[101]

3.4. Asymmetric Hydrogenation of N-Unprotected Pyrroles

Chiral 1-pyrrolines and related compounds are ubiquitous building blocks in many bioactive compounds, but no asymmetric hydrogenation of simple N-unprotected pyrroles

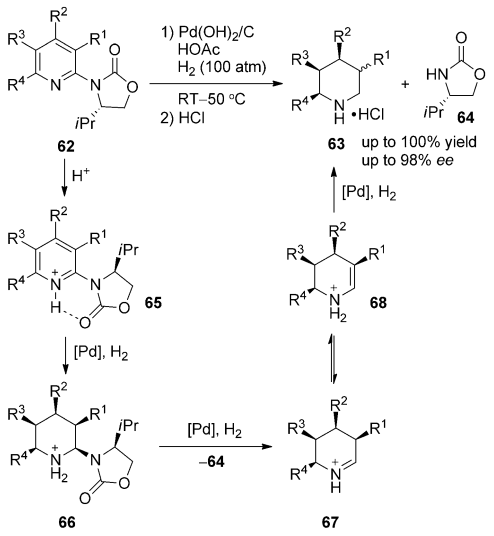
was successfully conducted, because of their very poor aromaticity, until 2011 as reported by Zhou and co-workers [Eq. (18)].[102] Based on the breakthrough work by Zhang et al.,[76] it was envisioned that electron-rich pyrroles could be



protonated by a strong Brønsted acid, which would destroy their aromaticity and make them suitable for catalytic hydrogenation. Thus, with ethylsulfonic acid as an activator enantioselective palladium-catalyzed partial hydrogenation of N-unprotected 2,5-disubstituted pyrroles **57** was successfully carried out in the presence of (*R*)-C_4-TunePhos (**58**), thus forming chiral 2,5-disubstituted 1-pyrrolines **59** with up to 92% *ee*. It is proposed that the N-unprotected simple pyrrole **57** initially reacts with the strong Brønsted acid $EtSO_3H$ to produce the intermediate iminium salt **60** by protonating one of its carbon–carbon double bonds, thereby destroying the aromaticity of the pyrrole substrate. The in situ generated iminium salt **60** is then partially hydrogenated to give enamine **61** which is additionally isomerized to the imine product **59** under the acidic conditions. The related theoretical studies have revealed that the final product **59** is more stable than enamine **61** and can survive in the presence of the acid. It is noteworthy that compounds **59** can be conveniently transformed into other compounds by imine chemistry in organic synthesis.

3.5. Asymmetric Hydrogenation of N-Unprotected Pyridines

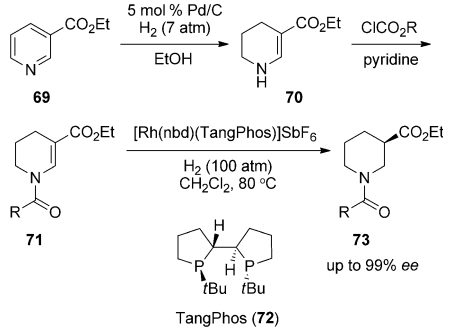
Transfer hydrogenation or hydrogenation of functionalized pyridines has been reported to proceed through organocatalysis,[70] transition-metal catalysis,[10,57,103] and heterogeneous catalysis.[104] Although asymmetric hydrogenation of imines, enamines, and polycyclic N-heteroaromatic compounds has received considerable attention, only very limited work has been directed toward that of monocyclic pyridine derivatives. A homogeneous rhodium catalyst promoted the asymmetric hydrogenation of monosubstituted pyridines to form the desired hydrogenation products with only 24–27% *ee*.[105] In 2004, Glorius and co-workers reported an efficient asymmetric hydrogenation of the unprotected pyridines **62** to prepare highly enantiopure piperidines **63** by introduction of a chiral oxazolidinone moiety as an auxiliary at the 2-position of the pyridine substrate (Scheme 6).[10] It is well known that heterogeneous catalytic hydrogenation of pyridines is usually carried out in acidic media.[106] Protonation not only activates a pyridine substrate for hydrogenation, but also suppresses catalyst poisoning by the resultant piperidine product. With



