ACCOUNTS of chemical research

Article

pubs.acs.org/accounts

# Benzothiazoline: Versatile Hydrogen Donor for Organocatalytic Transfer Hydrogenation

Chen Zhu,[†,‡] Kodai Saito,[‡] Masahiro Yamanaka,[§] and Takahiko Akiyama*[,‡]

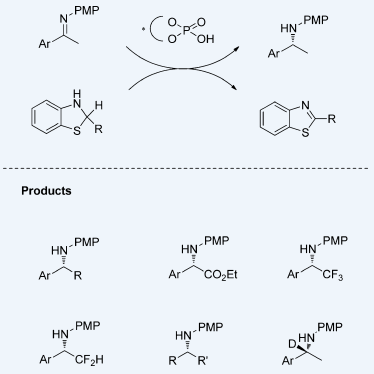
[†]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, 199 Ren-Ai Road, Suzhou, Jiangsu 215123, People's Republic of China

[‡]Department of Chemistry, Gakushuin University, 1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588, Japan

[§]Department of Chemistry and Research Center for Smart Molecules, Faculty of Science, Rikkyo University, 3-34-1 Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501, Japan

**CONSPECTUS:** The asymmetric reduction of ketimines is an important method for the preparation of amines in optically pure form. Inspired by the biological system using NAD(P)H, Hantzsch ester has been extensively employed as a hydrogen donor in combination with chiral phosphoric acid for the transfer hydrogenation of ketimines to furnish amines with high to excellent enantioselectivities.

We focused on 2-substituted benzothiazoline as a hydrogen donor in the phosphoric acid catalyzed transfer hydrogenation reaction of ketimines for the following reasons: (1) benzothiazoline is readily prepared just by mixing 2-aminobenzenethiol and aldehyde, (2) both reactivity (hydrogen donating ability) and enantioselectivity would be controlled by tuning the 2-substituent of benzothiazoline, and (3) benzothiazoline can be stored in a refrigerator under inert atmosphere without conceivable decomposition. Both the 2-position of benzothiazoline and the 3,3′-position of phosphoric acid are tunable in order to achieve excellent enantioselectivity.




Benzothiazoline proved to be useful hydrogen donor in combination with chiral phosphoric acid for the transfer hydrogenation reaction of ketimine derivatives to afford the corresponding amines with high to excellent enantioselectivities by tuning the 2-substituent of benzothiazoline. Ketimines derived from acetophenone, propiophenone, $\alpha$-keto ester, trifluoromethyl ketone, and difluoromethyl ketone derivatives proved to be suitable substrates. Benzothiazoline could be generated in situ starting from 2-aminobenzenethiol and aromatic aldehyde in the presence of ketimine and chiral phosphoric acid and successfully worked in the sequential transfer hydrogenation reaction. The reductive amination of dialkyl ketones also proceeded with high enantioselectivities. Use of 2-deuterated benzothiazoline led to the formation of $\alpha$-deuterated amines with excellent enantioselectivities. The kinetic isotope effect ($k_H/k_C$ = 3.8) was observed in the competitive reaction between H- and D-benzothiazoline, which explicitly implies that the cleavage of the C−H (C−D) bond is the rate-determining step in the transfer hydrogenation reaction.

Benzothiazoline yielded products with higher enantioselectivity in the transfer hydrogenation reaction of ketimines, particularly ketimines derived from propiophenone derivatives, than Hantzsch ester. DFT study elucidated the mechanism, as well as the difference in selectivity, between benzothiazoline and Hantzsch ester. The chiral phosphoric acid activates ketimines and benzothiazoline by means of the Brønsted acidic site (proton) and the Brønsted basic site (phosphoryl oxygen), respectively, to accelerate the hydride transfer reaction.

## 1. INTRODUCTION

Amines are an important class of structural motifs found in a vast array of natural products and biologically active compounds. The asymmetric hydrogenation of the carbon−nitrogen double bond (abbreviated as C=N bond hereafter) represents one of the most straightforward strategies for the construction of chiral amines.[1−8] In the last several decades, we have witnessed remarkable advances in the transition metal catalyzed asymmetric hydrogenation of ketimines. Despite those advances, its application has been limited particularly in the pharmaceutical industry due to inherent shortcomings, for example, the presence of metal contaminants and the high cost of removing trace metals from products. Inspired by naturally occurring hydrogenation processes mediated by nicotinamide adenine dinucleotide (NAD(P)H), Rueping,[9] List,[10] and MacMillan[11] independently reported the transfer hydrogenation of ketimines by the use of Hantzsch ester[12,13] as the hydrogen donor in combination with chiral phosphoric acid to afford the corresponding amines with high to excellent enantioselectivities. The combination of Hantzsch ester and chiral phosphoric acid proved to be useful for a range of enantioselective reduction reactions of C=N bonds (Scheme 1).[14−26] Although Hantzsch ester is an efficient hydrogen donor,[27] the development of a new type of versatile organic hydrogen source was still in demand.

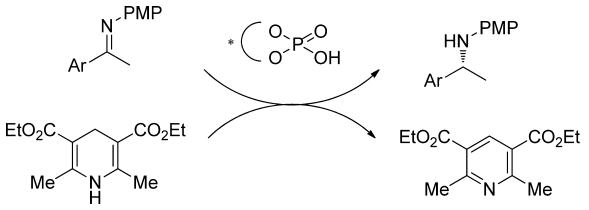
**Received:** November 17, 2014
**Published:** January 22, 2015





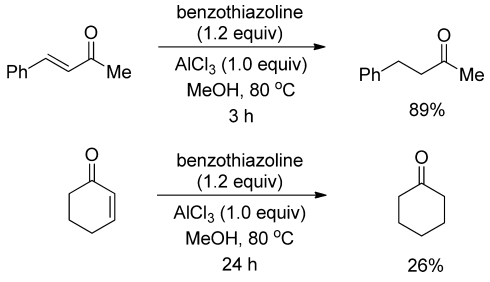
DOI: 10.1021/ar500414x
*Acc. Chem. Res.* 2015, 48, 388−398

**Scheme 1. Transfer Hydrogenation of Ketimines by Use of Hantzsch Ester as Hydrogen Donor Catalyzed by Chiral Phosphoric Acid**



Benzothiazoline exhibits reducing ability by releasing molecular hydrogen to form more stable benzothiazole. Chikashita and co-workers reported the reduction of $\alpha,\beta$-unsaturated carbonyl compounds in the presence of a stoichiometric amount of a Lewis acid by use of benzothiazoline as the reducing agent as early as in the 1980s (Scheme 2).[28,29] However, this pioneering

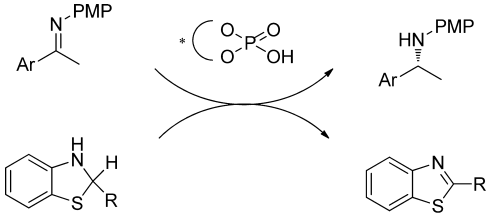
**Scheme 2. Benzothiazoline as Reducing Agent for the Reduction of $\alpha,\beta$-Unsaturated Carbonyl Compounds**




research failed to attract much attention over the last 20 years, and consequently, the utility of benzothiazoline had not been extensively investigated.

We hypothesized that benzothiazoline has unique features that contribute to the high enantioselectivity in the transfer hydrogenation: (1) reactivity (hydrogen-donating ability) would be controlled by tuning the electronic properties of the 2-substituent, and (2) the 2-substituent would improve the stereoselectivity because it is positioned geminal to the transferable hydrogen. Based on those ideas, we reported the transfer hydrogenation of ketimines derived from acetophenone derivatives by means of chiral phosphoric acid in 2009 (Scheme 3).

**Scheme 3. Benzothiazoline-Mediated Transfer Hydrogenation of C═N Bond**



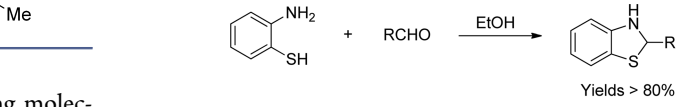
Subsequently, applications for the reduction of various types of molecules containing the C═N bond were developed. We discuss herein the transfer hydrogenation of the C═N bond by use of benzothiazoline as the hydrogen donor.[30]

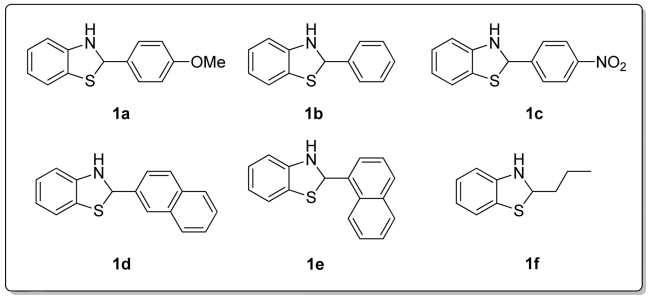
## 2. PERFORMANCE IN TRANSFER HYDROGENATION OF C═N BOND

### 2.1. Synthesis of Benzothiazolines

Benzothiazolines **1a**−**1f** were readily prepared in good yields by the condensation of 2-aminobenzenethiol with a variety of aldehydes in ethanol (Scheme 4). The ease of structural modification

**Scheme 4. Synthesis of Benzothiazolines**




at the 2-position is a beneficial advantage of benzothiazoline over Hantzsch ester because both benzothiazoline and phosphoric acid are tunable, thereby achieving high enantioselectivity. Although benzothiazoline has an *N*,*S*-acetal moiety and potentially undergoes autoxidation, it has reasonable stability that enables storage at 0 °C under an inert atmosphere for several months without appreciable decomposition.

