Asymmetric Catalytic Aldol-type Reaction with Ketene Silyl Acetals: Possible Intervention of the Silatropic Ene Pathway

Koichi Mikami* and Satoru Matsukawa

Department of Chemical Technology
Tokyo Institute of Technology
Meguro-ku, Tokyo 152, Japan

Received October 18, 1993

The aldol reaction constitutes one of the most fundamental bond construction processes in organic synthesis.[1] Therefore, the detailed understanding of the reaction mechanisms of aldol processes[2] and asymmetric catalysis thereof[3] has attracted much attention. The ketene silyl acetals (KSAs) of esters and thioesters can be used as storable (thio)ester enolate equivalents in the aldol-type processes and eventually provide β-hydroxy esters, a class of compounds of synthetic and biological importance. The "silatropic ene pathway",[4] in other words, direct silyl transfer from the KSA to the aldehyde, may be involved as a possible mechanism in the aldol-type reaction.[5] Herein, we report the silatropic ene approach to the asymmetric catalysis of the aldol-type reaction with KSA by a chiral binaphthol-derived titanium dichloride (BINOL–$TiCl_2$, **1**) (Scheme 1), an efficient asymmetric catalyst for the "prototropic" glyoxylate ene reaction.[6]

The reaction was carried out by adding the thioester-derived KSA **2** and aldehyde **3** at 0 °C to a solution of the chiral titanium dichloride **1** (5 mol %), prepared from (*R*)-binaphthol and diisopropoxytitanium dichloride.[6b] The reaction proceeded smoothly as determined by TLC monitoring. Careful hydrolytic workup with pH 7 buffer at 0 °C followed by flash column chromatography afforded the trimethylsilyl ether of the aldol product **4**. The enantiomeric purity of the product was determined by chiral HPLC (Daicel chiral OB column) analysis of the β-hydroxy thioesters obtained on protodesilylation of **4** and/or ^{1}H NMR (300 MHz) analysis of the (*S*)-(−)- and (*R*)-(+)-MTPA ester derivatives of the β-hydroxy thioesters (Table 1).[7]

Significantly, a range of structurally flexible β-hydroxy thioesters was obtained in high enantiomeric purity (Table 1). Enantiofacial selectivity was enhanced in the nonpolar solvent, toluene, compared to the more polar dichloromethane, propionitrile, and nitroethane solvents which have been used previously

Scheme 1

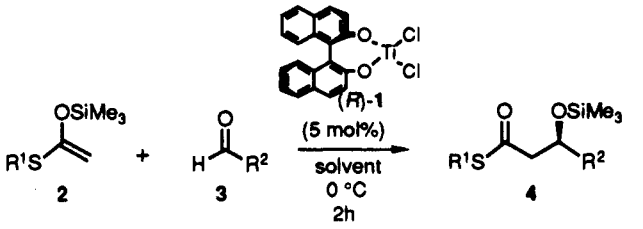
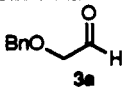
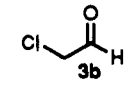
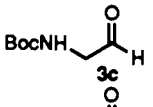
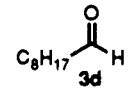
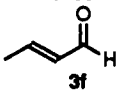
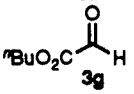


Table 1. Asymmetric Silatropic Ene Process Catalyzed by BINOL–Ti Complex (**1**)[a]

entry	2 (R^1)	3 (RCHO)	solvent	yield (%)	% ee (config)[b]
1	Et	 **3a**	toluene	81	94 (*R*)
2			CH_2Cl_2	71	91 (*R*)
3			C_2H_5CN	[c]	
4			$C_2H_5NO_2$	96	85 (*R*)
5	Bu^t		toluene	80	96 (*S*)[d]
6[e]	Bu^t	 **3b**	toluene	61	91 (*R*)
7[e]			CH_2Cl_2	60	81 (*R*)
8[e]	Et			47	80 (*R*)
9[e]		 **3c**		64	88 (*R*)
10	Bu^t	 **3d**	toluene	60	91 (*S*)[f]
11	Et			67	86 (*S*)[f]
12			CH_2Cl_2	60	60 (*S*)[f]
13	Et	 **3e**	toluene	61	85 (*R*)
14	Et	 **3f**	toluene	60	81 (*R*)
15	Et	 **3g**	toluene	84	95 (*R*)

[a] Conditions as in text. [b] Determined by analysis of 300-MHz ^{1}H NMR spectra of the (*S*)-(−)- and (*R*)-(+)-MTPA ester derivatives and/or HPLC analysis. [c] The reaction was quite sluggish. [d] (*S*)-**1** was used as the catalyst. [e] Run at −20 °C. [f] Due to the priority of groups attached to the chiral carbon.

(1) Reviews: (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2. (d) Masamune, S.; Choy, W.; Peterson, J.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *24*, 1. (e) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

(2) (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481. (b) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576. (c) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177.

(3) (a) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247. (b) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365. (c) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (d) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. (e) Kiyooka, S.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927.

