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Chiral Phosphoric-Acid-Catalyzed Transfer Hydrogenation of Ethyl Ketimine Derivatives by Using Benzothiazoline

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Abstract: Chiral phosphoric acid catalyzed transfer hydrogenation of ketimines derived from propiophenone derivatives and reductive amination of alkyl ethyl ketone derivatives were extensively examined in the presence of two representative hydrogen donors. The excellent enantioselective transfer hydrogenation was achieved by use of benzothiazoline as a hydrogen donor. The theoretical studies elucidated that the unsymmetrical structure of benzothiazoline plays an important role in high enantioselective hydrogenation.

The asymmetric hydrogenation of ketimines is an efficient method for the synthesis of chiral amines.[1] In this reaction, molecular hydrogen is normally used as the reducing agent in combination with chiral transition-metal catalysts.[2] A biomimetic asymmetric hydrogen-transfer approach employing nicotinamide adenine dinucleotide (NADH) mimics was recently developed and extensively studied by many researchers.[3] The groups of Rueping, List, and MacMillan independently reported the transfer hydrogenation of ketimines by using Hantzsch ester as the hydrogen donor and chiral phosphoric acid for the first time.[4] Hantzsch ester was recognized to be the most reliable hydrogen donor, and a range of transfer hydrogenation reactions, which use chiral phosphoric acid, has been developed.[5]

In 2009, we demonstrated that benzothiazoline is an efficient hydrogen donor in the chiral phosphoric-acid-catalyzed transfer hydrogenation of ketimines.[6a] The advantages of benzothiazoline lie in the ease of tuning both reactivity and enantioselectivity by altering the substituent at the second position of the molecule. The substituent effect of benzothiazoline was confirmed in many examples of the transfer hydrogenation of C=N bonds catalyzed by chiral phosphoric acid.[6b–j] Although we have recently reported that there are some differences in reactivity and enantioselectivity in transfer hydrogenation of trifluoromethylated ketimines by using those two hydrogen donors, the mechanistic insights and stereochemical outcome were not discussed.[6c,j] Hantzsch ester and benzothiazoline have large structural differences (Figure 1). In benzothiazoline,

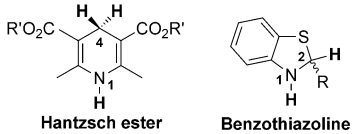

Figure 1. Representative hydrogen donors for transfer hydrogenation catalyzed by a Brønsted acid.

the hydrogen atom located at the sterically hindered C(2) position transfers to the substrate, whereas in Hantzsch ester having a symmetric and planar structure, the transferable hydrogen atom is located at the sterically less hindered C(4) position. The steric difference between the two hydrogen donors would be a vital factor affecting the enantioselectivity.[7]

Although the asymmetric transfer hydrogenation of ketimines was extensively investigated, the substrate scope was limited to mostly acetophenone derivatives, and there are few intensive studies on the generality and limitations of ketimines derived from propiophenone and other aromatic ketones containing long alkyl chains.[8] Herein, we report the chiral phosphoric acid catalyzed transfer hydrogenation of ketimine derivatives obtained from ethyl ketones by using the representative hydrogen donors. Interestingly, benzothiazoline exhibited excellent enantioselectivity in comparison with Hantzsch ester. We also conducted a theoretical study and elucidated the difference in enantiocontrol efficiency between those two hydrogen donors.

First, we focused on the applicability of benzothiazoline to the asymmetric transfer hydrogenation of non-methyl aromatic ketimine. An initial attempt of the transfer hydrogenation was carried out with ketimine **1a** prepared from propiophenone and *p*-anisidine by means of chiral phosphoric acid containing 2,4,6-triisopropylphenyl group (*R*)-**2** in benzene in the presence of benzothiazoline **3** at room temperature (Table 1).[9] Examination of the effect of the substituent at second position of benzothiazoline **3** revealed that **3b** containing a 2-naphthyl group resulted in the highest enantiomeric excess (*ee*; 85, 98% *ee*, Table 1, entry 3).