### 2.2. Brønsted Acid Catalyzed Reductive Amination of Aldehydes

The reductive amination of aldehydes was initially tested to assess the reducing ability of benzothiazoline.[31] Optimization of the reaction conditions revealed that in the presence of benzothiazoline **1a**, 20 mol % TFA promoted the reductive amination of benzaldehyde with *p*-anisidine, furnishing the corresponding amine in 93% yield at room temperature. A range of aromatic aldehydes bearing either electron-rich or electron-deficient groups proved to be suitable substrates (Scheme 5, **2a**−**2f**). The aldimine derived from cinnamaldehyde exclusively underwent 1,2-reduction (**2g**). Heteroaryl aldehyde and aliphatic aldehyde also gave products in good chemical yields by prolonging the reaction time (**2h**, **2i**). The reaction was compatible with other anilines than *p*-anisidine (**2j**−**2l**).

Subsequently, a one-pot reduction process was developed, which relied on the formation of both benzothiazoline and imine *in situ*. The reaction was carried out with aldehyde, aniline, and 2-aminobenzenethiol. With 2-aminobenzenethiol as the precursor of the reducing agent, the reductive amination proceeded readily with a variety of aldehydes, giving the corresponding amines in good yields (Scheme 6).

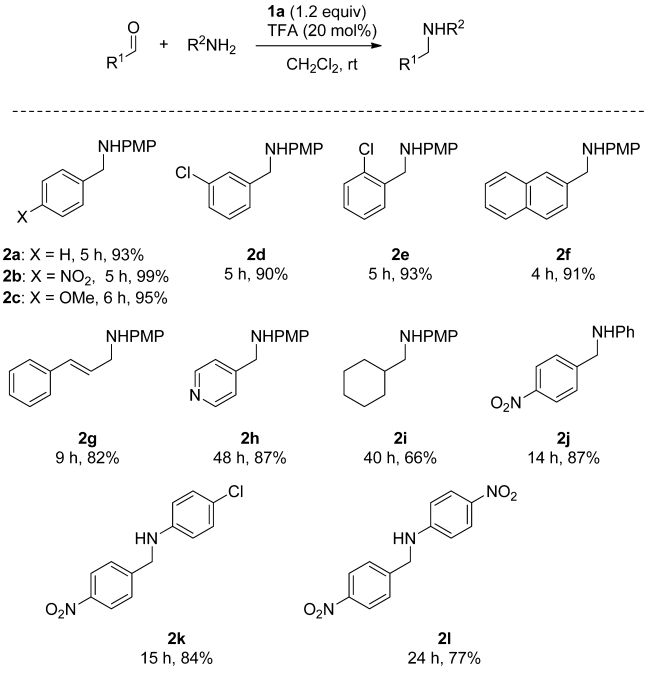
### 2.3. Asymmetric Transfer Hydrogenation of Ketimines

The asymmetric reduction of imine is a highly efficient approach for the preparation of amine in an optically pure form. We investigated the enantioselective transfer hydrogenation of ketimines by use of benzothiazoline as the hydrogen donor in combination with chiral phosphoric acids.[32−41] Phosphoric acid **3** (TRIP) exhibited the highest catalytic activity in the presence of benzothiazoline.[42] It is noted that TRIP (**3**) frequently provides the best stereocontrol in the benzothiazoline-mediated

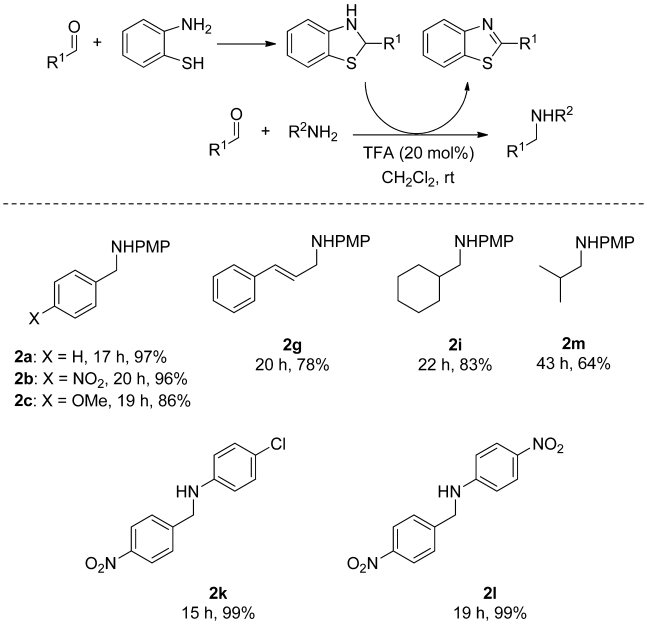


DOI: 10.1021/ar500414x
*Acc. Chem. Res.* 2015, 48, 388−398

**Scheme 5. Reductive Amination of Aldehydes**




**Scheme 6. One-Pot Reductive Amination with *in Situ* Generated Reducing Agents**

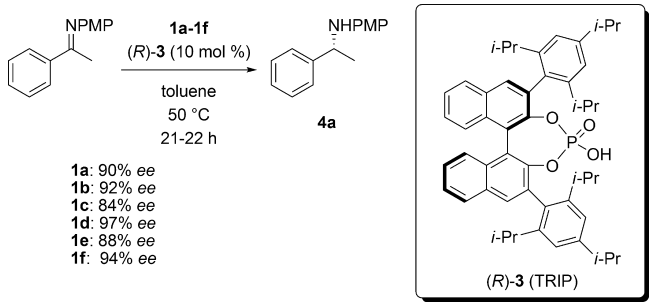



enantioselective transfer hydrogenation. The enantioselectivity can be further fine-tuned by modifying the 2-substituent of benzothiazoline. The enantioselectivities were variable with the use of different benzothiazolines **1a**–**f** (Scheme 7). Increasing the steric hindrance from phenyl (**1b**) to 2-naphthyl group (**1d**) improved the ee value to 97%.

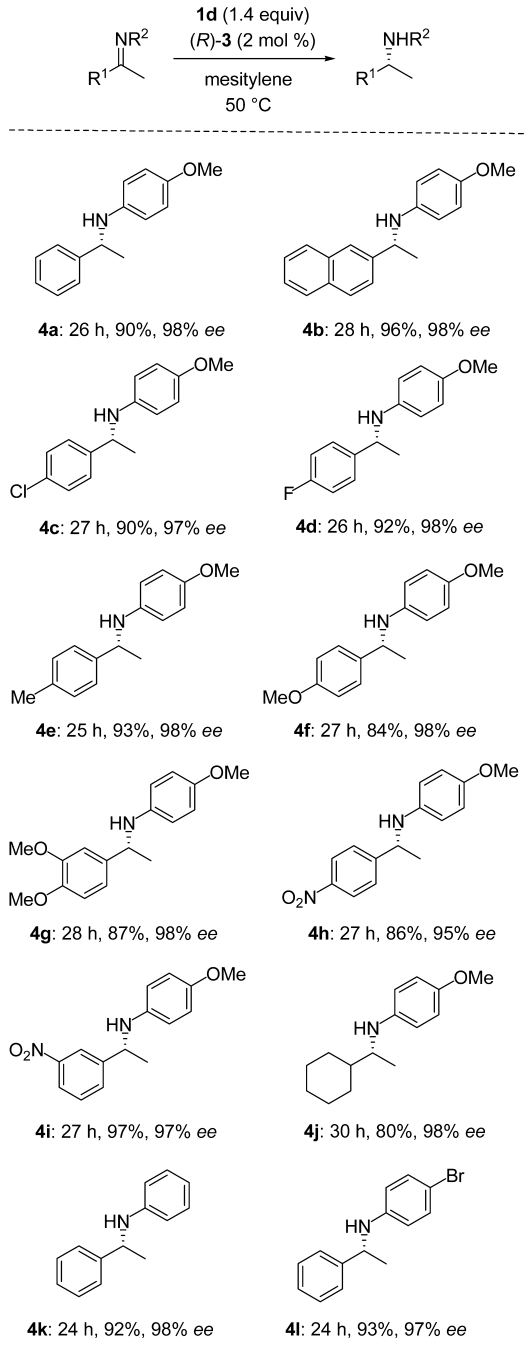
With benzothiazoline **1d** in hand, the substrate scope was defined. Excellent ee values (95–98% ee) as well as high chemical yields were obtained in all the cases examined (Scheme 8). Even the reduction of aliphatic ketimine proceeded smoothly without any loss of enantioselectivity (**4j**).