(4) Comprehensive reviews on ene reactions: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (b) Snider, B. B. *Comprehensive Organic Synthesis*; Pergamon: London, 1991; Vols. 2 and 5. (c) Fujita, Y.; Suzuki, S.; Kanehira, K. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 1152. (d) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 1984. (e) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (f) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1. (g) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556.

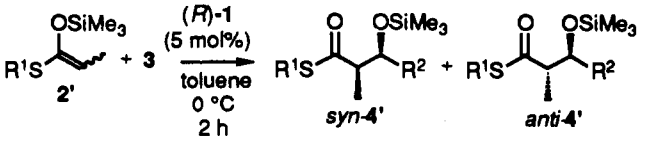
(5) Recently, Myers reported a silicon-directed aldol condensation of KSA without catalysis, which has implications for the pericyclic mechanism: Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *113*, 9672. Myers, A. G.; Widdowson, K. L.; Kukkola, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 2765. Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922. Also see: Denmark, S. E.; Griedel, B. D.; Coe, D. M. *J. Org. Chem.* **1993**, *58*, 988. Group-transfer mechanism has also been reported for the Michael addition of KSA: Webster, O. W.; Hertler, W.; R.; Sogah, D. Y.; Farnham, W. B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1983**, *105*, 5706. RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083.

(6) (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. (c) The prototropic ene reaction with ketone silyl enol ethers: Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039.

(7) The absolute stereochemistry of the product can be determined by the modified Mosher method: Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731. Trost, B. M.; Belletire, J. L.; Godelski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. Thus, the sense of asymmetric induction in the aldol reaction is consistent with that previously observed in the glyoxylate ene reaction;[6] (*R*)-**1** provides the (2*R*) products.

0002-7863/94/1516-4077$04.50/0

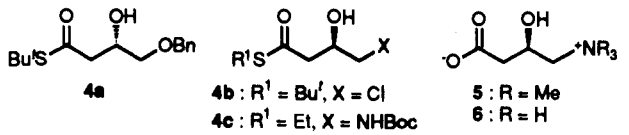
Table 2



entry	2 (R^1)	E/Z	3	yield (%)	syn/anti[a]	% ee (config)[b]
1	Et	77% E	**3a**	85	72:28	90 (*R*)
2			**3g**	64	92:8	98 (*R*)
3	Bu^t	95% E	**3g**	57	57:43	88 (*R*)
4	Et	95% Z	**3a**	80	48:52	86 (*R*)
5	Bu^t	93% Z	**3a**	72	8:92	90 (*R*)
6			**3g**	81	20:80	86 (*R*)

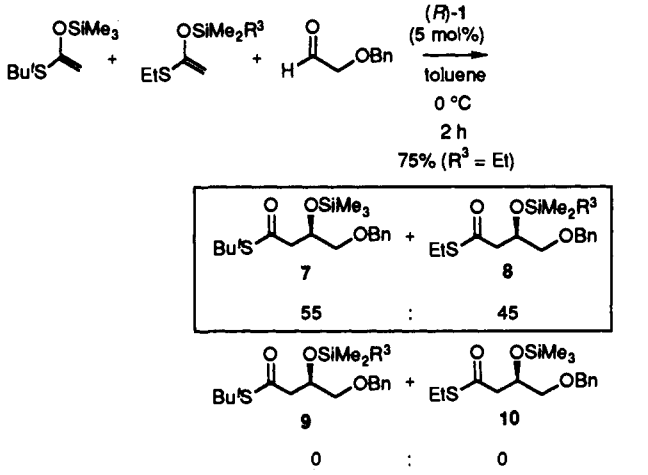
[a] The isomeric ratio was determined by analysis of 300-MHz ^{1}H NMR spectra. [b] The values correspond to the major diastereomer.

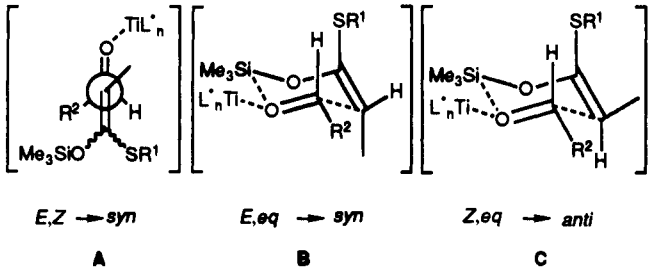
in the asymmetric catalytic aldol-type reaction with silyl enol ethers of thioesters,[3a] esters,[3b,e] and ketones[3c,d] (entries 1 *vs* 2–4, 6 *vs* 7, and 11 *vs* 12). A higher enantiomeric excess was obtained with *tert*-butylthio-KSA than with the ethylthio counterpart (entries 10 *vs* 11). Benzyloxy product (3*S*)-**4a** thus obtained with (*S*)-**1** in 96% ee (entry 5) is a building block for synthesis of the lactone portion of coenzyme A reductase inhibitors mevinolin and compactin.[8] Chloro and amino compounds (3*R*)-**4b** and -**4c** obtained in 91% ee and 88% ee, respectively (entries 6 and 9), are useful intermediates for the synthesis of carnitine **5**[9] and GABOB **6**.[10]



