Asymmetric Organocatalysis

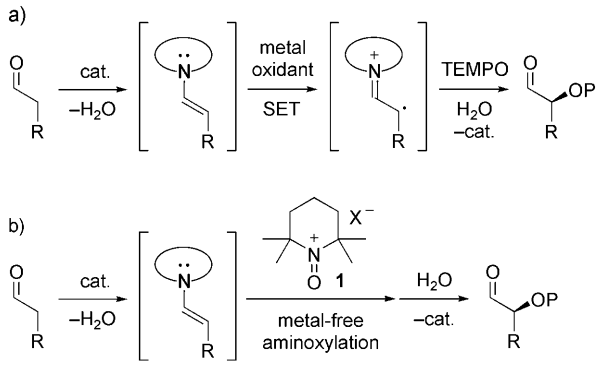
DOI: 10.1002/ange.201002965

Metal-Free Direct Asymmetric Aminoxylation of Aldehydes Catalyzed by a Binaphthyl-Based Chiral Amine**

*Taichi Kano, Haruka Mii, and Keiji Maruoka**

Chiral α-hydroxy carbonyl motifs are prevalent in natural products and biologically active compounds, and are versatile building blocks for the synthesis of structurally complex molecules. It is known that such chiral α-hydroxy carbonyl compounds are prepared by asymmetric oxygenations of preformed enolates and enamines, such as epoxidation,[1] dihydroxylation,[2] and aminoxylation.[3] Over the past several years, a number of direct asymmetric α-oxygenations of aldehydes and ketones catalyzed by chiral secondary amines have been reported.[4–8] In this area, nitroso compounds have been commonly utilized as an electrophile for asymmetric α-aminoxylation, and virtually optically pure α-aminoxy carbonyl compounds have been prepared. However, the α-aminoxy aldehydes and the reduced β-aminoxy alcohols produced are highly labile, probably owing to oligomerization and/or N–O bond cleavage.[4]

Recently, Sibi and Hasegawa reported the asymmetric α-aminoxylation of aldehydes using a stable radical, 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO),[5] which is considered to progress via a radical coupling pathway between TEMPO and the enamine radical cation generated from the enamine intermediate and a metal single electron oxidant (Scheme 1a).[9–11] Whilst this metal-promoted reaction requires further improvement of the reaction conditions and the substrate scope, the resulting aminoxy aldehydes are attractive chiral building blocks as O-protected α-hydroxy aldehydes because of their stability. Accordingly, we have been interested in the possibility of utilizing oxoammonium salt **1**, which could be generated in situ by oxidation from TEMPO, as a non-metal single-electron oxidant and an aminoxylating agent in the aminoxylation of aldehydes (Scheme 1b). Herein, we report a metal-free organocatalytic asymmetric aminoxylation of aldehydes using TEMPO and benzoyl peroxide (BPO) with high enantioselectivity and broad substrate scope.



Scheme 1. Aminoxylation of aldehydes via enamine intermediates. a) Previous work by Sibi and Hasegawa,[5] and b) this work. SET = single electron transfer.

To oxidize TEMPO into **1**, which is known as a catalyst in TEMPO oxidation,[12] BPO was chosen as an organic oxidant. In the presence of chiral pyrrolidine catalyst (*S*)-**2**,[8a] 3-phenylpropanal was first treated with TEMPO and BPO in dichloromethane at 0 °C. As expected, the reaction proceeded to give the desired α-aminoxy aldehyde. To determine the enantioselectivity of the reaction, the product was reduced in situ with $NaBH_4$ to the corresponding alcohol **6**, and the enantioselectivity was found to be moderate (Table 1,

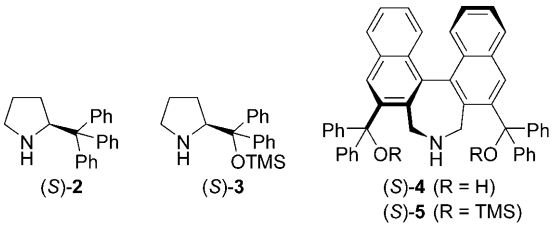
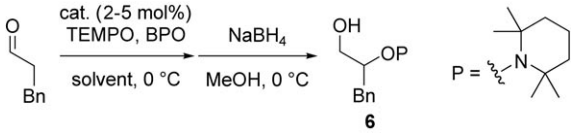


