Diphenylprolinol silyl ether as a catalyst in an asymmetric, catalytic and direct α-benzoyloxylation of aldehydes†

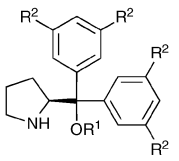
Hiroaki Gotoh[a] and Yujiro Hayashi*[ab]

Received (in Cambridge, UK) 3rd February 2009, Accepted 18th March 2009
First published as an Advance Article on the web 14th April 2009
DOI: 10.1039/b902287b

Diphenylprolinol silyl ether was found to promote asymmetric, catalytic and direct α-benzoyloxylation of aldehydes with benzoyl peroxide to afford oxidized products in good yields with excellent enantioselectivity.

Optically active α-acyloxy- or α-hydroxy-aldehydes are important intermediates in organic synthesis. α-Oxygenation of aldehydes is one of the direct and straightforward methods for their synthesis, and there are several enantioselective and catalytic methods. For instance, the nitroso aldol reaction of aldehyde and nitrosobenzene catalyzed by proline, which has been developed independently by three groups including our group, is one of the powerful methods for the formation of α-aminoxy aldehydes, which are easily transformed into α-hydroxy aldehydes.[1,2] Our group not only developed this reaction, but also applied it as a key reaction in the synthesis of complex natural products, such as fumagillol,[3] ovalicin,[3] panepophenanthrin[4] and cytotrienin A.[5] The aldehyde was also converted to α-hydroxyaldehydes using TEMPO as an oxidant with MacMillan's catalyst,[6] while $^1O_2$ is employed as an oxidant in the organocatalyst-mediated reaction.[7] In spite of these successful α-oxidations of aldehydes, there has been no direct, catalytic, α-acyloxylation of aldehydes so far. We have been interested in benzoyl peroxide as an oxidant. This reagent is widely employed as a radical initiator in organic synthesis, while there is one report in which it is used as a stoichiometric oxidant with a chiral metallo-enamine to afford an α-benzoyloxylated carbonyl compound.[8]

On the other hand, reactions using organocatalysts have been developing rapidly, and many types of organocatalysts with superior features have been devised.[9] Diphenylprolinol silyl ether,[10] which has been developed independently by our group[11] and Jørgensen's group,[12] is an effective organocatalyst, which has been employed in several asymmetric reactions. We have found highly enantioselective reactions catalyzed by diphenylprolinol silyl ether *via* an enamine mechanism such as the Michael reaction of aldehydes with nitroalkenes,[11a] tandem Michael/Henry reaction,[11d] Michael reaction[11g] and Mannich reaction[11i] of acetaldehyde. In the search for α-oxygenation of aldehydes using diphenylprolinol silyl ether as a catalyst, we have found the highly enantioselective



Catalyst	R^1	R^2
1	TMS	H
2	TBS	H
3	TMS	CF_3
4	TES	CF_3

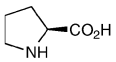
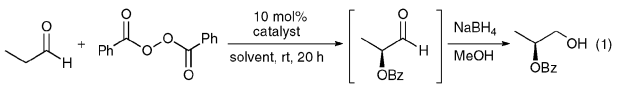


Fig. 1 The organocatalysts examined in this study.

α-benzoyloxylation of aldehydes, which will be described in this communication.[13]

We chose the reaction of propanal and benzoyl peroxide as a model reaction, and the catalysts were investigated first (Fig. 1). As the generated 2-benzoyloxypropanal is easily racemized, isolation and characterization were performed after conversion to the corresponding 2-benzoyloxypropanol by treatment of the reaction mixture with $NaBH_4$. The results are summarized in Table 1. Proline scarcely promoted the reaction, with very low enantioselectivity (entry 1) while diphenylprolinol trimethylsilyl ether **1** gave good enantioselectivity with low yield (38%, entry 2). The organocatalyst **1** reacts with benzoyl peroxide slowly, affording the *N*-benzoyloxy derivative as a side product, which was partially

Table 1 Effect of catalyst and solvent in α-benzoyloxylation of propanal[a]



Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	Proline	DMF	11	9
2	**1**	DMF	38	83
3	**2**	DMF	45	87
4	**3**	DMF	27	81
5	**4**	DMF	42	79
6	**2**	NMP	24	87
7	**2**	CH_3CN	15	86
8	**2**	MeOH	27	78
9	**2**	CH_2Cl_2	0	—
10	**2**	Et_2O	37	90
11	**2**	1,4-Dioxane	44	90
12	**2**	THF	59	88
13[d]	**2**	THF	68	92
14[e]	**2**	THF	78	92

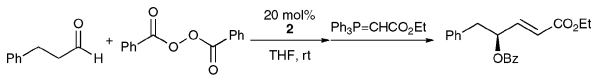
[a] Unless otherwise shown, the reaction was performed by employing propanal (0.81 mmol), benzoyl peroxide (0.27 mmol) and organocatalyst (0.027 mmol) in solvent (0.54 mL) at room temperature for 20 h. The reaction mixture was treated with $NaBH_4$ at 0 °C, and the product was isolated as an alcohol. [b] Isolated yield of alcohol. [c] Determined by HPLC analysis on a chiral phase. [d] Organocatalyst **2** was employed (20 mol%, 0.054 mmol) in THF (2.7 mL). [e] Organocatalyst **2** (10 mol%) was added at the start and also after 4 h.

[a] *Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo, 162-8601, Japan. E-mail: hayashi@ci.kagu.tus.ac.jp; Fax: +81-(0)3-5261-4631; Tel: +81-(0)3-5228-8318*
[b] *Research Institute for Science and Technology, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo, 162-8601, Japan*
† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b902287b

suppressed when bulkier *tert*-butyldimethyl silyl ether **2** was employed, in which better yield and enantioselectivity were realized (entry 3). Trifluoromethyl substituted diarylprolinol silyl ethers **3** and **4** are not effective in the present reaction (entries 4 and 5). Next, screening of the solvent was investigated. As shown in Table 1, among the solvents examined such as NMP, CH_3CN, THF, Et_2O, 1,4-dioxane, MeOH and CH_2Cl_2, THF was found to be the best choice (entry 12). When the reaction proceeds, an equimolar amount of benzoic acid would be generated, which might affect the reaction. Therefore, additives were investigated. Neither bases such as 2,6-lutidine, Et_3N, K_2CO_3, $NaHCO_3$ nor acids such as CF_3CO_2H, $TsOH{\cdot}H_2O$ and 2,4-dinitrophenylsulfonic acid are effective, decreasing the yield. By further screening the reaction conditions, yield and enantioselectivity were increased to 68% and 92% ee, when 20 mol% of diphenylprolinol *tert*-butyldimethyl silyl ether **2** was employed (entry 13). With successive addition of catalyst **2** after a 4 h interval, good yield (78%) was obtained with the excellent enantioselectivity (92% ee, entry 14).‡

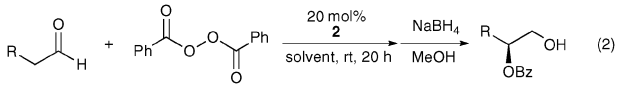
The reaction conditions were optimized using propanal as a model aldehyde, in which propanal as three equivalents with respect to benzoyl peroxide (condition A) was employed. This condition (condition A) would be suitable when the aldehyde is inexpensive. Next, we investigated the reaction conditions using 1.5 mol ratio of benzoyl peroxide to aldehyde, appropriate for the case of an expensive aldehyde, in which 3-phenylpropanal was selected as a model aldehyde. When benzoyl peroxide was employed as 1.5 equivalents to aldehyde in the presence of 20 mol% of catalyst **2** (condition B), the desired product was obtained in good yield with excellent enantioselectivity (Table 2, entry 3). Under both conditions A and B, the generality of the reaction was investigated, and the results are summarized in Table 2. Not only propanal, but also linear chain aldehydes such as *n*-butanal react with benzoyl peroxide, affording α-benzoyloxyaldehyde in moderate yield with excellent enantioselectivity (entry 2). Aldehydes containing aromatic or silyl ether moieties were successfully employed in this reaction (entries 3 and 4). Alkenes do not interfere with the reaction, affording the α-benzoyloxylated aldehyde in good yield with excellent enantioselectivity (entry 5).

