Direct Asymmetric Aminoxylation Reaction Catalyzed by Axially Chiral Amino Acids

Taichi Kano, Akihiro Yamamoto, Haruka Mii, Jun Takai, Seiji Shirakawa, and Keiji Maruoka*
Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502

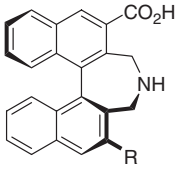
(Received November 27, 2007; CL-071314; E-mail: maruoka@kuchem.kyoto-u.ac.jp)

Binaphthyl-based amino acids were prepared and applied for the direct asymmetric aminoxylation of aldehydes with nitrosobenzene. The reaction catalyzed by (*S*)-**1e** proceeded smoothly to give the aminoxylated product in good yield and enantioselectivity. This method represents a rare example of the direct asymmetric aminoxylation by a non-proline-type catalyst.

Nitroso compounds are frequently utilized as a nitrogen and/or an oxygen source in synthetic organic chemistry,[1] and various catalytic asymmetric reactions, such as aminoxylation,[2–5] hydroxyamination,[4–6] and nitroso Diels–Alder reaction,[7] have recently been developed by exploiting their unique properties. In this area, highly enantioselective aminoxylation reactions using simple aldehydes and ketones were realized by organocatalysts through the in situ generation of the reactive enamine.[3] To the best of our knowledge, however, most of the reported organocatalysts for the aminoxylation reaction are proline and its derivatives, and structurally different catalysts have not yet been studied. Accordingly, we have been interested in the possibility of utilizing a binaphthyl-based amino acid catalyst (*S*)-**1a**,[8] which is an effective catalyst for the direct asymmetric aldol reaction, in the direct asymmetric aminoxylation of aldehydes. Herein, we wish to report a direct asymmetric aminoxylation reaction of aldehydes with nitrosobenzene by using binaphthyl-based amino acid catalysts (Figure 1).

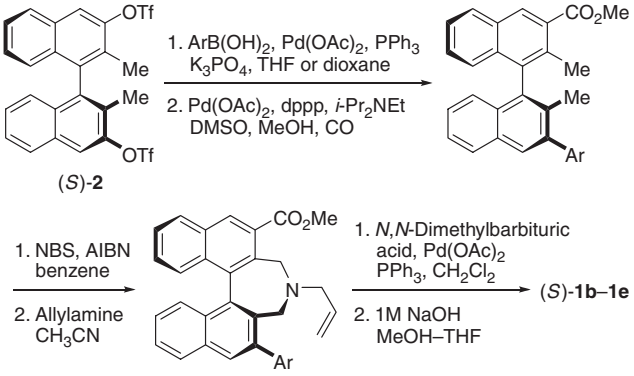
We first attempted to use (*S*)-**1a** as a catalyst for the direct asymmetric aminoxylation reaction. Thus, treatment of propanal with nitrosobenzene in the presence of 5 mol % of (*S*)-**1a** in $CHCl_3$ at 0 °C and subsequent reduction with $NaBH_4$ in $CHCl_3$/EtOH furnished the corresponding 2-aminoxy alcohol in good yield with moderate enantioselectivity (Table 1, Entry 1). We then designed and synthesized new binaphthyl-based amino acids (*S*)-**1b**–**1e** having an aromatic substituent at 3-position to improve the enantioselectivity. The requisite binaphthyl-based amino acids (*S*)-**1b**–**1e** were synthesized in a 6-step sequence from bistriflate (*S*)-**2**,[9] which was prepared from (*S*)-BINOL, as shown in Scheme 1.

With catalysts (*S*)-**1b**–**1e** in hand, the direct asymmetric aminoxylation of propanal with nitrosobenzene was carried out, and the results were summarized in Table 1. Introduction of an aromatic substituent at 3-position of the catalyst led to increases in enantioselectivity in all cases examined (Entries 2–5), and (*S*)-**1e** having 3,4,5-trifluorophenyl group was found to be



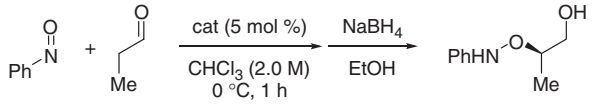
(*S*)-**1a** : R = H
(*S*)-**1b** : R = Ph
(*S*)-**1c** : R = 3,5-$Ph_2C_6H_3$
(*S*)-**1d** : R = 3,5-$(CF_3)_2C_6H_3$
(*S*)-**1e** : R = 3,4,5-$F_3C_6H_2$

Figure 1. Binaphthyl-based amino acid catalysts.



