Catalytic Asymmetric Synthesis of Both Syn- and Anti-β-Amino Alcohols

Shū Kobayashi,* Haruro Ishitani, and Masaharu Ueno

Department of Applied Chemistry, Faculty of Science
Science University of Tokyo (SUT)
CREST, Japan Science and
Technology Corporation (JST)
Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

Received October 8, 1997

β-Amino alcohol units are often observed in biologically interesting compounds, and several methods for the synthesis of these units have been developed.[1−5] Among them, catalytic asymmetric processes are the most effective and promising. Asymmetric ring opening of symmetric epoxides by nitrogen nucleophiles in the presence of a chiral Lewis acid catalyst[2] and ring opening of chiral epoxides or aziridines, which are prepared by catalytic asymmetric reactions, are useful methods.[3] Recent progress has been made by Sharpless to introduce direct asymmetric aminohydroxylation (AA) of alkenes.[4] The Sharpless AA method has realized a high degree of enantioselctivities to afford syn-β-amino alcohols directly. Herein, we describe an alternative approach for the synthesis of chiral β-amino alcohols using catalytic diastereo- and enantioselective Mannich-type reactions of α-alkoxy enolates with aldimines (Scheme 1). According to this methodology, both syn- and anti-β-amino alcohols can be obtained in high selectivities by simply choosing the protective groups of the α-alkoxy parts and of the R^2 (ester) part of the enolates, accompanied with formation of new carbon−carbon bonds.[5]

First, we tested the reaction of aldimine **2a** with α-TBSO-ketene silyl acetal **3a** using 10 mol % of zirconium catalyst **1**, which was prepared from $Zr(O^tBu)_4$, 2 equiv of (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol ((*R*)-Br-BINOL), and 1-methylimidazole (NMI) (Table 1).[6] The reaction proceeded smoothly to afford the corresponding α-alkoxy-β-amino ester in a 76% yield with moderate syn-selectivity,[7] and the enantiomeric excess of the syn-adduct was proven to be less than 10%. We then screened various reaction conditions. It was found that when 1,2-dimethylimidazole (DMI) was used instead of NMI, the selectivity increased dramatically. Moreover, the diastereo- and enantioselectivities were improved when the reaction was carried out at −78 °C. The O-substituents of ketene silyl acetals and solvents also influenced the yield and selectivity, and finally, the best result (quantitative, syn/anti = 96:4, syn = 95% ee) was obtained when the reaction was carried out in toluene using ketene silyl acetal **3b(E)**. It was also interesting from a mechanistic point of view that geometrically isomeric ketene silyl acetal **3b(Z)** also gave excellent diastereo- and enantioselectivities. We next tried other substrates, and the results are shown in Table 2. In all cases, the desired adducts including syn-β-amino alcohol units were obtained in high diastereo- and enantioselectivities.

On the other hand, it was found that anti-β-amino alcohol derivatives were obtained by the reaction of aldimine **2a** with α-benzyloxy-ketene silyl acetal **3c** under the same reaction conditions.[8] Namely, in the presence of 10 mol % of the above catalyst, aldimine **2a** reacted with **3c** smoothly to give the corresponding adduct quantitatively with anti-preference, and the enantiomeric excess (ee) of the anti-adduct was 95%. It was exciting that both syn- and anti-amino alcohol units were prepared

Scheme 1. Chiral β-Amino Alcohol Synthesis

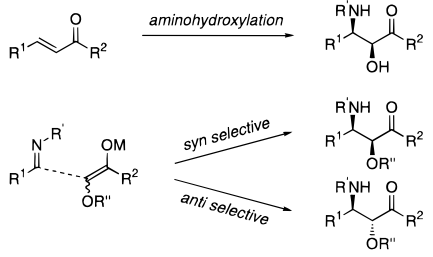
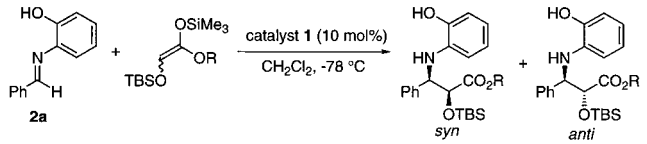
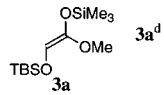
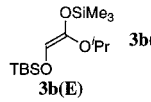
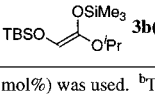
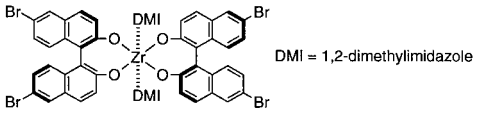


Table 1. Effects of Enolates and Solvents



entry	enolate		yield, %	*syn/anti*	ee, % (*syn*)
1[a,b]		**3a**[d]	76	66/34	6
2[b]		**3a**	62	90/10	63
3		**3a**	90	94/ 6	82
4		**3b(E)**[e]	90	91/ 9	89
5[c]		**3b(E)**	quant	96/ 4	95
6[c]		**3b(Z)**[f]	65	>99/ 1	96

[a]NMI (12 mol%) was used. [b]The reaction was carried out at -45 °C. [c]Toluene was used as a solvent. [d]E/Z = 93/7. [e]E/Z = 87/13. [f]E/Z = 1/99.



