Tetrahedron: Asymmetry Vol. 2, No. 7, pp. 635-638, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Catalytic Asymmetric Aldol Reaction of the Silyl Enol Ether of Acetic Acid Thioester with Aldehydes Using Chiral Tin(II) Lewis Acid

Shū KOBAYASHI, Minoru FURUYA, Akihiro OHTSUBO, and Teruaki MUKAIYAMA

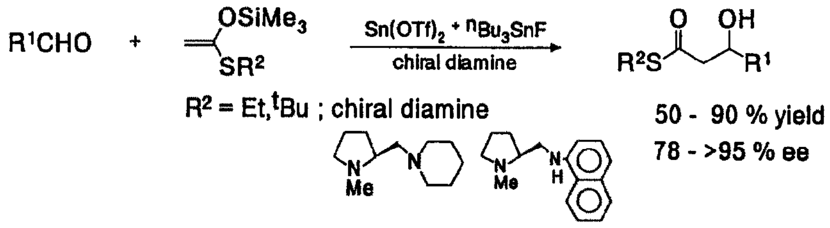
Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

(*Received* 29 *April* 1991)

Abstract: Catalytic asymmetric aldol reaction of the silyl enol ether derived from S-ethyl ethanethioate with achiral aldehydes is carried out by using chiral diamine-coordinated tin(II) triflate to afford the corresponding aldol-type adducts, α-unsubstituted β-hydroxy thioesters, in good yields with high ees.

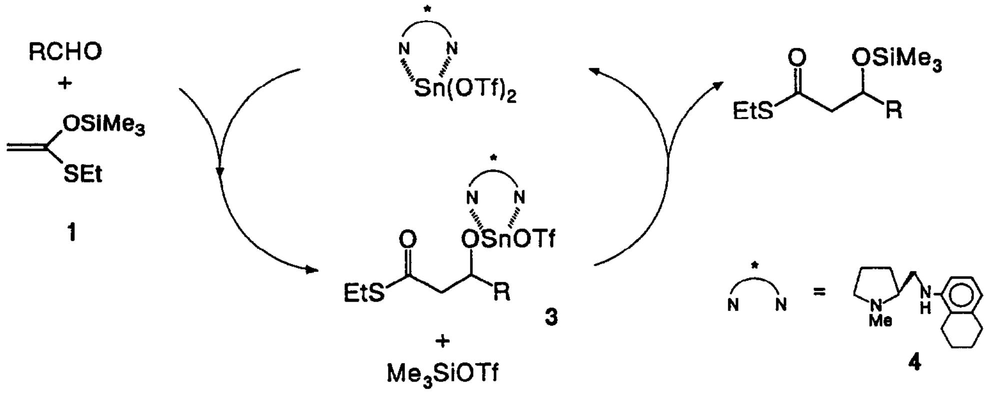
Optically active α-unsubstituted β-hydroxy esters are veratile chiral building blocks in organic synthesis. Asymmetric aldol reaction of the enolates derived from acetic acid esters with carbonyl compounds is one of the most important and convenient tools for the preparation of the esters, although the selectivity in this reaction has been generally low.[1] However, the corresponding reactions of α-substituted enolates with aldehydes proceed with a highly stereoselective manner,[2] and recently some improved methods for the preparation of α-unsubstituted-β-hydroxy ketone or ester equivalents have been reported, but in every case they require a stoichiometric amount of chiral source.[3]

We have already reported that the asymmetric aldol reaction of the silyl enol ethers of S-ethyl or S-t-butyl ethanethioate[4] or S-ethyl propanethioate with aldehydes may be performed with excellent diastereo- and enantioselectivities by the use of a new chiral promoter consisting of stoichiometric amounts of chiral diamine-coordinated tin(II) triflate and tributyltin fluoride[5] or dibutyltin diacetate.[6] Further, catalytic asymmetric aldol reaction of the silyl enol ether of S-ethyl propanethioate with aldehydes is also successfully carried out by using chiral diamine-coordinated tin(II) triflate.[7]



In this communication, we would like to describe the catalytic asymmetric aldol reaction of the silyl enol ether of acetic acid thioester with aldehydes, which is unprecedented as far as we know.

Initially, the reaction of the silyl enol ether of S-ethyl ethanethioate (**1**) with cyclohexanecarboxyaldehyde (**2**) served as a model system to test the influence of several reaction conditions. Our proposed catalytic cycle is shown in Scheme 1. The metal exchange reaction of **3** with trimethylsilyl triflate (TMSOTf) to regenerate the catalyst is considered as a key step, therefore, when this step is slow, undesirable achiral TMSOTf-mediated aldol reaction proceeds at the same time to result in lowering the selectivities. In order to keep TMSOTf in as low a concentration as possible during the reaction, the slow addition of the substrates to the catalyst was tried. When the dichloromethane solution solution of **1** and **2** was slowly added over 3.5 h to the dichloromethane solution of the catalyst consisting of tin(II) triflate and (S)-1-methyl-2-[(N-1-(5,6,7,8-tetrahydronaphtyl) amino)methyl]pyrrolidine (**4**),[8] the corresponding aldol-type adduct was obtained in 76% yield with 73% ee. The enantioselectivity was improved to 80% ee by prolonging the addition time (6 h). In addition, solvent is also quite crucial in this reaction and when propionitrile was employed as a solvent as shown in the previous paper,[7b] it was found that the optical purity was improved up to 92% ee.



Scheme 1.

Several examples of this catalytic asymmetric aldol reaction are listed in Table 1. In every case, aldol-type adducts, α-unsubstituted-β-hydroxy thioesters, are obtained in good yields with high enantiomeric excesses.

