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The Chiral Catalyst Control. A Significant Role of a Chiral Catalyst in the Diastereoselective Aldol Reaction Using Chiral Aldehydes

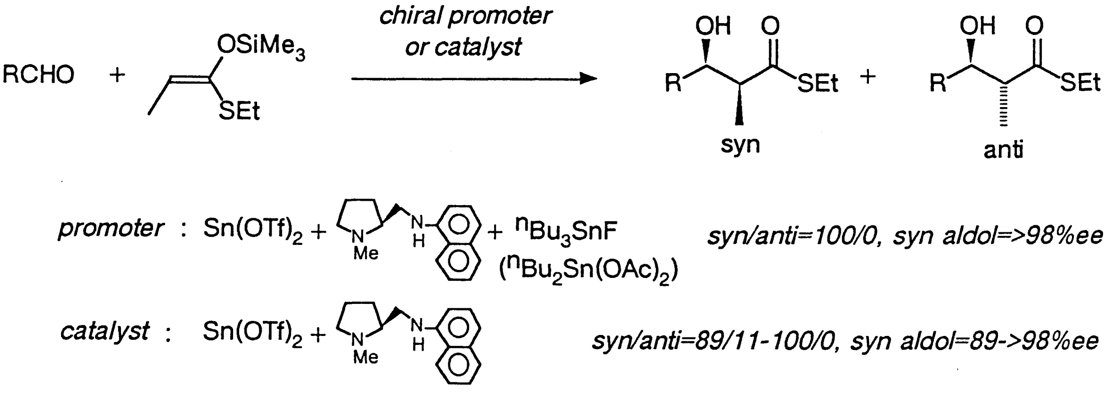
Shū KOBAYASHI, Akihiro OHTSUBO, and Teruaki MUKAIYAMA
Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

The stereochemistry in the aldol reaction of a silyl enol ether with chiral aldehydes is almost completely controlled by the chiral catalyst regardless of the inherent diastereofacial preference of the chiral aldehydes.

In the addition reaction of nucleophiles with chiral carbonyl compounds which has more than two π-faces, main diastereomers are predicted by the Cram's and related rules for asymmetric induction.1) The stereoselectivities in these reactions are mainly dependent on the inherent diastereofacial preference of the chiral carbonyl compounds even in the double stereodifferentiation (the double asymmetric reaction).2)

In this communication, we would like to report a role of a chiral catalyst in the diastereoselective aldol reaction of an achiral silyl enol ether with chiral aldehydes.

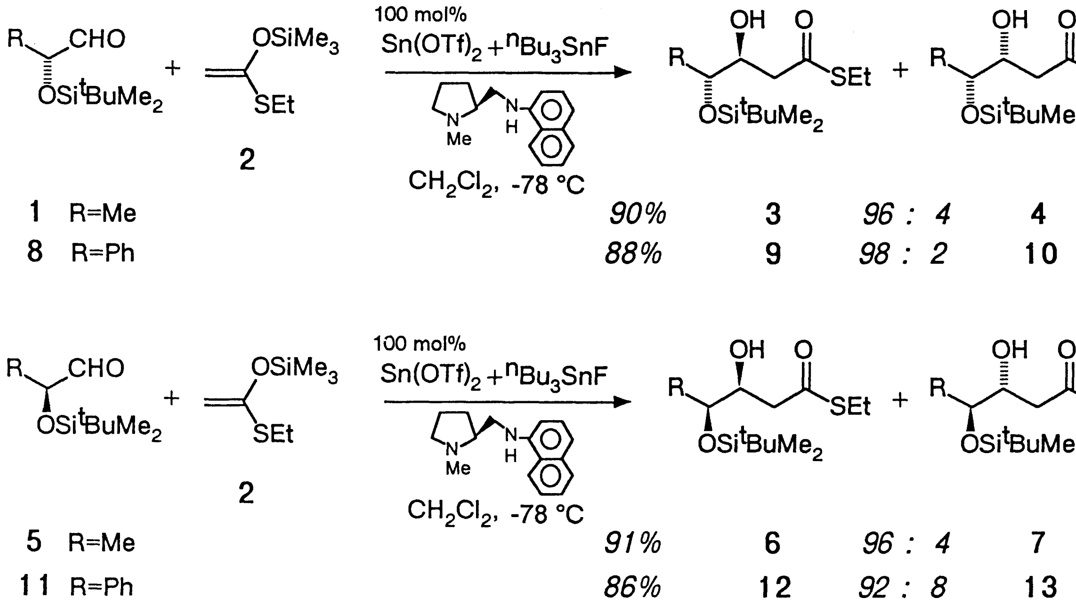
Recently we developed the highly enantioselective aldol reaction between achiral aldehydes and achiral silyl enol ethers by the use of a chiral promoter consisting of tin(II) triflate, a chiral diamine derived from (S)-proline and $^{n}Bu_3SnF$3) ($^{n}Bu_2Sn(OAc)_2$),4) or a chiral catalyst consisting of tin(II) triflate and a chiral diamine.5) A wide variety of aldehydes, including aliphatic, α,β-unsaturated and aromatic aldehydes, are successfully employed to achieve excellent diastereo- (syn) and enantioselectivities (2S, 3S). In our continuous study to extend the scope of this asymmetric reaction,6) the double asymmetric induction between the chiral catalyst and chiral aldehydes has been examined. Though the reactions of chiral aldehydes with chiral enolates have already been intensively studied



as the double stereodifferentiation (the double asymmetric reaction), the aldol reaction of chiral aldehydes with achiral enolates in the presence of a chiral catalyst is unprecedented as far as we know.

