J|A|C|S
COMMUNICATIONS

Published on Web 07/13/2004

# Catalytic Enantio- and Diastereoselective Aldol Reactions of Glycine-Derived Silicon Enolate with Aldehydes: An Efficient Approach to the Asymmetric Synthesis of *anti*-β-Hydroxy-α-Amino Acid Derivatives

Jun Kobayashi, Masayuki Nakamura, Yuichiro Mori, Yasuhiro Yamashita, and Shū Kobayashi*

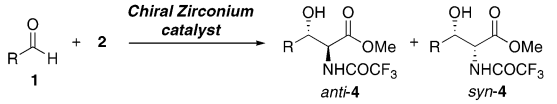
*Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

Received April 26, 2004; E-mail: skobayas@mol.f.u-tokyo.ac.jp

β-Hydroxy-α-amino acids are ubiquitous, important components of various nitrogen-containing biologically active compounds and natural products. For example, the vancomycin class of antibiotics[1] incorporates an *erythro*- and a *threo*-β-arylserine moiety, and the promising antifungal agents, sphingofungins,[2] contain a β-hydroxy-α-amino acid in the polar headgroup of their structure. In addition, β-hydroxy-α-amino carbonyl compounds are often used as intermediates for synthesis of 2-amino-1,3-diols, β-lactams,[3] aziridines,[4] and so on. Among a number of methods reported to date for the asymmetric synthesis of β-hydroxy-α-amino acids, the aldol reaction of glycine derivatives with aldehydes has been considered to be the most synthetically efficient approach.[5] However, there have been few successful examples demonstrating a catalytic asymmetric process: several groups reported Lewis acid-catalyzed asymmetric synthesis of 2-oxazoline-4-carboxylates as surrogates of β-hydroxy-α-amino acids,[6] while recently more direct approaches to β-hydroxy-α-amino carbonyl compounds have been developed using glycine Schiff base derivatives.[7] Although each of these approaches involves an elegant methodology, there still remain some limitations such as substrate generality, and very little is known concerning actual applications to efficient synthesis of biologically important compounds. Herein we describe a new synthetic protocol based on catalytic enantio- and diastereoselective aldol reactions of *N*-trifluoroacetylglycine-derived silicon enolate with aldehydes using a chiral zirconium catalyst.

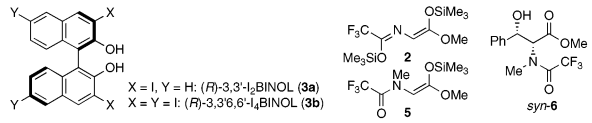
We have previously shown that chiral zirconium complexes prepared from zirconium alkoxide and BINOL derivatives activate both azomethine compounds and aldehydes effectively, and various catalytic asymmetric reactions such as Mannich-type reactions,[8a] Mukaiyama aldol reactions,[8b] hetero Diels−Alder reactions,[8c] etc. have been performed. In our initial investigations, we conducted aldol reactions of benzaldehyde with several types of glycine-derived silicon enolates under the conditions of toluene, 0 °C in the presence of a chiral zirconium catalyst prepared from $Zr(O^tBu)_4$ (10 mol %), (*R*)-3,3′-$I_2$BINOL (**3a**, 12 mol %), $^n$PrOH (80 mol %), and $H_2O$ (20 mol %), which are the optimal conditions for aldol reactions of propionate-derived silicon enolates.[8b] As a result, the reaction of silicon enolate **2**[9] prepared from *N*-trifluoroacetylglycine methyl ester proceeded to give the desired β-hydroxy-α-amino acid derivative **4a** (R = Ph) in good yield (71%) but with disappointing selectivity (anti/syn = 43/57, anti = 6% ee, syn = 46% ee, Table 1, entry 1). We also tested other trimethylsilyl enol ether derivatives of *tert*-butyl *N*-(diphenylmethylene)-glycinate[7a] or 2-oxazolin-5-ones;[10] however, they resulted in no reaction or very low yield with almost no selectivity. Silicon enolate **2** is particularly useful because it can be easily prepared in large scale from glycine methyl ester and stored over a long period. Moreover, the trifluoroacetyl group of the corresponding product is utilized as a useful protecting group for further transformations. As for reaction solvents, toluene was the best for the catalyst