1

(1) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Shioiri, T.; Hamada, Y. *Heterocycles* **1988**, *27*, 1035. (c) Barlow, C. B.; Bukhari, S. T.; Guthrie, R. D.; Prior, A. M. *Asymmetry in Carbohydrates*; Dekker: New York, 1979; pp 81−99.

(2) (a) Yamashita, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1213. (b) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. (c) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. For the stoichiometric use of a chiral source, see: (d) Emziane, M.; Sutowardoyo, K. I.; Sinou, D. *J. Organomet. Chem.* **1988**, *346*, C7. (e) Hayashi, M.; Kohmura, K.; Oguni, N. *Synlett* **1991**, 774.

(3) (a) DuBois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 317. (b) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420. (c) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (d) Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1993**, 469. (e) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792.

(4) (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451. (b) Li, G.; Sharpless, K. B. *Acta Chem. Scand.* **1996**, *50*, 649. (c) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810. (d) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813. (e) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483.

(5) (a) Shibasaki, M.; Sasai, H. *Pure Appl. Chem.* **1996**, *68*, 523. (b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785. (c) Hwang, G.-I.; Chung, J.-H.; Lee, W. K. *J. Org. Chem.* **1996**, *61*, 6183. (d) Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677. (e) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4469. (f) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623.

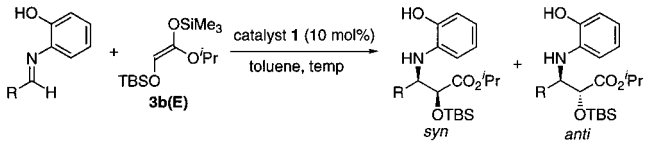
(6) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153.

(7) Relative configuration assignment was made after converting to the corresponding β-lactam (see the Supporting Information).

(8) We also observed similar dramatic changes in diastereoselectivities in chiral tin(II)-mediated asymmetric aldol reactions. (a) Kobayashi, S.; Horibe, M. *Synlett* **1994**, 147. (b) Kobayashi, S.; Horibe, M.; Saito, Y. *Tetrahedron* **1994**, *50*, 9629. (c) Kobayashi, S.; Kawasuji, T. *Tetrahedron Lett.* **1994**, 35, 3329. (d) Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1708. See also ref 5b.

S0002-7863(97)03527-0 CCC: $15.00
Published on Web 01/06/1998

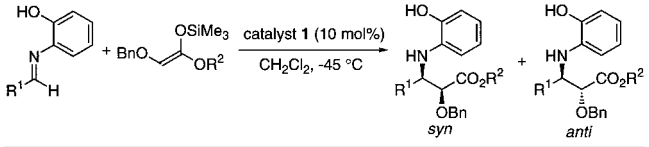
Table 2. Synthesis of Syn-Amino Alcohol Units



R	temp, °C	yield, %	*syn*/*anti*	ee, % (*syn*)
Ph (**2a**)	-78	quant	96/ 4	95
1-naphthyl	-78	65	>99/ 1	91
2-furyl	-45	68	82/18	92
p-ClPh[a)]	-78	73	92/ 8	98

a) Dichloromethane was used as solvent, and 30 mol% of DMI was added.

Table 3. Synthesis of Anti-Amino Alcohol Units



R^1	R^2	yield, %	*syn*/*anti*	ee, % (*anti*)
Ph (**2a**)[a]	^{i}Pr (**3c**)[e]	quant	32/68	95
Ph (**2a**)[b]	PMP[f,g]	91	6/94	80
1-naphthyl[c]	c-C_6H_{11}[e]	80	8/92	96
2-furyl[b]	PMP	68	13/87	80
p-ClPh[a,c]	^{i}Pr (**3c**)	quant	43/57	91
p-ClPh[b]	PMP	72	8/92	76
c-C_6H_{11}[d]	c-C_6H_{11}	41	18/82	92

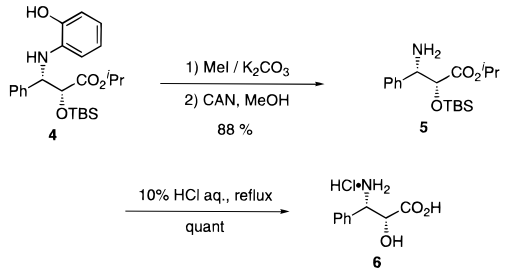
[a]DMI (30 mol%) was used. [b]NMI (20 mol%) was used. [c]The reaction was carried out at -78 °C. [d]The imine was prepared from cyclohexanecarboxaldehyde with 2-amino-3-methylphenol *in situ* in the presence of MS4A. See text. [e]E/Z = <1/>99. [f]E/Z = 4/96. [g]PMP = *p*-methoxyphenyl.

