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Enantioselective and Diastereoselective Catalysis of the Mukaiyama Aldol Reaction: Ene Mechanism in Titanium-Catalyzed Aldol Reactions of Silyl Enol Ethers

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The aldol process constitutes one of the most fundamental bond constructions in organic synthesis.[1] Therefore, the development of chiral catalysts that promote asymmetric aldol reactions in a highly stereocontrolled fashion has attracted much attention.[2] In the course of studies on the asymmetric catalysis of the Mukaiyama aldol reaction (the Lewis acid-promoted carbonyl addition of silyl enol ethers of ketones),[3] we made the unanticipated observation that aldol products were obtained exclusively as the silyl enol ether (ene-type product)[4] form by the catalysis of a chiral binaphthol-derived titanium dichloride (BINOL–Ti, **1**) (Scheme I).[5] The stereochemical and mechanistic features of the ene-type aldol reaction are the subject of this communication.

The reaction was carried out by adding the trimethylsilyl enol ether **2** of ketone and glyoxylate ester **3** at 0 °C to a dichloromethane solution containing 5 mol % of the chiral titanium dichloride **1**, prepared from (*R*)-binaphthol and diisopropoxytitanium dichloride as previously reported.[6] The reaction was completed within 30 min as determined by TLC monitoring.[7] Careful hydrolytic workup[8] with saturated sodium bicarbonate at 0 °C afforded the aldol product as the trimethylsilyl enol ether form **4**. Flash column chromatography gave the silyl enol ether product **4** as the sole stereoisomer.[9,10] The enantiomeric purity of the product was determined to be almost perfect (99% ee) by ^{1}H NMR (300 MHz) spectral analysis of the (*S*)-(–)- and (*R*)-(+)-MTPA ester derivatives of the β-hydroxy ketone obtained on hydrolysis of **4** (Table I, entry 1).[11]

Scheme I

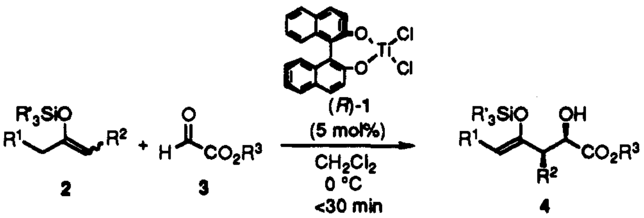
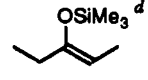
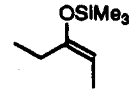
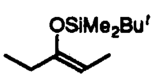
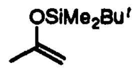
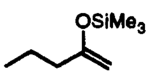


Table I. BINOL–Ti (**1**)-Catalyzed Aldol Reactions of Ketone Silyl Enol Ethers with Glyoxylates[a]

entry	silyl ethers	R^3	yield (%)	*syn*/*anti*[b]	(*Z*)/(*E*)[b]	% ee[c] (config)
1	 [d]	Bu	63	99/1	99/1	99 (*R*)
2		Me	58	98/2	94/6	99 (*R*)
3	 [e]	Me	54	98/2	96/4	99 (*R*)
4	 [f]	Me	73	73/27	84/16	77 (*R*)
5 [g]		Me	44	56/44		
6		Me	71			>99 (*R*)
7		Bu	73			>99 (*R*)
8		Bu	67		95/5	>99 (*R*)
9 [h]		Bu	72		79/21	

[a] Conditions as in text. [b] The isomeric ratio was determined by analysis of 300-MHz ^{1}H NMR spectra. [c] The values correspond to the major isomers. [d] (*E*)/(*Z*) = 14/86. [e] (*E*)/(*Z*) = 73/27. [f] (*E*)/(*Z*) = 10/90. [g] $Cl_2Ti(OPhBr\text{-}p)_2$ was used instead of **1**. [h] Me_3Al was used.

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

(2) Kiyooka, S.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927. Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247. Mukaiyama, T.; Kobayashi, S.; Sano, T. *Tetrahedron* **1990**, *46*, 4653. Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365 and references cited therein. For the asymmetric catalytic aldol reaction of isonitrilacetate, see: Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405.