A silatropic ene mechanism requires a cyclic transition state, which has implications for the relative stereochemistry of the reaction (Table 2). An acyclic antiperiplanar transition-state model (**A**) has been widely used to explain the formation of the *syn*-diastereomer, irrespective of the geometry of silyl enol ethers of (thio)esters and ketones.[11] The *syn*-diastereomer was mainly formed from the (*E*)-isomer of KSA **2'** (R^1 = Et) (entries 1 and 2[12]). However, the changeover of diastereoselection from *syn* to *anti* with (*Z*)-KSA (entries 4–6) is inconsistent with the extended transition-state structures (**A**). When the diastereoselectivity depends on the geometry of KSA, the Zimmerman–Traxler "pericyclic" transition states (**B** and **C**)[13] are much more likely. Thus, the *E* to *syn* and *Z* to *anti* diastereoselectivity can be rationalized by the *E*,*eq* (**B**) and *Z*,*ax* (**C**) silatropic ene transition states, respectively.

Scheme 2





We have further established that the reaction proceeds via "intramolecular" silyl transfer by the crossover experiment with 1-(*tert*-butylthio)-1-(trimethylsiloxy)ethylene and 1-(ethylthio)-1-(dimethylethylsiloxy)ethylene (R^3 = Et) (Scheme 2). The 55:45 mixture of the products **7** and **8** was obtained in 75% combined yield. Significantly, no crossover was observed by ^{1}H NMR and capillary GLC (PEG 20M, 25 m) analyses of the product mixture through comparison with the other possible isomers **9** and **10** independently prepared[14] (see the supplementary material). By contrast, use of *tert*-butyldimethylsiloxy acetal (R^3 = Bu^t) leads to considerable contamination (ca. 20%) of the β-trimethylsiloxy ethyl thioester (R^3 = Me) because of the low migratory aptitude of the bulky silyl group.

In summary, we have proposed the silatropic ene mechanism as a guiding principle for the asymetric catalysis of aldol-type reactions with KSA. Further studies along these lines, including theoretical calculations on the silatropic ene transition states, are now underway in our laboratory.

Acknowledgment. We are grateful to Prof. B. B. Snider of Brandeis University and Dr. T. V. RajanBabu of DuPont Central Research for their useful discussions and comments.

Supplementary Material Available: Typical experimental procedures for the silatropic ene reactions, physical data for the products, and ^{1}H NMR data for the MTPA esters of β-hydroxy thioester (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) Review: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.
(9) (a) Zhou, B.; Gopalan, A. S.; Van Middlesworth, F.; Shieh, W. R.; Sih, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 5925. (b) Seebach, D.; Zuger, M. F.; Giovannini, F.; Sonneleitner, B.; Fiechter, A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 151. (c) Gopalan, A. S.; Sih, C. J. *Tetrahedron Lett.* **1984**, *25*, 5235. (d) Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1985**, *26*, 101. (e) Pellegata, R.; Dosi, I.; Villa, M.; Lesma, G.; Palmisano, G. *Tetrahedron* **1985**, *41*, 5607. (f) Rajaskhar, B.; Kaiser, E. T. *J. Org. Chem.* **1985**, *50*, 5480. (g) Bianchi, D.; Gabri, W.; Gesti, P.; Flancalanci, F.; Ricci, M. *J. Org. Chem.* **1988**, *53*, 104. (h) Rosslein, L.; Tamm, C. *Helv. Chim. Acta* **1988**, *71*, 47. (i) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555.
(10) (a) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304. (b) Brehm, L.; Jacobsen, P.; Johansen, J. S.; Larsen, P. K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1459. (c) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707. (d) Renaud, P.; Seebach, D. *Synthesis* **1986**, 424. (e) Takano, S.; Yanase, M.; Sekiguchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1987**, *28*, 1783. (f) Bongini, A.; Gardillo, G.; Orena, M.; Porzi, G.; Sandtri, S. *Tetrahedron* **1987**, *43*, 4377. (g) Braun, M.; Waldmuller, D. *Synthesis* **1989**, 856. (h) Larcheveque, M.; Henrot, S. *Tetrahedron* **1990**, *46*, 4277.
(11) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, *21*, 4607. Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.
(12) The use of more polar solvents leads to a decrease in *syn*-diastereoselectivity on going from dichloromethane (88% *syn*) to nitroethane (80% *syn*), which may imply the partial intervention of a polar rather than concerted reaction pathway in the polar solvents.
(13) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920. For the skewed modification, see: Dubois, J. E.; Dubois, M. *Chem. Commun.* **1968**, 1567. *Bull. Soc. Chim. Fr.* **1969**, 3120. Fellmann, P.; Dubois, J. E. *Tetrahedron* **1978**, *34*, 1349. Also see ref 1c.
(14) t_R (230 °C): **7**, 10.67 min; **8**, 14.02 min; **9**, 12.37 min; **10**, 11.23 min.