CHEMISTRY LETTERS, pp. 1001-1004, 1989.

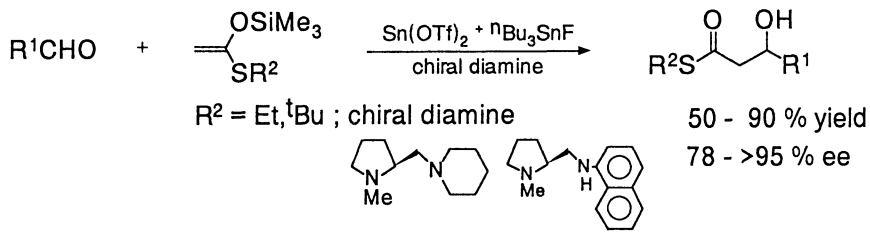
Perfect Stereochemical Control in the Synthesis of syn-α-Methyl-β-hydroxy Thioesters by Asymmetric Aldol Reaction of Silyl Enol Ethers with Aldehydes

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

Perfect stereochemical control in the synthesis of syn-α-methyl-β-hydroxy thioesters are achieved by the asymmetric aldol reaction between silyl enol ether of S-ethyl propanethioate and aldehydes by the use of a chiral promoter consisted of chiral diamine coordinated tin(II) triflate and tributyltin fluoride.

Enantioselective synthesis of α-methyl-β-hydroxy ester equivalents is one of the most challenging tasks in organic synthesis.[1] Aldol reaction is a prospective tool for this purpose and recently several metal enolates, such as boron,[2] silicon,[3] lithium,[4] zirconium,[5] or tin(II),[6] etc.,[7] have been developed to realize high syn/anti selections and diastereofacial selectivities. However, most of these approaches depend on substrate-based asymmetric induction by employing chiral enolates (including metal enolates which have chiral substituents on metals) or chiral aldehydes. Asymmetric aldol reaction for the preparation of syn or anti-α-methyl-β-hydroxy carboxylic acid derivatives, starting from two prochiral reactants by the use of a chiral promoter which activates carbonyl compounds, have never reached the practical level.[6,8]

In the previous paper,[9] we have shown that high enantiomeric excesses could be realized in the aldol reaction between prochiral silyl enol ethers derived from S-ethyl ethanethioate or S-t-butyl ethanethioate and prochiral aldehydes by the use of a new chiral promoter, a combined use of chiral diamine coordinated tin(II) triflate and tributyltin fluoride. In this communication, we would like to



describe on further possible extention of this enantioselective reaction for the synthesis of syn-α-methyl-β-hydroxy thioesters.

In the first place, the reaction of benzaldehyde with 1-trimethylsiloxy-1-ethylthiopropene was chosen as a model and several reaction conditions were examined in the presence of stoichiometric amounts of tin(II) triflate, (S)-methyl-

2-[(piperidin-1-yl)methyl]-pyrrolidine (chiral diamine A) and tributyltin fluoride. It was shown that the geometry of the silyl enol ether strongly influenced both reactivity and selectivity, and that E silyl enol ether[10] smoothly reacted with benzaldehyde to afford the corresponding aldol adduct in 80% yield with high selectivity (syn/anti=93/7, syn aldol=80% ee). Appropriate choice of chiral diamines, which are easily prepared from (S)-proline, also improved both reactivity and selectivity. When (S)-1-methyl-2-[(N-1-naphthylamino)methyl]-pyrrolidine (chiral diamine B) was employed, only syn aldol was obtained with excellent enantiomeric excess (>98%) (Table 1).

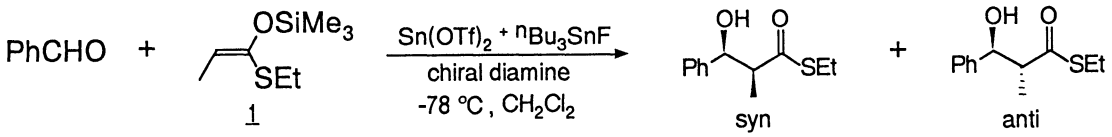
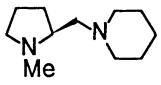
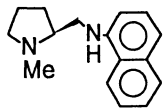
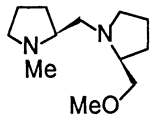


Table 1. Effect of chiral diamine

Chiral diamine	Time/h	Yield/%	syn : anti	ee/%
 (A)	20	80	93 : 7	80
 (B)	3	86	100 : 0	> 98
 (C)	20	77	88 : 12	44

Several aldehydes were successfully employed in the present asymmetric aldol reaction (Table 2). In every case, syn-α-methyl-β-hydroxy thioesters were prepared in good yields with almost perfect diastereo- and enantionselectivities (syn/anti= 100/0, syn aldol=>98% ee).

