ORGANIC LETTERS

2009
Vol. 11, No. 18
4180−4183

Benzothiazoline: Highly Efficient Reducing Agent for the Enantioselective Organocatalytic Transfer Hydrogenation of Ketimines

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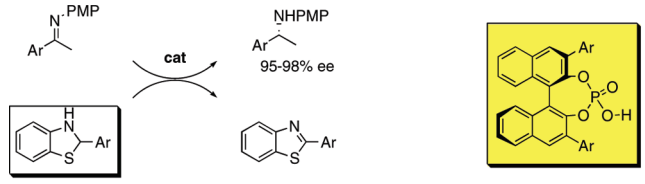
Received July 31, 2009

ABSTRACT



Benzothiazoline proved to be an efficient reducing agent for the phosphoric acid-catalyzed enantioselective transfer hydrogenation reaction of imines. Corresponding amines were obtained with excellent enantioselectivities.

The asymmetric reduction of imines is an important reaction for the preparation of amines in the optically pure form.[1] Although methods employing transition metal catalysts have been reported,[2] metal-free approaches that involve the reduction of ketimines,[3] α-imino esters,[4] etc.,[5] have been developed only recently: in those cases, the reducing agent is limited to Hantzsch esters, which are the most well-used cofactors in biochemical hydrogenation reactions.[6−8] Thus, the development of a novel biomimetic hydrogen source is strongly desired.

We focused on benzothiazolines, which are efficient antioxidants[9] with potent reducing ability,[10] as the hydrogen source. We hypothesized that the exposure of ketimine **1** to benzothiazoline **3** in the presence of catalytic amounts of chiral Brønsted acid would result in the formation of chiral amine **2**. Meanwhile, benzothiazoline **3** would be converted into the corresponding more stable aromatic benzothiazole **4** after liberating hydride (Scheme 1). Because of our previous success in strong Brønsted acid catalysis,[11−13] we studied the reduction of ketimine **1a** by means of chiral

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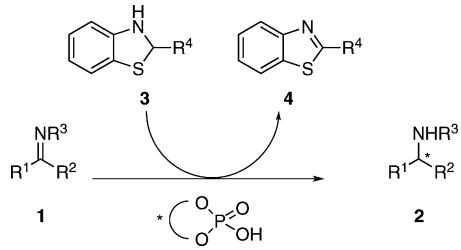
10.1021/ol901762g CCC: $40.75
Published on Web 08/19/2009

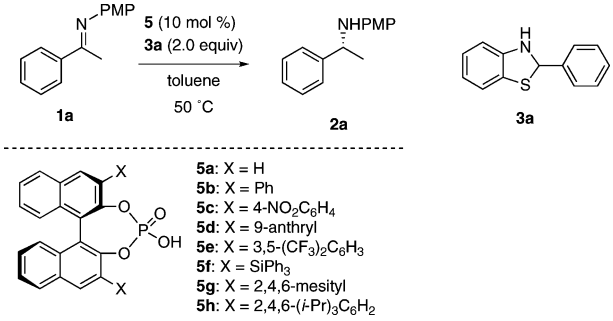
Scheme 1. Hydrogen Transfer Reaction



phosphoric acids. Herein, we reveal the first example of utilizing benzothiazoline as a novel hydrogen source for the asymmetric transfer hydrogenation of imines.

Although the exposure of ketimine **1a** with 2-phenylbenzothiazoline **3a** (2 equiv) in the presence of phosphoric acid **5a** furnished amine **2a** with low enantioselectivity (Table 1, entry 1), increasing the size of the substituents at 3,3′-positions of the catalyts significantly improved both chemical yields and enantioselectivities (entries 2−6). Gratifyingly, phosphoric acid **5h** gave the best result with 97% yield and 92% ee (entry 8).

Table 1. Enantioselective Transfer Hydrogenation Mediated by Benzothiazoline

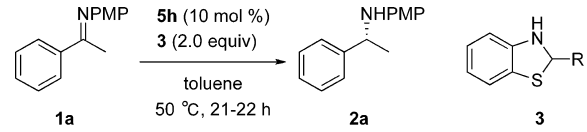


entry	catalyst	time (h)	yield (%)[a]	ee (%)[b]
1	**5a**	22	63	11
2	**5b**	21	67	79
3	**5c**	22	91	75
4	**5d**	21	93	62
5	**5e**	21	96	84
6	**5f**	24	53	84
7	**5g**	22	94	84
8	**5h**	21	97	92

[a] Isolated yield. [b] Enantiomeric excess was determined by chiral HPLC analysis.

We further examined a range of 2-substituted benzothiazolines in the asymmetric transfer hydrogenation reaction by means of phosphoric acid **5h** (Table 2). Gratifyingly, ee could be increased to 97% by using **3d** bearing a 2-naphthyl group (entry 4). Conversely, replacement with a 1-naphthyl group reduced the enantioselectivity (entry 5). Interestingly, alkyl group substituted benzothiazoline **3f** also exhibited high reactivity without steric hindrance (entry 6).