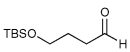
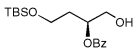
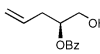
Optically active α-benzoyloxyaldehydes are important synthetic intermediates, because several additional transformations are possible. The following example is a successful transformation of this key intermediate to a more functionalized synthetic intermediate in the same pot without isolation of the intermediate with tendency of racemization. A Wittig reagent was added to the reaction mixture of 3-phenylpropanal, benzoyl peroxide and catalyst **2**, affording γ-benzoyloxy α,β-unsaturated ester **5** in good yield without compromising the enantioselectivity (eqn (3)). It should be noted that it is a synthetic advantage to perform several transformations in a single pot without isolation of the racemizable α-benzoyloxyaldehydes.



(3)

Table 2 Catalytic, asymmetric α-benzoyloxylation of aldehydes



Entry	Aldehyde	Condition[a]	Product	Yield[b] (%)	ee[c] (%)
1		A		78	92
2		A		54	90
3		B		72	94
4		B		58	91
5		B		77	92

[a] Condition A: The reaction was performed by employing aldehyde (0.81 mmol) and benzoyl peroxide (0.27 mmol) in THF (2.7 mL) at room temperature for 20 h. Catalyst **2** (0.027 mmol) was added at the start and also after 4 h. Condition B: The reaction was performed by employing aldehyde (0.27 mmol) and benzoyl peroxide (0.40 mmol) in THF (2.7 mL) at room temperature for 20 h. Catalyst **2** (0.027 mmol) was added at the start and also after 4 h. [b] Isolated yield of alcohol. [c] Determined by HPLC analysis on a chiral phase.

The absolute configuration of 2-benzoyloxypropanol was determined to be *S* by comparison with the data in the literature.[14] The reaction is thought to proceed *via* a transition state in which benzoyl peroxide approaches the face opposite the bulky diphenyl(*tert*-butyldimethylsiloxy)methyl group.

In summary, we have found a highly enantioselective α-benzoyloxylation of aldehydes with benzoyl peroxide catalyzed by diphenylprolinol silyl ether. Because the oxidant is inexpensive, and excellent enantioselectivity has been obtained, the present method would be one of the more useful enantioselective α-oxidation methods of aldehydes.

Notes and references

‡ Typical procedure of asymmetric α-benzoyloxylation of propanal (Table 1, entry 14, condition A).

To a solution of benzoyl peroxide (88.0 mg, 0.27 mmol, contains 25% water) and propanal (58.0 μL, 0.81 mmol) in THF (2.7 mL) was added catalyst **2** (9.9 mg, 0.027 mmol, 10 mol%) at the room temperature. After stirring the reaction mixture at room temperature for 4 h, further catalyst **2** (9.9 mg, 0.027 mmol, 10 mol%), was added. After stirring the reaction mixture at room temperature for an additional 16 h, MeOH (2.7 mL) and an excess amount of $NaBH_4$ was added at 0 °C to the reaction mixture, which was stirred for 5 min. The resulting mixture was quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted with AcOEt and dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt–hexane = 1 : 20–1 : 3) to afford (*S*)-1-hydroxypropan-2-yl benzoate (39.3 mg, 78%).

Enantiomeric excess was determined by HPLC using a Chiralpak AS-H column (10 : 1 hexane–*i*-PrOH; flow rate 1.0 mL min^{-1}, major enantiomer; t_R = 4.5 min, minor enantiomer; t_R = 5.3 min.)

1 Review, see: (*a*) H. Yamamoto and N. Momiyama, *Chem. Commun.*, 2005, 3514; (*b*) Y. Yamamoto and H. Yamamoto, *Eur. J. Org. Chem.*, 2006, 2031.

2 (*a*) G. Zhong, *Angew. Chem., Int. Ed.*, 2003, **42**, 4247; (*b*) S. P. Brown, M. P. Brochu, C. J. Sinz and D. W. C.

MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 10808; (*c*) Y. Hayashi, J. Yamaguchi, K. Hibino and M. Shoji, *Tetrahedron Lett.*, 2003, **44**, 8293; (*d*) Y. Hayashi, J. Yamaguchi, T. Sumiya and M. Shoji, *Angew. Chem., Int. Ed.*, 2004, **43**, 1112; (*e*) Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino and M. Shoji, *J. Org. Chem.*, 2004, **69**, 5966.

3 J. Yamaguchi, M. Toyoshima, M. Shoji, H. Kakeya, H. Osada and Y. Hayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 789.