A typical experimental procedure is described for the reaction of **1** with an aldehyde; to a solution of tin(II) triflate (0.08 mmol, 20 mol%) in propionitrile (1 ml) was added **4** (0.088 mmol) in propionitrile (1 ml). The mixture was cooled to -78°C, then a mixture of **1** (0.4 mmol) and an aldehyde (0.4 mmol) was slowly added to this solution over an appropriate time (see Table 1). The mixture was further stirred for 2 h, then quenched with saturated aqueous sodium hydrogen carbonate. After usual work up, the aldol-type adduct was isolated as the corresponding trimethylsilyl ether.

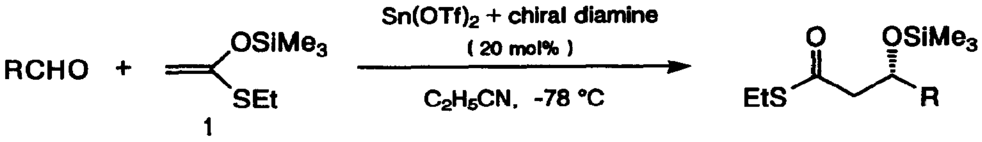
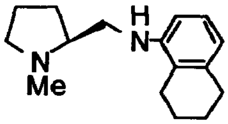


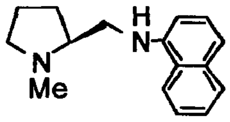
Table 1. Catalytic Asymmetric Aldol Reaction of the Silyl Enol Ether of S-Ethyl Ethanethioate with Aldehydes

Aldehyde	Diamine	Addition time/h	Yield/%	ee/%[a]
$CH_3(CH_2)_6CHO$	4	4	79	93[b]
$CH_3(CH_2)_3CHO$	4	6	79	91
$c\text{-}C_6H_{11}CHO$	4	4.5	81	92
i-PrCHO	4	4	48	90
$CH_3(CH_2)_2CH{=}CHCHO$	5	20	65	72
$^{n}BuC{\equiv}CCHO$	4	5	68	88[b]
$Me_3SiC{\equiv}CCHO$	4	3	75	77[c]
$PhC{\equiv}CCHO$	4	6	71	79[b]
C_6F_5CHO	5	20	90	68

Diamine: 4



5



a) Determined by HPLC analysis (Daicel Chiralcel).

b) Dichloromethane was used as a solvent.

c) 30mol% of tin(II) triflate and chiral diamine was employed.

Thus, the catalytic asymmetric aldol reaction of 1 with several aldehydes by the use of chiral diamine coordinated tin(II) triflate, is successfully attained. Several synthetically valuable α-unsubstituted-β-hydroxy thioesters are prepared in high optical purities according to the present procedure.

The present research is partially supported by Grant-in-Aids for Scientific Research on Priority Areas (Multiplex Organic Systems) from the Ministry of Education, Science and Culture.

References

1) M. Braun, *Angew. Chem., Int. Ed. Engl.*, **26**, 24 (1987), and references cited therein.

2) C. H. Heathcock, "Asymmetric Synthesis, Vol. 3, Part B," ed by J. D. Morrison, Academic Press, New York (1984), Chap. 2; I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, and R. D. Norcross, *Tetrahedron*, **46**, 4663 (1990), and references cited therein.

3) S. Masamune, T. Sato, B. Kim, and T. A. Wollmann, *J. Am. Chem. Soc.*, **108**, 8279 (1986), and references cited therein. See also ref. 1).

4) S. Kobayashi and T. Mukaiyama, *Chem. Lett.*, **1989**, 297.

5) T. Mukaiyama, H. Uchiro, and S. Kobayashi, *Chem. Lett.*, **1989**, 1001.

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

7) a) T. Mukaiyama, S. Kobayashi, H. Uchiro, and I. Shiina, *Chem. Lett.*, **1990**, 129; b) S. Kobayashi and Y. Fujishita, and T. Mukaiyama, *ibid.*, **1990**, 1455. For catalytic asymmetric aldol reaction, see Y. Ito, M. Sawamura, H. Hamashima, T. Emura, and T. Hayashi, *J. Am. Chem. Soc.*, **111**,938 (1989); T. Mukaiyama, H. Uchiro, and S. Kobayashi, *Chem. Lett.*, **1990**, 1147; T. Mukaiyama, A. Inubushi, S. Suda, R. Hara, and S. Kobayashi, *ibid.*, **1990**, 1015; T. Mukaiyama, T. Takashima, H. Kusaka, and T. Shimpuku, *ibid.*, **1990**, 1777; K. Furuta, T. Maruyama, and H. Yamamoto, *J. Am. Chem. Soc.*, **113**, 1041 (1991).

8) This chiral diamine was prepared according to the standard procedure.[9] **4**: bp: 144 °C/0.7 mmHg; $[\alpha]_D^{22}$ -27.1 ° (c 0.88, EtOH); IR (neat) 3375, 2920, 1590, 1500, 1465 cm^{-1}; ^1H NMR (CCl_4) 1.40-2.20 (m, 8H), 2.20-2.90 (m, 6H), 2.25 (s, 3H), 2.90-3.25 (m, 3H), 3.95 (brs, 1H), 6.10-6.45 (m, 2H), 6.65-7.00 (m, 1H). Precise mass calc for $C_{16}H_{24}N_2$ m/z 244.1939. Found 244.1921.

9) T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, *Tetrahedron*, **40**, 1381 (1984); T. Mukaiyama, S. Kobayashi, and T. Sano, *ibid.*, **46**, 4653 (1990); S. Kobayashi, H. Uchiro, Y. Fujishita, I. Shiina, and T. Mukaiyama, *J. Am. Chem. Soc.*, in press.