Benzothiazoline could be generated *in situ* in the transfer hydrogenation reaction. A three-component reaction involving

**Scheme 7. Improvement of Enantioselectivity by Modifying 2-Substituent of Benzothiazoline**




**Scheme 8. Asymmetric Transfer Hydrogenation of Ketimines**

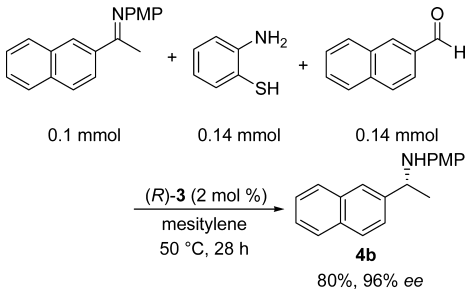





DOI: 10.1021/ar500414x
*Acc. Chem. Res.* 2015, 48, 388–398

ketimine, 2-naphthalenecarbaldehyde, and 2-aminobenzenethiol furnished corresponding amine **4b** in high yield with excellent enantioselectivity (Scheme 9).

**Scheme 9. Transfer Hydrogenation of Ketimine by Use of *in Situ* Generated Benzothiazoline**




## 2.4. Enantioselective Reductive Amination of Aliphatic Ketones

Ketimines derived from dialkyl ketones are, in general, unstable and difficult to isolate in pure form. Thus, the enantioselective reduction of ketimines, particularly those derived from aliphatic ketones, is nontrivial. In this regard, enantioselective reductive amination is an efficient approach to obviate the need for the isolation of dialkyl ketimines.

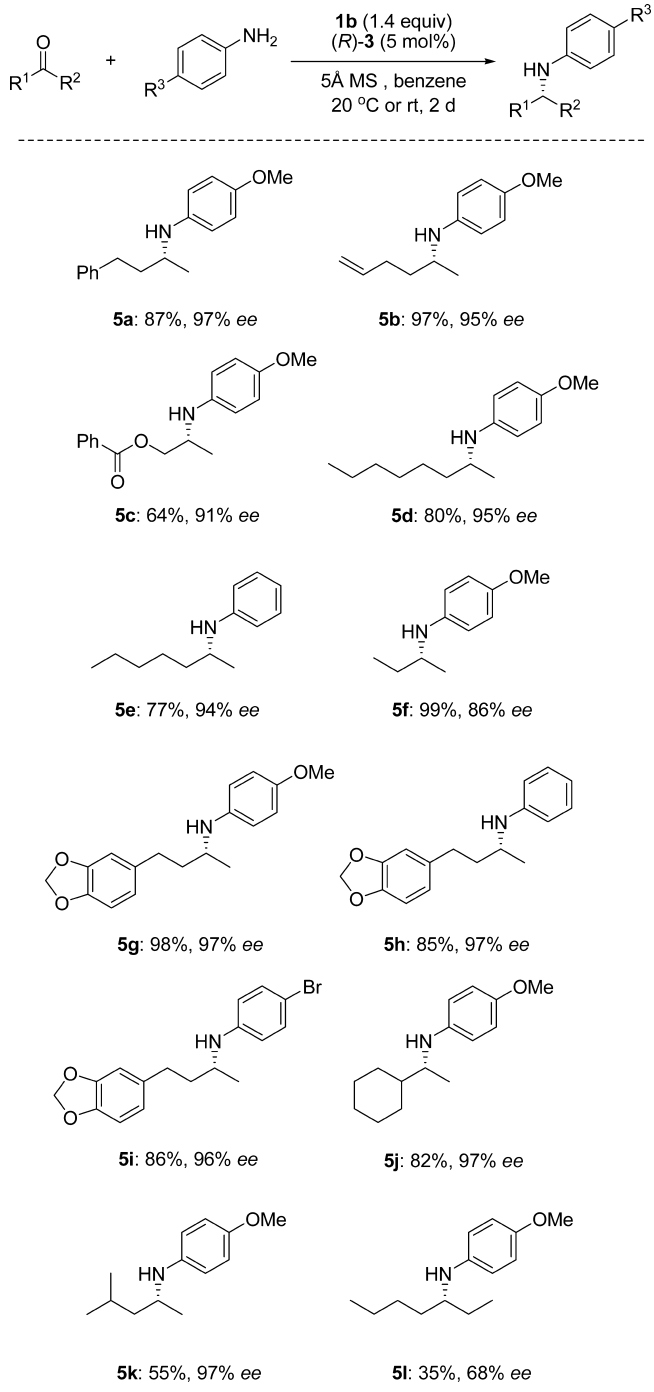
The reductive amination was carried out with benzylacetone, *p*-anisidine, and benzothiazoline **1b** in benzene in the presence of a catalytic amount of chiral phosphoric acid (5 mol %) and 5 Å MS at room temperature.[43] During the screening for phosphoric acid, TRIP (**3**) once again exhibited the highest catalytic activity, giving **5a** with 97% ee.[44] When this reaction was performed at 20 °C instead of rt, the enantioselectivity of **5a** was not affected but the yield was slightly improved from 76% to 87%. The applicability of the reactions to a range of aliphatic ketones and anilines was subsequently explored (Scheme 10). Methyl ketones bearing various substituents on the carbonyl group reacted smoothly to afford corresponding amines **5a–f** in good yields with excellent enantioselectivities. Both electron-rich and electron-deficient anilines were suitable substrates, giving amines **5g–i** in satisfactory yields. Sterically hindered methyl ketones also adapted well to the reaction conditions, and products **5j** and **5k** were obtained with 97% ee. In contrast, ethyl ketone gave corresponding amine **5l** in low yield with moderate enantioselectivity.

Recently, Enders and co-workers reported the asymmetric synthesis of *trans*-1,3-disubstituted tetrahydroisoquinolines via a reductive amination/aza-Michael addition sequence.[45] The performance of benzothiazoline **1g** in the reductive amination step catalyzed by TRIP (**3**) was superior to that of Hantzsch ester with respect to the enantioselectivity (Scheme 11).

## 2.5. Asymmetric Transfer Hydrogenation of Ketimines Derived from Propiophenones

Although the enantioselective reduction of ketimines derived from acetophenone derivatives by organocatalysis as well as metal catalysis has been extensively studied, the reduction of ketimines derived from propiophenone derivatives is under-investigated. We studied the enantioselective transfer hydrogenation of ketimine derived from propiophenone and found that the combination of 2-naphthylbenzothiazoline **1d** and TRIP (**3**) was the most efficient.[46] Corresponding amine **6a** was obtained in 85% yield with 98% ee. The reaction has a broad

**Scheme 10. Asymmetric Reductive Amination of Aliphatic Ketones**

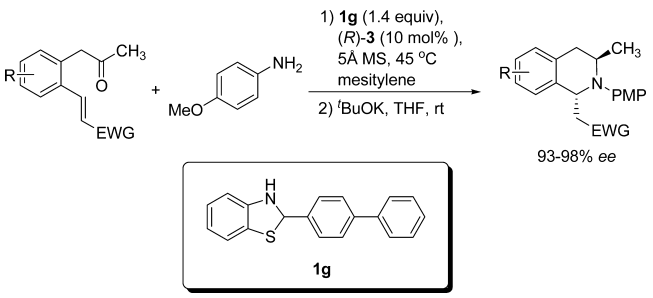



substrate scope (**6b–6p**): electron-rich and electron-deficient aryl and heteroaryl substrates, such as 2- and 3-thienyl, were compatible with the reaction conditions. The protocol was applied to a range of ketimines derived from propiophenones to afford the corresponding amines with high to excellent enantioselectivities (Scheme 12). In sharp contrast, the use of Hantzsch ester under identical conditions led to a significant deterioration of the enantioselectivities. This was the first time that the performance of benzothiazoline and Hantzsch ester in the asymmetric transfer hydrogenation of ketimines was systematically compared.

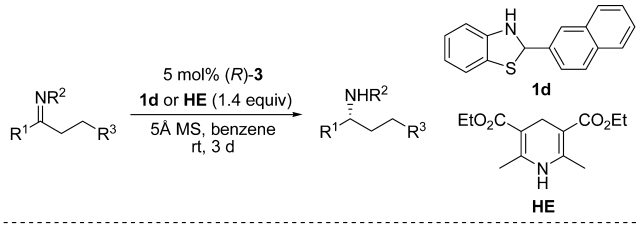


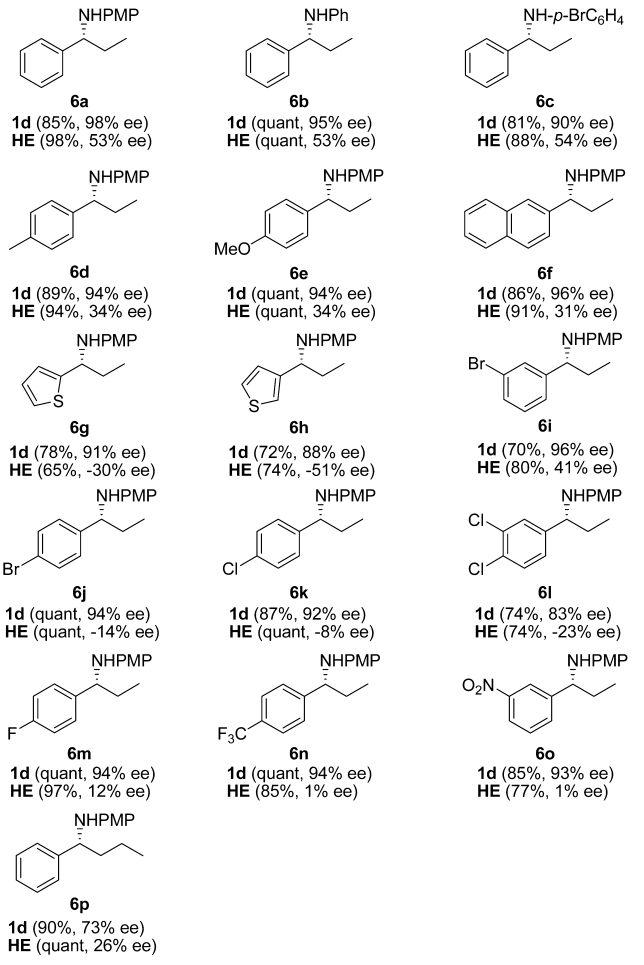
DOI: 10.1021/ar500414x
*Acc. Chem. Res.* 2015, 48, 388–398

