J|A|C|S
COMMUNICATIONS

Published on Web 12/04/2008

Complete Switch of Product Selectivity in Asymmetric Direct Aldol Reaction with Two Different Chiral Organocatalysts from a Common Chiral Source

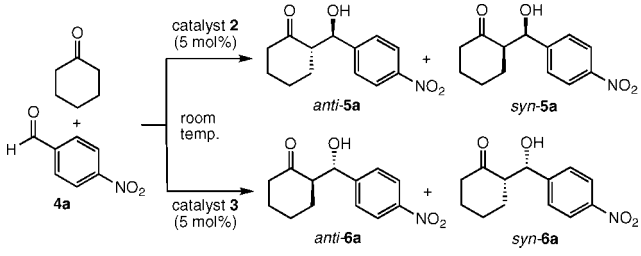
Keiji Nakayama[†] and Keiji Maruoka*[,‡]

Process Technology Research Laboratories, Daiichi Sankyo Co., LTD, Hiratsuka, Kanagawa 254-0014, Japan, and Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

Received October 3, 2008; E-mail: maruoka@kuchem.kyoto-u.ac.jp

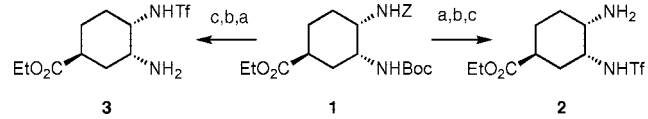
Design of new chiral organocatalysts to achieve efficient asymmetric transformations has become increasingly important in current asymmetric organocatalysis.[1] In particular, development of a novel approach for asymmetric synthesis of both enantiomers would be very useful from a practical viewpoint by designing two different chiral organocatalysts from a readily available compound as a common chiral source. We here wish to report our case study on this subject by the preparation of chiral organocatalysts **2** and **3** starting from common chiral intermediate **1** with the unique cis-diamine structure.[2] The chiral efficiency of these organocatalysts was evaluated by their application to asymmetric direct aldol reactions.[3−5]

The requisite catalysts **2** and **3** can be easily prepared from **1** in a 3-step sequence as shown in Scheme 1. Asymmetric direct aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde catalyzed by **2** was first carried out as a model experiment to find the optimum reaction condition.[6] Treatment of cyclohexanone and *p*-nitrobenzaldehyde (**4a**) with 5 mol % of **2** in polar solvents (DMSO, DMF, or CH_3CN) at room temperature gave aldol products **5a** in very low yields, but the major isomer *anti*-**5a** was found to exhibit high enantioselectivity (entries 1−3 in Table 1). Without solvent, the reaction proceeded smoothly to furnish *anti*-**5a** as a major product with high enantioselectivity (entry 6). A noticeable increase in the reaction rate was attained by the use of MeOH and *i*-PrOH (entries 7 and 8), and water solvent was found to be superior in terms of reactivity and selectivity (entries 9 and 10).[7] Finally, the mixed solvents such as aqueous DMSO, DMF, CH_3CN, and THF were examined (entries 12−15), and among these use of aqueous THF gave aldol products **5a** in almost quantitative yield with excellent enantioselectivity after shorter reaction time (entry 15). In marked contrast, however,



switching catalyst **2** to **3** resulted in formation of the enantiomeric aldols **6a** in 96% yield (anti/syn = 91:9), and the major anti isomer *anti*-**6a** was found to be 98% ee with the opposite absolute configuration.

Scheme 1. Synthesis of Two Different Chiral Organocatalysts



Reagents and conditions: (a) MsOH, CH_3CN; (b) Tf_2O, Et_3N; (c) Pd/C, H_2.

With the optimal reaction condition at hand, we further studied the generality of asymmetric direct aldol reaction of various cyclic ketones and substituted benzaldehydes in the presence of catalyst **2** or **3** as shown in Table 2. Both catalysts exhibited generally high anti selectivity and excellent enantioselectivity in the asymmetric direct aldol reactions. Here, use of catalyst **2** always gave anti aldol products *anti*-**5a**∼**i**, *anti*-**7a**, and *anti*-**9a** with the (2*S*,1′*R*) configuration, while use of catalyst **3** afforded *anti*-**6a**∼**i**, *anti*-**8a**, and *anti*-**10a** with the (2*R*,1′*S*) configuration.[8] In case of cyclopentanone substrate, the catalyst loading could be further reduced to 1 mol % without losing the high anti selectivity and enantioselectivity (entries 20 and 22).