Scheme 1. Synthesis of binaphthyl-based amino acid catalysts.

Table 1. Direct asymmetric aminoxylation of propanal with nitrosobenzene catalyzed by (*S*)-**1**[a]



Entry	Cat	Yield/%[b]	ee/%[c]	Entry	Cat	Yield/%[b]	ee/%[c]
1	(*S*)-**1a**	82	49	4	(*S*)-**1d**	88	62
2	(*S*)-**1b**	99	64	5	(*S*)-**1e**	87	79
3	(*S*)-**1c**	82	60				

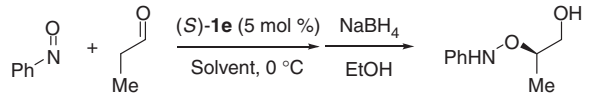
[a]The reaction of propanal (3 equiv.) with nitrosobenzene was carried out in $CHCl_3$ in the presence of catalyst (*S*)-**1** at 0 °C. [b]Isolated yield. [c]Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).

the catalyst of choice (Entry 5).

We then examined the effects of solvents on the yield and enantioselectivity. The results of the reaction using various solvents are shown in Table 2. When other halogenated solvents were used instead of $CHCl_3$, similar results were obtained (Entries 2 and 3). Switching the solvent to acetonitrile resulted in no improvement (Entry 4). In the case of amide solvents DMF and NMP as well as THF, significant decreases in yield were observed, although the enantioselectivities were increased to >90% ee (Entries 5–7). Aromatic solvents benzene, toluene, and mesitylene were found to be effective both in terms of the yield and enantioselectivity (Entries 8, 9, and 12). It should be noted that the reaction performed at lower concentration afforded the aminoxylated product with good enantioselectivity, albeit with moderate yield (Entries 11, 13, and 14). Toluene proved to be optimal for the present reaction due to the ease of handling and was selected for further studies.

The reactions using other aldehydes were then carried out under optimized conditions and some selected examples are summarized in Table 3. Similar high levels of yield and enantioselectivity were obtained when hexanal was used (Entry 2). In

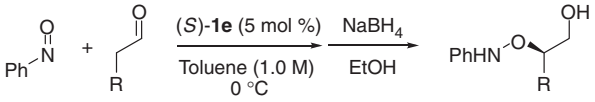
Table 2. Solvent effects in direct asymmetric aminoxylation of propanal with nitrosobenzene catalyzed by (*S*)-**1e**[a]



Entry	Solvent	Conc/M	Time/h	Yield/%[b]	ee/%[c]
1	$CHCl_3$	2.0	1	87	79
2	CH_2Cl_2	2.0	1	86	77
3	$ClCH_2CH_2Cl$	2.0	1	88	76
4	CH_3CN	1.0	1	81	77
5	DMF	2.0	1	<10	90
6	NMP	2.0	2	30	92
7	THF	2.0	2	40	90
8	Benzene	1.0	1	85	85
9	Toluene	2.0	1	86	83
10	Toluene	1.0	1	89	86
11	Toluene	0.5	1	70	89
12	Mesitylene	1.0	1.5	94	86
13	Mesitylene	0.5	1.5	62	91
14	Mesitylene	0.2	5	64	91

[a]The reaction of propanal (3 equiv.) with nitrosobenzene was carried out in the solvent mentioned above in the presence of catalyst (*S*)-**1e** at 0 °C. [b]Isolated yield. [c]Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).