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(4) Reviews on ene reactions: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (b) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vols. 2 and 5. (c) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (d) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556.

(5) Reviews on asymmetric catalysis by chiral titanium complexes: Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807. Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255. Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986. Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer: Berlin, 1983; Vol. 3, p 217.

(6) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949; **1989**, *111*, 1940.

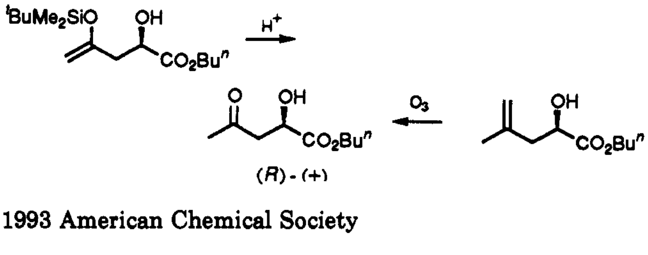
(7) The silyl enol ether product (R_f = 0.68) is clearly distinguishable from the desilylated β-hydroxy ketone (R_f = 0.33) (Merck kieselgel 60F_{254}, EtOAc/hexane = 1:3) (Table I, entry 1). The silyl enol ether was found to decompose to the β-silyloxy derivative at longer reaction times. However, control experiments showed that essentially no change was observed in the (*E*)/(*Z*) ratio of the remaining silyl enol ether and the *syn*/*anti* ratio of the product in 36 and 45% conversions (CD_2Cl_2, 0 °C).

(8) The usual workup with dilute (1 N) hydrochloric acid gave the desilylated β-hydroxy ketones.

(9) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923. Silica gel: Merck kieselgel 60, 70–230 mesh, batch no., e.g., TA210034 and TA362034.

(10) No change was observed in the stereochemical integrity by ^{1}H NMR spectroscopy after the column chromatography.

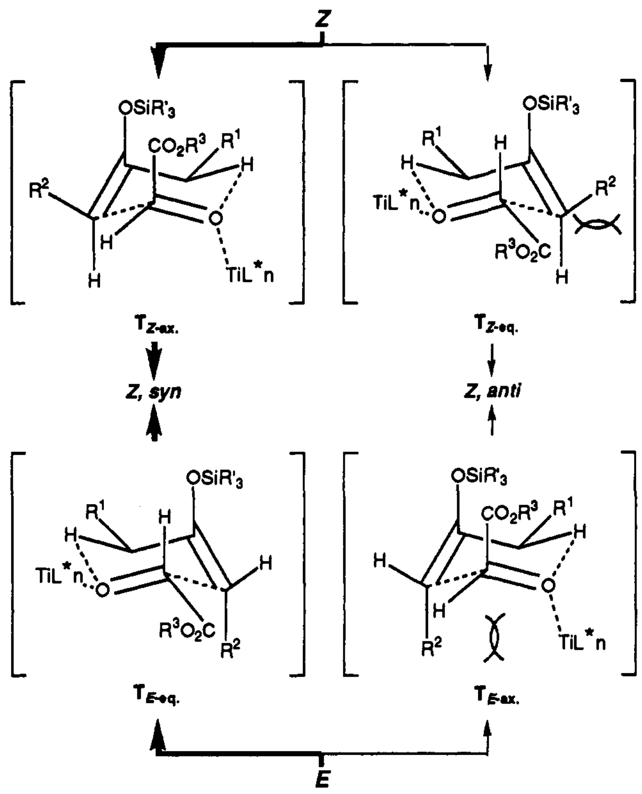
(11) Thus, the absolute stereochemistry of the product can be determined by the modified Mosher method: Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. 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. The absolute configuration of the aldol product was further confirmed by the comparison of the $[\alpha]_D$ value with that of authentic (*R*)-ketone obtained from the (2*R*)-glyoxylate ene product via ozonolysis as shown below. 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.



