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Highly Enantioselective Synthesis of syn-α, β-Dihydroxy Thioesters by the Asymmetric Aldol Reaction Using a Chiral Tin(II) Lewis Acid

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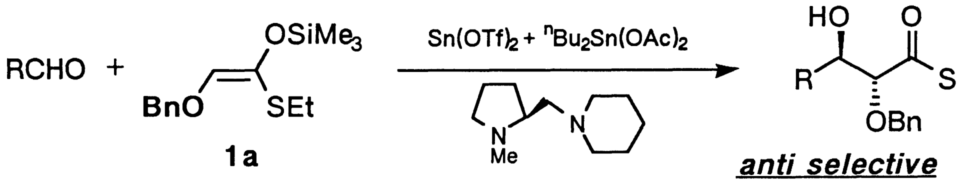
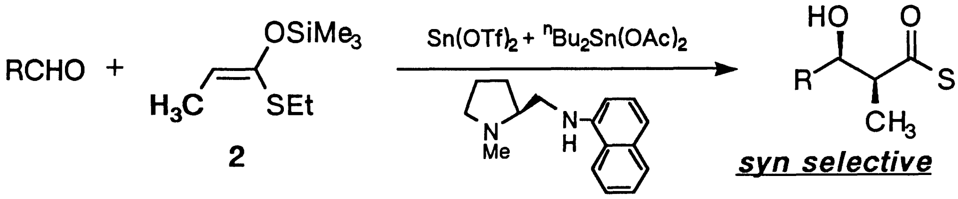
syn-α, β-Dihydroxy thioesters are prepared in good yields with high diastereo- and enantioselectivities by the asymmetric aldol reaction of 1-trimethylsiloxy-1-ethylthio-2-t-butyldimethylsiloxyethene with aldehydes using a chiral promoter consisting of tin(II) triflate, a chiral diamine and dibutyltin diacetate.

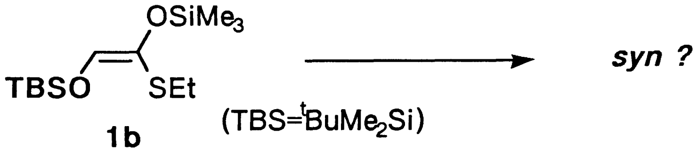
The asymmetric aldol reaction of α-alkoxy ester enolates with aldehydes is one of the most powerful methods for the synthesis of optically active 1, 2-diol units.[1] In the previous paper,[2] we have already shown that anti-α, β-dihydroxy thioesters are prepared by the asymmetric aldol reaction of the silyl enol ether derived from the α-benzyloxy thioester **1a** with aldehydes under the influence of a chiral promoter consisting of tin(II) triflate, a chiral diamine and a tin(IV) compound (Eq. 1). The high anti selectivities attained in this reaction are unexpected and interesting results, because the excellent syn selective aldol-type reaction of the silyl enol ether derived from S-ethyl propanethioate (**2**) with aldehydes using the above chiral promoter had already been widely developed (Eq. 2).[3] The consideration on the transition states of these enantioselective aldol reactions led us to assume that (i) the coordination of the oxygen atom of the α-benzyloxy group of the silyl enol ether **1a** to tin(II) atom of tin(II) triflate was essential in the anti selective transition state and this coordination did change the corse of the



(1)



(2)



diastereofacial selectivity,[4] (ii) thus syn α,β-dihydroxy thioesters would be prepared if this coordination was restrained. In this communication, we would like to report the experimental results carried out according to this hypothesis, providing a convenient method for the preparation of optically active syn-α,β-dihydroxy thioesters.

In order to restrain the coordination of the oxygen atom of the α-alkoxy group in the silyl enol ether **1a** to tin(II) metal, 1-trimethylsiloxy-1-ethylthio-2-t-butyldimethylsiloxyethene (**1b**), which has t-butyldimethylsiloxy group instead of benzyloxy group at 2-position, was prepared. It was found then that **1b** smoothly reacted with benzaldehyde in dichloromethane at -78 °C, in the coexistence of tin(II) triflate, (S)-1-methyl-2-[(N-naphthylamino)methyl]pyrrolidine (**3**) and dibutyltin diacetate, to afford the corresponding aldol-type adduct in 73% yield with syn preference (syn/anti=73/27). The enantiomeric excesses of the syn and anti aldol-type adducts were proved to be 70% and 60%, respectively, determined by HPLC analysis (Daicel Chiralcel OD). It is noteworthy to point out that the syn aldol-type adduct was preferentially produced as expected by using **1b**,[5] though the diastereo- and enantioselectivities were not so high. These selectivities were remarkably improved after examination of effects of chiral diamines and tin(IV) compounds (Table 1). The best result was obtained (86% yield, syn/anti=88/12, syn aldol=90%ee) when (S)-n-propyl-2-[(1-piperidin-1-yl)methyl]pyrrolidine (**4**) and dibutyltin diacetate were employed. Other examples are listed in Table 2, and in every case aldol-type adducts are obtained in good yields with high diastereo- and enantioselectivities.