Table 1: Aminoxylation of 3-phenylpropanal.[a]



Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	(*S*)-**2**	CH_2Cl_2	0	3	62	44 (*S*)
2	(*S*)-**3**	CH_2Cl_2	0	5	28	47 (*S*)
3[d]	(*S*)-**4**	CH_2Cl_2	0	9	53	30 (*S*)
4	(*S*)-**5**	CH_2Cl_2	0	7	33	94 (*R*)
5[e]	(*S*)-**5**	CH_2Cl_2	−10	24	99	95 (*R*)
6[e]	(*S*)-**5**	THF	−10	23	40	92 (*R*)
7[e]	(*S*)-**5**	toluene	−10	23	47	95 (*R*)

[a] The reaction of 3-phenylpropanal (0.1 mmol), TEMPO (0.11 mmol), and BPO (0.11 mmol) was carried out in 0.5 mL solvent in the presence of 0.005 mmol catalyst. [b] Yield of isolated product. [c] The *ee* value of **6** was determined by HPLC analysis using a chiral column. [d] 10 mol% of (*S*)-**4**. [e] 3-Phenylpropanal (0.1 mmol), TEMPO (0.13 mmol), BPO (0.06 mmol), and a solvent (0.2 mL). TMS = trimethylsilyl.

[*] Dr. T. Kano, H. Mii, Prof. K. Maruoka
Department of Chemistry, Graduate School of Science
Kyoto University, Sakyo, Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-4041
E-mail: maruoka@kuchem.kyoto-u.ac.jp

[**] This work was supported by a Grant-in-Aid for Scientific Research from MEXT (Japan). H.M. thanks the Japan Society for the Promotion of Science for Young Scientists for Research Fellowships.

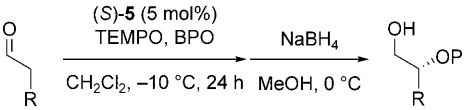
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201002965.

entry 1). Another pyrrolidine-type catalyst (*S*)-**3**[13] gave a lower yield and similar enantioselectivity (Table 1, entry 2). In terms of enantioselectivity, no improvement was observed with the binaphthyl-based amino alcohol catalyst (*S*)-**4**[14] (Table 1, entry 3). We assumed that the poor enantioselectivity might arise from the sterically less-hindered oxygen atom of **1**. Thus, a binaphthyl-based secondary amine catalyst (*S*)-**5**, containing bulky substituents at the 3,3′-positions, was synthesized by the introduction of trimethylsilyl groups into (*S*)-**4**. Gratifyingly, using the sterically more-congested catalyst (*S*)-**5**, the desired aminoxylation product was obtained in excellent enantioselectivity albeit with low yield (Table 1, entry 4).

Encouraged by this promising result, the reaction conditions were then optimized. Under the reaction conditions at 0 °C, 3-phenylpropanal was found to be oxidized into 3-phenylpropanoic acid, and the catalyst could also be deactivated via oxidation by **1** and/or BPO. These undesired side-reactions could be suppressed somewhat by lowering the reaction temperature and decreasing the amount of BPO; higher concentration also resulted in an improved yield (Table 1, entry 5). Switching solvent from dichloromethane to tetrahydrofuran and toluene did not improve the yield (Table 1, entries 6 and 7).

This reaction system was then applied to various aldehydes (Table 2). Under the optimized conditions, the corresponding α-aminoxylated products were obtained with good to excellent enantioselectivity in all cases examined.

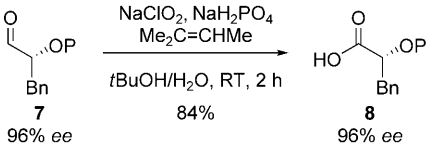
Table 2: Aminoxylation of various aldehydes.[a]



Entry	R	Yield [%][b]	*ee* [%][c]	Entry	R	Yield [%][b]	*ee* [%][c]
1[d]	Me	75	91	5	allyl	89	95
2	Et	88	92	6	*i*Pr	94	99
3	Bu	77	93	7	Cy	95	98
4	Bn	99	95				