4 M. Matsuzawa, H. Kakeya, J. Yamaguchi, M. Shoji, R. Onose, H. Osada and Y. Hayashi, *Chem.–Asian J.*, 2006, **1**, 845.

5 Y. Hayashi, M. Shoji, H. Ishikawa, J. Yamaguchi, T. Tamura, H. Imai, Y. Nishigaya, K. Takabe, H. Kakeya and H. Osada, *Angew. Chem., Int. Ed.*, 2008, **47**, 6657.

6 M. P. Sibi and M. Hasegawa, *J. Am. Chem. Soc.*, 2007, **129**, 4124.

7 A. Cordova, H. Sunden, M. Engqvist, I. Ibrahem and J. Casas, *J. Am. Chem. Soc.*, 2004, **126**, 8914.

8 J. Lee, S. Oya and J. K. Snyder, *Tetrahedron Lett.*, 1991, **32**, 5899.

9 Reviews on organocatalysis, see: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*b*) *Asymmetric Organocatalysis*, ed. A. Berkessel and H. Groger, Wiley-VCH, Weinheim, 2005; (*c*) Y. Hayashi, *J. Synth. Org. Chem., Jpn.*, 2005, **63**, 464; (*d*) B. List, *Chem. Commun.*, 2006, 819; (*e*) M. Marigo and K. A. Jørgensen, *Chem. Commun.*, 2006, 2001; (*f*) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug Discovery Today*, 2007, **12**, 8; (*g*) *Enantioselective Organocatalysis*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2007; (*h*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (*i*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638; (*j*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138.

10 Selected examples of other group's application of diarylprolinol ether, see: (*a*) D. Enders, M. R. M. Huttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861; (*b*) J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios and A. Cordova, *Angew. Chem., Int. Ed.*, 2007, **46**, 778; (*c*) H. Xie, L. Zu, H. Li, J. Wang and W. Wang, *J. Am. Chem. Soc.*, 2007, **129**, 10886; (*d*) N. T. Vo, R. D. M. Pace, F. O'Hara and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 404. Review, see ; (*e*) C. Palomo and A. Mielgo, *Angew. Chem., Int. Ed.*, 2006, **45**, 7876; (*f*) A. Mielgo and C. Palomo, *Chem.–Asian J.*, 2008, **3**, 922.

11 (*a*) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212; (*b*) H. Gotoh, R. Masui, H. Ogino, M. Shoji and Y. Hayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 6853; (*c*) H. Gotoh and Y. Hayashi, *Org. Lett.*, 2007, **9**, 2859; (*d*) Y. Hayashi, T. Okano, S. Aratake and D. Hazelard, *Angew. Chem., Int. Ed.*, 2007, **46**, 4922; (*e*) H. Gotoh, H. Ishikawa and Y. Hayashi, *Org. Lett.*, 2007, **9**, 5307; (*f*) Y. Hayashi, H. Gotoh, R. Masui and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 4012; (*g*) Y. Hayashi, T. Itoh, M. Ohkubo and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 4722; (*h*) Y. Hayashi, S. Samanta, H. Gotoh and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 6634; (*i*) Y. Hayashi, T. Okano, T. Ioth, T. Urushima, H. Ishikawa and T. Uchimaru, *Angew. Chem., Int. Ed.*, 2008, **47**, 9053; (*j*) Y. Hayashi, M. Toyoshima, H. Gotoh and H. Ishikawa, *Org. Lett.*, 2009, **11**, 45; (*k*) Y. Hayashi, K. Obi, Y. Ohta, D. Okamura and H. Ishikawa, *Chem.–Asian J.*, 2009, **4**, 246.

12 (*a*) M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 794; (*b*) M. Marigo, D. Fielenbach, A. Braunton, A. Kjasgaard and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 3703; Recent reports, see: (*c*) P. T. Franke, R. L. Johansen, S. Bertelsen and K. A. Jørgensen, *Chem.–Asian J.*, 2008, **3**, 216.

13 During the review process, a similar paper has appeared, see; T. Kano, H. Mii and K. Maruoka, *J. Am. Chem. Soc.*, 2009, **131**, 3450.

14 E. Santaniello, S. Casati, P. Ciuffreda and L. Gamberoni, *Tetrahedron: Asymmetry*, 2005, **16**, 1705.