Table 3. Direct asymmetric aminoxylation of aldehydes with nitrosobenzene catalyzed by (*S*)-**1e**[a]



Entry	R	Time/h	Yield/%[b]	ee/%[c]
1	Me	1	89	86
2	Bu	2	81	88
3	*i*-Pr	1.5	69	86

[a]The reaction of an aldehyde (3 equiv.) with nitrosobenzene was carried out in toluene in the presence of catalyst (*S*)-**1e** at 0 °C. [b]Isolated yield. [c]Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).

the case of less reactive 3-methylbutanal, the corresponding aminoxylated product was obtained in slightly lower yield with good enantioselectivity (Entry 3).

In all cases examined in this study, the absolute configuration of the aminoxylated products was determined to be *R*. On the basis of the observed stereochemistry, a plausible transition state is proposed (Figure 2). The activated and directed nitrosobenzene by carboxyl group on (*S*)-**1e** would approach the *Re* face of the enamine. Hence, the reaction of an aldehyde with nitrosobenzene catalyzed by (*S*)-**1e** provides *R* isomer predominantly, while at present we have no clear rationale for increases in enantioselectivity by the aromatic substituent at 3-position.

In summary, we have shown that the binaphthyl-based amino acid (*S*)-**1e** prepared from (*S*)-BINOL can be utilized as an organocatalyst in the direct asymmetric aminoxylation reaction of aldehydes. Further investigations to clarify the role of the aromatic substituent on the catalyst and efforts toward development of other enantioselective reactions using this catalyst are in progress.

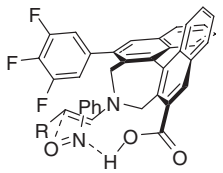


Figure 2. A transition state model for the direct asymmetric aminoxylation reaction catalyzed by (*S*)-**1e**.

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References and Notes

1 For reviews, see: a) W. Adam, O. Krebs, *Chem. Rev.* **2003**, *103*, 4131. b) P. Merino, T. Tejero, *Angew. Chem., Int. Ed.* **2004**, *43*, 2995. c) J. M. Janey, *Angew. Chem., Int. Ed.* **2005**, *44*, 4292. d) H. Yamamoto, N. Momiyama, *Chem. Commun.* **2005**, 3514. e) H. Yamamoto, M. Kawasaki, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595.

2 N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6038.

3 Representative papers: a) G. Zhong, *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808. c) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293. d) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem., Int. Ed.* **2004**, *43*, 1109. e) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem., Int. Ed.* **2004**, *43*, 1112. f) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962. g) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374. h) W. Wang, J. Wang, H. Li, L. Liao, *Tetrahedron Lett.* **2004**, *45*, 7235. i) D. B. Ramachary, C. F. Barbas, III, *Org. Lett.* **2005**, *7*, 1577. j) S. Kumarn, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Lett.* **2005**, *7*, 4189. k) K. Huang, Z.-Z. Huang, X.-L. Li, *J. Org. Chem.* **2006**, *71*, 8320. l) D. Font, A. Bastero, S. Sayalero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 1943.

4 N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080.

5 N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5360.

6 a) H.-M. Guo, L. Cheng, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Chem. Commun.* **2006**, 429. b) T. Kano, M. Ueda, J. Takai, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 6046. c) S.-G. Kim, T.-H. Park, *Tetrahedron Lett.* **2006**, *47*, 9067. d) C. Palomo, S. Vera, I. Velilla, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem., Int. Ed.* **2007**, *46*, 8054. e) J. López-Cantarero, M. B. Cid, T. B. Poulsen, M. Bella, J. L. García Ruano, K. A. Jørgensen, *J. Org. Chem.* **2007**, *72*, 7062.

7 a) Y. Yamamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 4128. b) Y. Yamamoto, H. Yamamoto, *Angew. Chem., Int. Ed.* **2005**, *44*, 7082. c) C. K. Jana, A. Studer, *Angew. Chem., Int. Ed.* **2007**, *46*, 6542.

8 a) T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Angew. Chem., Int. Ed.* **2005**, *44*, 3055. b) T. Kano, O. Tokuda, J. Takai, K. Maruoka, *Chem. Asian J.* **2006**, *1*, 210.

9 T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 5139.

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