**Scheme 11. Reductive Amination/Aza-Michael Addition Sequence**




**Scheme 12. Asymmetric Transfer Hydrogenation of Ketimines Derived from Propiophenones**



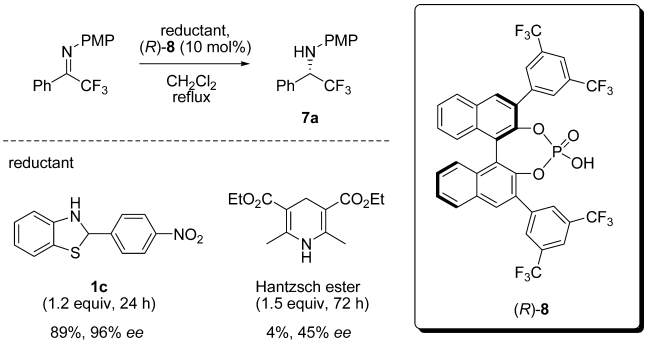




## 2.6. Asymmetric Transfer Hydrogenation of Trifluoromethyl and Difluoromethyl Ketimines

Fluorinated compounds have attracted much attention in academia and industry in the past decade. A general and efficient method for the preparation of fluorinated compounds, which was based on the transfer hydrogenation by use of benzothiazolines, was developed in order to meet the growing demand for new and structurally diverse trifluoromethylated and difluoromethylated amines for pharmaceutical and agrochemical purposes.[47]

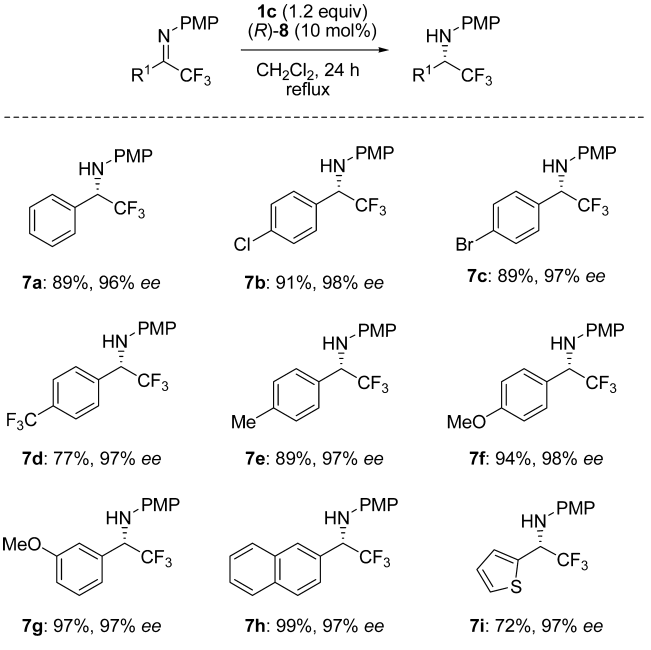
In the asymmetric transfer hydrogenation of trifluoromethyl ketimine, screening for chiral phosphoric acid catalysts and benzothiazolines revealed that catalyst **8** and the more electron-deficient 4-nitrophenyl benzothiazoline **1c** were the most effective to furnish corresponding trifluoromethylated amine **7a** in 89% yield with 96% ee (Scheme 13). In sharp contrast, use of Hantzsch ester as the reducing agent under identical reaction conditions gave a trace amount of **7a** (4% yield) with poor enantioselectivity (45% ee).

**Scheme 13. Distinct Differences in Reactivity between Two Reducing Agents**




Satisfactory outcomes of the transformation were achieved with a variety of trifluoromethyl ketimines. In the case of electron-rich/electron-deficient aryl and heteroaryl ketimines, products with 96−98% ee were furnished (Scheme 14).

**Scheme 14. Asymmetric Transfer Hydrogenation of Trifluoromethyl Ketimines**



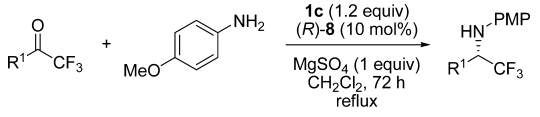

The asymmetric reductive amination of trifluoromethyl ketones was also successfully achieved. Subjection of a mixture of trifluoromethyl ketone and *p*-anisidine to the standard



DOI: 10.1021/ar500414x
*Acc. Chem. Res.* 2015, 48, 388−398

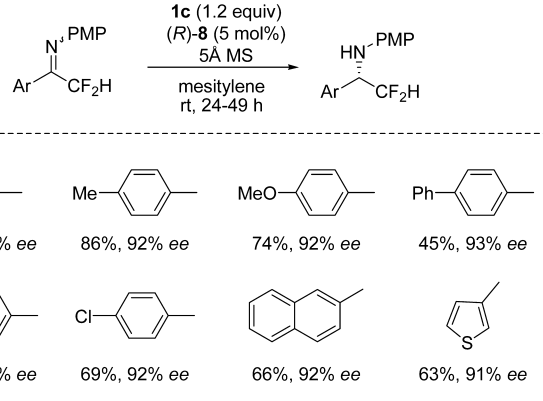
conditions in the presence of a dehydrating agent ($MgSO_4$) gave rise to the corresponding trifluoromethylated amines with 93−96% ee, which was similar to the case of preformed trifluoromethyl ketimines (Scheme 15).

**Scheme 15. Asymmetric Reductive Amination of Trifluoromethyl Ketones**




In addition to trifluoromethylated amines, difluoromethylated amines are also important scaffolds particularly in biologically active molecules. However, the asymmetric reduction of difluoromethyl ketimines had not been achieved with satisfactory enantioselectivity.[48,49] Under identical reaction conditions to the transfer hydrogenation of trifluoromethyl ketimines, difluoromethyl ketimines also proved to be suitable substrates.[50] In the presence of phosphoric acid **8** and benzothiazoline **1c**, both aryl- and heteroaryl-containing difluoromethyl ketimines underwent transfer hydrogenation to furnish difluoromethylated amines with high enantioselectivities (Scheme 16).

**Scheme 16. Asymmetric Transfer Hydrogenation of Difluoromethyl Ketimines**

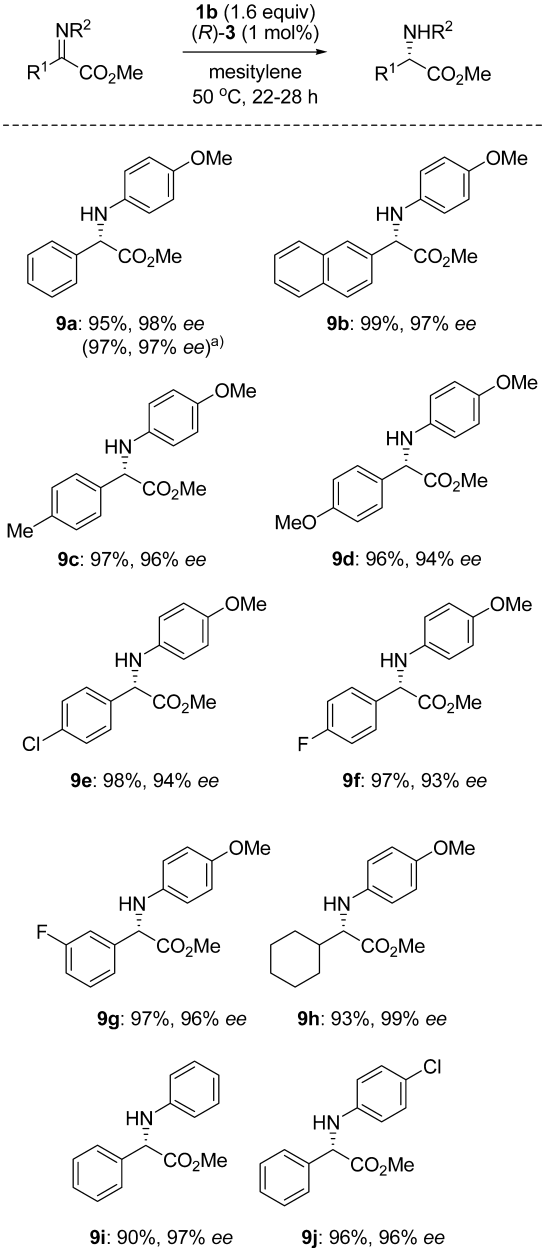



## 2.7. Asymmetric Transfer Hydrogenation of α-Imino Esters

α-Amino acids are widely found in natural products and biological systems and extensively utilized as building blocks in biochemistry and pharmaceutical chemistry. The reduction of α-imino esters is one of the most direct approaches to afford α-amino esters, the precursor of α-amino acids. Apart from the original efforts for the asymmetric reduction of α-imino esters by means of chiral phosphoric acid and Hantzsch ester by Antilla[51] and You,[52,53] comparable results from our group indicated that benzothiazoline was just as competent for the reduction of α-imino esters, yielding the corresponding α-amino esters with high enantiopurity.[54]

