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Organocatalytic asymmetric transfer hydrogenation of imines

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The asymmetric organocatalytic transfer hydrogenation of imines can be accomplished in good yields with high enantioselectivities through the use of BINOL-derived phosphoric acids as catalysts and Hantzsch esters or benzothiazoles as the hydride source. The same method can also be applied to the enantioselective reduction of benzo-fused heterocycles, such as quinolines, benzoazinones, benzoxazinones, quinoxalines, quinoxalinones and a limited number of pyridines containing electron-withdrawing groups. Cascade reactions involving multiple reductions and rearrangements have been reported as well as combinations of metal-catalysed reactions, such as gold-catalyzed hydroaminations of alkynes combined with the reduction of the ensuing enamine. Although turnover frequencies in the organocatalytic imine hydrogenations are still lower than those of metal-catalyzed hydrogenations, there are several advantages. Mild and environmentally friendly conditions as well as excellent selectivity make this method a valuable approach to enantiopure amine building blocks.

Introduction

Although the efficiency and selectivity of many organocatalytic reactions meets the standards of established organic reactions,1 use of metal catalysts often leads to higher turnover frequencies in the asymmetric hydrogenation of imines compared to the use of organocatalysts. However, to the best of our knowledge there is no metal catalyzed asymmetric imine hydrogenation as part of an industrial process with the exception of the Metolachlor process.2 There are several disadvantages of metal catalysts that often preclude industrial applications. These are related to the cost of the catalyst, relatively low turnover numbers—the Metolachlor process is an exception—and possible contamination of the product with metals. Organocatalytic reactions have several advantages; they can be performed under aerobic conditions, organocatalysts are also more stable than enzymes and can be anchored to a solid support and reused more conveniently than organometallic/bioorganic analogues. Organocatalysts also offer alternatives with respect to the activation of the substrate. Although organocatalytic reactions have passed through a flourishing decade, their origins started much earlier.3

Organocatalytic hydride transfers are inspired by reduction processes in nature.4 In biological systems, reductions are done in the cascade reactions using enzymes and organic hydride reduction cofactors, such as nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH_2). The first metal-free enantioselective imine reduction was reported in 1989 by Singh and Batra.5 With the use of amino acids as catalysts and Hantzsch esters (HE) as hydrogen sources, up to 62% ee was obtained. Hantzsch esters are bio-inspired hydride donors, commonly known as synthetic analogues of reduced nicotinamide adenine dinucleotide (NADH).6

Over the last decade, Brønsted acids have become a successful alternative to metal catalysts.7 Brønsted acid catalysis relies on enantioselective protonation or formation of a directed hydrogen bond by the catalyst. The interaction between the catalyst and the substrate is noncovalent and the chiral ion pair is the active species. Fig. 1 represents phosphoric acid catalysts and Hantzsch esters that have been successfully employed in the organocatalytic transfer hydrogenation of imines over the last 5 years.

N-Aryl imines

In 2005, Rueping et al. reported the first enantioselective Bronsted acid catalyzed reduction of N-aryl ketimines using a phosphoric acid catalyst derived from the Akiyama–Terada family of BINOL-derived catalysts (Scheme 1).8 Hantzsch ester 6 was used as the hydrogen source and various BINOL-derived 3,3′-arylated phosphoric acids were screened. Both steric and electronic effects of the substituents on the BINOL backbone were shown to influence the asymmetric induction. A strong solvent effect was observed, with non-polar solvents such as benzene leading to the best enantioselectivity and yield. Using 20 mol% of Bronsted acid
N-aryl ketimines 9 were reduced with up to 84% ee and good yields.

Rueping proposed a mechanism in which the ketimine is activated by protonation through Brønsted acid 1a, which generates the iminium compound A (Scheme 1). Subsequent hydrogen transfer from the Hantzsch ester 6 yields a chiral amine and pyridinium salt B, which undergoes proton transfer to regenerate the Brønsted acid 1a. The authors assigned the absolute configuration of the products based on the stereochemical model derived from the X-ray crystal structure of the catalyst. They propose that in the transition state, the ketimine is activated by the Brønsted acid 1a, favouring the nucleophile to approach the substrate from the less hindered si face. The re face is shielded by the aryl group of the catalyst.