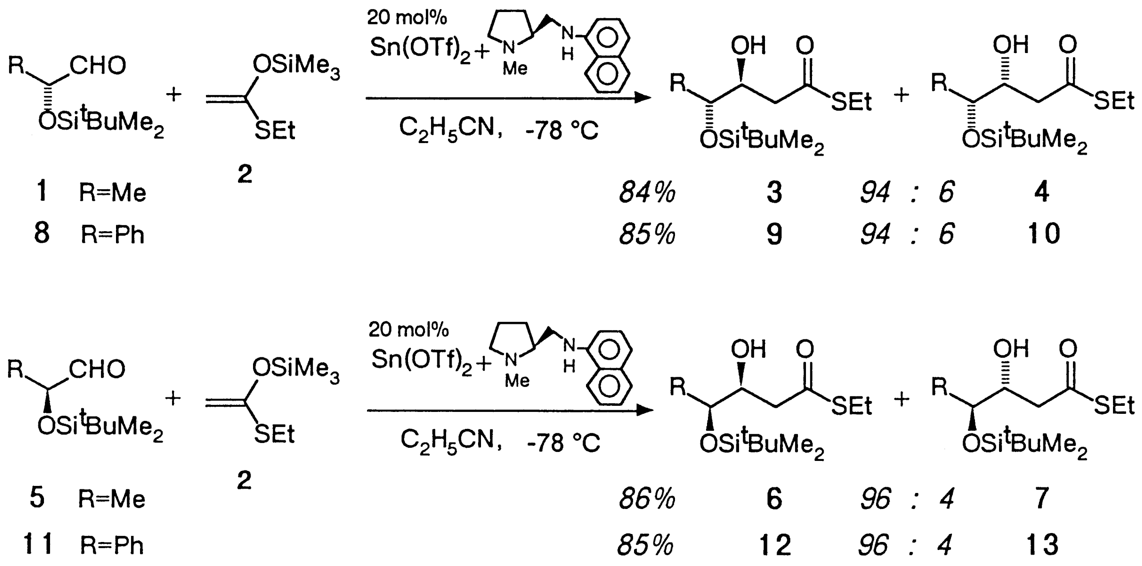
Firstly, the reaction of (R)-2-t-butyldimethylsiloxypropionealdehyde (**1**) with 1-ethylthio-1-trimethylsiloxyethene (**2**) was carried out in dichloromethane at -78 °C in the presence of tin(II) triflate, (S)-1-methyl-2-[(N-naphthylamino)methyl]pyrrolidine and tributyltin fluoride. The reaction smoothly proceeded to give the corresponding diastereomeric aldol-type adducts, **3** and **4**, with a ratio of 96/4 in 90% yield, different from the results obtained by using the achiral promoters.[7] Next, (S)-2-t-butyldimethylsiloxypropionealdehyde (**5**), an enantiomer of **1**, was employed under the same reaction conditions, and in this case again, the diastereomers **6** and **7** were obtained in excellent yield (91%) with excellent selectivity (96/4). *It is noteworthy to refer that the created chiral centers in the major diastereomers have S-configuration in both cases indicating that the stereochemistry in these reactions is controlled not by the chiral aldehydes but by the chiral promoter; the reactions apparently proceeded independent of the chirality of the aldehyde under the chiral catalyst control.*

Almost same yields and selectivities were obtained in the reactions of (R)- and (S)-2-t-buthyldimethylsiloxy-2-phenylacetaldehyde (**8**, **11**) (Scheme 1).

