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Facile Synthesis of Optically Active anti-α,β-Dihydroxy Ester Derivatives

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Anti-α,β-dihydroxy thioesters are prepared with excellent enantioselectivities by the asymmetric aldol reaction between both achiral aldehydes and silyl enol ethers derived from α-benzyloxy thioesters in the presence of a chiral promoter consisted of chiral diamine coordinated tin(II) triflate and dibutyltindiacetate.

Optically active 1,2-diol units are widely distributed in natural products such as macrolides, polyethers and carbohydrates, etc. Recently several asymmetric oxidation reactions of olefins by using osmium tetraoxide with a chiral ligand has been developed in high optical yields,$^{1,2)}$ however, there still remain some severe problems such as the preparation of optically active anti-1,2-diols.

In the previous papers,$^{3,4)}$ we have demonstrated that the asymmetric aldol reaction between both achiral silyl enol ethers of thioesters and aldehydes is performed with almost perfect diastereo- and enantioselectivities by using a new chiral promoter, combination of chiral diamine coordinated tin(II) triflate and tributyltinfluoride (dibutyltindiacetate). Then this asymmetric reaction was intended to apply to the reaction of silyl enol ether derived from α-benzyloxy thioester with aldehydes in order to introduce two hydroxy groups simultaneously accompanied with stereoselective carbon-carbon bond formation.$^{5)}$

In the first place, the reaction of benzaldehyde with trimethylsilyl enol ether of S-ethyl 2-benzyloxyethanethioate$^{6)}$ was carried out in dichloromethane by using a chiral promoter consisted of tin(II) triflate, (S)-1-methyl-2-[(N-1-naphthylamino)methyl]pyrrolidine and tributyltinfluoride. The reaction smoothly proceeded at -78 °C to afford the corresponding aldol-type adduct in 69% yield with anti preference (syn/anti=26/74). The enantiomeric excesses of syn and anti aldols proved to be 30% and 97%, respectively. It is noteworthy to point out that the anti aldol-type adduct was predominantly obtained with excellent ee in this case, while in the case of asymmetric aldol reaction of silyl enol ether of S-ethyl propanethioate with aldehydes, syn aldol-type adducts were obtained (syn/anti=100/0. syn aldol=>98%ee).$^{4)}$

Next, several chiral diamines were examined in order to improve the diastereoselectivity. When (S)-1-methyl-2-[(1-piperidin-1-yl)methyl]pyrrolidine was employed, the aldol-type adduct was obtained in 54% chemical yield with excellent diastereo- and enantioselectivity (syn/anti=1/99, anti aldol=97%ee). Further, the chemical yield was improved without loosing the stereoselectivities when combination of (S)-1-ethyl-2-[(1-piperidin-1-yl)methyl]pyrrolidine and dibutyltindiacetate was employed as a promoter (Table 1).

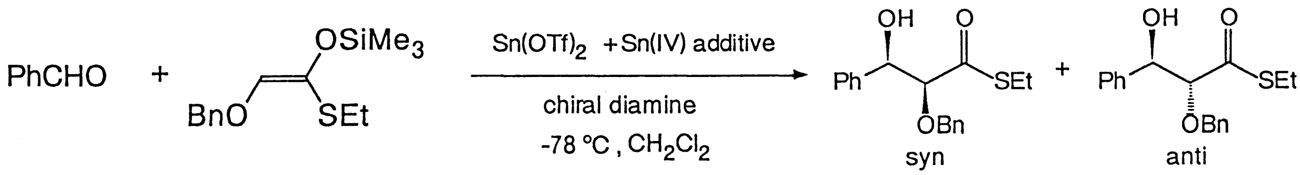
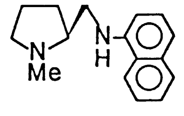
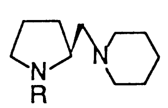
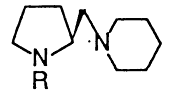


Table 1. Effect of Chiral Diamine

Chiral diamine	Additive	Yield / %	syn : anti	ee / % (anti)
	^{n}Bu$_3$SnF	69	26 : 74	97
 R = Me	^{n}Bu$_3$SnF	70	1 : 99	97
Et	^{n}Bu$_3$SnF	54	1 : 99	>98
^{n}Pr	^{n}Bu$_3$SnF	54	1 : 99	>98
^{n}Pen	^{n}Bu$_3$SnF	38	1 : 99	97
 R = Me	^{n}Bu$_2$Sn(OAc)$_2$	74	1 : 99	96
Et	^{n}Bu$_2$Sn(OAc)$_2$	83	1 : 99	96

The results of the present asymmetric aldol reaction by using several kinds of aldehydes such as aromatic, aliphatic, α,β-unsaturated aldehydes and a dienal, are shown in Table 2. In every case, anti-α,β-dihydroxy thioesters are obtained in high yields with excellent diastereo- and enantioselectivities.

