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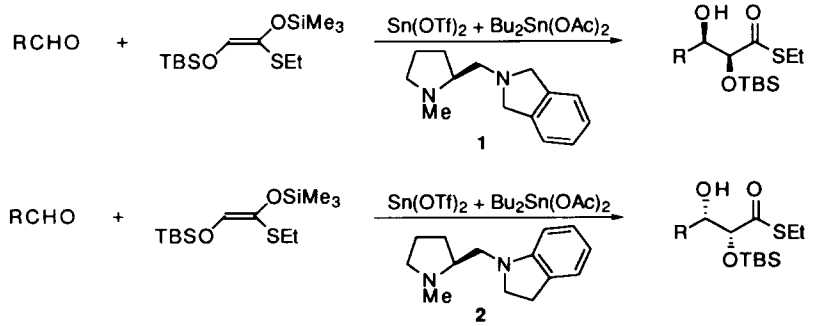
Preparation of Both Enantiomers of 2-Methyl-3-hydroxythioesters Based on Chiral Lewis Acid-Controlled Synthesis

Shū Kobayashi* and Mineko Horibe

Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo (SUT), Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

Abstract: Both enantiomers of 2-methyl-3-hydroxythioesters have been synthesized by using chiral tin(II) Lewis acid-mediated aldol reactions of (*Z*)-1-ethylthio-1-trimethylsiloxypropene (**4**) with aldehydes, based on chiral Lewis acid-controlled synthesis. The key to this synthesis is in choosing similar types of chiral sources, (*S*)-1-methyl-2-[(1-benz[*cd*]indolinyl)methyl]pyrrolidine (**3**) and (*S*)-1-methyl-2-[(1-naphthylamino)methyl]pyrrolidine (**5**), derived from *L*-proline. Evaluation of new chiral ligand **3** in the asymmetric aldol reactions is also described.

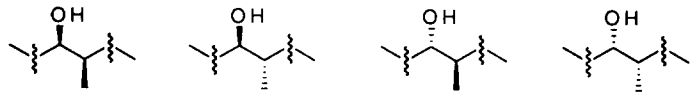
Synthesis of both enantiomers of a chiral compound is a very important task in organic synthesis.[1] However, traditional methods often require sources of enantiomeric precursors, auxiliaries, or catalysts, and both enantiomers of the sources are often hard to obtain (for example, alkaloids, amino acids, sugars, etc.). We have recently reported[2] a new method for the preparation of both enantiomers of optically active *syn*-2,3-dihydroxythioester derivatives based on "chiral Lewis acid-controlled synthesis (CLAC synthesis)." CLAC synthesis[3] means the synthesis of both individual diastereomers or enantiomers from the same starting materials by designing chiral Lewis acids. We have prepared new chiral tin(II) Lewis acids in the asymmetric aldol reactions of the silyl enol ether of S-ethyl 2-*t*-butyldimethylsiloxyethenethioate with aldehydes to obtain both enantiomers of the corresponding aldol adducts by using similar types of chiral sources, **1** and **2** (Scheme 1).



Scheme 1. Synthesis of Both Enantiomers of 2,3-Dihydroxythioester Derivatives

In this paper, we describe an application of CLAC synthesis to the preparation of α-methyl-β-hydroxy units by designing a new chiral ligand, (*S*)-1-methyl-2-[(1-benz[*cd*]indolinyl)methyl]pyrrolidine (**3**).[4] Evaluation of **3** in the asymmetric aldol reactions is also reported.

Optically active α-methyl-β-hydroxy units (see Scheme 2) are often observed in various important natural and unnatural products, and development of efficient methods for the preparation of these units has been strongly desired.[5] In particular, a requirement is a new reaction which can prepare both enantiomers of the above units, because the biological activities of the compounds containing the units have been shown to be quite different between enantiomers in some cases. While several protocols have already been reported and asymmetric aldol reactions of enolate components derived from propionate derivatives with aldehydes provide one of the most prospective routes for their preparation,[6] both enantiomers of chiral sources are required according to conventional methods.

