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Enantioselective Organocatalytic Transfer Hydrogenation of α-Imino Esters by Utilization of Benzothiazoline as Highly Efficient Reducing Agent

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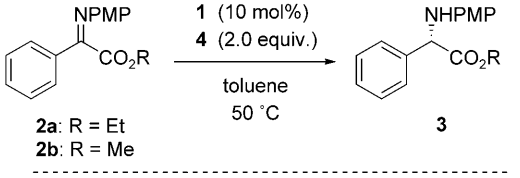
Abstract: Benzothiazoline was employed as an efficient and versatile reducing agent for the chiral phosphoric acid-catalyzed transfer hydrogenation of α-imino esters. The corresponding α-amino esters were furnished with excellent enantioselectivities. Novel and readily removable benzothiazolines bearing a hydroxy group were also investigated.

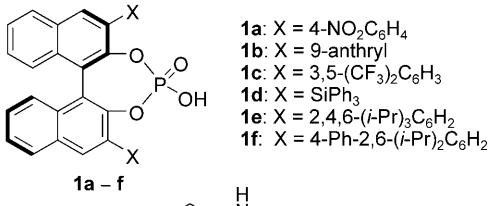
Keywords: amino esters; benzothiazolines; imino esters; organocatalysis; transfer hydrogenation

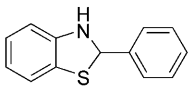
α-Amino acids are found widely in natural products and biological systems. They are broadly utilized in biochemistry and pharmaceutical chemistry because of their intriguing biological activities.[1] The synthesis of α-amino acids and their derivatives in the optically pure form has attracted much attention in the last decade.[2] The reduction of α-imino esters is one of the most direct approaches to afford the α-amino esters. In addition to the transition metal-catalyzed method reported by Zhang,[3] Antilla and You independently reported the asymmetric reduction of α-imino esters by means of a chiral Brønsted acid catalyst[4] and Hantzsch esters,[5] which are the most well-used cofactors in biochemical hydrogenation reactions. Although Hantzsch esters have been extensively employed as a hydrogen source, in asymmetric organocatalyzed reactions lately,[6,7] the development of novel hydrogen sources has been expected. We have recently reported that benzothiazoline[8] functioned as a novel reducing agent in the asymmetric transfer hydrogenation of ketimines,[9] giving rise to the corresponding amines with excellent enantioselectivities. As a result of our continuing efforts towards the development of chiral Brønsted acid-catalyzed reactions,[10,11,12] we wish to report herein the phosphoric acid-catalyzed asymmetric transfer hydrogenation of α-imino esters using benzothiazoline as the reducing agent.

Preliminary experiments were carried out with the combination of ethyl imino ester **2a** and benzothiazoline **4** (Table 1). We examined the effects of a variety

Table 1. Enantioselective transfer hydrogenation of α-imino ester mediated by benzothiazoline.







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Entry	2	Catalyst	Time [h]	Yield [%][a]	*ee* [%][c]
1	**2a**	**1a**	21	60	0
2	**2a**	**1b**	24	86	−10
3	**2a**	**1c**	21	83	48
4	**2a**	**1d**	24	57	34
5	**2a**	**1e**	20	99	58
6	**2a**	**1f**	20	99	44
7	**2b**	**1e**	24	99 (92)[b]	93

[a] Determined by ^{1}H NMR.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

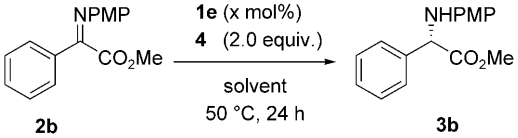
of chiral phosphoric acids and found that catalyst **1e**, bearing the 2,4,6-triisopropylphenyl substituent exhibited the highest catalytic activity (entry 5). Gratifyingly, the *ee* value rose to 93% when methyl ester **2b** was used in place of ethyl ester **2a** (entry 7).

Then we tried to optimize the reaction conditions. The investigation of different benzothiazolines demonstrated that benzothiazoline **4**, bearing a 2-phenyl group was the hydrogen source of choice with respect to the enantioselectivity.[13] Although no remarkable solvent effect was observed, mesitylene gave slightly higher enantioselectivity than the other solvents (Table 2, entries 1–4). It is noted that lowering the catalyst loading of **1e** to 1 mol% improved *ee* to 98% (entry 5). The catalyst loading could be reduced to as little as 0.5 mol% without sacrificing both chemical yield and enantioselectivity (entry 6).

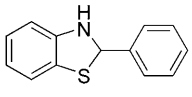
With the optimized reaction conditions in hand, we set out to define the scope of the transfer hydrogenation reaction. Excellent enantioselectivities (93–99% *ee*) as well as high chemical yields were realized in all the cases examined (Table 3).[14] A range of α-imino esters bearing electron-donating, electron-withdrawing, and bulky aromatic groups as R^1 furnished the corresponding α-amino esters **3** with excellent yields and enantioselectivities (entries 1–7). Remarkably, even the transfer hydrogenation of an aliphatic imino ester proceeded smoothly without compromising the enantioselectivity (entry 8). Both *N*-phenyl- and *N*-4-chlorophenylimines also proved to be suitable substrates (entries 9 and 10).