List et al. reported independently the use of only 1 mol% of the (S)-BINOL-derived phosphoric acid 1b and Hantzsch ester 6 as the hydrogen source in the transfer hydrogenation of N-PMP-protected aromatic and aliphatic ketimines, with up to 93% ee and high yields. Moreover, imine generation could be performed in situ in the presence of molecular sieves. After the subsequent deprotection with CAN (cerium(IV) ammonium nitrate), the primary amine was isolated with 88% ee and 81% yield. Following these results reported by Rueping et al. and List et al. several groups reported BINOL-derived phosphoric acids to lead to excellent results in the metal-free transfer hydrogenation of the C=N bond. The steric hindrance in the 3,3′-position was shown to play an important role in the asymmetric induction.

Enantiomerically pure α-amino acids and their derivatives are the building blocks for the synthesis of peptides and chiral pharmaceuticals. One straightforward approach to the synthesis of enantiopure α-amino acids is the asymmetric hydrogenation of α-imino esters. Antilla and co-workers and You and co-workers reported the organocatalytic asymmetric transfer hydrogenation of N-PMP protected α-imino esters 11 and 13 using chiral phosphoric acids as a catalyst and Hantzsch esters as the hydrogen source (Scheme 2).

Using 5 mol% of the VAPOL-derived catalyst 4 Antilla et al. found excellent enantioselectivities and yields in the hydrogenation of α-aryl and α-alkyl substituted imino esters 11 (up to 99% ee). The use of in situ prepared imino esters gave lower overall yields, however with identical enantioselectivities. You et al. reported the use of 1 mol% of the hindered 9-anthracenyl-substituted phosphoric acid (S)-1c which resulted in excellent yields and ee’s (up to 98% ee). Enantioselectivities were strongly dependant on the 3,3′-substituents on the phosphoric acid catalyst and the ester group of the substrate. The more bulky the ester group was, the higher the enantioselectivity.

Antilla and co-workers described a highly enantioselective hydrogenation of aromatic enamides catalyzed by phosphoric acid 4.

**Scheme 1** Rueping’s organocatalytic reduction of imines and the proposed mechanism.

**Scheme 2** Organocatalytic transfer hydrogenation of α-imino esters.
acid (S)-1c. The authors found it was possible to speed up the reaction substantially by the addition of 10 mol% of acetic acid. A range of aromatic enamides was reduced with ee’s ranging from 41–95% ee. Apparently, the hydrogenation proceeds through the protonated iminium intermediate.15

You et al. reported the asymmetric transfer hydrogenation of N-PMP-substituted β,γ-alkynyl α-imino esters 15 using 1 mol% of Bronsted acid 1c. Both the alkyne and imine moieties were reduced with Hantzsch ester 6 to afford trans-alkenyl α-amino esters with up to 96% ee (Scheme 3).16 Yields were moderate and highly dependent on the variation of the ester group of the substrate, while enantioselectivity was unaffected. Mechanistic investigation showed that the reduction of the carbon–carbon triple bond is faster than that of the imine bond.

Recently, Zhu and Akiyama reported the use of benzo-thiazolines 17 and 21 as hydrogen donors in the asymmetric transfer hydrogenation of N-PMP-protected ketimines 17 and α-imino-esters 10 (Scheme 4).18 With the use of up to 2 mol% of 3,3′-disubstituted-BINOL-derived phosphoric acid catalyst 1b, excellent yields and enantioselectivities were achieved. Once again both the yields and enantioselectivities were dependent on the substrate in the 3,3′-position of the BINOL backbone of the catalyst.

Akiyama has shown that benzothiazolines can be generated in situ. Introduction of a hydroxy group onto the benzo-thiazoline as in 21 leads to the formation of benzothiazole 22 that precipitates from the reaction mixture. Thus, 22 is easily removed by filtration, which simplifies the ensuing purification of the product. This is the major advantage over the use of the Hantzsch esters.