Scheme 6. Pd(OH)$_2$/C-catalyzed hydrogenation of pyridines.[10]

Pd(OH)$_2$/C as a catalyst in acetic acid, hydrogenation of **62** afforded chiral piperidines **63** in up to 98% *ee*. The reaction is suggested to proceed via the activated form of the pyridine substrate, the pyridinium salt **65**, which is initially hydrogenated to intermediate **66**. Conversion of **66** into oxazolidinone **64** and iminium salt **67** which is in equilibrium with the enaminium salt **68**, is followed by hydrogenation of the resulting C=N or C=C bond to give the desired product **63**. The piperidinium hydrochloride and the auxiliary can be easily separated by extraction and then the auxiliary can be recycled.

[{Ir(cod)Cl}$_2$]/**44**/I_2[107] and [{Ir(cod)Cl}$_2$]/(*R*)-DifluorPhos/I_2[103] catalyst systems were successfully applied in the asymmetric hydrogenation of functionalized pyridines, that is, bicyclic 7,8-dihydroqui-nolin-5(6*H*)-ones, in good yields and up to 98% *ee*. Through a three-step procedure chiral nipecotic acid derivatives **73** were synthesized (Scheme 7).[104] Under Pd/C catalysis,the nicotinic acid ethyl ester **69**, was partially hydrogenated to 1,4,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (**70**) which was then transformed into the N-acetyl vinylogous amide **71** through functionalization by an acid chloride. Using a rhodium(I)/TangPhos (**72**) catalyst, **71** was efficiently hydrogenated to **73**. An iridium(I)/



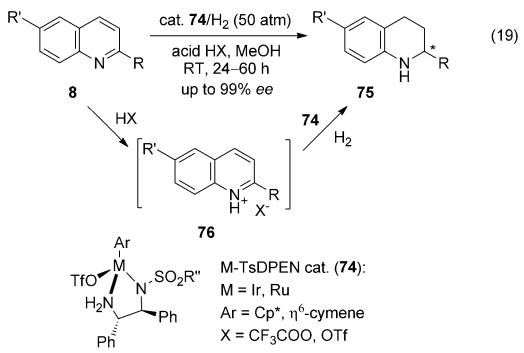
Scheme 7. Pd/C- and rhodium-catalyzed hydrogenation of pyridines.[104] nbd = norbornadiene.

[4,4′-bis(diphenylphosphino)-2,2′,6,6′-tetramethoxy-3,3′-bipyridine]/I_2 catalyst system was applied in the asymmetric hydrogenation of trisubstituted pyridines, that is, 2-substituted 7,8-dihydroquinolin-5(6*H*)-ones, to afford chiral hexahydroquinolinone derivatives in nearly quantitative yields and up to 99% *ee*,[108] thus presenting rare examples of asymmetric hydrogenation of N-unprotected pyridines.

3.6. Asymmetric Hydrogenation of N-Unprotected Quinolines

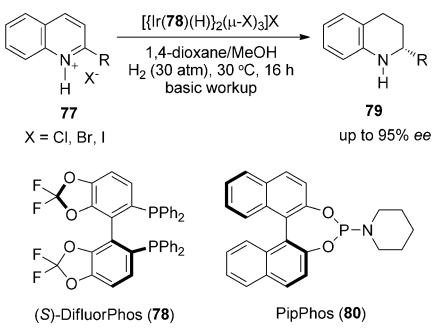
Quinolines are also challenging substrates for enantioselective hydrogenation because of their low aromaticity. In 2006, Rueping et al. reported the first metal-free Brønsted acid catalyzed transfer hydrogenation of quinolines using the Hantzsch ester as the hydrogen source.[72,73] The reaction is presumably initiated by protonation of the substrate to form its iminium salt.[66] Various chiral phosphoric acids have been developed for this purpose.