The experiments were carried out in the presence of TRIP (**3**) and benzothiazoline **1b**. The type of ester was crucial: whereas ethyl ester furnished a reduced product with 58% ee, methyl ester resulted in a product with 93% ee. Interestingly, the ee value was improved to 98% by decreasing catalyst loading from 10 to 1 mol %. Then, a series of α-imino esters bearing different functional groups were examined and found to produce corresponding α-amino esters **9** in excellent yields and enantioselectivities (Scheme 17). The reduction of an aliphatic imino ester also proceeded

**Scheme 17. Asymmetric Transfer Hydrogenation of α-Imino Esters**




[a]Result of reductive amination of α-keto ester shown in parenthesis.

smoothly without compromising the enantioselectivity (**9h**). Both *N*-phenyl- and *N*-4-chlorophenylimines proved to be suitable substrates (**9i,j**). Compound **9a** could also be successfully synthesized by the reductive amination of α-keto ester, furnishing **9a** in 97% yield with 97% ee.

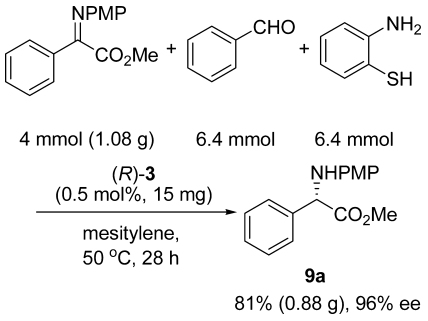
In order to demonstrate the synthetic utility of the method, benzothiazoline **1b** was generated *in situ* and used in the gram-scale reduction in the presence of 0.5 mol % TRIP **3**. The three-component reaction starting from 1.08 g of α-imino ester, benzaldehyde, and 2-aminobenzenethiol furnished the



DOI: 10.1021/ar500414x
Acc. Chem. Res. 2015, 48, 388−398

corresponding $\alpha$-amino ester **9a** without compromising yield and enantioselectivity (Scheme 18).

**Scheme 18. Gram-Scale Reduction by Use of *in Situ* Generated Benzothiazoline**




## 2.8. Readily Removable Hydrogen Source

The difficulty of separating the products from the pyridine derivative generated by the dehydrogenation is one of the disadvantages in the transfer hydrogenation by use of hydrogen donor. In order to resolve this issue, additional functional groups were introduced into benzothiazolines to modify their chemical or physical properties. Hydroxy-attached benzothiazolines **1h**−**1k** and carboxy-attached benzothiazoline **1l** were synthesized (Figure 1). It was found that **1h**−**1k** and the resulting

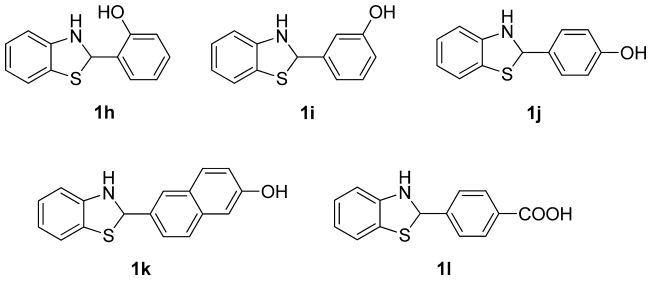
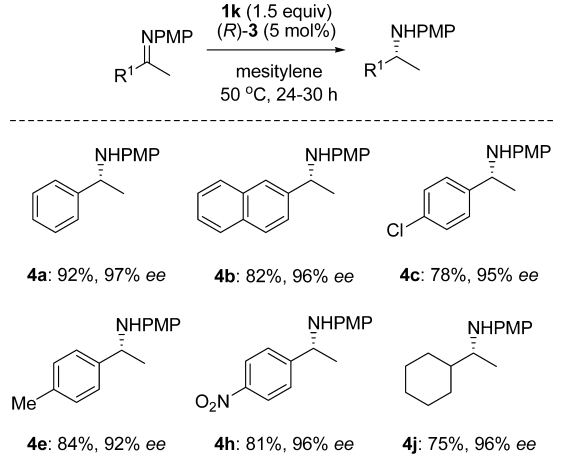



**Figure 1.** Readily removable benzothiazolines.

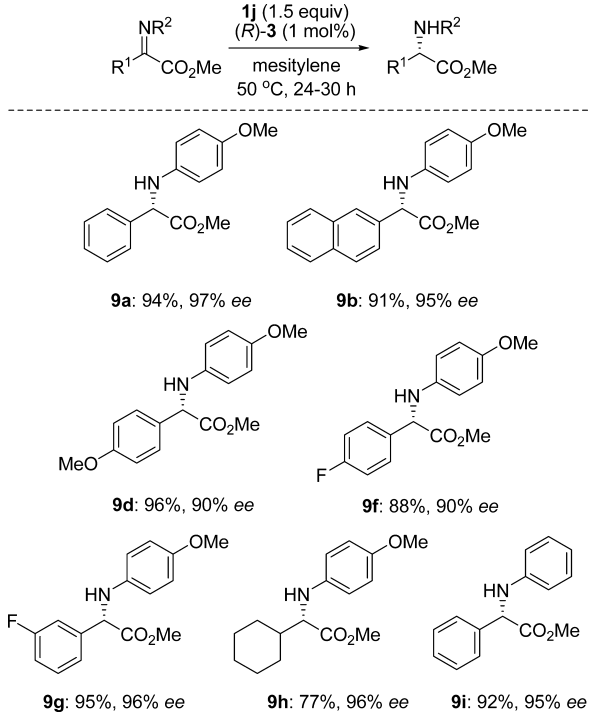
byproduct benzothiazoles were precipitated in organic solvents, whereas **1l** and its byproduct were readily eliminated by washing with aqueous basic solution. As a result, benzothiazoles along with excess benzothiazolines could be removed by simple treatment in a workup procedure.

The performance of benzothiazolines **1h**−**1l** in the asymmetric transfer hydrogenation of ketimines and $\alpha$-imino esters is demonstrated in Schemes 19 and 20, respectively. Benzothiazoline **1k** proved to be the most efficient reducing agent for the reduction of ketimines in the presence of TRIP (**3**) (Scheme 19).[55] All aryl and cyclohexyl ketimines gave rise to the corresponding amines in good yields with excellent enantioselectivities. Benzothiazoline **1j** exhibited the highest selectivity in the reduction of $\alpha$-imino esters (Scheme 20).[54] A range of $\alpha$-imino esters underwent transfer hydrogenation by the combined use of **1j** and TRIP (**3**) to furnish chiral $\alpha$-amino esters in a highly enantioselective manner regardless of the electronic features of the substrates. Notably, these results were comparable to those obtained by the use of non-hydroxy-attached benzothiazolines **1b** and **1d** (Schemes 8 and 17). The advantage of hydroxy-benzothiazolines is 3-fold: (1) the benzothiazole byproduct appears as a precipitate in the reaction and is readily removable by filtration, (2) further purification by chromatography is

**Scheme 19. Transfer Hydrogenation of Ketimines by Use of Hydroxy-benzothiazolines**




**Scheme 20. Transfer Hydrogenation of $\alpha$-Imino Esters by Use of Hydroxy-benzothiazolines**




facilitated due to the presence of a polar hydroxy group, and (3) application of the polymer-supported benzothiazoline is expected due to the facile modification of the hydroxy group.

Preliminary studies of carboxy-attached benzothiazoline **1l** demonstrated that **1l** also possessed good reducing ability and could efficiently accomplish the reduction of $\alpha$-imino esters and aldimines, as well as the reductive amination of aldehydes.[56] The introduction of the carboxy group significantly facilitated the removal of residual benzothiazoline and benzothiazole by simply washing with 10% aqueous NaOH solution. This eco-friendly approach reduced the volume of organic solvents used for the purification process and offered a convenient access to amines.

