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*REVIEW*

# Recent Advances in Enantioselective Organocatalytic Reduction of C=N Bonds with Hantzsch Esters as the Hydride Source

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Reduction of C=N bonds with metal-free chiral organocatalysts is an attractive approach to get optically active amines. This review focuses on the recent developments in enantioselective organocatalytic reduction of C=N bonds by Brønsted acids with Hantzsch esters as the hydride source. The studies of several research groups such as Rueping, List, MacMillan, Antilla, You and Du are involved and the potential strengths of the catalysts as well as the weaknesses are discussed.

**Key Words: Organocatalysts, Hantzsch esters, Reduction, Brønsted acids.**

## INTRODUCTION

Catalytic enantioselective reduction of C=N bonds represents one of the most straightforward and efficient methods for the preparation of chiral amines, an important intermediate for the synthesis of natural products and chiral drugs[1-4]. However, asymmetric reduction of C=N bonds remains a big challenge comparing with the reduction of C=O and C=C bonds due to the weak reactivity of the C=N bonds and the existence of inseparable mixtures of E/Z isomers. Great attention has been attracted to the field just because of the challenge. As a result, many of successful approaches have been developed. The main methods for the enantioselective reduction of C=N bonds currently are the chiral transition metal complexes, which are limited by the rigorous reaction conditions, metal leaching and the cost. Another significant advance in the reduction of C=N bonds are the metal-free organocatalysts, which has attracted special attentions due to the friendly reaction conditions and the high enantioselectivity[5-8]. Organocatalysts for reduction of C=N bonds reported so far include the Lewis bases for the hydrosilation with trichlorosilane ($HSiCl_3$)[9-20] and the Brønsted acids for the transfer hydrogenation with Hantzch esters[21-33]. The latter attracts more attention because of its asymmetric transfer hydrogenation using NADH-like Hantzsch esters which makes the reaction seem to mimic biochemical reductions. Since the first report of enantioselective C=N bonds reduction using Hantzsch esters in the presence of Brønsted acids to afford amines with moderate enantioselectivities (up to 63 % ee) in 1989 by Singh and Batra[34], great progress

has been made in the field recently. This review is to focus on the topic while other concerning reviews have been published only part of the results on asymmetric transfer hydrogenation of C=N bonds[35-39]. In this paper, the researches of several groups such as Rueping, List, MacMillan, Antilla, You and Du will be involved and potential strengths of the catalysts as well as the weaknesses will be discussed.

**Studies of Rueping and coworkers:** Rueping and coworkers found that enantioselective phosphoric acid derived from dinaphthol can catalyze hydrogenation of ketimines with the Hantzsch esters as the hydride source first in 2005[21]. After testing a series of phosphoric acids, catalyst **1a** (Fig. 1) was found to be promising in both the reactivity and the enantioselectivity. Under the optimized conditions they explored the scope of **1a** with various imines and the results showed in Fig. 2. Although the highest enantioselectivity was only 84 % ee and the catalyst loading was 20 mol %, that was the first example enantioselective phosphoric acid catalyzed the reduction of ketimines with Hantzsch esters and made a big progress comparing with the reports by Singh and Batra[34].

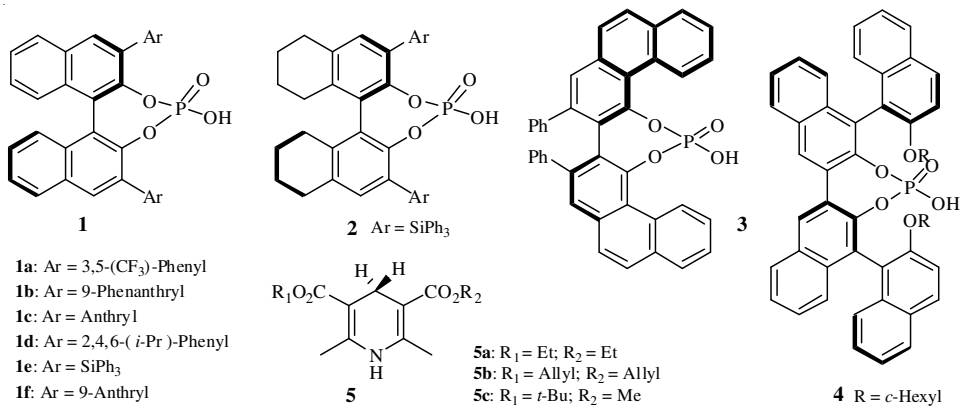
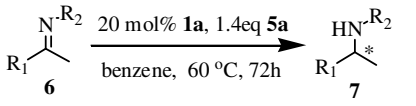