Guéritte and co-workers developed a protocol for the enantioselective transfer hydrogenation of unprotected ortho-hydroxyaryl alkyl N–H imines 23 using 10 mol% of (S)-1e as a catalyst and Hantzsch ester 7 as the hydride source. A variety of ortho-hydroxybenzylamines was obtained with good to excellent yields and enantioselectivities (Scheme 5).19

Nitrogen heterocycles

Rueping has reported the organocatalytic cascade transfer hydrogenation of nitrogen heterocycles. Bronsted acid catalyzed cascade transfer hydrogenation of quinolines,20 quinoxalines,21 pyridines,22 benzoazines, benzoazinones and benzothiazines23 provides direct access to valuable enantio-enriched saturated heterocyclic compounds that are of considerable importance as intermediates for pharmaceuticals and agrochemicals and for use in the material sciences.24

In the reduction of 2-substituted quinolines 25, enantioselectivities of >99% ee were obtained using 2 mol% of catalyst 1d (Scheme 6). In general, 2-substituted quinolines with aromatic, heteroaromatic and aliphatic substituents were well tolerated. This is one of the first examples of metal-free asymmetric reduction of heteroaromatic compounds. The method was applied to the two-step synthesis of the natural products (−)-angustureine, (+)-cuspareine and (+)-galipinine in 90–91% ee and high yields. Rueping and Theissmann recently reported the first highly enantioselective Bronsted acid catalyzed reaction in an aqueous medium.25 Various

Scheme 3 You’s organocatalytic transfer hydrogenation of β,γ-alkynyl α-imino esters.

Scheme 4 Benzo-thiazolines as a hydrogen source in the organo-catalytic transfer hydrogenation of imines and imino-esters.
2-substituted quinolines and a benzoaxazine were reduced using 2 mol% of \(1b\) and Hantzsch ester 7 in brine as a solvent. Good yields and enantioselectivities of 83–97% were obtained.

Rueping and co-workers used Brønsted acid 2 derived from H\(_{8}\)-BINOL as a catalyst for the enantioselective transfer hydrogenation of 3- and 2,3-substituted quinolines 27 and 29, with good yields and enantioselectivities/diastereoselectivities (up to 86% ee and 99% ee, respectively).

The Brønsted acid 2 was recently used successfully by the same authors as a catalyst in the 4-step metal-free synthesis of the fluoroquinolone antibiotic flumequine and levofloxacin with high ee’s and yields.27 Whereas in the Brønsted catalyzed enantioselective transfer hydrogenation of 2- and 4-substituted quinolines the authors proposed that the enantioselectivity is introduced in the hydride addition, in the case of 3-substituted quinolines the enantiodetermining step was assumed to be the protonation by the Brønsted acid catalyst (Scheme 7).

Du and co-workers have also reported the organocatalytic transfer hydrogenation of quinolines (Scheme 8). As in previous cases they showed that the steric bulk of the substituent on the BINOL backbone of the phosphoric acid catalysts is crucial for obtaining good reactivity and selectivity. They employed double axially chiral phosphoric acids as catalysts, where substituents in the 3,3’-positions posses double axial chirality.28 The use of 0.2 and 1 mol% of catalyst 5, respectively, resulted in excellent enantioselectivities, diastereoselectivities and yields in the transfer hydrogenation of 2- and 2,3-substituted quinolines 25 and 31 (up to 98% ee and 92% ee, respectively).

Rueping and co-workers reported that excellent enantioselectivities and high yields were obtained in the reduction of benzoaxazines 33, benzoathiazines 34 and benzoazinones 37 using 0.1–1 mol% of phenanthryl-substituted BINOL-derived phosphoric acid 1d (Scheme 9).23 Enantiopure dihydrobenzoxazinones 38 could be ring opened using benzylamine to yield the \(N\)-aryl amino acid benzylamide 39 with preservation of stereochemical integrity.

Rueping and co-workers recently reported the first organocatalytic transfer hydrogenation of 2-aryl substituted quinoxalines 40 and quinoxalinones 42, with the use of up to 10 mol% of the Brønsted acid 1c and Hantzsch ester 6 as the hydride source.21 Enantioselectivities were high for both classes of substrates, with good to excellent yields (Scheme 10). The authors proposed a mechanism in which, similar to their previously reported quinoline reductions, the substrate is activated through Brønsted acid catalyzed protonation, followed by double 1,2-hydride addition.8

Rueping and Antonchick also reported the first Brønsted acid catalyzed cascade reduction of pyridines.22 With the use of 5 mol% of the phosphoric acid 1c various azadecalinones 45 and tetrahydropyridines 47 were obtained in good yields and excellent enantioselectivities (Scheme 11).