To expand the practicality of the current method, benzothiazoline was generated *in situ* and subjected to the transfer hydrogenation reaction. Then, we examined a gram-scale reaction using 0.5 mol% of phos-

Table 2. Examination of solvents and catalyst loading.



2b **3b**



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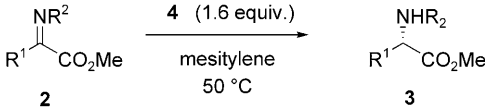
Entry	Solvent	X	Yield [%][a]	*ee* [%][b]
1	$(CH_2Cl)_2$	10	96	94
2	benzene	10	93	92
3	toluene	10	92	93
4	mesitylene	10	97	95
5	mesitylene	1	95	98
6	mesitylene	0.5	94	96

[a] Isolated yield.
[b] Determined by chiral HPLC analysis.

Table 3. Substrate scope of the asymmetric transfer hydrogenation of α-imino esters.



2 **3**

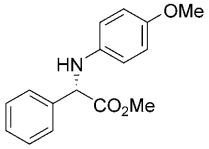
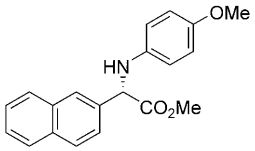
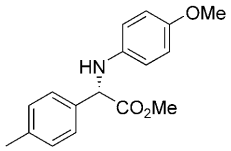
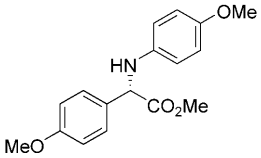
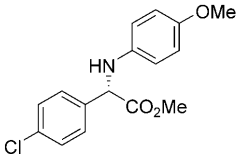
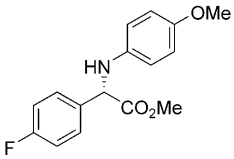
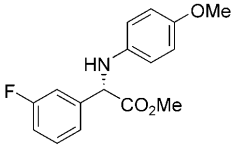
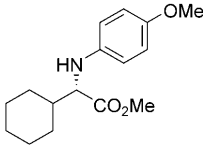
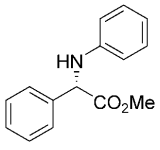
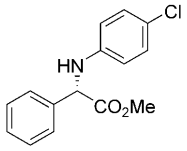
Entry	**3**	Time [h]	Yield [%][a]	*ee* [%][b]
1	**3b** 	24	95	98
2	**3c** 	24	99	97
3	**3d** 	25	97	96
4	**3e** 	28	96	94
5	**3f** 	24	98	94
6	**3g** 	24	97	93
7	**3h** 	24	97	96
8	**3i** 	27	93	99
9	**3j** 	22	90	97

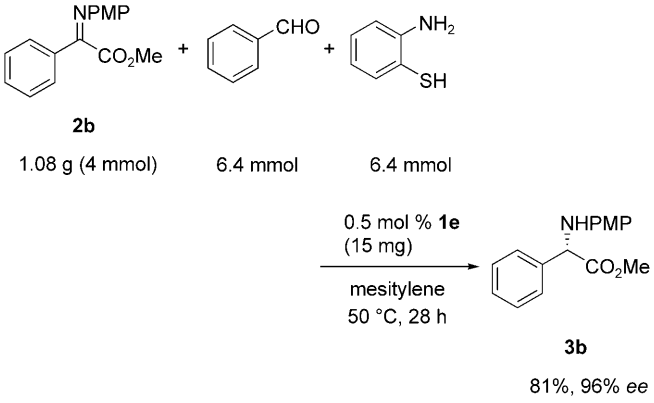
Table 3. (Continued)

Entry	3	Time [h]	Yield [%][a]	*ee* [%][b]
10	**3k** 	23	96	96

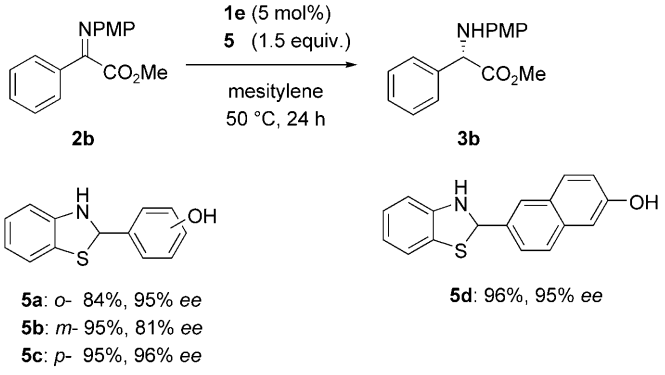
[a] Isolated yield.
[b] Determined by chiral HPLC analysis.

phoric acid **1e**. The three-component reaction starting from α-imino ester **2b**, benzaldehyde, and 2-aminothiophenol furnished the corresponding α-amino ester **3b** in high yield along with excellent enantioselectivity (Scheme 1).