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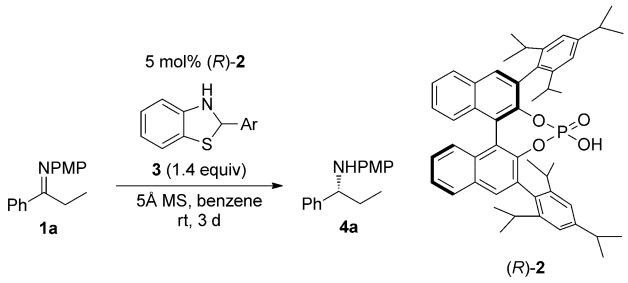
Table 1. Optimization of reaction conditions.[a]

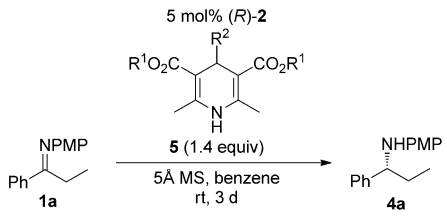


Entry	Benzothiazoline	Ar	Yield [%][b]	*ee* [%][c]
1	**3a**	Ph	90	85
2[d]	**3a**	Ph	36	90
3	**3b**	2-naphthyl	85	98
4	**3c**	PMP	94	89
5	**3d**	4-HOC_6H_4	quant.	70
6	**3e**	4-$NO_2C_6H_4$	78	72
7	**3f**	4-$CF_3C_6H_4$	70	84

[a] Reaction conditions: ethyl ketimine **1a** (0.10 mmol), benzothiazoline **3** (0.14 mmol), (*R*)-**2** (5 mol%), and benzene (2 mL) in the presence of 5 Å MS (100 mg) at room temperature. [b] Unless otherwise noted, the yield is that of isolated product **4a** after preparative TLC. [c] Determined by HPLC on a chiral stationary phase. [d] Without 5 Å MS. PMP = *p*-methoxyphenyl.

Next, we investigated the transfer hydrogenation of ketimine **1a** by using (*R*)-**2** and Hantzsch ester **5** as the hydrogen donor after the examination of the effect of the phosphoric-acid catalysts.[10] Ethyl ester **5a** gave amine **4a** quantitatively with 53% *ee* (Table 2, entry 1). Changing the ester substituent did not improve *ee* (Table 2, entries 2 and 3). Introducing a substituent at fourth position of Hantzsch ester dramatically decreased the reactivity (Table 2, entries 4 and 5). It was found that tuning the fourth substituent of Hantzsch ester did not have a beneficial effect on the reactivity and enantioselectivity, in contrast to the case of benzothiazoline.[11]

Table 2. Asymmetric transfer hydrogenation by using Hantzsch ester.[a]



Entry	Hantzsch ester	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	**5a**	Et	H	quant.	53
2	**5b**	*i*Pr	H	quant.	52
3	**5c**	*t*Bu	H	quant.	37
4	**5d**	Et	Ph	67	51
5	**5e**	Et	2-naphthyl	0	–

[a] Reaction conditions: ethyl ketimine **1a** (0.10 mmol), Hantzsch ester **5** (0.14 mmol), (*R*)-**2** (5 mol%), and benzene (2 mL) in the presence of 5 Å MS (100 mg) at room temperature. [b] Unless otherwise noted, the yield is that of isolated product **4a** after preparative TLC. [c] Determined by HPLC on a chiral stationary phase.

To elucidate the difference between benzothiazoline and Hantzsch ester in terms of stereocontrol efficiency, as well as reaction mechanism, DFT calculations were carried out (computational details are provided in the Supporting Information). On the basis of Goodman's[12] and our previous computational studies,[13] we investigated the dicoordinated cyclic transition state (TS),[14] in which the Brønsted acidic proton and the basic phosphoryl oxygen activate the ketimine and the hydride donor (e.g., Hantzsch ester or benzothiazoline), respectively. After exploring the possible transition structures for Hantzsch ester and benzothiazoline (see the Supporting Information), the most stable diastereomeric **TSα** (affording the major enantiomer) and **TSβ** (affording the minor enantiomer) for each hydride donor (**TS-1**: benzothiazoline **3a**, **TS-2**: Hantzsch ester **5c**) were compared (Figure 2). In **TS-1** for the benzothiazoline-mediated hydrogenation, **3a** showed a significant substituent effect, which induced the energetic differentiation between **TSα** and **TSβ**. The chiral space constructed by the 3,3′-2,4,6-