Following the pioneering work on Brønsted acid activation of unprotected six-membered N-heteroaromatic compounds by Glorius et al.[10] and Rueping et al.,[70,72,73] the substrate activation strategy with Brønsted acids has been applied in the enantioselective transition-metal-catalyzed hydrogenation of quinolines. It was established that quinolines and isoquinolines, upon activation by strong acids such as CF_3SO_3H/SbF_5 and $HCl/AlCl_3/CH_2Cl_2$, etc., can lead to N,C-diprotonated dications.[109] In the presence of a strong Brønsted acid such as CF_3COOH (10 mol%)[110] or TfOH (0.1 mol%),[111] chiral cationic [Cp*Ir(OTf)(CF_3TsDPEN)] and [Ru(OTf)(TsDPEN)(η^6-cymene)] complexes (**74**, TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) catalyzed phosphine-free asymmetric hydrogenation of quinolines **8** to afford 1,2,3,4-tetrahydroquinoline derivatives **75** in up to 99% *ee* [Eq. (19)]. The experimental and theoretical studies by Fan, Chan, and co-workers suggest that the enantioselective hydrogenation of **8** is initiated by their protonation with the Brønsted acid activator to form the quinolinium ion **76**, which is then hydrogenated to **75**.[112,113]



(19)

In 2009, Ohshima et al. developed the direct catalytic asymmetric hydrogenation of 2-substituted quinolinium salts, that is, quinoline·HX (X = Cl, Br, I) adducts (**77**), by iridium complex catalysts bearing DifluorPhos (**78**) and halide ligands [Eq. (20)].[114] The hydrogenation reaction produced 2-substituted tetrahydroquinolines **79** in up to 95% *ee*, which is much better than those from the corresponding neutral 2-arylquinolines,[115] and the 2-alkylquinolinium salts could also be hydrogenated to the corresponding tetrahydroquinoline derivatives with up to 95% *ee*. A notable feature of this catalytic system is the unexpected superiority of chloro- and bromo-iridium catalysts over the iodo-iridium catalyst, a trend that is opposite to the known halide effect. With a library of modular iridium complexes derived from the P-OP ligands as catalysts, 10% anhydrous HCl was also used as an activator for the same purpose.[116] In this aspect, the Brønsted acid activation strategy has been extended to synthesize various tetrahydroquinolines through asymmetric hydrogenation of functionalized quinolines.[117,118] In a fashion similar to the asymmetric hydrogenation of pyridines bearing an auxiliary (**62**),[10] the stereoselective hydrogenation of the substituted quinolines **81** was used to access partially saturated and saturated N-heterocycles in up to 99% *ee* [Eq. (21); TFA = trifluoroaceteic acid].[119]



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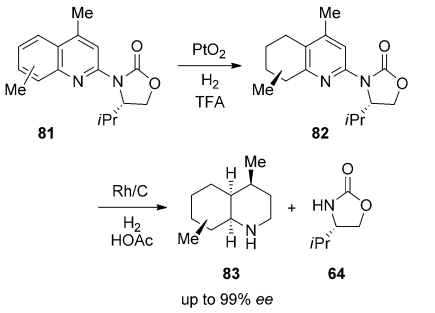
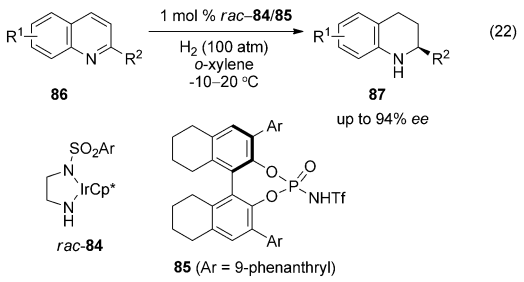
As the alternative to a Brønsted acid, its ammonium salt may also play the same role as a substrate activator. In 2008,