Table 2. Survey of Benzothiazolines for the Asymmetric Transfer Hydrogenation



entry	reducing agent	R	yield (%)[a]	ee (%)[b]
1	**3a**	Ph	97	92
2	**3b**	4-$MeOC_6H_4$	93	90
3	**3c**	4-$NO_2C_6H_4$	96	84
4	**3d**	2-naphthyl	89	97
5	**3e**	1-naphthyl	84	88
6	**3f**	*n*-propyl	96	94

[a] Isolated yield. [b] Enantiomeric excess was determined by chiral HPLC analysis.

Further screening for the reaction conditions revealed that the catalyst loading could be reduced to 2 mol % without compromising the enantioselectivity. Thus, exposure of imine **1a** to 1.4 equiv of benzothiazoline **3d** in the presence of **5h** in mesitylene at 50 °C for 26 h provided reduction product **2a** in 90% yield with 98% ee.[14] With the optimized reaction conditions in hand, we set out to define the scope of the

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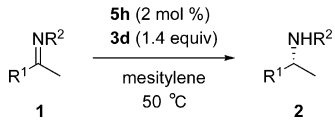
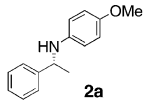
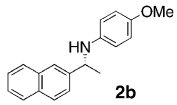
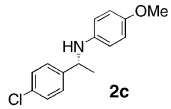
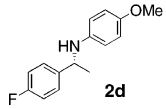
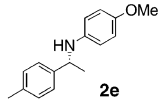
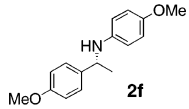
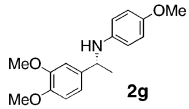
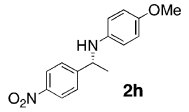
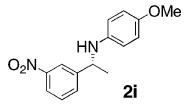
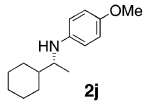
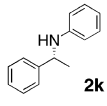
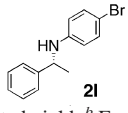
Table 3. Substrate Scope of the Asymmetric Transfer Hydrogenation



entry	product	time (h)	yield (%)[a]	ee (%)[b]
1	 **2a**	26	90	98
2	 **2b**	28	96	98
3	 **2c**	27	90	97
4	 **2d**	26	92	98
5	 **2e**	25	93	98
6	 **2f**	27	84	98
7	 **2g**	28	87	98
8	 **2h**	27	86	95
9	 **2i**	27	97	97
10	 **2j**	30	80	98
11	 **2k**	24	92	98
12	 **2l**	24	93	97

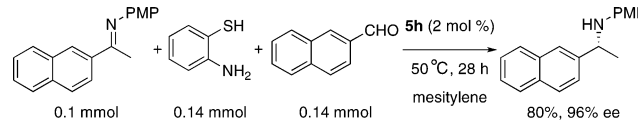
[a] Isolated yield. [b] Enantiomeric excess was determined by chiral HPLC analysis.

transfer hydrogenation reaction. Excellent ee values (95−98% ee) as well as high chemical yields were obtained in all the cases examined (Table 3).

Both R^1 and R^2 functional groups were well tolerated. Significantly, even the reduction of aliphatic ketimine **1j** proceeded smoothly without any loss of enantioselectivity (entry 10). It is noted that the present protocol for the phosphoric acid-catalyzed reduction of ketimines uniformly gave higher enantioselectivities than with the previous reports,[3] in which Hantzsch ester was employed as the hydrogen source.

Benzothiazoline may be generated in situ and subjected to the reduction reaction. Thus, three-component reaction starting from ketimine **1b**, 2-naphthalenecarbaldehyde, and 2-aminothiophenol gave the corresponding reduction product **2b** in a high yield with excellent enantioselectivity (Scheme 2).

Scheme 2. Hydrogen Transfer Reaction by Use of Benzothiazoline Generated in Situ



According to the resulting *R* configuration of amines, we speculated a ten-membered transition state[15] wherein the hydride was transferred from benzothiazoline to attack the imine via *Si*-face (Figure 1).

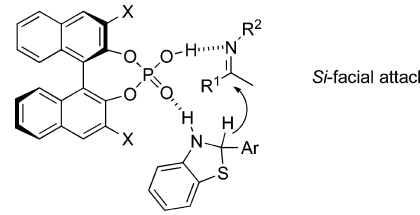


Figure 1. Proposed transition state.

In summary, we have described the first example of the use of benzothiazoline as the hydrogen source in the

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asymmetric transfer hydrogenation of ketimines. This is a simple and complementary approach that gives higher enantioselectivity in the imine reduction and that may widen the scope of catalytic transfer hydrogenation chemistry in general. Mechanistic studies and further applications are ongoing.

(14) For details, see Supporting Information.

(15) For the theoretical studies on the phosphoric acid-catalyzed reduction of imines, see: (a) Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741–8747. (b) Marcelli, T.; Hammar, P.; Himo, F. *Chem.—Eur. J.* **2008**, *14*, 8562–8571.

Acknowledgment. This work was partially supported by a Grant-in Aid for Scientific Research from the Japan Society for the Promotion of Science.

Supporting Information Available: Experimental procedures, characterization data, copies of NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901762G