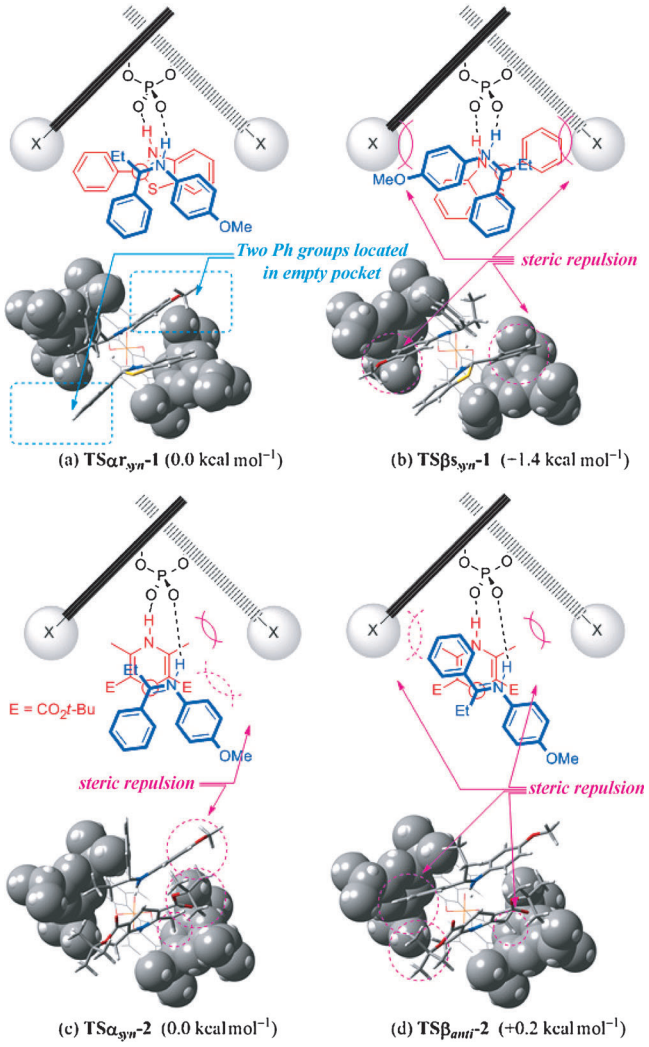
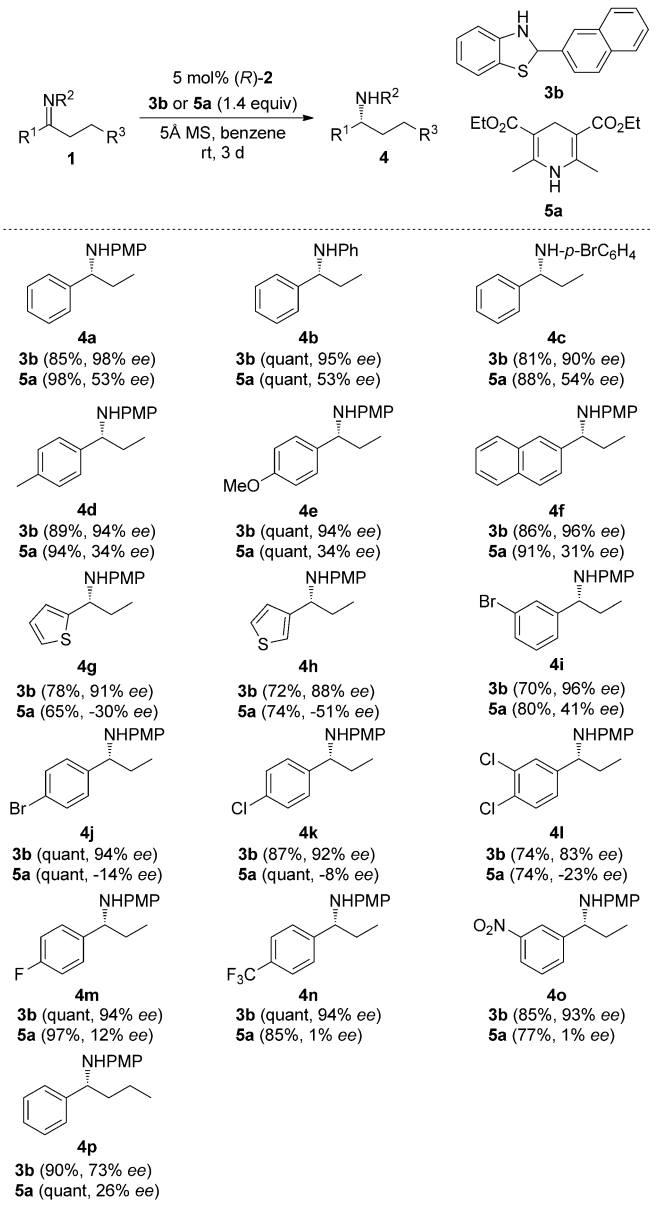