A typical experimental procedure is described for the reaction of silyl enol ether derived from S-ethyl 2-benzyloxyethanethioate with benzaldehyde; to a solution of tin(II) triflate (0.4 mmol) and (S)-1-ethyl-2-[(piperidin-1-yl)methyl]pyrrolidine (0.48 mmol) in dichloromethane (1 ml) was added dibutyltindiacetate (0.44 mmol) at room temperature. The mixture was stirred for 30 min and then cooled to -78 °C. Dichloromethane solutions (0.5 ml each) of silyl enol ether of S-ethyl 2-benzyloxyethanethioate (0.4 mmol) and benzaldehyde (0.27 mmol) were successively added. The reaction mixture was further stirred for 20 h, and quenched with aqueous sodium hydrogen carbonate. After usual work up, S-ethyl 2,3-dihydroxy-3-phenylpropanethioate was obtained in 83% yield (syn/anti=1/99, anti aldol=96%ee).[7]

Thus, the present asymmetric aldol-type reaction makes it possible to introduce two hydroxy groups in 1,2-trans possition stereoselectively during new carbon-carbon bond formation. It is noteworthy to mention that thus obtained aldol-type adducts, optically active anti-α,β-dihydroxy ester derivatives, are generally difficult to prepare by the conventional methods of asymmetric oxidation because it is hard to obtain starting materials, cis-α,β-unsaturated ester equivalents.[8] Further investigation concerning application of this asymmetric aldol reaction to synthesis of natural products are in progress.

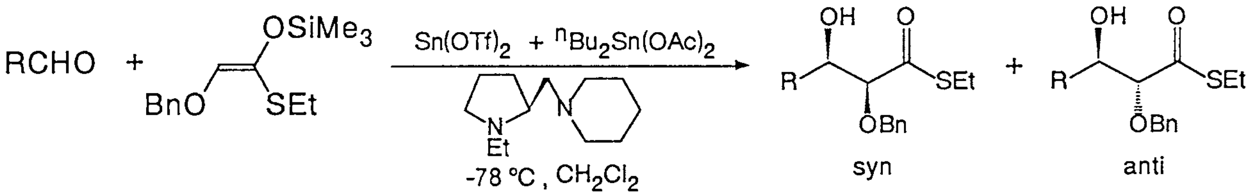


Table 2. Synthesis of anti-α,β-Dihydroxy Thioesters

Aldehyde	Yield / %	syn : anti	ee / % a) (config.)
PhCHO	83	1 : 99	96 (2R, 3R)
CH_3CH_2CHO	72	2 : 98	97
c-$C_6H_{11}CHO$	59	9 : 91	96
(E)-PhCH=CHCHO	88	2 : 98	98
(E)-CH_3CH=CHCHO	85	2 : 98	97
(E,E)-CH_3CH=CHCH=CHCHO	83	2 : 98	95

a) Determined by HPLC analysis of the corresponding acetyl derivatives.

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References

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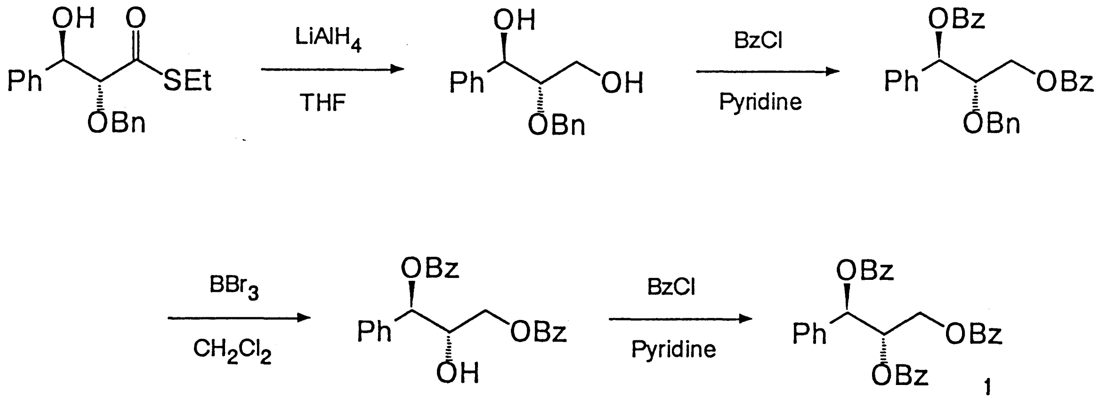
5) It was reported from this laboratory that chiral diamine coordinated tin(II) enolate of 3-(2-benzyloxyacetyl)-thiazolidine-2-thione reacted with aldehydes to afford the corresponding anti aldol-type adducts in good diastereo- and enantioselectivities; T. Mukaiyama and N. Iwasawa, Chem. Lett., **1984**, 753.

6) This silyl enol ether was prepared from S-ethyl 2-benzyloxyethanethioate by the usual procedure (1. LDA/THF, -78 °C, 2. TMSCl; 80%yield, E/Z=72/28). In this paper, the stereochemical description E and Z of silyl enol ethers of thioesters are employed as they correspond to ketene silyl acetals.

7) The absolute configuration was detemined by the comparison of the authentic tribenzoate **1** after the following derivations.



1

anti , (1R , 2S)

$[\alpha]_{546}^{23}$ + 82.6 ° (c 0.89, benzene)

(lit. $[\alpha]_{546}$ - 81 ° (c 2.00, benzene))[9]

8) Recently, Corey et al. reported that anti-α,β-diols were difficult to prepare in high ees via the asymmetric dioxyosmylation, according to the consideration of their mechanistic model; ref. 2).

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