A possible transition state model has been proposed as shown in Figure 1 to account for the observed absolute configuration of aldol product **5** (R = H) or **6** (R = H) and the high selectivity of the catalyst **2** or **3**.

Table 1. Asymmetric Direct Aldol Reaction of Cyclohexanone and *p*-Nitrobenzaldehyde Catalyzed by **2**[a]

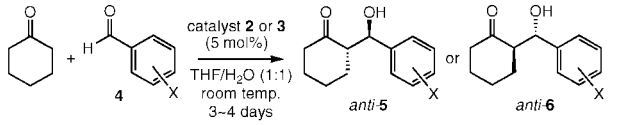
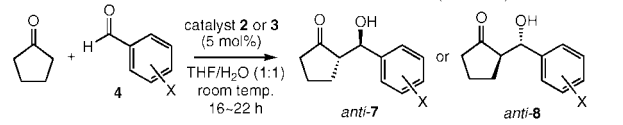
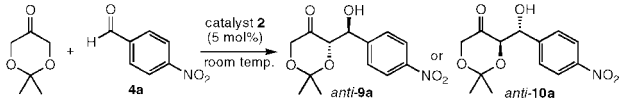
entry	solvent	time (h)	% yield (anti/syn)[b,c]	% ee[d]
1	DMSO	68	4 (−/−)	98/−
2	DMF	68	6 (−/−)	99/−
3	MeCN	68	1 (−/−)	94/−
4	THF	68	54 (75/25)	88/40
5	toluene	68	28 (−/−)	82/−
6	neat[e]	68	65 (76/24)	92/20
7	MeOH	68	89 (80/20)	92/50
8	*i*-PrOH	68	85 (90/10)	97/49
9	H_2O	68	64 (91/9)	97/62
10		94	90 (93/7)	98/75
11	sat NaCl	46	94 (87/13)	96/75
12	DMSO/H_2O	94	92 (91/9)	98/80
13	DMF/H_2O	75	73 (85/15)	98/51
14	MeCN/H_2O	75	95 (88/12)	97/48
15	THF/H_2O	48	95 (94/6)	98/51

[a] Unless otherwise specified, asymmetric direct aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde in the presence of 5 mol % of catalyst **2** at room temperature under the given reaction conditions. [b] Isolated yield of **5**. [c] The anti/syn ratio of **5** was determined by ^1H NMR analysis. [d] Enantiopurity of aldol product **5** was determined by HPLC analysis using a chiral column [DAICEL Chiralpak AD-H] with hexane-isopropyl alcohol as solvent. [e] In cyclohexanone.

[†] Daiichi Sankyo Co.
[‡] Kyoto University.

10.1021/ja807807p CCC: $40.75

Table 2. Asymmetric Direct Aldol Reaction of Cyclic Ketone and Substituted Benzaldehyde Catalyzed by **2** or **3**[a]

entry	aldehyde **4**	catalyst	aldol	% yield (*anti*/*syn*)[b,c]	% ee[d]
					
1	X = *p*-NO_2	**2**	**5a**	99 (93 / 7)	97
2		**3**	**6a**	96 (91 / 9)	98
3	X = *p*-CN	**2**	**5b**	98 (92 / 8)	97
4		**3**	**6b**	95 (95 / 5)	97
5	X = *p*-CF_3	**2**	**5c**	99 (92 / 8)	96
6		**3**	**6c**	99 (83 / 17)	94
7	X = *p*-Br	**2**	**5d**	96 (93 / 7)	98
8		**3**	**6d**	86 (87 / 13)	96
9	X = *p*-Cl	**2**	**5e**	89 (89 / 11)	97
10		**3**	**6e**	83 (85 / 5)	94
11	X = *p*-CO_2Me	**2**	**5f**	99 (89 / 11)	93
12		**3**	**6f**	94 (85 / 15)	94
13	X = *m*-NO_2	**2**	**5g**	90 (97 / 3)	98
14		**3**	**6g**	72 (98 / 2)	99
15	X = *o*-NO_2	**2**	**5h**	52 (93 / 7)	99
16		**3**	**6h**	34 (93 / 7)	99
17	X = H	**2**	**5i**	53 (96 / 4)	98
18		**3**	**6i**	25 (89 / 11)	76
					