A typical experimental procedure is described for the reaction of **1b** with benzaldehyde: To a suspension of tin(II) triflate (0.4 mmol) in dichloromethane (0.5 ml) were added chiral diamine **4** (0.48 mmol) in dichloromethane (0.5 ml) and dibutyltin diacetate (0.44 mmol) successively at room temperature. The mixture

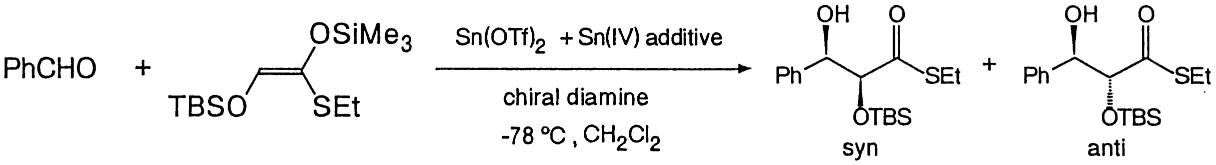
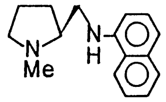
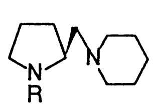


Table 1. Effect of Chiral Diamine and Sn(IV) Additive

Chiral diamine	Sn(IV) Additive	Yield / %	syn : anti	ee / % syn	ee / % anti
 3	^{n}Bu$_2$Sn(OAc)$_2$	73	73 : 27	94	83
	^{n}Bu$_3$SnF	56	70 : 30	90	85
 R = Me	^{n}Bu$_2$Sn(OAc)$_2$	83	91 : 9	49	76
Me	^{n}Bu$_3$SnF	81	86 : 14	49	35
Et	^{n}Bu$_2$Sn(OAc)$_2$	83	86 : 14	90	68
^{n}Pr (4)	^{n}Bu$_2$Sn(OAc)$_2$	86	88 : 12	90	65
^{n}Bu	^{n}Bu$_2$Sn(OAc)$_2$	75	87 : 13	89	68
^{n}Pen	^{n}Bu$_2$Sn(OAc)$_2$	63	83 : 17	89	57

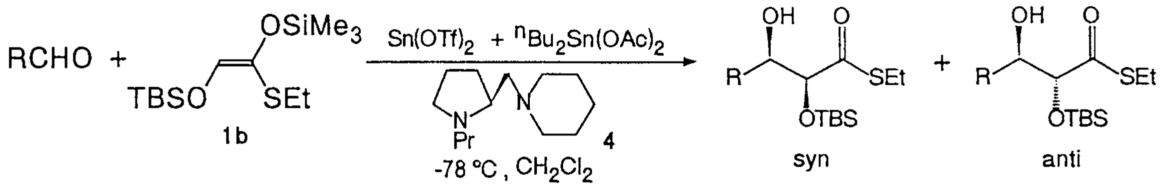
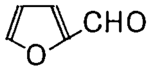
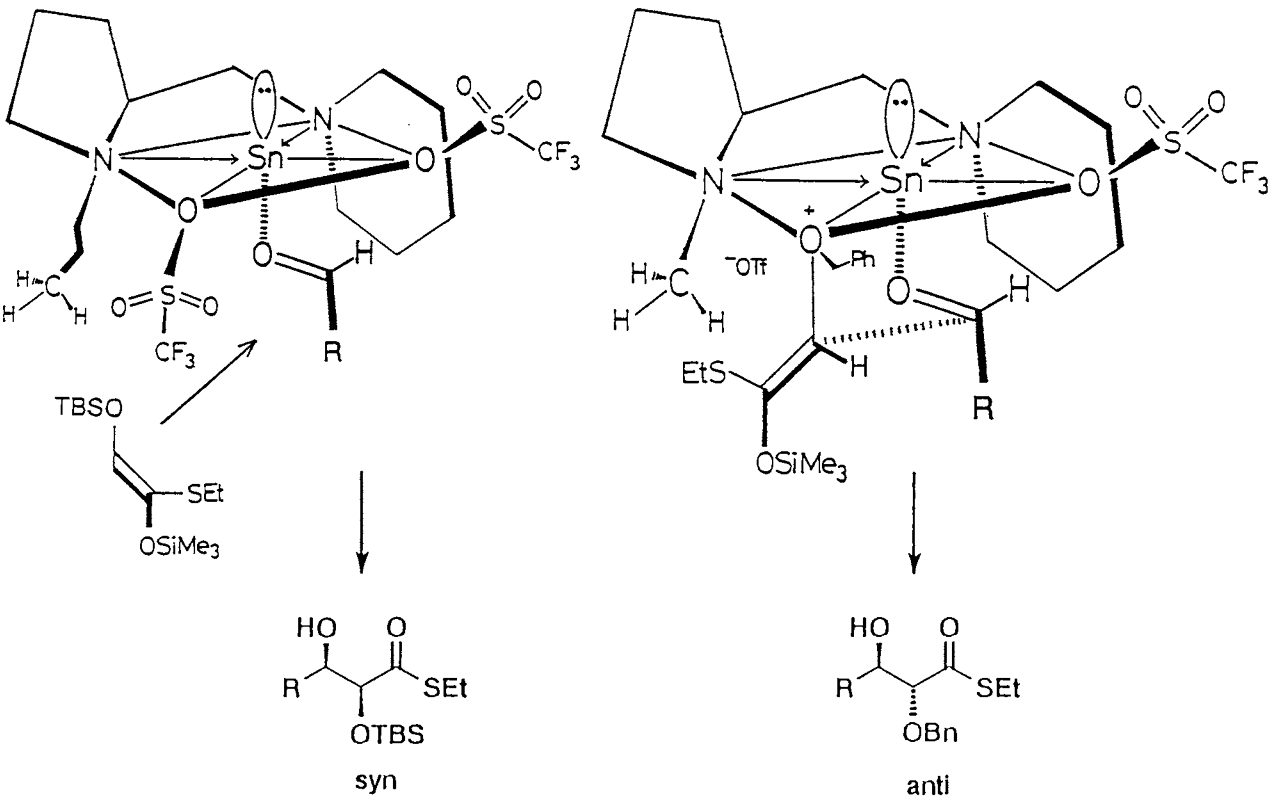