A typical procedure is described for the reaction of silyl enol ether of S-ethyl propanethioate(1) with benzaldehyde; to a solution of tin(II) triflate (0.4 mmol) and (S)-1-methyl-2-[(N-1-naphthylamino)methyl]-pyrrolidine (chiral diamine B, 0.48 mmol) in dichloromethane (1 ml) was added tributyltin fluoride (0.44 mmol) at room temperature. After the mixture was cooled to -78 °C, 1 in dichloromethane (0.5 ml) was added and the mixture was further stirred for 30 min. Then, benzaldehyde in dichloromethane (1 ml) was added and the reaction mixture was stirred for 3 h, then quenched with aqueous sodium hydrogen carbonate. After the aqueous layer was extracted with dichloromethane, the organic layer was dried and the solvent was removed under reduced pressure. The crude product was purified by thin layer chromatography (silica gel) to yield S-ethyl 2-methyl-3-hydroxy-3-phenylpropanethioate (82%, syn aldol). Anti aldol was not detected by TLC, HPLC, and ^{1}H NMR. The enantiomeric excess of syn aldol was determined to be >98% by measurement of the ^{1}H NMR spectrum of the corresponding MTPA ester.[11]

Thus, perfect control of stereochemistry in aldol reaction starting from two prochiral reactants, silyl enol ethers and aldehydes, was achieved by the use of

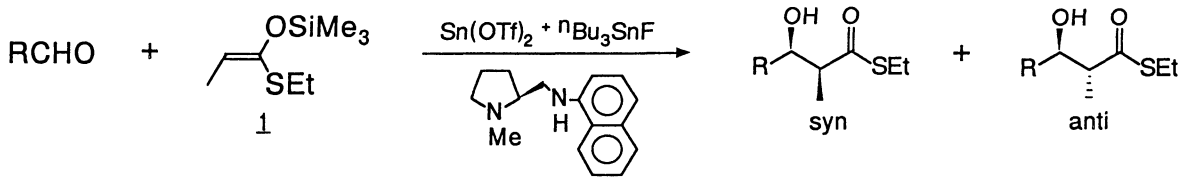
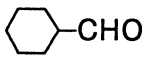


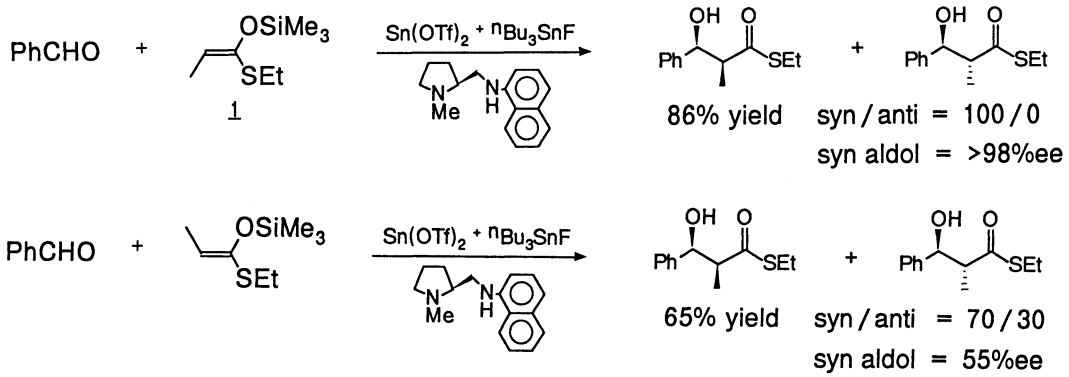
Table 2. Synthesis of syn-α-methyl-β-hydroxy thioesters