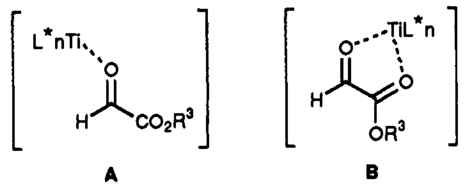
(*R*)-(+)

0002-7863/93/1515-7039$04.00/0

Scheme II



This asymmetric catalytic aldol reaction is characterized by the exclusive ene regioselectivity and unique stereoselectivity. The (*Z*) (namely, *trans*)-silyl enol ether is formed with high stereoselectivity (entries 1–3 and 8).[4,12,13] The *syn*-diastereomer is formed with high selectivity from either isomer of the starting trimethylsilyl enol ethers (entries 1–3).[14] This *syn*-selectivity is analogous to that observed in the alkylaluminum triflate-promoted glyoxylate ene reaction with *trans*- and *cis*-2-butene.[15] This suggests that the present reaction also proceeds through monodentate complex A via cyclic transition states (Scheme II).[4a,15]



Thus, the decrease in *syn*-diastereoselectivity with the more bulky *tert*-butyldimethylsilyl ether (entry 4) would be due to developing 1,3-diaxial repulsion with the axial ester moiety in the (*Z*)-*ax*-transition state. The more Lewis acidic titanium bis(*p*-bromophenoxide) gave a 1:1 diastereomer mixture (entry 5). The *anti*-diastereomer might be formed via the bidentate complex B.[4a,15]

In summary, we have discovered that the Mukaiyama aldol reactions of ketone silyl enol ethers with glyoxylate esters catalyzed by titanium complex **1** afford ene-type products with control of absolute and relative stereochemistry. The formation of ene-type products is also observed with α-benzyloxy aldehydes.[16] The ene process has not been previously considered as a possible mechanism in the Mukaiyama aldol reactions. This mechanism provides, however, another rationale for the *syn*-diastereoselection irrespective of the starting silyl ether geometry.[17] Further studies along these lines are now underway in our laboratory.

Acknowledgment. We are grateful to Professor Barry B. Snider of Brandeis University for his comments and useful discussions.

Supplementary Material Available: Typical experimental procedure for the aldol reactions, physical data for the silyl enol ether products, and ^{1}H NMR data for the MTPA esters of β-hydroxy ketones (7 pages). Ordering information is given on any current masthead page.

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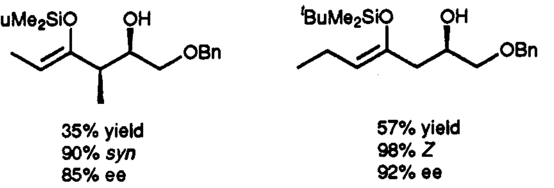
(12) The (*Z*)-geometry was confirmed by ^{13}C NMR analysis through comparison with the (*E*)-isomer obtained with Me$_3$Al as the Lewis acid (*e.g.*, entry 9); the C-3 of the (*Z*)-isomer absorbs downfield from that of the (*E*)-diastereomer (see ref 1b).

(13) The formation of ene-type adducts has been reported in the reaction of silyl enol ether with CH$_2$=O·Me$_3$Al complex: Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1983**, *48*, 2789. For the use of methylaluminum bis(2,6-diphenylphenoxide) instead of Me$_3$Al, see: Maruoka, K.; Concepcion, A. B.; Hirayama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 7422.

(14) The *syn*-stereochemistry of the β-hydroxy ketones was established by ^{13}C NMR analysis through comparison with the *anti*-diastereomer; the 3-methyl and C-2 and C-3 on the *syn*-isomer absorb further upfield than those of the *anti*-diastereomer (see refs 1b and c).

(15) Mikami, K.; Loh, T.-P.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 6305.

(16)



(17) Noyori et al. have proposed an acyclic extended transition state to explain the formation of the *syn*-diastereomer from either silyl enol ether isomer in their TMSOTf-catalyzed aldol reactions with acetals: (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.