by simply choosing the protective groups of the α-alkoxy parts of the silyl enolates. Several aldimines were then tested and the results are summarized in Table 3. In most cases, the desired anti-adducts were obtained in high yields with high diastereo- and enantioselectivities. While higher diastereoselectivities were obtained using a ketene silyl acetal derived from a *p*-methoxyphenyl (PMP) ester, higher enantiomeric excesses were observed in the reactions using a ketene silyl acetal derived from isopropyl or cyclohexyl ester. In the reaction of the aldimine derived from cyclohexanecarboxaldehyde, use of 2-amino-3-methylphenol instead of 2-aminophenol was effective in affording the corresponding anti-adduct in high selectivities.[9]

A typical experimental procedure is described for the reaction of aldimine **2a** with ketene silyl acetal **3b(E)**. To $Zr(O^tBu)_4$ (0.04 mmol) in toluene (0.25 mL) were added (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol (0.088 mmol) in toluene (0.5 mL) and 1,2-dimethylimidazole (0.08 mmol) in toluene (0.25 mL) at room temperature. The mixture was stirred for 1 h at the same temperature and then cooled to −78 °C. Toluene solutions (0.75 mL) of **2a** (0.4 mmol) and **3b(E)** (0.5 mmol) were successively added. The mixture was stirred for 20 h, and saturated aqueous $NaHCO_3$ was then added to quench the reaction. The aqueous layer was extracted with dichloromethane, and the crude adduct was treated with THF/1 N HCl (10:1) at 0 °C for 30 min. After a usual workup, the crude product was chromatographed on silica gel to give the desired adduct. The diastereomer ratio was determined by ^{1}H NMR analysis, and the optical purity was determined by HPLC analysis using a chiral column (see the Supporting Information).

(9) The NMR spectra of the corresponding aldimine indicated that most of them existed as stable benzoxazolidine forms. This is only for the electrophile derived from cyclohexanecarboxaldehyde and 2-amino-3-methylphenol.

Scheme 2. Synthesis of (2*R*,3*S*)-3-Phenylisoserine·Hydrochloride (**6**)



Finally, to demonstrate the utility of these reactions, we undertook the synthesis of (2*R*,3*S*)-3-phenylisoserine•hydrochloride (**6**), which is a precursor of the C-13 side chain of paclitaxel, known to be essential for its biological activity.[10] The key catalytic asymmetric Mannich-type reaction of aldimine **2a** with ketene silyl acetal **3b(E)** using the chiral zirconium catalyst prepared using (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol proceeded smoothly in toluene at −78 °C to afford the corresponding syn-adduct quantitatively in excellent diastereo- and enantioselectivities (syn/anti = 95:5, syn = 94% ee). Methylation (MeI, K_2CO_3) of the phenolic OH of the adduct **4** and deprotection using cerium ammonium nitrate (CAN) gave β-amino ester **5**. Hydrolysis of the ester and deprotection of the *tert*-butyldimethylsilyl (TBS) group were performed using 10% HCl to afford **6** quantitatively.[11−12]

In conclusion, we have developed an efficient method for the synthesis of both syn- and anti-amino alcohol units with high yields and high selectivities via catalytic asymmetric Mannich-type reactions of aldimines with α-alkoxy silyl enolates. The protocol includes catalytic diastereo- and enantioselective carbon−carbon bond-forming processes, and the syn- and anti-selectivities were controlled by simply choosing the protective groups of the α-alkoxy parts and of the ester parts of the silyl enolates. Since both enantiomers of the chiral source, (*R*)- and (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol, are commercially available, all four stereoisomers of β-amino alcohol units can be prepared according to this method. The utility of this protocol has been demonstrated by the concise synthesis of (2*R*,3*S*)-3-phenylisoserine•hydrochloride (a precursor of the C-13 side chain of paclitaxel).

Acknowledgment. H.I. thanks the JSPS fellowship for Japanese Junior Scientists. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan, and a SUT Special Grant for Research Promotion.

Supporting Information Available: Experimental procedures and NMR and HPLC data (10 pages). See any current masthead page for ordering and Internet access instructions.

JA973527T

(10) (a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15. (b) Escalante, J.; Juaristi, E. *Tetrahedron Lett.* **1995**, *36*, 4397. (c) Wang, Z.-M.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 5104. (d) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320. (e) Georg, G. I.; Mashava, P. M.; Akgün, E.; Milstead, M. W. *Tetrahedron Lett.* **1991**, *32*, 3151. (f) Denis, J.-N.; Correa, A. E.; Greene, A. *J. Org. Chem.* **1990**, *55*, 1957. See also ref 4b,e.

(11) Mp 223−225 °C (dec.) (lit. 222−224 °C (dec);[12] 224−226 °C[4e]). $[\alpha]^{29}_D$ −13.7 (*c* 0.83, 6 N HCl) (lit. $[\alpha]^{20}_D$ −14.6 (*c* 1.03, 6 N HCl);[12] $[\alpha]^{29}_D$ −14.9 (*c* 0.55, 6 N HCl)[4e]).

(12) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.