Figure 2. 3D structures and schematic representation models for benzothiazoline hydrogenation (**TS-1**); a) **TSαr$_{syn}$-1**; b) **TSβs$_{syn}$-1**; and Hantzsch ester hydrogenation (**TS-2**); c) **TSα$_{syn}$-2**; d) **TSβ$_{anti}$-2** (3,3′-substituents of 1,1′-Bi-2-naphthol (BINOL)–phosphoric acid, ball model; substrates, tube model).

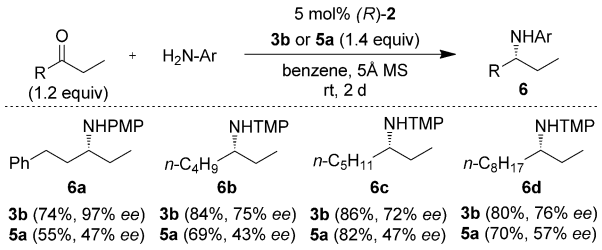
(iPr)$_3$C$_6$H$_2$ groups of (*R*)-**2** is sufficient for the orientation of the 2-aryl and the N-aryl substituents of the substrates in **TSαr$_{syn}$-1** as the most stable TS (Figure 2a). In contrast, these aryl substituents of the substrates would induce a repulsive interaction with the 3,3′-2,4,6-(iPr)$_3$C$_6$H$_2$ groups to destabilize **TSβs$_{syn}$-1** and achieve high enantioselectivity (purple curves in Figure 2b). On the other hand, the substituent effect of Hantzsch ester was found to be inefficient for differentiating the diastereomeric TSs. In both **TSα$_{syn}$-2** and **TSβ$_{anti}$-2**, the 2-methyl group of **5c** is located in proximity to the 3,3′-2,4,6-(iPr)$_3$C$_6$H$_2$ group to induce unfavorable steric interaction (purple curves in Figure 2c and d). The repulsive interactions caused by the ester substituent (e.g., *t*Bu group) of **5c** and the 3,3′-substituent of (*R*)-**2** for the PMP group and the phenyl group of ketimine **1a** in **TSα$_{syn}$-2** and **TSβ$_{anti}$-2**, respectively, also affect the stability of the diastereomeric TSs (dotted purple curves in Figure 2c and d). The small energy differences between **TSα$_{syn}$-2** and **TSβ$_{anti}$-2** would be attributed to these steric repulsions. These computational results are consistent with the experimental results. The unsymmetrical structure of benzothiazoline induces a matched or mismatched pair of substrate orientations to maximize the difference in terms of steric interaction in the diastereomeric TSs in **TS-1**. In contrast, the steric effect generated by C_2-symmetrical Hantzsch ester would be approximately the same on each diastereomeric TS in **TS-2**. These differences in the steric effect caused by the structural properties of the hydride donors are the reason for the major advantage of benzothiazoline over Hantzsch ester.

To confirm this proof of principle, we set out to investigate the transfer hydrogenation of a range of ethyl ketimines **1b–p** and compared the enantioselectivity between benzothiazoline **3b** and Hantzsch ester **5a** (Scheme 1). Although ketimines having a phenyl group and an electron-withdrawing group substituted aromatic ring on the nitrogen atom could be employed as substrates to give corresponding amines **4b** and **c** in high yields with excellent enantioselectivities by using benzothiazoline **3b**, the use of Hantzsch ester in the same reaction deteriorated the enantioselectivities. Next, we examined the substituent effect on an aryl group connected to an imine carbon. Although excellent enantioselectivities were realized by using benzothiazoline in all cases, the use of Hantzsch ester resulted in much lower enantioselectivities. In particular, when substrates **1j–o** containing an electron-withdrawing group were employed for this reaction, a remarkable difference in enantioselectivity was observed. Ketimine **1p** derived from butyrophenone could also be hydrogenated with better enantioselectivity by using benzothiazoline (90%, 73% *ee*) rather than Hantzsch ester.