Enantioselectivity was highly dependant on the substituent on the phosphoric acid catalyst and the ester group of the Hantzsch ester. The authors also applied their method to the
The synthesis of the alkaloid diepi-pumiliotoxin C. The proposed mechanistic cycle of the transfer hydrogenation of pyridines starts with the protonation of the pyridine by the phosphoric acid, resulting in the chiral ion pair A (Scheme 11). Subsequent hydride transfer from Hantzsch ester 6 gives the adduct B, which is transformed into the iminium ion C through an acid-catalyzed isomerization. A second hydride transfer results in the desired product, and the phosphate catalyst 1c is regenerated.

The same authors developed a protocol for the enantioselective transfer hydrogenation of 3H-indoles.30 Using 1 mol% of 1c as catalyst, various substituted indolines were isolated with high yields and 70–99% ee (Scheme 12).

Recently, Rueping and co-workers described the asymmetric organocatalytic hydrogenation of quinolines and benzoxazines using polymer-supported chiral BINOL-derived phosphoric acids.31 These catalysts were shown to be as stable and effective as their homogenous counterparts and could be easily removed from the reaction mixture and reused in up to 11 consecutive reactions with preservation of both enantioselectivity and reactivity.

In 2008, Metallinos et al. described the first asymmetric organocatalytic transfer hydrogenation of 2- and 2,9-substituted 1,10-phenanthrolines 50 (Scheme 13).32 They applied “Rueping’s conditions”; using up to 10 mol% of the phosphoric acid catalyst 1d and 1f and Hantzsch ester 6 (6 eq.) and obtained octahydrophenanthrolines 51 in 40–88% yield and good to excellent enantioselectivities (78–99% ee).

Rueping and co-workers recently reported the highly enantioselective synthesis of benzodiazepinones via organocatalytic hydrogenation.33 A one-pot procedure involving the in situ generation of benzodiazepin-2-ones 52 and subsequent hydrogenation furnished benzodiazepinones 53 in moderate to high yields and excellent enantioselectivities (83–99% ee, Scheme 14).

Gong and co-workers described a dynamic kinetic transfer hydrogenation of 2-methyl-2,4-diaryl-2,3-dihydrobenzo[b][1,4]diazepines with 8 using the 3,3’-phenyl-substituted BINOL-derived phosphoric acid catalyst.34 Using 10 mol% of the catalyst at −10 °C, optically active 1,3-diamines were isolated with high yields and moderate to good diastereoselectivities (2:1 to 8:1; syn is the major isomer) and good enantioselectivities (63–86% ee).

**Direct reductive amination**

The direct reductive amination is a biomimetic reaction that allows the asymmetric coupling of complex fragments...
containing a ketone functionality into amines by the use of a chiral hydrogen-bonding catalyst and a hydrogen donor. Direct reductive amination enables access to enantio-enriched amines without the isolation of the imine substrates. This is a great advantage in the case of imines that are too unstable to be isolated.

The first enantioselective organocatalytic direct reductive amination was described by MacMillan and co-workers in 2006 (Scheme 15). They were able to achieve the reductive amination of aromatic and aliphatic ketones with various aromatic and heteroaromatic amines. Exposing ketone 54 and amine 55 to 10 mol% of the chiral catalyst 1e, in the presence of molecular sieves, resulted in the formation of an intermediate iminium species that in the presence of a suitable Hantzsch ester underwent enantioselective hydride reduction with excellent enantioselectivities and moderate to good yields. Based on the X-ray structure of the catalyst, as well as on calculated and experimental data, the authors concluded that the catalyst is particularly selective for the reduction of iminium ions derived from methyl ketones. Ethyl ketones reacted substantially slower. Remarkably, aliphatic methyl ketones could also be reductively aminated with a variety of anilines with ee’s between 83–94%. List and co-workers described the asymmetric Bronsted acid catalyzed reductive amination of ketones using benzylamine. With the use of 5 mol% of (S)-1c moderate to good yields and enantioselectivities were obtained with four different substrates (26–88% ee). Reactions were slow and took 7 days.

The scope of the organocatalytic direct reductive amination was extended by List and co-workers to α-branched aldehydes and ketones (Schemes 16 and 17). Enolizable α-branched aldehydes were subjected to direct reductive amination to give β-branched amines via an enantiomer-differentiating kinetic resolution. Under reductive amination conditions the α-branched aldehyde 57 undergoes a fast racemization in the presence of the amine and an acid catalyst via an imine/enamine tautomerization. The reductive amination of one of the two imine enantiomers is faster than that of the other, resulting in an enantiomerically enriched product via a dynamic kinetic resolution (DKR).