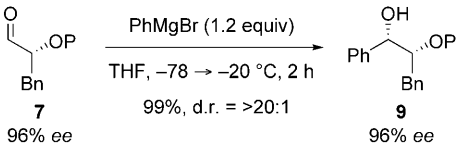
[a] The reaction of an aldehyde (0.1 mmol), TEMPO (0.13 mmol), and BPO (0.06 mmol) was carried out in CH_2Cl_2 (0.2 mL) in the presence of (*S*)-**5** (0.005 mmol). [b] Yield of isolated product. [c] The *ee* value of the product was determined by HPLC analysis using a chiral column. [d] The reaction time was 12 h.

It should be noted that an α-aminoxyl aldehyde could be isolated by column chromatography without reduction of the carbonyl group,[15] and neither decomposition nor racemization was observed. For instance, the isolated α-aminoxy aldehyde **7** (89% yield, 96% *ee*) was stored in [D]chloroform for 60 hours without any change observed by ^{1}H NMR and HPLC analyses (see the Supporting Information). To examine the synthetic utility of this aminoxylation reaction, an optically enriched α-aminoxy aldehyde **7** was converted into its corresponding α-hydroxy acid derivative [Eq. (1)]. Thus, treatment of the α-aminoxy aldehyde **7** with $NaClO_2$ in the presence of NaH_2PO_4 and 2-methyl-2-butene resulted in clean formation of α-aminoxy acid **8** without loss of optical purity. In this transformation, the 2,2,6,6-tetramethylpiperidinyl group was not oxidized and acted as a protecting group.



(1)

The reaction of α-aminoxy aldehyde **7** with PhMgBr in tetrahydrofuran proceeded smoothly to give the corresponding half-protected 1,2-diol **9** in excellent diastereoselectivity without loss of optical purity [Eq. (2)]. The observed



(2)

diastereoselectivity can be explained by non-chelation control, which might be attributable to the bulky and non-protic aminoxyl group of **7** (Figure 1, left), and contrasted sharply with that observed in the chelate-controlled reactions between Grignard reagents and α-aminoxy aldehydes generated in situ from nitroso compounds (Figure 1, right).[16]

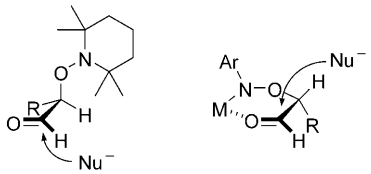
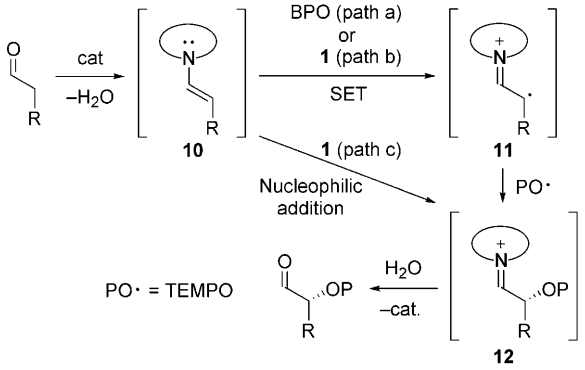


Figure 1. Possible transition-state models for diastereoselective nucleophilic addition to α-aminoxy aldehydes.

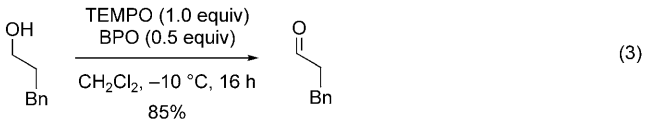
For this aminoxylation reaction, two radical reaction pathways and an ionic reaction pathway could be suggested: 1) The enamine radical cation **11**, which is generated by oxidation of the enamine intermediate **10** with BPO, reacts with a TEMPO radical to give the iminium intermediate **12** (Scheme 2, path a). 2) The enamine **10** is oxidized by oxoammonium salt **1**, which is generated from TEMPO and BPO, to give the enamine radical cation **11** (path b). 3) Enamine **10** reacts directly with **1** in an ionic (nucleophilic addition) pathway, giving **12** (path c).