## 2.9. Enantioselective Transfer Deuteration of Ketimines

Because deuterated compounds are an important class of materials that are used in a number of scientific areas and occasionally

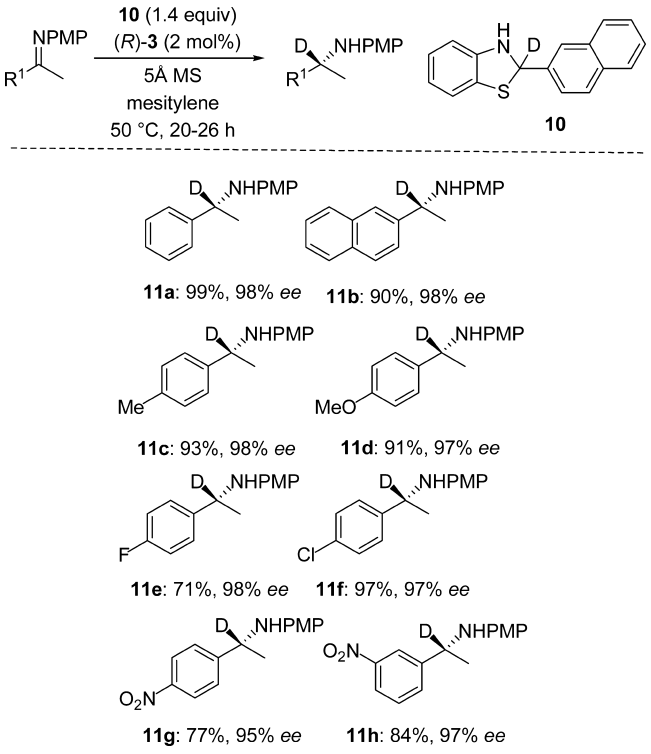


DOI: 10.1021/ar500414x
Acc. Chem. Res. 2015, 48, 388−398

exhibit better stability or bioavailability than their hydrogen analogues, the incorporation of deuterium into molecules is of great significance. Although many practical methods for the deuteration have been documented, asymmetric deuteration is underexplored.[57] Inspired by the accomplishments in the transfer hydrogenation with benzothiazoline as the reducing agent, we developed an efficient access to the optically active deuterated amines by use of deuterated benzothiazoline, which was readily accessible from $D_1$-aldehyde.[58]

Upon treatment of ketimines with 2-deuterio-2-(2-naphthyl)-benzothiazoline (**10**) in the presence of TRIP (**3**) in mesitylene at 50 °C, the transfer deuteration proceeded to give the corresponding $\alpha$-deuterated amines **11** with excellent enantioselectivities (95%−98% ee) regardless of the electronic characters of the different substituents (Scheme 21). Deuterium was incorporated

**Scheme 21. Asymmetric Deuteration of Ketimines by Use of 2-Deuteriobenzothiazoline**



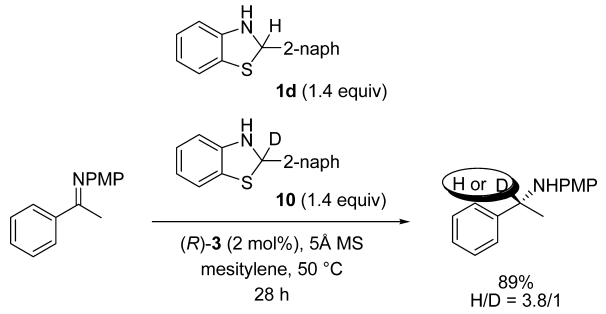

at the position $\alpha$ to nitrogen. The kinetic isotope effect ($k_H/k_D$ = 3.8) was observed in the competitive reaction between H- and D-benzothiazolines, which explicitly implies that the cleavage of the C−H (or C−D) bond is the rate-limiting step in this transfer hydrogenation reaction (Scheme 22).

The deuteride reduction was also successfully applied to $\alpha$-imino esters (Scheme 23). 2-Deuterio-2-phenylbenzothiazoline **12** proved to be the most efficient hydrogen donor. The electron-rich, electron-deficient, and heterocyclic substrates gave the corresponding $\alpha$-amino esters **13** with excellent enantioselectivities.

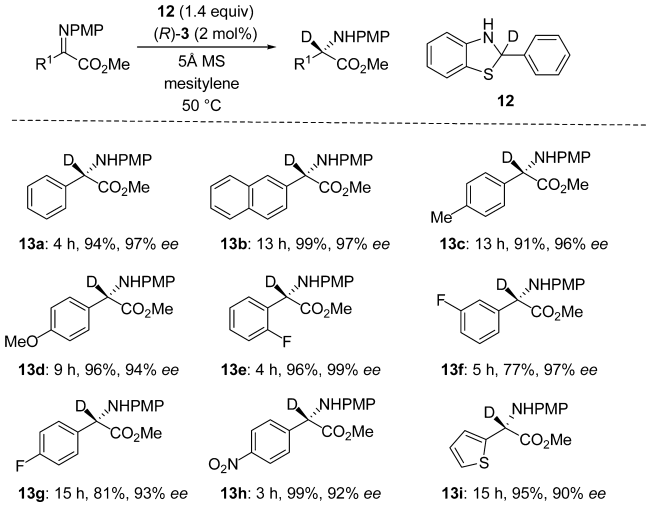
## 3. COMPUTATIONAL STUDY FOR MECHANISTIC ELUCIDATION

DFT studies of the chiral BINOL−phosphoric acid catalyzed asymmetric transfer hydrogenation of ketimine and $\alpha$-imino ester with benzothiazoline enabled the elucidation of the reaction mechanism, as well as the origin of the stereocontrol.[59] The chiral

**Scheme 22. Competition Experiments between H- and D-Benzothiazolines**




**Scheme 23. Asymmetric Deuteration of $\alpha$-Imino Esters by Use of D-Benzothiazoline**




BINOL−phosphoric acid activates ketimine and benzothiazoline by means of the Brønsted acidic site (proton) and the Brønsted basic site (phosphoryl oxygen), respectively, to accelerate hydride transfer. This reaction mechanism, which involves a two-point catalyst−substrate interaction, is very similar to that reported in the transfer hydrogenation of ketimines with Hantzsch ester.[60−62] In both cases, the bifunctionality of BINOL−phosphoric acid plays a significant role in the simultaneous activation of ketimines and the hydride source (Figure 2). The results of the deuteride reduction and the KIE experiment (Scheme 22) support the mechanism.

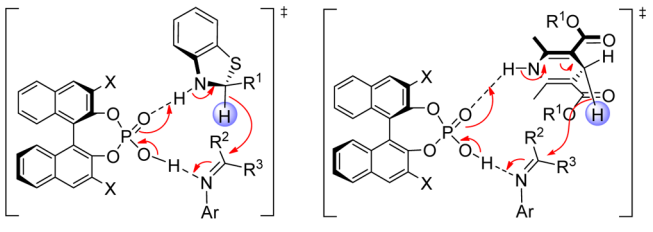



**Figure 2.** Reaction mechanism of the BINOL−phosphoric acid catalyzed transfer hydrogenation of ketimine with (a) benzothiazoline and (b) Hantzsch ester.

On the basis of the two-point catalyst−substrate interaction mechanism, there are eight possible transition states (TSs) corresponding to the enantiofacial selection (leading to major and



DOI: 10.1021/ar500414x
Acc. Chem. Res. 2015, 48, 388−398

minor enantiomers, favored TS and disfavored TS), two geometric conformations of the imino group (*anti* and *syn* conformations of ketimine), and two absolute configurations of benzothiazoline (*S* and *R*). In the relatively more stable diastereomeric TSs, *syn*-ketimine is preferred to *anti*-ketimine because of conformational matching with the compact chiral space constructed by the 3,3′-substituents of BINOL−phosphoric acid (Figure 3). The steric interactions with the sterically

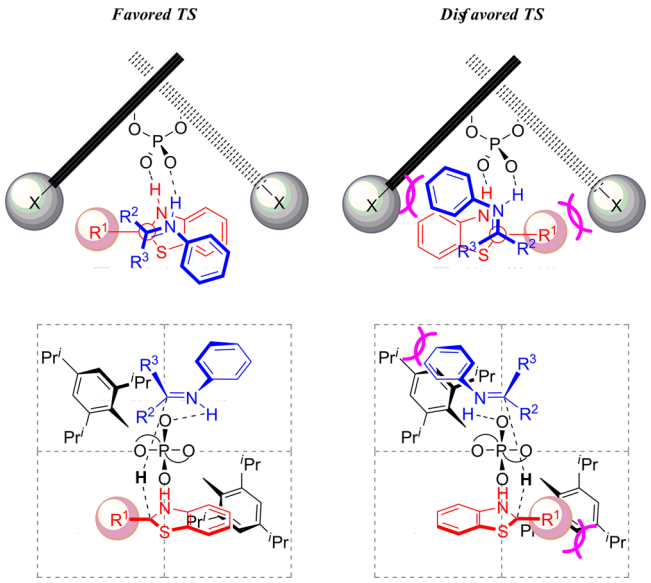



**Figure 3.** Diastereomeric transition states in the BINOL−phosphoric acid catalyzed transfer hydrogenation of ketimine.

demanding 2,4,6-$(i\text{-Pr})_3C_6H_2$ groups at the 3,3′-positions are responsible for the high stereocontrol. The *N*-aryl group of ketimine and the 2-substituent of benzothiazoline ($R^1$) are oriented toward the empty pocket of BINOL−phosphoric acid in the favored TS. In contrast, these substituents of the substrates are located close to the 2,4,6-$(i\text{-Pr})_3C_6H_2$ groups to induce large repulsive interactions in the disfavored TS. These computational results well account for the 2-substituent effect of benzothiazoline, in which the 2-naphthyl group exhibited higher enantioselectivity (97% ee) than the phenyl group (92% ee) as the 2-aryl substituent of benzothiazoline. Sterically fine-tuning the 2-aryl substituent of benzothiazoline increases the repulsive interaction with the 2,4,6-$(i\text{-Pr})_3C_6H_2$ groups in the disfavored TS to enhance the enantioselectivity. The steric effect of Hantzsch ester is approximately the same on each diastereomeric TS due to its $C_2$-symmetric structure. Such differences in steric effects between unsymmetrical benzothiazoline and $C_2$-symmetric Hantzsch ester result in the major advantage of benzothiazoline.