Fig. 1. Structure of Brønsted acids organocatalysts and Hantzsch esters in the reduction of C=N bonds




46-91% yield, 68-84% ee, 13 examples

$R_1$ = 2-Naphthyl, 4-$CF_3C_6H_4$, $C_6H_5$, 2-$FC_6H_4$, 2-$MeC_6H_4$, 2,4-$Me_2C_6H_4$, 4-$PhC_6H_4$

$R_2$ = $C_6H_5$, 4-$MeOC_6H_4$

Fig. 2. Reduction of imines with **1a**

In 2006, they found that the compound **1b** (Fig. 1) was an excellent catalyst for reduction of quinoline derivatives which involved a cascade transfer hydrogenation in the presence of **5a** (Fig. 1)[22]. Excellent enantioselectivities and yields were observed

in the exploring scope of **1b** just with 1-5 mol % catalyst loading, especially for the 2-aryl-substituted tetrahydroquinolines (Fig. 3). They also applied the new methodology to the synthesis of biologically active tetrahydroquinoline alkaloids such as galipinine, cuspareine and angustureine with high enantioselectivities. The discovery was very important because it was the first example of a metal-free reduction of heteroaromatic compounds and the methodology provided an alternative access to optically pure tetrahydroquinoline derivatives.

Later, Rueping and coworkers extended the biomimetic approach to the reduction of benzoxazines, benzothiazines and benzoxazinones successfully[23]. **1b** was found to be the most efficient catalyst again. The catalyst loading can be decreased to 0.01 mol % without a considerable loss in reactivity and selectivity, which is, to date, the lowest catalyst loading reported for an organocatalytic enantioselective transformation. With 1.25 equivement of **5a**, 0.1 mol % catalyst loading, they explored the scope of **1b** in $CHCl_3$ at room temperature. Differently substituted 3-aryl dihydro-2*H*-benzoxazines and 3-aryl dihydro-2*H*-benzothiazines were catalyzed by **1b** in good yields and with excellent enantioselectivities (93-99 % ee, Fig. 4). The procedure of reduction of dihydro-2*H*-benzothiazines showed the advantage of organocatalytic hydrogenation over most of the metal catalysts, which were known to be poisoned by sulfur-containing substrates. Catalyst **1b** was also proved to be efficient to transfer hydrogenation of benzoxazinones which can obtained the valuable cyclic aryl-substituted amino acid derivatives with high enantioselectivities.

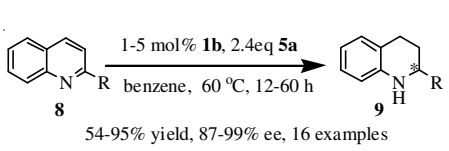



Fig. 3. Reduction of quinoline derivatives with **1b**

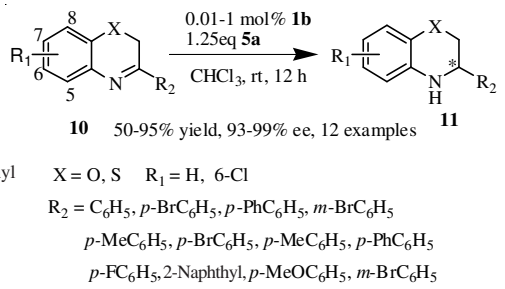



Fig. 4. Reduction of benzoxazines and benzothiazines with **1b**

Subsequently, they found that the compound **1c** (Fig. 1) was the best catalyst in the reduction of pyridines which obtained the hexahydroquinolinones and tetrahydropyridines with good yields and excellent enantioselectivities (up to 92 % ee, Fig. 5)[24]. The newly developed method not only was the first enantioselective reduction of pyridines catalyzed by Brønsted acids but also made a big progress in contrast to the metal-catalyzed enantioselective hydrogenation of pyridines.