(21)

Feringa, et al. reported the asymmetric hydrogenation of quinolines **8** catalyzed by iridium complexes bearing monodentate binol-derived phosphoramidite ligands (**80**) in the presence of 10 mol% piperidine hydrochloride ($C_5H_{11}N$·HCl) as an activator, thus producing tetrahydroquinolines **75** in up to 89% *ee*.[120] Upon optimizing the reaction conditions, Zhou et al. performed the same reaction by using piperidine triflate ($C_5H_{11}N$·TfOH) as the substrate activator, thus increasing the best enantioselectivity of **75** to 92% *ee*.[121]

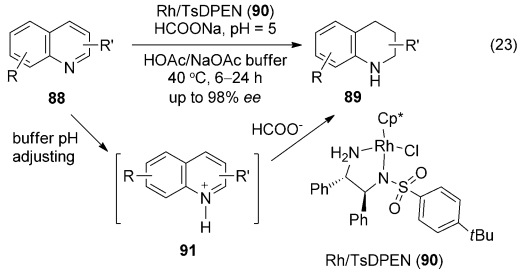
In 2011, Rueping et al. documented the first Brønsted acid differentiated, transition-metal-catalyzed hydrogenation by kinetic discrimination [Eq. (22)].[122] By using a chiral acidic triflylphosphoramide (**85**) as an activator, an achiral iridium complexe (*rac*-**84**) catalyzed the enantioselective hydrogena-



(22)

tion of polysubstituted quinolines **86** to generate substituted tetrahydroquinolines **87** with up to 94% *ee*.

The Brønsted acid activation strategy can also be applied to the transformation of C=N bonds in aqueous solutions. In 2009, Xiao et al. reported the first examples of transition-metal-catalyzed asymmetric transfer hydrogenation of quinolines in an acidic aqueous phase.[123] Through adjusting the pH value of the buffer to 5, the substituted quinolines **88** were efficiently reduced to tetrahydroquinolines (**89**) by the rhodium(III)/TsDPEN catalyst **90** with HCOONa as the hydrogen source in water, thus revealing that a Brønsted acid facilitates the transfer hydrogenation in water [Eqs. (23)–25). The HOAc/NaOAc system exhibited the maximum buffer capacity at an approximate pH value of 5. A plausible explanation for this phenomenon is demonstrated in the two conflicting equilibria [Eqs. (24) and (25)]. At high



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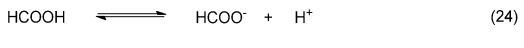

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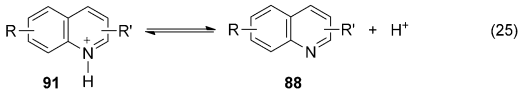
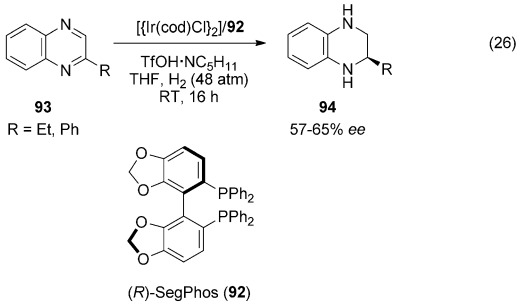


(25)

pH values (pH > 5.4), the concentration of protonated **88**, that is, **91**, becomes low, whereas at low pH values (pH < 3.6) the concentration of formate ($HCOO^-$) decreases. Only a pH value between 3.6 and 5.4 may provide a high enough concentration for both of the reactants, thereby leading to high reaction rates. This system was applied to the asymmetric transfer hydrogenation of various substituted quinolines **88**, thus affording chiral tetrahydroquinoline derivatives **89** in up to 97% yields and 98% *ee*.