## 4. CONCLUSION

In this Account, we have summarized the achievements of benzothiazolines as the reducing agent in the chiral phosphoric acid catalyzed transfer hydrogenation of the C═N bond. Applications include (1) the reductive amination of aldehydes and the enantioselective reductive amination of aliphatic ketones, (2) the asymmetric reduction of ketimines and trifluoromethyl/difluoromethyl ketimines, as well as α-imino esters, and (3) the asymmetric transfer deuteration of ketimines. The remarkable advantages of benzothiazolines are also referred to easy synthesis and modification. Based on that, hydroxy- and carboxy-attached benzothiazolines were developed to simplify the purification process. Moreover, theoretical studies were conducted to elucidate the reaction mechanism, as well as the origin of the high enantioselectivity. Benzothiazolines are expected to have diverse applications in the future, particularly in the reduction of unsaturated functional groups other than the C═N bond and transition metal catalyzed reductions.[63,64]

## AUTHOR INFORMATION

### Corresponding Author

*E-mail: takahiko.akiyama@gakushuin.ac.jp.

### Author Contributions

The manuscript was written through contributions of all the authors. All the authors have given their approval for the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

### Biographies

**Chen Zhu** received his B.S. degree from Xiamen University in 2003 and his Ph.D. degree from Shanghai Institute of Organic Chemistry in 2008 under the supervision of Professor Guo-Qiang Lin. After doing postdoctoral research at Gakushuin University, Japan, with Professor Takahiko Akiyama, he moved to the University of Texas Southwestern Medical Center where he worked with Professor John R. Falck and Professor Chuo Chen. He was appointed professor at Soochow University, China, in December 2013. His current research interests include transition-metal-free transformations and their applications in the construction of natural products and biologically active compounds.

**Kodai Saito** received his Ph.D. degree from Tokyo Institute of Technology in 2010 under the supervision of Professor Nobuharu Iwasawa. After completing postdoctoral work with Professor Jun-ichi Yoshida at Kyoto University, he joined Professor Akiyama's group as a postdoctoral fellow in 2011. His current research interests include the development of organocatalyzed asymmetric transformation reactions.

**Masahiro Yamanaka** received his Ph.D. from the University of Tokyo under the supervision of Professor Eiichi Nakamura in 2001. Thereafter, he was appointed assistant professor at Tokyo Institute of Technology. He joined Rikkyo University as a lecturer in 2004 and was promoted to full professor in 2014. Research in his group is focused on the mechanistic understanding, rational design, and development of asymmetric catalysts.

**Takahiko Akiyama** received his Ph.D. degree from the University of Tokyo under the supervision of Professor Teruaki Mukaiyama in 1985. Thereafter, he joined Shionogi Research Laboratories, Shionogi Inc. as a research chemist. In 1988, he was appointed assistant professor at Ehime University. He joined Professor B. M. Trost's group at Stanford University in 1992 as a visiting scholar. He was appointed associate professor at Gakushuin University in 1994 and was promoted to full professor in 1997. Research in his group is focused on the development of novel reactions employing organocatalysts and metal catalysts.

## ACKNOWLEDGMENTS

T.A. acknowledges financial support in the form of a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Transformation by Organocatalysis" from MEXT, Japan, and a Grant-in-Aid for Scientific Research from JSPS. C.Z. acknowledges the support from Soochow University and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).



DOI: 10.1021/ar500414x
*Acc. Chem. Res.* 2015, 48, 388−398

## REFERENCES


(1) Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003**, *103*, 3029−3070.
(2) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. Selective Hydrogenation for Fine Chemicals: Recent Trends and New Developments. *Adv. Synth. Catal.* **2003**, *345*, 103−151.
(3) Tararov, V. I.; Börner, A. Approaching Highly Enantioselective Reductive Amination. *Synlett* **2005**, 203−211.
(4) Gladiali, S.; Alberico, E. Asymmetric Transfer Hydrogenation: Chiral Ligands and Applications. *Chem. Soc. Rev.* **2006**, *35*, 226−236.
(5) Nugent, T. C.; El-Shazly, M. Chiral Amine Synthesis - Recent Developments and Trends for Enamide Reduction, Reductive Amination, and Imine Reduction. *Adv. Synth. Catal.* **2010**, *352*, 753−819.
(6) Fleury-Brégeot, N.; Fuente, V.; Castillón, S.; Claver, C. Highlights of Transition Metal-Catalyzed Asymmetric Hydrogenation of Imines. *ChemCatChem* **2010**, *2*, 1346−1371.
(7) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. Transition Metal-Catalyzed Enantioselective Hydrogenation of Enamines and Imines. *Chem. Rev.* **2011**, *111*, 1713−1760.
(8) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. Asymmetric Hydrogenation of Heteroarenes and Arenes. *Chem. Rev.* **2012**, *112*, 2557−2590.
(9) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. Enantioselective Brønsted Acid Catalyzed Transfer Hydrogenation: Organocatalytic Reduction of Imines. *Org. Lett.* **2005**, *7*, 3781−3783.
(10) Hoffman, S.; Seayad, A. M.; List, B. A Powerful Brønsted Acid Catalyst for the Organocatalytic Asymmetric Transfer Hydrogenation of Imines. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424−7427.
(11) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. Enantioselective Organocatalytic Reductive Amination. *J. Am. Chem. Soc.* **2006**, *128*, 84−86.
(12) Yang, J. W.; Fonseca, M. T. H.; List, B. A Metal-Free Transfer Hydrogenation: Organocatalytic Conjugate Reduction of $\alpha,\beta$-Unsaturated Aldehydes. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660−6662.
(13) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. Enantioselective Organocatalytic Hydride Reduction. *J. Am. Chem. Soc.* **2005**, *127*, 32−33.
(14) Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. C. Enantioselective Organocatalytic Transfer Hydrogenation Reactions using Hantzsch Esters. *Acc. Chem. Res.* **2007**, *40*, 1327−1339.
(15) You, S.-L. Recent Developments in Asymmetric Transfer Hydrogenation with Hantzsch Esters: A Biomimetic Approach. *Chem.—Asian J.* **2007**, *2*, 820−827.
(16) Connon, S. J. Asymmetric Organocatalytic Reductions Mediated by Dihydropyridines. *Org. Biomol. Chem.* **2007**, *5*, 3407−3417.
(17) Rueping, M.; Sugiono, E.; Schoepke, F. R. Asymmetric Brønsted Acid Catalyzed Transfer Hydrogenations. *Synlett* **2010**, 852−865.
(18) Rueping, M.; Dufour, J.; Schoepke, F. R. Advances in Catalytic Metal-free Reductions: From Bio-inspired Concepts to Applications in the Organocatalytic Synthesis of Pharmaceuticals and Natural Products. *Green Chem.* **2011**, *13*, 1084−1105.
(19) de Vries, J. G.; Mršić, N. Organocatalytic Asymmetric Transfer Hydrogenation of Imines. *Catal. Sci. Technol.* **2011**, *1*, 727−735.
(20) Zheng, C.; You, S.-L. Transfer Hydrogenation with Hantzsch Esters and Related Organic Hydride Donors. *Chem. Soc. Rev.* **2012**, *41*, 2498−2518.
(21) Saito, K.; Shibata, Y.; Yamanaka, M.; Akiyama, T. Chiral Phosphoric Acid-Catalyzed Oxidative Kinetic Resolution of Indolines Based on Transfer Hydrogenation to Imines. *J. Am. Chem. Soc.* **2013**, *135*, 11740−11743.
(22) Saito, K.; Miyashita, H.; Akiyama, T. Asymmetric Transfer Hydrogenation of Ketimines by Indoline as Recyclable Hydrogen Donor. *Org. Lett.* **2014**, *16*, 5312−5315.
(23) Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. Dihydrophenanthridine: A New and Easily Regenerable NAD(P)H Model for Biomimetic Asymmetric Hydrogenation. *J. Am. Chem. Soc.* **2012**, *134*, 2442−2448.
(24) Lu, L.-Q.; Li, Y.; Junge, K.; Beller, M. Iron-Catalyzed Hydrogenation for the In Situ Regeneration of an NAD(P)H Model: Biomimetic Reduction of $\alpha$-Keto-/$\alpha$-Iminoesters. *Angew. Chem., Int. Ed.* **2013**, *52*, 8382−8386.
(25) Wang, S.-G.; Zhang, W.; You, S.-L. Construction of Spirotetrahydroquinolines via Intramolecular Dearomatization of Quinolines: Free of a Preinstalled Activation Group. *Org. Lett.* **2013**, *15*, 1488−1491.
(26) Wang, S.-G.; You, S.-L. Hydrogenative Dearomatization of Pyridine and an Asymmetric Aza-Friedel−Crafts Alkylation Sequence. *Angew. Chem., Int. Ed.* **2014**, *53*, 2194−2197.
(27) Wakchaure, V. N.; Nicoletti, M.; Ratjen, L.; List, B. Towards a Practical Brønsted Acid Catalyzed and Hantzsch Ester Mediated Asymmetric Reductive Amination of Ketones with Benzylamine. *Synlett* **2010**, 2708−2710.
(28) Chikashita, H.; Miyazaki, M.; Itoh, K. 2-Phenylbenzothiazoline as a Reducing Agent in the Conjugate Reduction of $\alpha,\beta$-Unsaturated Carbonyl Compounds. *Synthesis* **1984**, 308−310.
(29) Chikashita, H.; Miyazaki, M.; Itoh, K. Lewis Acid-promoted Conjugate Reduction of $\alpha,\beta$-Unsaturated Carbonyl Compounds by 2-Phenylbenzothiazoline (2-Phenyl-2,3-dihydrobenzothiazole). *J. Chem. Soc., Perkin Trans. 1* **1987**, 699−706.
(30) Zhu, C.; Falck, J. R. Benzothiazoline: The Surrogate of Hantzsch Ester. *ChemCatChem* **2011**, *3*, 1850−1851.
(31) Zhu, C.; Akiyama, T. Brønsted Acid Catalyzed Reductive Amination with Benzothiazoline as a Highly Efficient Hydrogen Donor. *Synlett* **2011**, 1251−1254.
(32) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich−type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568.
(33) Uraguchi, D.; Terada, M. Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357.
(34) Akiyama, T.; Itoh, J.; Fuchibe, K. Recent Progress in Chiral Brønsted Acid Catalysis. *Adv. Synth. Catal.* **2006**, *348*, 999−1010.
(35) Akiyama, T. Stronger Brønsted Acids. *Chem. Rev.* **2007**, *107*, 5744−5758.
(36) Terada, M. Binaphthol-derived Phosphoric Acid as a Versatile Catalyst for Enantioselective Carbon−carbon Bond Forming Reactions. *Chem. Commun.* **2008**, 4097−4112.
(37) Terada, M. Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Transformations. *Synthesis* **2010**, 1929−1982.
(38) Rueping, M.; Kuenkel, A.; Atodiresei, I. Chiral Brønsted Acids in Enantioselective Carbonyl Activations - Activation Modes and Applications. *Chem. Soc. Rev.* **2011**, *40*, 4539−4549.
(39) Yu, J.; Shi, F.; Gong, L.-Z. Brønsted-Acid-Catalyzed Asymmetric Multicomponent Reactions for the Facile Synthesis of Highly Enantioenriched Structurally Diverse Nitrogenous Heterocycles. *Acc. Chem. Res.* **2011**, *44*, 1156−1171.
(40) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047−9153.
(41) Zhu, C.; Akiyama, T. Benzothiazoline: Highly Efficient Reducing Agent for the Enantioselective Organocatalytic Transfer Hydrogenation of Ketimines. *Org. Lett.* **2009**, *11*, 4180−4183.
(42) Use of *N*-aryl ketimine is required. Ketimine derived from acetophenone and *N*-benzylamine did not undergo the transfer hydrogenation reaction by use of TRIP and 2-phenylbenzothiazoline.
(43) Saito, K.; Akiyama, T. Enantioselective Organocatalytic Reductive Amination of Aliphatic Ketones by Benzothiazoline as Hydrogen Donor. *Chem. Commun.* **2012**, *48*, 4573−4575.
(44) Use of Hantzsch ester resulted in the formation of the amine in 80% yield and 92% ee.
(45) Enders, D.; Liebich, J. X.; Raabe, G. Organocatalytic Asymmetric Synthesis of trans-1,3-Disubstituted Tetrahydroisoquinolines via a Reductive Amination/Aza-Michael Sequence. *Chem.—Eur. J.* **2010**, *16*, 9763−9766.