Furthermore, they examined the hydrogenation of 3-substituted tetrahydroquinolines which involved a cascade reaction with a new catalyst **2** (Fig. 1)[25]. Different from the reduction of 2-substituted tetrahydroquinolines, here the stereodetermining

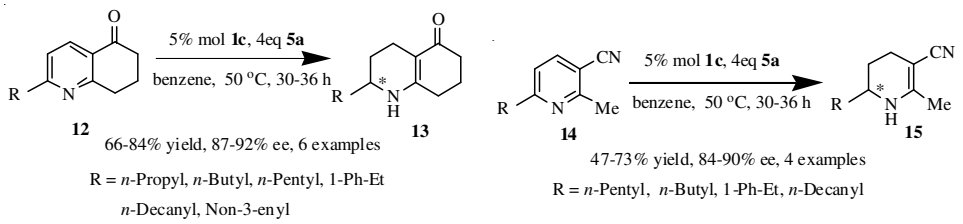



Fig. 5. Reduction of pyridines derivatives with **1c**

step was an enantioselective Brønsted acid catalyzed proton transfer. Influence of solvent, catalyst loading, solvent concentration and different Hantzsch esters on the enantioselectivity were investigated. Hantzsch ester **5b** (Fig. 1) bearing an allyl group was found to be the best one for getting a higher enantioselectivity. With the optimized conditions, they explored the scope of **2** with various 3-substituted quinolines (Fig. 6). Moderate to high enantioselectivities and yields of several 3-aryl- and heteroaryl- substituted tetrahydroquinolines were obtained. Although the highest enantioselectivity was only 86 % ee, that was the first example of an organocatalytic protonation in a cascade reaction.

**Studies of List and coworkers:** Shortly following Rueping's first reports in 2005, List and coworkers reported the same hydrogenation of ketimines with the Hantzsch esters as the hydride source[26]. Brønsted acid **1d** (Fig. 1) was found to be more efficient than **1a**. Compared with the research of Rueping, the higher yields and enantioselectivities were obtained with generally shorter reaction time, lower reaction temperature and lower catalyst loading (Fig. 7). The enantioselectivity was up to 93 % ee in the presence of 1 mol % catalyst loading. Moreover, **1d** can reduce aliphatic ketimines highly enantio- selectively and reduce imine generating in situ with high ee. Although there was just one example, it was the first example of enantioselective reductive amination with organocatalyst.

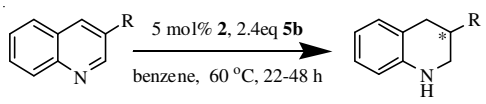



Fig. 6. Reduction of 3-substituted tetrahydroquinolines with **2**

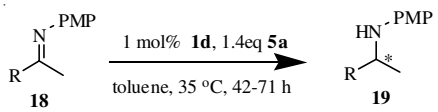



Fig. 7. Reduction of imines with **1d**

In succession, they applied the methodology to the asymmetric reductive amination of α-branched aldehydes which afforded β-branched amines *via* an enantiomer-differentiating kinetic resolution[27]. Catalyst **1d** turned out to be the most effective catalyst again. The highest enantioselective was up to 98 % ee for aromatic

substrates under the optimized conditions (Fig. 8). But the limitation of the transformation was that only 40-80 % ee for simple aliphatic aldehydes were obtained and the reaction time was a little longer.