3.7. Asymmetric Hydrogenation of N-Unprotected Quinoxalines

Quinoxalines are rarely explored substrates for asymmetric hydrogenation because of their very poor aromaticity. The Brønsted acid activation strategy has recently been documented in a few examples of enantioselective hydrogenation of quinoxalines. In 2010, Zhou et al. reported that with an iridium complex catalyst, generated in situ by treatment of $[\{Ir(cod)Cl\}_2]$ with (*R*)-SegPhos (**92**), in the presence of 5 mol% piperidine·TfOH in THF, 2-ethyl and 2-phenyl-substituted quinoxalines (**93**) were hydrogenated to the tetrahydroquinoxalines **94** in 57–65% *ee* [Eq. (26)].[121] Vidal-Ferran et al. carried out the asymmetric hydrogenation of 2-methylquinoxaline (**95**) in the presence of 10% anhydrous HCl in toluene using the $[\{Ir(cod)Cl\}_2]$/**96** catalyst to prepare tetrahydroquinoxaline **97** in 70% *ee* [Eq. (27)].[116]



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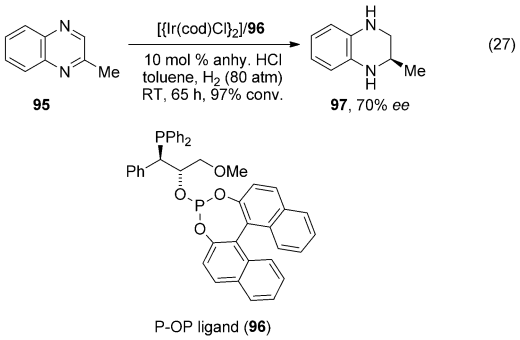
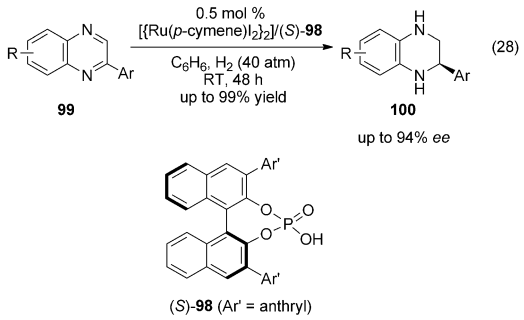
In 2011, Zhou et al. developed a ruthenium(II)/Brønsted acid relay catalysis procedure for the synthesis of chiral tetrahydroquinoxalines **100** by means of a convergent asymmetric disproportionation of the reaction intermediate, that

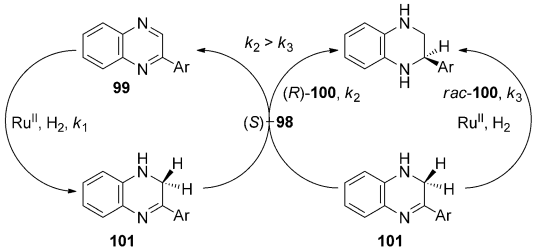


(27)

is, dihydroquinoxalines (**101**) from the enantioselective hydrogenation of 2-aryl-substituted quinoxalines **99** in the presence of chiral phosphoric acid (*S*)-**98** as an activator [Eq. (28) and Scheme 8].[124] Use of H_2 gas as the reductant makes the convergent disproportionation an ideal atom-economical process, thus affording the desired products **100** in up to 94% *ee*. Theoretical studies suggests that the ruthenium(II)-catalyzed hydrogenation of **99** first delivers the intermediate **101**, which subsequently interacts with chiral phosphoric acid (*S*)-**98** to activate its C=N bond through hydrogen bonding.[125] The hydrogen bonds and steric effect lead to a "three-point contact model" which determines the selectivity in the disproportionation of **101**. In the catalytic