DOI: 10.1021/ar500414x
*Acc. Chem. Res.* 2015, 48, 388−398

(46) Saito, K.; Horiguchi, K.; Shibata, Y.; Yamanaka, M.; Akiyama, T. Chiral Phosphoric-Acid-Catalyzed Transfer Hydrogenation of Ethyl Ketimine Derivatives by Using Benzothiazoline. *Chem.—Eur. J.* **2014**, *20*, 7616−7620.
(47) Henseler, A.; Kato, M.; Mori, K.; Akiyama, T. Chiral Phosphoric Acid Catalyzed Transfer Hydrogenation: Facile Synthetic Access to Highly Optically Active Trifluoromethylated Amines. *Angew. Chem., Int. Ed.* **2011**, *50*, 8180−8183.
(48) Abe, H.; Amii, H.; Uneyama, K. Pd-Catalyzed Asymmetric Hydrogenation of α-Fluorinated Iminoesters in Fluorinated Alcohol: A New and Catalytic Enantioselective Synthesis of Fluoro α-Amino Acid Derivatives. *Org. Lett.* **2001**, *3*, 313−315.
(49) Chen, M.-W.; Duan, Y.; Chen, Q.-A.; Wang, D.-S.; Yu, C.-B.; Zhou, Y.-G. Enantioselective Pd-Catalyzed Hydrogenation of Fluorinated Imines: Facile Access to Chiral Fluorinated Amines. *Org. Lett.* **2010**, *12*, 5075−5077.
(50) Sakamoto, T.; Horiguchi, K.; Saito, K.; Mori, K.; Akiyama, T. Enantioselective Transfer Hydrogenation of Difluoromethyl Ketimines Using Benzothiazoline as a Hydrogen Donor in Combination with a Chiral Phosphoric Acid. *Asian J. Org. Chem.* **2013**, *2*, 943−946.
(51) Li, G.; Liang, Y.; Antilla, J. C. A Vaulted Biaryl Phosphoric Acid-Catalyzed Reduction of α-Imino Esters: The Highly Enantioselective Preparation of α-Amino Esters. *J. Am. Chem. Soc.* **2007**, *129*, 5830−5831.
(52) Kang, Q.; Zhao, Z.-A.; You, S.-L. Highly Enantioselective Transfer Hydrogenation of α-Imino Esters by a Phosphoric Acid. *Adv. Synth. Catal.* **2007**, *349*, 1657−1660.
(53) Kang, Q.; Zhao, Z.-A.; You, S.-L. Asymmetric Transfer Hydrogenation of β,γ-Alkynyl α-Imino Esters by a Brønsted Acid. *Org. Lett.* **2008**, *10*, 2031−2034.
(54) Zhu, C.; Akiyama, T. Enantioselective Organocatalytic Transfer Hydrogenation of α-Imino Esters by Utilization of Benzothiazoline as Highly Efficient Reducing Agent. *Adv. Synth. Catal.* **2010**, *352*, 1846−1850.
(55) Zhu, C.; Akiyama, T. Unpublished results.
(56) Zhu, C.; Akiyama, T. Transfer Hydrogenation of Imines with Carboxyl-tailed Benzothiazoline as Readily Removable Hydrogen Donor. *Tetrahedron Lett.* **2012**, *53*, 416−418.
(57) Miyazaki, D.; Nomura, K.; Yamashita, T.; Iwakura, I.; Ikeno, T.; Yamada, T. Enantioselective Borodeuteride Reduction of Aldimines Catalyzed by Cobalt Complexes: Preparation of Optically Active Deuterated Primary Amines. *Org. Lett.* **2003**, *5*, 3555−3558.
(58) Sakamoto, T.; Mori, K.; Akiyama, T. Chiral Phosphoric Acid Catalyzed Enantioselective Transfer Deuteration of Ketimines by Use of Benzothiazoline As a Deuterium Donor: Synthesis of Optically Active Deuterated Amines. *Org. Lett.* **2012**, *14*, 3312−3315.
(59) Shibata, Y.; Yamanaka, M. DFT Study of the Mechanism and Origin of Enantioselectivity in Chiral BINOL-Phosphoric Acid Catalyzed Transfer Hydrogenation of Ketimine and α-Imino Ester Using Benzothiazoline. *J. Org. Chem.* **2013**, *78*, 3731−3736.
(60) Simon, L.; Goodman, J. M. Theoretical Study of the Mechanism of Hantzsch Ester Hydrogenation of Imines Catalyzed by Chiral BINOL-Phosphoric Acids. *J. Am. Chem. Soc.* **2008**, *130*, 8741−8747.
(61) Marcelli, T.; Hammar, P.; Himo, F. Phosphoric Acid Catalyzed Enantioselective Transfer Hydrogenation of Imines: A Density Functional Theory Study of Reaction Mechanism and the Origins of Enantioselectivity. *Chem.—Eur. J.* **2008**, *14*, 8562−8571.
(62) Marcelli, T.; Hammar, P.; Himo, F. Origin of Enantioselectivity in the Organocatalytic Reductive Amination of α-Branched Aldehydes. *Adv. Synth. Catal.* **2009**, *351*, 525−529.
(63) Zhou, J.-Q.; Sheng, W.-J.; Jia, J.-H.; Ye, Q.; Gao, J.-R.; Jia, Y.-X. Chiral Phosphoric Acid Catalyzed Asymmetric Hydrogenolysis of Racemic 3-Aryl-3-hydroxyisoindolin-1-ones. *Tetrahedron Lett.* **2013**, *54*, 3082−3084.
(64) Wang, Z.; Ai, F.; Wang, Z.; Zhao, W.; Zhu, G.; Lin, Z.; Sun, J. Organocatalytic Asymmetric Synthesis of 1,1-Diarylethanes by Transfer Hydrogenation. *J. Am. Chem. Soc.* **2015**, *137*, 383−389.


DOI: 10.1021/ar500414x
*Acc. Chem. Res.* 2015, 48, 388−398