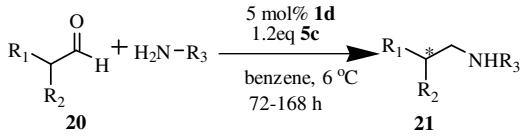



Fig. 8. Asymmetric reductive amination of α-branched aldehydes with **1d**

Recently, they successfully synthesized *cis*-3-substituted (hetero)-cyclohexylamines from 2,6-diones through new triple organocatalytic cascade reaction which combined both enamine and iminium catalysis with asymmetric Brønsted acid catalysis[28] (Fig. 9). High diastereoselectivities and excellent enantioselectivities were obtained for different substituted 2,6-diketones in the presence of 10 mol % Brønsted acid **1d**. For most of the studied reactions, the ee exceeds 90 % (dr > 95:5) especially with the aliphatic substituents. Heterocyclic substrates can also be obtained in high enantioselectivity. The new methodology provided a powerful strategy for organocatalytic cascade reactions.

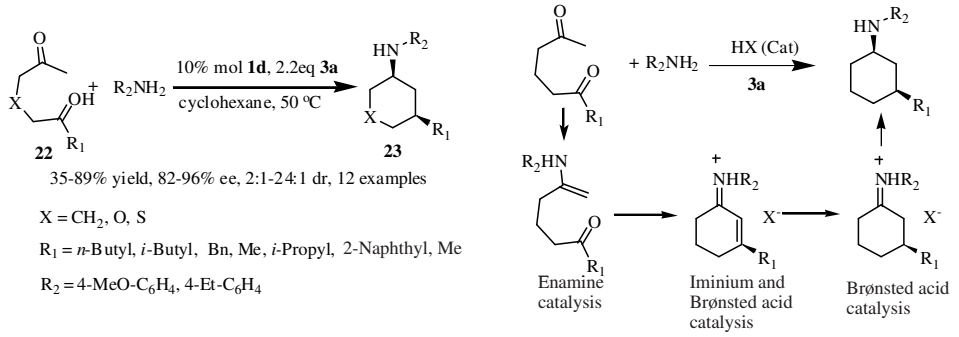



Fig. 9. Triple organocatalytic cascade reaction with **1d**

**Studies of MacMillan and coworkers:** Soon after List's disclosure in 2005, MacMillan and co-workers reported organocatalytic reductive amination using chiral catalyst **1e** (Fig. 1) and Hantzsch esters in details[29]. They found that 10 mol % **1e** facilitate the reaction in high conversion and excellent enantiocontrol at 40 ºC in the presence of 5 Å sieves with benzene as the solvent. Under the optimal conditions,

they examined the scope of the ketone and amines component, respectively (Fig. 10). A variety of ketone including substituted aromatic ketones and aliphatic ketones can be successfully coupled with *p*-anisidine afforded the products with excellent enantioselectivities. Different electronically diverse aryl and heteroaromatic amines in combination with arylketones were also accomplished by **1e** with excellent enantioselectivities. The broad substrate spectrum of catalyst **1e** was unprecedented even in asymmetric imine reduction catalysis. The one-pot asymmetric reductive amination starting directly from the ketone was of considerable importance which provided a simple way for the synthesis of chiral amines.

**Studies of Antilla and coworkers:** The direct reduction of α-imino esters is the most straightforward and desirable means to produce chiral amino acid derivatives which are important small molecules in biological systems. Metal-catalysis is the main efficient method to synthesize α-amino acids. However, Antilla and coworkers found that the chiral phosphoric acid was efficient organocatalyst for the hydrogenation of α-imino esters and their derivatives[30]. Chiral vapol (2,2'-diphenyl-[3,3'-biphenanthrene]-4,4'- diol) derived phosphoric acid **3** (Fig. 1) was proved to be efficient catalyst for the hydrogenation firstly. In the presence of 5 mol % **3**, several α-imino esters were reduced in toluene with high reactivity (93-98 % yield, Fig. 11) and excellent selectivity (93-98 % ee, Fig. 11). What's more, the methodology can be adapted to a general one-pot procedure which three cases utilizing alkyl-substituted α-imino esters generated *in situ* were reduced with 96-99 % ee.