Then, we examined the reductive amination of alkyl ethyl ketones (Scheme 2). After optimization of the reaction conditions with slight modification of the transfer hydrogenation of aromatic ketimines (see the Supporting Information), we investigated the scope of aliphatic ketones. Although the use of ethyl ketone containing a phenethyl moiety gave a product with excellent *ee* values, which was similar to the *ee* obtained when an aromatic ketimine was used as substrate, and benzothiazoline was used as the hydrogen donor, the Hantzsch ester-mediated hydrogenation resulted in much lower enantioselectivity. A similar tendency was observed in the reaction of other alkyl ethyl ketones with 3,4,5-trimethoxyaniline.



Scheme 1. Substrate scope for chiral phosphoric-acid-catalyzed transfer hydrogenation of aromatic ketimines.



Scheme 2. Substrate scope for chiral phosphoric-acid-catalyzed reductive amination of aliphatic ethyl ketones. TMP = 3,4,5-trimethoxyphenyl.

In conclusion, we have demonstrated a chiral phosphoric-acid-catalyzed asymmetric transfer hydrogenation of ketimines derived from ethyl ketone derivatives. The products obtained using benzothiazoline and Hantzsch ester exhibited remarkable differences in enantioselectivity. A highly enantioselective transfer hydrogenation was efficiently achieved by the use of benzothiazoline as the hydrogen donor. We could rationalize the difference in enantioselectivity by conducting a theoretical study by using DFT calculations. Further investigations of the mechanism and applications to the synthesis of more complex molecules are underway.

Experimental Section

Typical procedure for the transfer hydrogenation of ketimines

A magnetic stirrer and powdered molecular sieves 5 A (5 Å MS; 100 mg) were placed in a test tube under nitrogen atmosphere. The 5 Å MS were dried with a heat gun under reduced pressure, and the test tube was refilled with nitrogen. Ketimine **1a** (23.9 mg, 0.10 mmol), phosphoric acid (*R*)-**1** (3.8 mg, 5.0 μmol), and benzothiazoline **3b** (34.5 mg, 0.14 mmol) were added to the test tube successively under nitrogen atmosphere at RT. Then benzene (2 mL) was added. After being stirred for three days at RT, the mixture was filtered through Celite pad and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and the residue was purified by preparative thin-layer chromatography on silica gel (CH_2Cl_2/hexanes 1:3) to give 20.5 mg (0.085 mmol, 85%) of **4a** as a pale yellow oil. The *ee* of **4a** was determined by HPLC on a chiral stationary phase (Daicel CHIRALCEL OD-H, 98% *ee*).

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Keywords: hydrogen donor · hydrogenation · organocatalysis · reductive amination · theoretical studies

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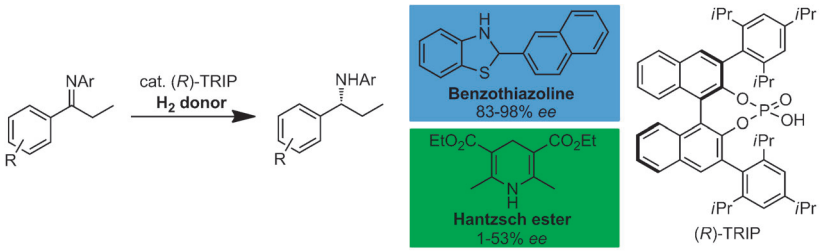
Chiral Phosphoric-Acid-Catalyzed Transfer Hydrogenation of Ethyl Ketimine Derivatives by Using Benzothiazoline



Asymmetric transfer hydrogenation of aromatic and aliphatic ketimines derived from ethyl ketone derivatives was examined by the combined use of a chiral phosphoric-acid catalyst and a hydrogen donor. The hydrogen donor had a remarkable effect on the enantioselectivity: excellent enantioselectivity was achieved when benzothiazoline was used as the hydrogen donor (see scheme, TRIP=3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diylhydrogenphosphate).