***Table 1.*** Catalytic Enantio- and Diastereo Selective Aldol Reactions of Silicon Enolate **2** with Benzaldehyde (**1a** (R = Ph))[a]




| entry | BINOL derivative | PrOH (mol %) | time (h)[b] | yield (%) | anti/syn | ee (%) (anti) |
|---|---|---|---|---|---|---|
| 1[c] | **3a** | 80 | 0 | 71 | 43/57 | 46[d] |
| 2[e] | **3a** | 80 | 0 | 80 | 29/71 | 63[d] |
| 3[e,f] | **3a** | 80 | 0 | 18 | 17/83 | 93[d] |
| 4 | **3a** | 150 | 0 | 50 | 55/45 | 75 |
| 5 | **3b** | 150 | 0 | 74 | 58/42 | 32 |
| 6 | **3b** | 150 | 1 | 97 | 72/28 | 71 |
| 7 | **3b** | 150 | 4 | 92 | 75/25 | 77 |
| 8 | **3b** | 150 | 8 | 93 | 78/22 | 87 |
| 9 | **3b** | 300 | 8 | 92 | 90/10 | 95 |

[a] Unless noted otherwise, the reaction was carried out with 1.5 equiv of **2** in toluene−$^t$BuOMe (1:1) at −20 °C for 12 h in the presence of a chiral zirconium catalyst prepared from $Zr(O^tBu)_4$ (10 mol %), (*R*)-BINOL derivative **3** (12 mol %), PrOH, and $H_2O$ (10 mol %). [b] Addition time of silicon enolate. [c] In toluene at 0 °C. [d] Ee of syn isomer. [e] At 0 °C. [f] Silicon enolate **5** was used, and the major product was *syn*-**6**.




preparation, and cosolvents used during addition of silicon enolates were next examined. When $^t$BuOMe was used (final solvent ratio: toluene/$^t$BuOMe = 1/1), the yield was increased to 80% and the selectivity was also improved; syn selectivity was raised to anti/syn = 29/71, and the enantiomeric excess of the syn adduct was 63% ee (entry 2). Instead of **2**, we also tested silicon enolate **5**[9b] derived from *N*-methyl-*N*-trifluoroacethylglycine methyl ester. Although the reactivity of **5** was much lower than that of **2**, the diastereo- and enantioselectivity were remarkably increased to anti/syn = 17/83, syn = 93% ee (entry 3). To improve the yield and selectivity, we investigated the reaction conditions further and obtained very surprising results concerning the diastereoselectivity. Thus, when the amount of $^n$PrOH was increased to trap the cationic silicon species more efficiently, the diastereoselectivity was reversed (toluene−$^t$BuOMe, −20 °C, anti/syn = 55/45, entry 4). With the use of (*R*)-3,3′,6,6′-$I_4$BINOL bearing electron-withdrawing iodo groups at the 6,6′-positions, a slight increase of the yield and anti selectivity was obtained, although enantioselectivity was decreased under these reaction conditions (entry 5). Moreover, when silicon enolate **2** was slowly added over 1 h to the reaction solution of the catalyst and aldehyde, the result was dramatically improved favoring the anti-isomer (97%, anti/syn = 72/28, anti = 71% ee, entry 6). The slow addition method was found to be particularly effective in this reaction. Extension of the addition time resulted in marked

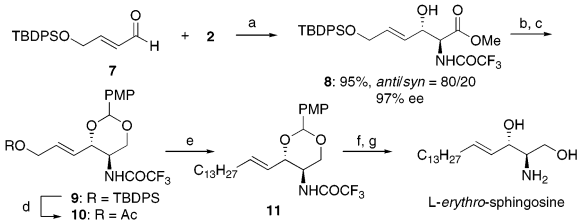

10.1021/ja047597t CCC: $27.50 

***Table 2.*** Catalytic Enantio- and Diastereoselective Aldol Reactions of Silicon Enolate **2** with Various Aldehydes[a]