Generation of oxoammonium salt **1** from TEMPO and BPO was confirmed by an experiment in which treatment of 3-phenylpropanol with TEMPO (1 equiv) and BPO (0.5 equiv) in dichloromethane led to the formation of 3-phenylpropanal in 85% yield [Eq. (3)]. In addition, when the aminoxylation of butanal was performed in the presence of 3-phenylpropanol, the formation of α-aminoxy butanal **13** was accompanied by oxidation of 3-phenylpropanol and the aminoxylation of the resulting 3-phenylpropanal [Eq. (4)].

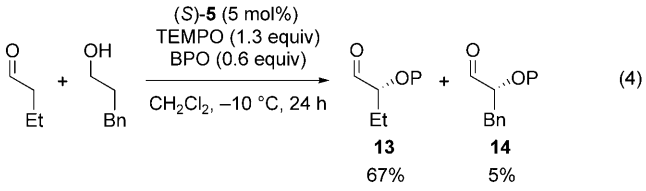


Scheme 2. Possible reaction pathways.

These observations strongly suggest the generation of oxoammonium salt **1** under the reaction conditions, and **1** might participate in the present aminoxylation, thus suggesting that the reaction proceeds through path b or path c.[17] Although the partial generation of the radical intermediate **11** by BPO (path a) is possible, we believe that BPO would preferentially react with a stoichiometric amount of TEMPO to generate **1**.

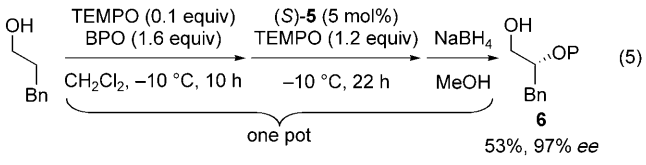


(3)



(4)

During the mechanistic investigation described above, TEMPO was found to serve the dual roles of oxidation catalyst and aminoxylating agent [Eqs. (3) and (4)]. Thus, we then investigated the one-pot oxidation–aminoxylation of an alcohol [Eq. (5)].[18,19] 3-Phenylpropanol was first treated with BPO (1.6 equiv) and a catalytic amount of TEMPO (0.1 equiv) in dichloromethane at −10 °C for 10 hours, and the resulting 3-phenylpropanal underwent aminoxylation with (*S*)-**5** (5 mol %) and TEMPO (1.2 equiv). The obtained α-aminoxy aldehyde was reduced with $NaBH_4$ to determine the enantioselectivity, giving the corresponding alcohol (*R*)-**6** in 53 % yield with 97 % *ee*.



(5)

The absolute configuration of the product in this reaction catalyzed by (*S*)-**5** was determined to be *R* by comparison of the HPLC retention time with the literature data.[5] Based on the observed stereochemistry, transition-state models can be proposed, as shown in Figure 2. In either the radial or ionic pathway, one face of the enamine radical cation or the enamine intermediate is effectively shielded by the bulky substituent of (*S*)-**5**, and consequently, the reaction of an aldehyde with TEMPO or **1** catalyzed by (*S*)-**5** provides the *R* isomer predominantly.

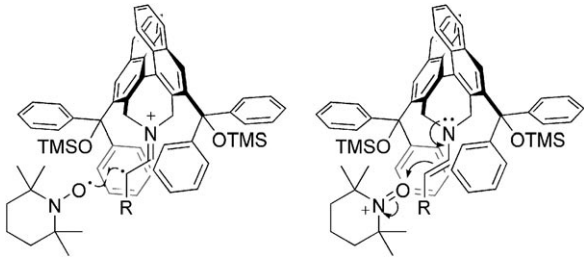


Figure 2. Plausible transition-state models.

In summary, we have developed the first metal-free direct aminoxylation reaction of aldehydes with an oxoammonium salt **1**, catalyzed by the novel binaphthyl-based amine (*S*)-**5**. This method represents a rare example of the catalytic and highly enantioselective synthesis of bench-stable α-aminoxy aldehydes. The synthetic utility of the obtained stable α-aminoxy aldehydes has also been demonstrated by taking advantage of their characteristic features. We are currently working to expand the scope of this methodology, as well as to ascertain mechanistic details of the aminoxylation.