19	X = *p*-NO_2	**2**	**7a**	99 (92 / 8)	93
20				90 (89 / 11)[e]	92
21		**3**	**8a**	96 (95 / 5)	96
22				99 (92 / 8)[e]	91
					
23		**2**	**9a**	99 (90 / 10)	98
24		**3**	**10a**	48 (89 / 11)	97

[a] Unless otherwise specified, asymmetric direct aldol reaction of cyclohexanone and substituted benzaldehyde **4** in the presence of 5 mol % of catalyst **2** or **3** at room temperature for 3−4 days. [b] Isolated yield. [c] The anti/syn ratio was determined by ^{1}H NMR analysis. [d] Enantiopurity of anti aldol products was determined by HPLC analysis using a chiral column [DAICEL Chiralpak AD-H, AS-H, and Chiralcel OD-H] with hexane-isopropyl alcohol as solvent. [e] Use of 1 mol % of catalyst **2** or **3** for 108 h.

In summary, we have succeeded in obtaining both enantiomeric aldol products by using two different chiral organocatalysts **2** and **3**, which are easily derived from common chiral source **1** with the unique cis-diamine structure. This strategy is in principle applicable to another catalytic system, and further effort to this end is currently underway in our laboratory.

Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

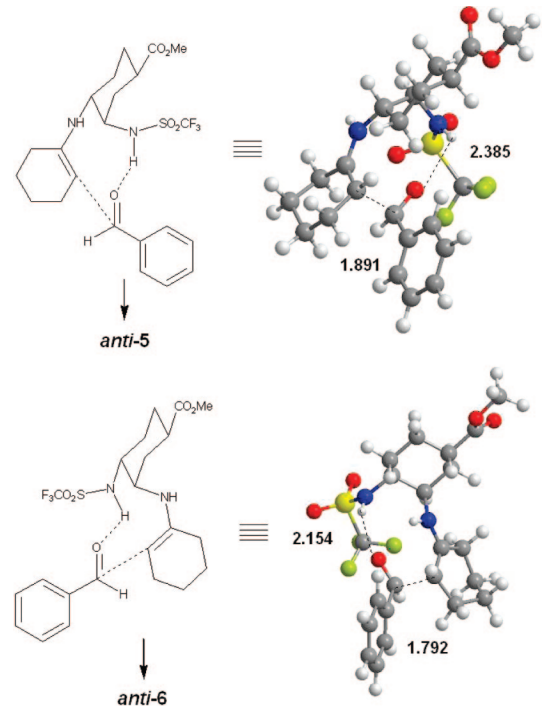


Figure 1. Proposed transition state of aldol reaction of cyclohexanone with benzaldehyde catalyzed by **2** and **3**. The geometry was optimized by the PM5 method.

References

(1) Recent reviews (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2007. (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2.

(2) (a) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095. (b) Yoshino, T.; Nagata, T.; Haginoya, N.; Yoshikawa, K.; Kanno, H.; Nagamochi, M. PCT Int. Appl. WO2001074774, 2001.

(3) Recent reviews (a) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Mlynarski, J.; Paradowska, J. *Chem. Soc. Rev.* **2008**, *37*, 1502.

(4) Recent selected examples of direct asymmetric aldol reactions: (a) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288. (b) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074. (c) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247. (d) Xu, X.-Y.; Wang, Y.-Z; Gong, L.-Z. *Org. Lett.* **2007**, *9*, 4247. (e) Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654. (f) Luo, S.; Xu, H.; Zhang, L.; Li, J.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 653. (g) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Barbas, C. F., III *Org. Lett.* **2008**, *10*, 1621. (h) Luo, S.; Xu, H.; Chen, L.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 1775. (i) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082.

(5) (a) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055. (b) Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem. Asian. J.* **2006**, *1*−*2*, 210. (c) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1738. See also: (d) Kano, T.; Tokuda, O.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 7423.

(6) (a) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. (b) Kano, T.; Hato, Y.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 8467 (see also ref 5c)

(7) (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100. (b) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103, and references therein.

(8) The absolute and relative configuration of the aldol products **5**−**10** was determined by comparison with the following references (a) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., Jr *Org. Lett.* **2005**, *7*, 1383. (b) Gryko, D.; Lipiński, R. *Eur. J. Org. Chem.* **2006**, 3864. (c) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., Jr *J. Am. Chem. Soc.* **2006**, *128*, 734.

JA807807P