Aldehyde	Yield / %	syn : anti	ee / % (config.) [a]
PhCHO	86	100 : 0	> 98 (2R,3S)
p-Cl PhCHO	86	100 : 0	> 98
p-CH_3 PhCHO	91	100 : 0	> 98
p-MeO PhCHO	80	100 : 0	> 98
^{i}PrCHO	52	100 : 0	> 98
	54	100 : 0	> 98
n-C_7H_{15}CHO	48	99 : 1 [b]	> 98

a) Determined by measurement of the ^{1}H-NMR spectrum of the corresponding MTPA ester and/or the acetyl derivatives using Eu(hfc)$_3$ as a chiral shift reagent. No separation could be detected at all by ^{1}H-NMR analysis. The methoxy or methyl peaks cleanly separated in all cases for racemic forms.

b) Determined by HPLC.

the chiral three components promoter. Another characteristic point of this aldol reaction is its high syn selectivities starting from E silyl enol ether. As shown below, (E)-1-trimethylsiloxy-1-ethylthiopropene smoothly reacted with benzaldehyde to afford the corresponding aldol adduct with excellent syn selectivity, while the reaction of the corresponding Z-enolate is slower and the aldol adduct was obtained



with lower syn selectivity. These stereoselectivity may not be explained by considering the transition states hitherto adovocated.[8,12] Precise reaction mechanism is not yet clear at this stage, however, we postulate the formation of an active complex which consists of three components, tin(II) triflate, chiral diamine and tributyltin fluoride. This complex would be able to activate both an aldehyde and a silyl enol ether (double activations); namely, the cationic center of tin(II) triflate activates an aldehyde and, at the same time, the electronegative fluoride interacts with a silicon atom of a silyl enol ether. The unique stereoselectivity would be dependent on the formation of this entropically advantageous intermediate.

Further investigations to clarify the transition state of the present stereocontrolled aldol reaction are now in progress.

References

1) cf. I. Paterson and J. M. Goodman, Tetrahedron Lett., 30, 997 (1989), and references cited therein.
2) T. Mukaiyama and T. Inoue, Chem. Lett., 1976, 559; S. Masamune, T. Sato, B. Kim, and T. A. Wollmann, J. Am. Chem. Soc., 108, 8279 (1986); D. A. Evans, J. Bartroli, and T. L. Shi, ibid., 103, 2127 (1981); A. I. Meyers and Y. Yamamoto, Tetrahedron, 40, 2309 (1984); M. T. Reetz, F. Kunisch, P. Heitmann, Tetrahedron Lett., 27, 4271 (1986); I. Paterson, M. A. Lister, and C. K. McClure, ibid., 27, 4787 (1986).
3) T. Mukaiyama, K. Bannno, and K. Narasaka, Chem. Lett., 1973, 1011; C. Gennari, A. Bernardi, L. Colombo, and C. Scolastico, J. Am. Chem. Soc., 107, 5812 (1985); G. Helmchen, U. Leikauf, and I. T-Knopfel, Angew. Chem., Int. Ed. Engl., 24, 874 (1985).
4) C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, and J. E. Sohn, J. Am. Chem. Soc., 101, 7077 (1979).
5) D. A. Evans and L. R. McGee, J. Am. Chem. Soc., 103, 2876 (1981).
6) T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, Tetrahedron, 40, 1381 (1984).
7) H. Eichenauer, E. Friedrich, W. Lutz, and D. Enders, Angew. Chem., Int. Ed. Engl., 17, 206 (1978); S. G. Davies, I. M. D-Hedgecock, and P. Warner, Tetrahedron Lett., 26, 2125 (1985); K. Narasaka and T. Miwa, Chem. Lett., 1985, 1217.
8) C. H. Heathcock, "Asymmetric Synthesis, Vol. 3, Part B," ed by J. D. Morrison, Academic Press, New York (1984), Chap. 2.
9) S. Kobayashi and T. Mukaiyama, Chem. Lett., 1989, 297.
10) In this paper, the stereochemical descriptors E and Z of silyl enol ethers of thioesters are employed as they correspond to ketene silyl acetals.
11) J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969).
12) cf. M. Braun, Angew. Chem., Int. Ed. Engl., 26, 24 (1987), and references cited therein.
13) Simple diastereoselection in the aldol reaction of silyl enol ethers of thioesters with aldehydes was discussed, C. Gennari, M. G. Beretta, A. Bernardi, G. Moro, C. Scolastico, and R. Todeschini, Tetrahedron 42, 893 (1986).

(Received March 28, 1989)