Table 2. Synthesis of syn-α,β-Dihydroxy Thioesters

Aldehyde	Yield / %	syn : anti	ee / %
PhCHO	86	88 : 12	90
CH_3CH_2CHO	46	92 : 8	82
	93	94 : 6	93
(E)-PhCH=CHCHO	76	90 : 10	92
(E)-CH_3CH=CHCHO	75	97 : 3	94
(E,E)-CH_3CH=CHCH=CHCHO	73	93 : 7	94



Scheme 1.

was stirred for 30 min at rt and then cooled to -78 °C. Dichloromethane solutions (0.5 ml each) of **1b** (0.4 mol) and benzaldehyde (0.27 mmol) were successively added and the mixture was stirred for 20 h. Sat. aqueous sodium hydrogen carbonate was added to quench the reaction, and after usual work up, S-ethyl 2-t-butyldimethylsiloxy-3-hydroxy-3-phenylpropanethioate was obtained in 86% yield (syn/anti=88/12, syn aldol=90%ee).

The high selectivity attained in this aldol reaction can be explained by assuming the transition states shown in Scheme 1.6) In the reaction of the silyl enol ether derived from α-t-butyldimethylsiloxy thioester **1b**, chiral diamine-coordinated tin(II) triflate has the rigid bicycle structure and its conformation is highly controlled by mutual interaction between pyrrolidyl, piperidyl and trifluoromethanesulfonyl groups, and re face of an approaching aldehyde is almost completely shielded and a silyl enol ether attacks this aldehyde via the acyclic transition state.7) On the other hand, in the previously reported reaction of the silyl enol ether derived from α-benzyloxy thioester, preference is given to the coordination of this oxygen to tin(II) atom. The reaction would proceed via the five membered cyclic transition state to give the anti aldol-type adducts in high enantioselectivities.

It should be noted that now it becomes possible to control the enantiofacial selectivity of the silyl enol ethers derived from the α-alkoxy thioesters **1a** and **1b** by just choosing the protective groups of the alkoxy parts of the silyl enol ethers, and that both diastereomers of optically active α,β-dihydroxy thioesters can be synthesized. Since the utility of the anti selective asymmetric aldol reaction in the syntheses of monosaccharides has been demonstrated,8) the present syn selective reaction will lead to further progress in this field.

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4) T. Mukaiyama, S. Kobayashi, H. Uchiro, and I. Shiina, *Chem. Lett.*, **1990**, 129.
5) Relative configuration assignment was made by comparison to the authentic sample similar to Ref. 2.
6) We proposed similar transition states in the reaction of the silyl enol ether derived from S-ethyl propanethioate with aldehydes using the chiral tin(II) Lewis acid. See, Ref. 4.
7) C. H. Heathcock, "Aymmetric Synthesis, Vol. 3," ed by J. D. Morrison, Academic Press, New York (1983), Chap. 2.
8) T. Mukaiyama, I. Shiina, and S. Kobayashi, *Chem. Lett*, **1990**, 2201.

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