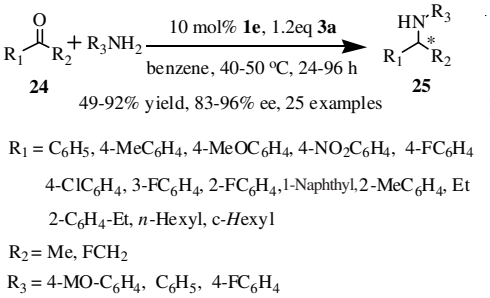



Fig. 10. Organocatalytic reductive amination with **1e**

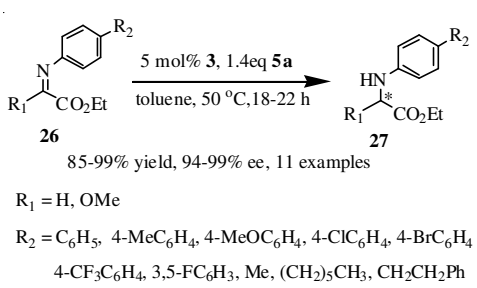
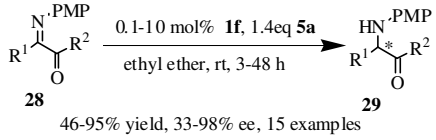



Fig. 11. Reduction of α-imino esters with **3**

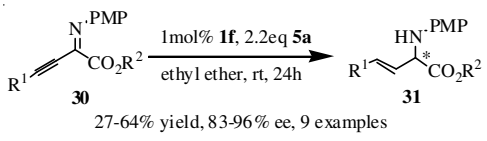
**Studies of You and coworkers:** Almost the same time with Antilla's report, You and coworkers found that **1f** (Fig. 1) was an efficient catalyst for the hydrogenation of α-imino esters in ethyl ether with Hantzsch ester **5a** as the hydrogen donor[31]. The catalyst loading was lower to 0.1 mol % and the enantioselectivity was up to 98 % ee. They examined the effect of different esters and found that the enantioselectivity was highly dependent on the steric size of the ester group. Higher ee values were obtained for those bearing a relatively bulky ester group. For most of the substrates including the thienyl-derived imino ester and imino amide can afford the hydrogenated products with high to excellent enantioselectivities (Fig. 12).

Whereafter, they applied the methodology to reduce β,γ-alkynyl α-imino acid derivatives and optically pure β,γ-alkenyl α-amino acids, a valuable intermediate for synthesis of further β,γ-position of α-amino acids were obtained[32]. 1f was also found to be the most efficient catalyst in ethyl ether. They also examined the influences of the ester groups' size and found that the steric size of ester groups had little impact on the selectivity but great on the reactivity. Greater ester group was in favor of higher reactivity. In the presence of 1 mol % of **1f** and 2.2 equiv of **5a**, several alkynyl-substituted α-imino esters had been tested and excellent ees were obtained (83-96 % ee, Fig. 13). But the reactivity for all the system was moderate (27-64 % yield) and no reactivity for aliphatic substituent substrate ($R_1$ = $C_6H_4$-$CH_2CH_2$). For all this, the method provided a promising way to synthesize α-amino acids and its derivatives.




$R_1$ = $C_6H_5$, 4-Br$C_6H_4$, 4-Cl$C_6H_4$ ,4-F$C_6H_4$ ,4-$CH_3C_6H_4$
4-Me$OC_6H_4$, 3-$CH_3C_6H_4$, 2-Naphthyl, *c*-Hexyl, Thienyl
$R_2$ = OEt, OMe, OBn, O-*i*-Pr, O-*t*-Bu, NH-*t*-Bu

Fig. 12. Reduction of α-imino esters with **1f**




$R_1$ = $C_6H_5$, 4-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-Cl-$C_6H_4$
3-F-$C_6H_4$, 1-Naphthyl
$R_2$ = Me, Et, *i*-Pr, *t*-Bu