| entry | R | yield (%) | anti/syn | ee (%)[b] |
|---|---|---|---|---|
| 1 | Ph (**1a**) | 92 | 90/10 | 95 |
| 2 | 4-$MeC_6H_4$ (**1b**) | 87 | 85/15 | 94 |
| 3 | 4-$ClC_6H_4$ (**1c**) | 91 | 84/16 | 94 |
| 4 | 3-$MeC_6H_4$ (**1d**) | 83 | 91/9 | 93 |
| 5 | 3-$ClC_6H_4$ (**1e**) | 93 | 92/8 | 96 |
| 6 | 3-$MeOC_6H_4$ (**1f**) | 93 | 91/9 | 95 |
| 7[c] | 3,5-$(MeO)_2C_6H_3$ (**1g**) | 93 | 87/13 | 97 |
| 8[c] | 2-Naphthyl (**1h**) | 93 | 94/6 | 95 |
| 9 | 2-Furyl (**1i**) | 71 | 87/13 | 90 |
| 10 | $Ph(CH_2)_3C{\equiv}C$ (**1j**) | 81 | 78/22 | 85 |
| 11 | $TBDPSOCH_2C{\equiv}C$ (**1k**) | 85 | 80/20 | 95 |

[a] Reaction was performed according to the conditions of Table 1, entry 9. [b] Ee of the anti isomer. [c] Amount of $H_2O$ was 20 mol %, and 2.0 equiv of **2** was added over 10 h.

***Scheme 1.*** Efficient Asymmetric Synthesis of L-*erythro*-Sphingosine[a]




[a] Conditions: (a) Chiral zirconium catalyst (10 mol %), toluene−$^t$BuOMe, −20 °C. (b) $NaBH_4$, MeOH, rt (87%). (c) (i) $PMPCH(OMe)_2$, TsOH, DMF, rt (71%); (ii) isolation of *trans*-isomer. (d) (i) TBAF, THF, rt; (ii) $Ac_2O$, DMAP, pyridine, 0 °C (90%, two steps); (iii) recrystallization (72%, >99% ee). (e) $C_{12}H_{25}MgBr$, $Li_2CuCl_4$, THF, −15 °C (57%). (f) 2 N NaOH−EtOH, 80 °C (99%); 1 N HCl−THF, 40 °C (75%).

improvement of both yield and selectivity (entries 7 and 8). Finally, when 300 mol % of $^n$PrOH was used and **2** was added over 8 h, the reaction proceeded smoothly in high yield and high anti selectivity with excellent enantioselectivity (92%, anti/syn = 90/10, anti = 95% ee, entry 9).[11]

We then examined reactions of other aldehydes under the optimal conditions, in which silicon enolate **2** (1.5−2.0 equiv) was slowly added over 8−10 h (toluene−$^t$BuOMe, −20 °C), and the results are summarized in Table 2. In most cases, the reactions proceeded smoothly to provide the desired $\beta$-hydroxy-α-amino acid derivatives in high yields with good anti selectivity and excellent enantioselectivity. Various types of benzaldehyde derivatives containing electron-withdrawing or -donating substituents at the para or meta positions were found to be good substrates. Furfural also afforded the corresponding product in good yield with high stereoselection (entry 9). The reaction of propargyl aldehydes cleanly produced *anti*-$\beta$-hydroxy-α-amino acid derivatives in good yield with good enantio- and diastereoselectivity (entries 10 and 11), which can be converted to various compounds.[12]

Finally, to demonstrate the synthetic utility of this aldol reactions, we performed efficient asymmetric synthesis of L-*erythro*-sphingosine.[13] Sphingosine is the backbone of an essential cell membrane component, sphingolipid, and has been widely studied from both biological and chemical points of view.[14] As shown in Scheme 1, the aldol reaction of **2** with aldehyde **7** was conducted in the presence of the chiral zirconium catalyst affording the desired *anti*-aldol adduct **8** in high yield (95%) with high stereoselectivity (anti/syn = 80/20, anti = 97% ee). Reduction of **8** with $NaBH_4$, followed by protection of the resulting 1,3-diol as its *p*-methoxybenzylidene acetal and isolation of the trans isomer provided **9**. The $^t$butyldiphenylsilyl ether was converted to the corresponding acetate **10**, which was recrystallized to an optically pure form (>99% ee) and treated with $C_{12}H_{25}MgBr$ in the presence of a catalytic amount of $Li_2CuCl_4$ to afford **11**. Finally, deprotection of 2-amino-1,3-diol gave L-*erythro*-sphingosine. Compound **8** is highly functionalized and considered to be a potentially useful intermediate for more complex compounds containing a $\beta$-hydroxy-α-amino carbonyl moiety.