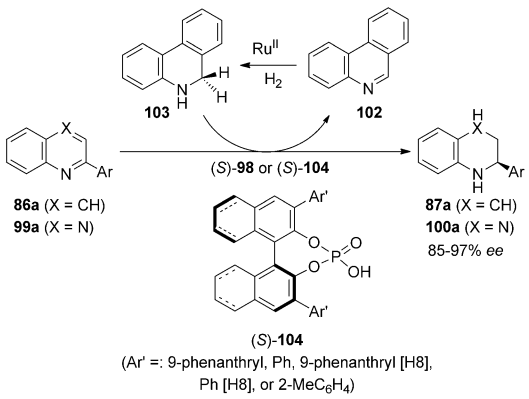
cycle (Scheme 8), the first hydrogenation process (k_1) is confirmed as the rate-determining step with $k_2 > k_3$. Therefore, excellent enantioselective control can be achieved because formation of the undesired hydrogenation side product, *rac*-**100**, is limited.



Scheme 8. Excellent enantioselective control.[124]

Xu, Xiao, and co-workers also developed pH-regulated transfer hydrogenation of multisubstituted quinoxalines with a [Cp*Ir]/monotosylated ethylenediamine catalyst and $HCOO^-$ as the hydrogen source in a HOAc/NaOAc buffer.[126] It is suggested that protonation of a quinoxaline substrate to its corresponding quinoxalinium by the buffer initiates the reaction sequence.

Very recently, Zhou et al. reported a ruthenium(II)-catalyzed, chiral phosphoric acid activated biomimetic asymmetric hydrogenation of benzoxazinones by means of catalytic amount of the in situ regenerative Hantzsch ester **16** under 70 atm of hydrogen gas.[127] During the reaction, the Hantzsch ester **16** can be recycled. In a similar fashion, the same group developed a more efficient protocol for the biomimetic asymmetric hydrogenation of benzoxazinones, benzoxazines, quinolines **86a**, and quinoxalines **99a** by using the readily regenerative dihydrophenanthridine (DHPD, **103**) from a catalytic amount of phenanthridine (**102**) with excellent activities (Scheme 9).[128] With $[\{Ru(p\text{-cymene})I_2\}_2]$ (0.5–1.0 mol%) as the catalyst and a chiral Brønsted acid (1–5 mol%) such as (*S*)-**98** or (*S*)-**104** as an activator in the presence of 10 mol% phenanthridine (**102**), **86a** and **99a** were efficiently hydrogenated to the corresponding chiral amines with 85–97% *ee* under 3–34 atm of H_2 gas. The proposed mechanism suggests that compound **102** is hydrogenated to DHPD first under the ruthenium(II) catalysis, and Brønsted acid (*S*)-**98** or (*S*)-**104** then promotes the transfer hydrogenation of the N-heteroaromatic substrate with DHPD to form the desired product and **102** for the next catalytic cycle.



Scheme 9. Biomimetic asymmetric hydrogenation.[128]

The use of hydrogen gas as the reductant makes this biomimetic asymmetric hydrogenation an ideal atom-economical process.

4. Conclusions

In conclusion, the recent breakthrough work by Zhang et al. has demonstrated excellent examples of how to construct an efficient transition-metal catalytic system for the enantioselective hydrogenation of the challenging C=N and C=C-N-bearing compounds through substrate activation using Brønsted acids as activators. Although Brønsted acid catalysis has been extensively explored in the pure organocatalytic transformations of some relevant substrates, cooperative transition-metal and chiral Brønsted acid catalysis remains a relatively unexplored topic. Applying a Brønsted acid to activate a Lewis basic substrate can increase the substrate reactivity and reaction selectivity through protonation of the substrate or hydrogen-bonding interactions between the substrate and Brønsted acid activator,[13,14,125] thus initiating novel transition-metal-catalyzed transformations which cannot easily occur under currently available reaction conditions. It is reasonable to expect that the present substrate activation strategy by means of a Brønsted acid is promising for the application of a wide range of organic reactions involving C=N bond activation.

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