Using 5 mol% of catalyst 1b and Hantzsch ester 7 as a hydrogen source different aryl, alkyl-substituted aldehydes were reduced to β-branched amines 58 with up to 98% ee and high yields. Aliphatic aldehydes can also be employed although with lower enantioselectivity.

This approach was extended to the first example of the direct catalytic asymmetric reductive amination of α-branched ketones using DKR (Scheme 17). Treating cyclohexanones 59 with para-anisidine 60, Hantzsch ester 6 and Bronsted acid 1d provided 2-alkyl, 2-aryl and 2-chloro-substituted N-PMP-protected cyclohexylamines 61 in good to excellent diastereo- and high enantioselectivity. The catalyst loading used depended on the steric demand of the substituent (1–10 mol%). Ketones with different ring sizes gave less successful results. Whereas 2-substituted cyclopentanone underwent reductive amination with lower selectivity, cycloheptanone did not undergo reductive amination. This approach was successfully used for the preparation of a key intermediate for the synthesis of Perindopril, an ACE inhibitor.

Enders and co-workers recently reported the organocatalytic asymmetric synthesis of trans-1,3-disubstituted tetrahydro-isoquinolines via a reductive amination/aza-Michael reaction sequence (Scheme 18). When methylketone enoates 62 and 64 were subjected to the reductive amination conditions using 10 mol% of the Bronsted acid 1b and a hydride source (Hantzsch ester or benzothiazole) in the
The presence of p-anisidine and molecular sieves, the amines 63 and 65 were obtained with high yields and enantioselectivities. Use of the benzothiazole reductant 66 resulted in higher yields and enantioselectivities when compared with the use of the Hantzsch ester. Treating the resulting amines with strong bases induced the cyclization reaction, resulting in the trans-diastereomer of the tetrahydro-isoquinoline product in good yields. Starting from an indole-derived keto enolate 64 the corresponding trans-disubstituted β-carboline 65 was obtained in excellent yield and stereoselectivity.

Recently Akiyama et al. reported the use of BINOL-derived phosphoroselenoic acids as organocatalysts in the imine hydrogenation and direct reductive amination of acetophenone, with up to 62% ee.41 The first nucleotide-catalyzed reductive amination of acetophenone, using the Hantzsch ester as the hydrogen donor, was described by Kumar and co-workers. With the use of up to 5 mol% of catalyst, they were able to obtain the products in good yields with up to 79% ee.42

**Domino reactions**

Over the last few years, organocatalytic domino reactions attracted significant attention.43 In nature, enzymatic multi-step sequences often take the form of domino and multi-component reactions. As the advantage of the formation of several bonds in a single reaction is evident, many groups have pursued organocatalytic domino reactions. In particular, amines and their salts trigger cascade reactions via enamine and/or iminium ion formation. The first example of an enantioselective phosphoric acid catalyzed domino reaction was the enantioselective cascade transfer hydrogenation of quinolines established by Rueping et al.44

In 2007, List et al. reported a domino reaction involving a Bronsted acid catalyzed transfer hydrogenation (Scheme 19).44 The authors combined enamine and iminium catalysis with asymmetric Brønsted catalysis in order to obtain pharmaceutically relevant cis-1,3-substituted cyclohexylamines 68 in high diastereo- and enantioselectivities, starting from linear diketones 67. The reaction proceeds via an intramolecular aldol condensation followed by a conjugate reduction and reductive amination cascade that is catalyzed by a Bronsted acid 1b and accelerated by the amine substrate. The authors proposed a catalytic cycle that was recently verified by mass spectrometry.45 The initial aldolization step involves formation of the enamine A, which reacts intramolecularly to form the iminium salt B. B undergoes conjugate reduction to C and a final reduction thereof furnishes the cyclohexylamine product 68.