Fig. 13. Reduction of β,γ-alkynyl α-imino acid derivatives with **1f**

**Studies of Du and coworkers:** In 2008, Du and coworkers designed and synthesized the novel double axially chiral phosphoric acid catalyst **4** (Fig. 1)[33]. With this new catalyst, they examined the asymmetric transfer hydrogenation of quinolines with Hantzsch ester **5a** as the hydride source. Comparing with the reports by Rueping, the efficiency of **4** was higher than **1b**. Excellent enantioselectivities and yields for both 2-aryl- and 2-alkyl-substituted quinolines were obtained with lower catalyst loading (0.2-1 mol %) (Fig. 14). Furthermore, 2,3-disubstituted quinolines were also reduced with excellent enantioselectivities. The novel backbone scaffolds of catalyst **4** obviously increased the variety of chiral phosphoric acid.

**General mechanism:** Enatioselective reduction of acetophenone imine by a chiral phosphoric acid with the Hantzsch esters was used to illustrate the general mechanism. Rueping, List and MacMillan generally assumed that ketimine was activated by protonation with a chiral Brønsted acid catalyst. The resulting iminium ion pair was chiral and reacted with the Hantzsch esters (Fig. 15 mechanism A). Structures derived from X-ray diffraction experiments of crystals of the Brønsted acid and of the imine-Brønsted acid complex have been used to explain the enantioselectivity of this reaction. However, Goodman thought that the single H-bond between imine and the catalyst was not fixed which leading to small energy differences in opposite enantiomers. They proposed an alternative mechanism, in

which the catalyst established H-bonds with both the imine and the Hantzsch esters (Fig. 15 mechanism B)[40]. Through calculations, mechanism B was proved to be much more effective than mechanism A in explaining the experimentally determined enantioselectivities. hydrogenation of imines.

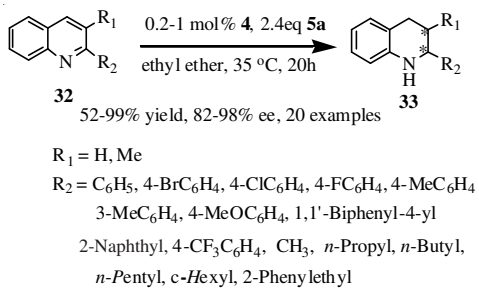



Fig. 14. Reduction of quinolines derivatives with **4**

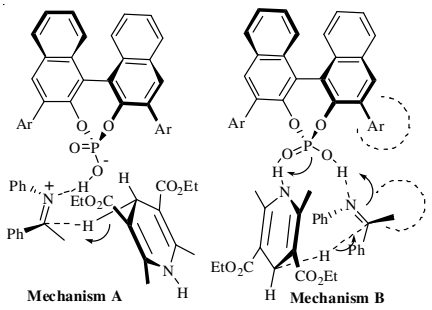



Fig. 15. Possible mechanisms for the Hantzsch esters

## Conclusion

As shown in this review, it is obviously that significant progresses in the enantioselective organocatalytic reduction of C=N bonds with Hantzsch esters have been made in recent five years. The scope of the substrate, the catalyst loading as well as the reactivity and selectivity have been considerably improved. Compared with the traditional hydrogen gas and metal hydride source, Hantzsch esters posses more superiorities such as mild reaction conditions, easy to handle and practicability. However, there are still problems existing in the field. Firstly, the type of Brønsted acid organocatalysts is rare which almost all the efficient catalysts reported are enantioselective phosphoric acid derivatives. Secondly, all the reported reactions are carried through in organic solvent while various reactions are catalyzed under aqueous conditions by naturally enzymes with the NADH as the hydride source. Thus, efforts toward the preparation of new type of Brønsted acid organocatalysts adapted to the reduction of C=N bonds with Hantzsch esters in water will be greatly desirable. It is very important both from the academic as well as industrial perspective.

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