Received: May 17, 2010
Published online: July 29, 2010

Keywords: aldehydes · aminoxylation · asymmetric catalysis · organocatalysis

[1] For reviews, see: a) W. Adam, R. T. Fell, V. R. Stegmann, C. R. Saha-Möller, *J. Am. Chem. Soc.* **1998**, *120*, 708; b) W. Adam, R. T. Fell, C. R. Saha-Möller, C.-G. Zhao, *Tetrahedron: Asymmetry* **1998**, *9*, 397; c) Y. Zhu, Y. Tu, H. Yu, Y. Shi, *Tetrahedron Lett.* **1998**, *39*, 7819; d) M. Koprowski, J. Łuczak, E. Krawczyk, *Tetrahedron* **2006**, *62*, 12363.

[2] a) K. Morikawa, J. Park, P. G. Andersson, T. Hashiyama, K. B. Sharpless, *J. Am. Chem. Soc.* **1993**, *115*, 8463; b) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

[3] a) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6038; b) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080; c) M. Kawasaki, P. Li, H. Yamamoto, *Angew. Chem.* **2008**, *120*, 3855; *Angew. Chem. Int. Ed.* **2008**, *47*, 3795.

[4] a) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379; *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.

[5] M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, *129*, 4124.

[6] a) A. Córdova, H. Sundén, M. Engqvist, I. Ibrahem, J. Casas, *J. Am. Chem. Soc.* **2004**, *126*, 8914; b) I. Ibrahem, G.-L. Zhao, H. Sundén, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 4659.
[7] M. Engqvist, J. Casas, H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 2053.
[8] a) T. Kano, H. Mii, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 3450; b) M. J. P. Vaismaa, S. C. Yau, N. C. O. Tomkinson, *Tetrahedron Lett.* **2009**, *50*, 3625; c) H. Gotoh, Y. Hayashi, *Chem. Commun.* **2005**, 3083.
[9] a) T. D. Beeson, A. Mastracchio, J. B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582; b) H.-Y. Jang, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004; c) H. Kim, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 398; d) T. H. Graham, C. M. Jones, N. T. Jui, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 16494; e) M. Amatore, T. D. Beeson, S. P. Brown, D. W. C. MacMillan, *Angew. Chem.* **2009**, *121*, 5223; *Angew. Chem. Int. Ed.* **2009**, *48*, 5121; f) J. E. Wilson, A. D. Casarez, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11332; g) J. C. Conrad, J. Kong, B. N. Laforteza, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11640.
[10] a) K. Narasaka, T. Okauchi, K. Tanaka, M. Murakami, *Chem. Lett.* **1992**, 2099; b) J. Cossy, A. Bouzide, *J. Chem. Soc. Chem. Commun.* **1993**, 1218.
[11] a) T. Koike, M. Akita, *Chem. Lett.* **2009**, *38*, 166; b) N.-N. Bui, X.-H. Ho, S.-i. Mho, H.-Y. Jang, *Eur. J. Org. Chem.* **2009**, 5309; c) K. Akagawa, T. Fujiwara, S. Sakamoto, K. Kudo, *Org. Lett.* **2010**, *12*, 1804.
[12] For reviews, see: a) P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559; b) A. E. J. de Nooy, A. C. Besemer, H. van Bekkum, *Synthesis* **1996**, 1153.
[13] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.
[14] a) T. Kano, M. Ueda, J. Takai, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 6046; b) T. Kano, M. Ueda, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 3728.
[15] Only a trace amount of the α-aminoxy aldehyde, obtained from the reaction between 3-phenylpropanal and nitrosobenzene, was isolated by column chromatography on silica gel. See Ref. 4 and the Supporting Information.
[16] P. Jiao, M. Kawasaki, H. Yamamoto, *Angew. Chem.* **2009**, *121*, 3383; *Angew. Chem. Int. Ed.* **2009**, *48*, 3333.
[17] M. Schämann, H. J. Schäfer, *Synlett* **2004**, 1601.
[18] T. Inokuchi, K. Nakagawa, S. Torii, *Tetrahedron Lett.* **1995**, *36*, 3223.
[19] R. Barhdadi, C. Comminges, A. P. Doherty, J. Y. Nédélec, S. O'Toole, M. Troupel, *J. Appl. Electrochem.* **2007**, *37*, 723.