In summary, we have developed an efficient process for the asymmetric synthesis of *anti*-$\beta$-hydroxy-α-amino acid derivatives based on highly enantio- and diastereoselective aldol reactions of a glycine-derived silicon enolate with aldehydes using a chiral zirconium catalyst. This is the first example of enantioselective aldol reactions using silicon enolates prepared from *N*-trifluoroacetylglycinate. The resulting *N*-trifluoroacetyl group is easily cleaved under either acidic or basic conditions and can be used directly as a protecting group for further transformations. Further improvement of the efficiency and the generality of the process, as well as exploration of the interesting features of silicon dienolate **2**, are now under investigation.

**Acknowledgment.** This work was partially supported by CREST, SORST, and ERATO, Japan Corporation of Science and Technology, and by a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Science.

**Supporting Information Available:** Experimental procedures and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Recent reviews: (a) Nicolaou, K. C.; Boddy, C. N.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096. (b) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1172.
(2) (a) VanMiddlesworth, F.; Durfresne, C.; Wincott, F. E.; Mosley, R. T.; Wilson, K. E.; *Tetrahedron Lett.* **1992**, *33*, 297. (b) Horn, W. S.; Smith, J. L.; Bills, G. F.; Raghoobar, S. L.; Helms, G. L.; Kurtz, M. B.; Marrinan, J. A.; Frommer, B. R.; Thornton, R. A.; Mandala, S. M. *J. Antibiot.* **1992**, *45*, 1692.
(3) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.
(4) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599.
(5) Recent examples: (a) Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron* **2001**, *57*, 6615. (b) Belokon, Y. N.; Kochetkov, K. A.; Ikonnikov, N. S.; Strelkova, T. V.; Harutyunyan, S. R.; Saghiyan, A. S. *Tetrahedron: Asymmetry* **2001**, *12*, 481. (c) Felice, P. D.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2191.
(6) With α-isocyano acetates: (a) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253. With 5-alkoxyoxazoles: (b) Suga, H.; Ikai, K.; Ibata, T. *J. Org. Chem.* **1999**, *64*, 7040. (c) Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884.
(7) With enolates of glycine Schiff base: (a) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843. Direct use of glycine Schiff base: (b) Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 8289. (c) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542.
(8) (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180. (b) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292. (c) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793.
(9) For the synthesis and utilization of **2**: (a) Oesterle, T.; Simchen, G. *Synthesis* **1985**, 403. (b) Simchen, G.; Schulz, D.; Seethaler, T. *Synthesis* **1988**, 127. (c) Seethaler, T.; Simchen, G. *Liebigs Ann. Chem.* **1991**, 11.
(10) Takagaki, H.; Tanabe, S.; Asaoka, M.; Takei, H. *Chem. Lett.* **1979**, 347.
(11) For further discussion on the stereochemistry, see Supporting Information.
(12) Aliphatic aldehydes reacted sluggishly (<30% yield) under the conditions.
(13) Asymmetric syntheses of sphingosine based on aldol reactions: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 239. (b) Nicolaou, K. C.; Caulfield, T.; Kataoka, H.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 7910. (c) Groth, U.; Schöllkopf, U.; Tiller, T. *Tetrahedron* **1991**, *47*, 2835. (d) Solladié-Cavallo, A.; Koessler, J. L. *J. Org. Chem.* **1994**, *59*, 3240. (e) Kobayashi, S.; Hayashi, T.; Kawasuji, T. *Tetrahedron Lett.* **1994**, *35*, 9573. (f) Spanu, P.; Rassu, G.; Pinna, L.; Battistini, L.; Casiraghi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 3237. (g) Corey, E. J.; Choi, S. *Tetrahedron Lett.* **2000**, *41*, 2765.
(14) (a) Hannun, Y. A.; Loomis, C. R.; Merrill, A. H., Jr.; Bell, R. M. *J. Biol. Chem.* **1986**, *261*, 12604. (b) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075.

JA047597T