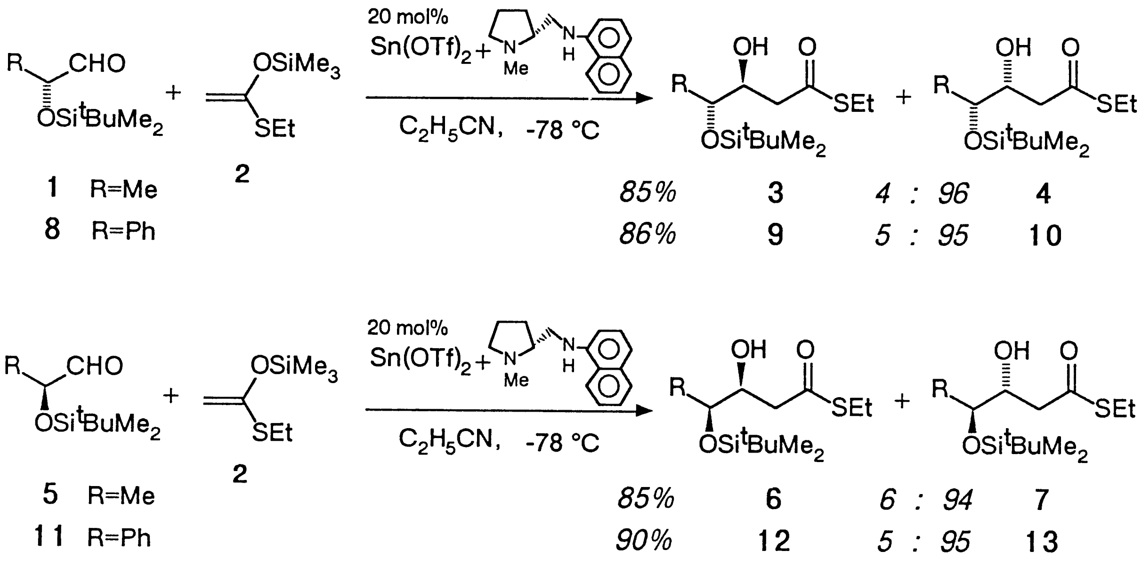


Scheme 1.

Next, we examined the catalytic asymmetric aldol reaction of the chiral aldehydes.[5] The reactions of the chiral aldehydes, **1**, **5**, **8**, and **11**, with **2** were carried out in propionitrile at -78 °C in the presence of a catalytic amount of tin(II) triflate and the chiral diamine according to the slow addition procedure. The results are summarized in Scheme 2, and again the stereochemistry of the main products was controlled by the catalyst. On the other hand, reverse diastereoselectivities are obtained when (R)-1-methyl-2-[(N-naphthylamino)-methyl]pyrrolidine was employed (Scheme 3). Therefore, the optically active four diastereomers can be easily prepared by the suitable combination of the chiral aldehydes and the catalysts.



Scheme 2.



Scheme 3.

A typical experimental procedure is described for the catalytic asymmetric aldol reaction of **1** with **2**; to a solution of tin(II) triflate (0.08 mmol, 20 mol%) in propionitrile (1 ml) was added (S)-1-methyl-2-[(N-naphthylamino)methyl]pyrrolidine (0.088 mmol) in propionitrile (1 ml). The mixture was cooled to -78 °C, then a mixture of **1** (0.4 mmol) and **2** (0.4 mmol) was slowly added to this solution over 6 h. The mixture was further stirred for 15 h, then quenched with saturated aqueous sodium hydrogencarbonate. After usual work-up, the aldol-type adduct was isolated as the corresponding trimethylsilyl ether.

Further investigations employing other chiral aldehydes are now in progress.

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References

1) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); G. J. Karabatsos, *ibid.*, **89**, 1367 (1967); M. Chrest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, **1968**, 2199; N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, **1**, 61 (1977);

2) C. H. Heathcock, "*The Aldol Addition Reaction*," in "*Asymmetric Synthesis*," ed by J. D. Morrison, Academic Press, New York (1984), Vol. 3, Chap. 2, pp.111-212.

3) S. Kobayashi and T. Mukaiyama, *Chem. Lett.*, **1989**, 297; T. Mukaiyama, H. Uchiro, and S. Kobayashi, *ibid.*, **1989**, 1001.

4) T. Mukaiyama, H. Uchiro, and S. Kobayashi, *Chem. Lett.*, **1989**, 1757.

5) T. Mukaiyama, S. Kobayashi, H. Uchiro, and I. Shiina, *Chem. Lett.*, **1990**, 129; S. Kobayashi, Y. Fujishita, and T, Mukaiyama, *ibid.*, **1990**, 1455.

6) S. Kobayashi, T. Sano, and T. Mukaiyama, *Chem. Lett.*, **1989**, 1319; T. Mukaiyama, S. Kobayashi, and T. Sano, *Tetrahedron*, **46**, 4653 (1990); S. Kobayashi, Y. Fujishita, and T. Mukaiyama, *Chem. Lett.*, **1989**, 2069; T. Mukaiyama, H. Uchiro, I. Shiina, and S. Kobayashi, *ibid.*, **1990**, 1019; T. Mukaiyama, I. Shiina, and S. Kobayashi, *ibid.*, **1990**, 2201.

7) The mixture of **3** and **4** was produced in the reaction of **1** with **2** using tin(II) triflate alone (98% yield, **3**/**4**=14/86) or tin(II) triflate and an achiral diamine, N, N, N', N'-tetramethylethylenediamine (TMEDA) (82% yield, **3**/**4**=49/51).

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