One of the disadvantages of the transfer hydrogenation reaction that used the Hantzsch ester lies in the difficulty of separating the product from the pyridine derivatives generated by dehydrogenation. The present transfer hydrogenation reaction that used benzothiazoline also faced similar isolation problems.

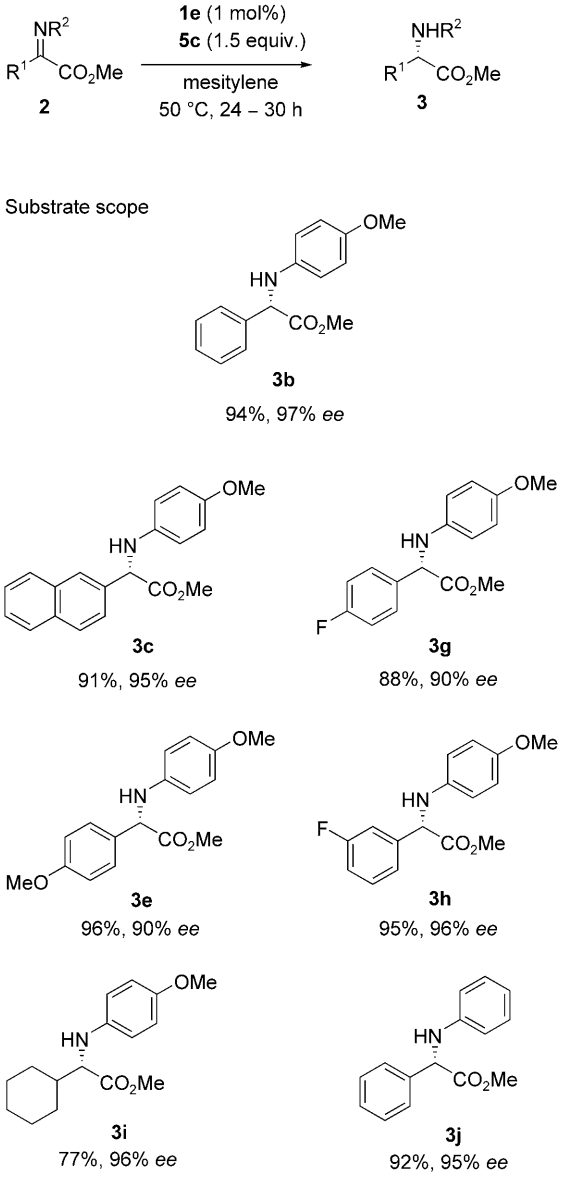


Scheme 1. Transfer hydrogenation reaction by use of *in-situ* generated benzothiazoline.



Scheme 2. Survey of hydroxy group-substituted benzothiazolines.

In order to overcome the difficulties associated with the purification of the compounds from benzothiazole generated as the by-product, we introduced a hydroxy group onto the 2-aryl group of the benzothiazoline. A screening experiment of hydroxy group-substituted benzothiazolines **5a–5d** revealed that **5c** was the most effective in terms of enantioselectivity (Scheme 2). The substrate scope of the transfer hydrogenation reaction with **5c** is shown in Scheme 3. Cyclohexylimino as well as arylimino esters proved to be suitable substrates. The advantage of **5c** is three-fold: (i) the benzothiazole by-product appears as a precipitate in the reaction and is readily removable by filtration, (ii) further purification by chromatography is facilitated due to the presence of polar hydroxy group, and (iii) ap-



Scheme 3. Transfer hydrogenation by use of hydroxy group-substituted benzothiazoline **5c**.

plication of the polymer-supported benzothiazoline is anticipated due to the facile modification of the hydroxy group.

In summary, we have described the first example of the use of benzothiazoline as the hydrogen source in the asymmetric transfer hydrogenation of α-imino esters. The use of hydroxy group-substituted benzothiazoline as the hydrogen source significantly facilitated the purification procedure. This is a simple and complementary approach that may widen the scope of catalytic transfer hydrogenation chemistry in general. Mechanistic studies and further applications are ongoing.

Experimental Section

Typical Procedure for the Transfer Hydrogenation of 2b

A 10-mL dry Schlenk flask was charged with 0.1 mmol imino ester **2b** (26.9 mg), 0.16 mmol benzothiazoline **4** (34 mg) and 0.001 mmol phosphoric acid **1e** (0.8 mg, 1 mol%). After the addition of 1 mL of mesitylene, the reaction mixture was heated to 50 °C under nitrogen for 24 h. Upon completion of the reaction, amino ester **3b** was purified by flash column chromatography (hexane/ethyl acetate = 14/1) in 95% yield with 98% *ee*.

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[13] For details, see Supporting Information.

[14] The absolute configuration was determined by comparing the optical rotation of **3** with those of reports of Antilla[4a] and You.[4b]