Rueping and co-workers developed an asymmetric organocatalytic cascade reaction in which multiple steps are catalyzed by a chiral Bronsted acid catalyst 1c and which provides tetrahydropyridines and aza-decalinones with good yields and excellent enantioselectivities (Scheme 20). The sequence comprises a one-pot Michael addition-isomerization-cyclization–elimination–isomerization–transfer hydrogenation in which each step is catalyzed by the same chiral Brønsted acid.46 The authors propose a mechanism in which exposure of a mixture of enamine 69 and vinyl ketone 70 to catalytic amounts of the Bronsted acid leads to the formation of the corresponding 1,4-addition products 72 and 73. Subsequent Bronsted acid catalyzed cyclization of 72, which is in an acid-catalyzed equilibrium with 73, gives the hemiaminal 74 which upon rapid water elimination results in the formation of the dihydropyridine 75. The following Brønsted acid catalyzed protonation isomerizes the enamine to the iminium ion 76, which is activated for an enantioselective hydride transfer to give the desired product. The requirement is that the last Bronsted acid catalyzed step in the sequence proceeds with high enantiocontrol. This domino reaction consists of six reaction steps catalyzed by the same catalyst which represents a direct and efficient access to useful tetrahydropyridines and azadecaliones from simple and readily available starting materials with the highest levels of enantiocontrol.

**Scheme 18** Synthesis of trans-1,3-disubstituted tetrahydroisoquinolines via a reductive amination/aza-Michael reaction sequence.

**Scheme 19** Preparation of cyclohexylamines via a cascade reaction.
The concept of combining metal catalyzed reactions with organocatalysis has emerged as a promising field since it enables transformations that previously could not be achieved. The challenge is to find reaction conditions suitable for the optimal performance of both metal-catalyzed and organocatalytic steps in one pot. A hydroamination/transfer hydrogenation cascade reaction reported by Gong and co-workers involved conversion of 2-(2-propynyl)aniline derivatives to tetrahydroquinolines (Scheme 21). The reaction is initiated by a gold catalyzed hydroamination-cyclization to quinoline, which is then hydrogenated with the use of Brønsted acid catalyst to give the tetrahydroquinolines with excellent yield and enantioselectivities. Catalysts tolerated both aryl and alkyl substituents on the propynyl bond, with the alkyl substituents leading to somewhat lower ee’s (87–88% ee compared to 94–99% in case of aryl substituents).

The silver salt of the Brønsted acid was also prepared and tested, but its use led to poor reactivity (35% yield, 90% ee, 80 h). The authors therefore concluded that the stereochemistry was controlled by the phosphoric acid. This method is nicely complimentary to the direct reduction of 2-substituted quinolines as described above in view of the different starting materials.

Che independently reported a highly enantioselective synthesis of chiral secondary amines by gold/chiral Brønsted acid catalyzed tandem intermolecular hydroamination and transfer hydrogenation reactions of alkynes, in good to excellent yields and excellent enantioselectivities (Scheme 22). The authors proposed a mechanism which involves the gold(I)-catalyzed intramolecular hydroamination of the alkyne to generate the ketimine intermediate and the subsequent chiral phosphoric acid catalyzed transfer hydrogenation thereof. The authors revealed that in the presence of AuI the hydroamination reaction proceeds smoothly, whereas in the presence of only the Brønsted acid the hydroamination is completely inhibited. Although Au complexes can catalyze the transfer hydrogenation of imines, the transfer hydrogenation only takes place if the Brønsted acid is present. Control experiments showed that upon treatment of the gold catalyst with the chiral gold phosphate, similar reactivity and enantioselectivities were observed. Thus the authors claim that there is a possible exchange of the metal counter ion, leading to the formation of a AuI complex cation/chiral counter ion pair which carries out the subsequent reaction. Comparing this method to the reduction of the preformed imine or the direct reductive amination the only disadvantage is the accessibility of starting alkynes. Whereas the substituted aceophenones are readily available, the aromatic alkynes need to be prepared via a Sonogashira reaction.

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**Conclusions**

The field of organocatalytic transfer hydrogenation has been developing at an extraordinary pace over the last decade. Although turnover frequencies of the organocatalytic imine hydrogenations are still lower than those of metal-catalyzed...
hydrogenations, there are several advantages. Mild, environmentally friendly conditions such as the avoidance of the use of high pressure hydrogenation conditions make this method synthetically useful. The challenges, such as the issue of the catalyst recycling, lowering the amount of catalyst, the reduction of reaction times and the complexity of the catalyst synthesis, remain to be overcome to allow large-scale application.

Notes and references