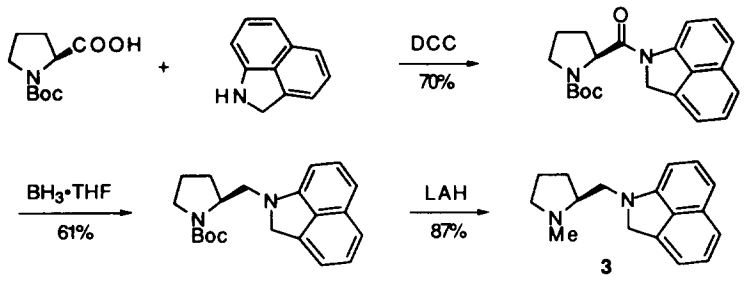


Scheme 2. α-Methyl-β-hydroxy Units

First, we performed the reaction of (*Z*)-1-ethylthio-1-trimethylsiloxypropene (**4**) with benzaldehyde in the presence of tin(II) triflate, chiral diamine **1**, and dibutyltin diacetate ($Bu_2Sn(OAc)_2$). The reaction proceeded smoothly at -78 °C in dichloromethane to afford the corresponding adduct including the α-methyl-β-hydroxy unit in a high yield with a high *syn*-selectivity, and the enantiomeric excess of the *syn*-adduct was 66% with a 2*S*, 3*S* absolute configuration. The diastereo- and enantioselectivities were improved when (*S*)-1-ethyl-2-[(2-isoindolinyl)methyl]pyrrolidine was used as the chiral source. On the other hand, when chiral diamine **2** was used, a high yield and a high *syn*-selectivity were also observed. The absolute configuration of the *syn*-adduct was reversed (2*R*, 3*R*), but the enantiomeric excess was low. The *N*-alkyl group reversed the absolute configuration in this case, and the *syn*-adduct was obtained in a 66% ee with a 2*S*, 3*S* absolute configuration by using (*S*)-1-ethyl-2-[(1-indolinyl)methyl]pyrrolidine. The high diastereoselectivity and rather low enantioselectivity indicated that in order to improve the selectivity, development of a chiral ligand with the increased enantiofacial selectivity of an aldehyde was necessary. We designed and synthesized several chiral ligands, and found that (*S*)-1-methyl-2-[(1-benz[*cd*]indolinyl)methyl]pyrrolidine (**3**) was suitable for our purpose.

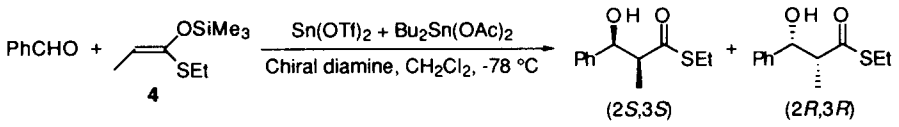
Chiral ligand **3** was prepared from Boc-proline and benz[*cd*]indoline according to the standard procedure (Scheme 3); DCC coupling afforded an amide, which was reduced via two steps (BH_3•THF and then $LiAlH_4$) to give the desire ligand (**3**) as an oil.

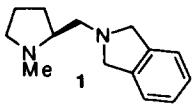
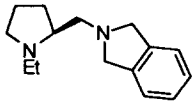
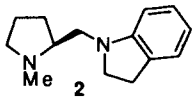
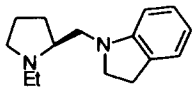
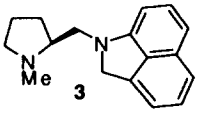
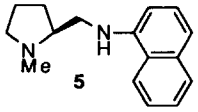
In the presence of tin(II) triflate, chiral diamine **3**, and $Bu_2Sn(OAc)_2$, silyl enolate **4** was treated with benzaldehyde at -78 °C in dichloromethane. The reaction proceeded smoothly to afford the corresponding adduct in a high yield with an excellent *syn*-selectivity. The enantiomeric excess of the *syn*-adduct was 82% with a 2*R*, 3*R* absolute configuration. On the other hand, higher 2*S*, 3*S* selectivity was observed when chiral diamine **5** was used.[7] These results are summarized in Table 1.



Scheme 3. Synthesis of chiral Ligand **3**

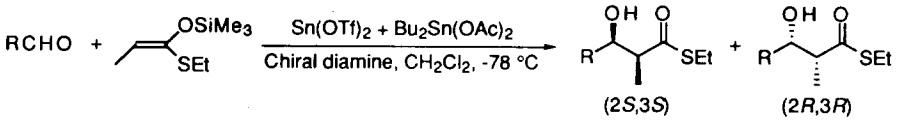
Table 1. Effect of Chiral Diamines



Chiral diamine	Yield/%	*syn*/*anti*	2*S*,3*S*/2*R*,3*R* (ee/%)
	98	99/ 1	83.0/17.0 (66)
	84	97/ 3	97.5/ 2.5 (95)
	90	93/ 7	35.0/65.0 (30)
	90	88/12	83.0/17.0 (66)
	80	>99/ 1	9.0/91.0 (82)
	85	>99/ 1	>99.5/<0.5 (>99)

We tested several aldehydes including aromatic, aliphatic, α,β-unsaturated, and heterocyclic aldehydes (Table 2). In every case, *syn*-2-methyl-3-hydroxythioesters with a 2*R*, 3*R*[8] absolute configuration were obtained in high selectivities by using chiral ligand **3**. Since *syn*-adducts with the reverse absolute configuration (2S, 3S)[9] have been obtained in high diastereo- and enantioselectivities,[7] both enantiomers of *syn*-2-methyl-3-hydroxythioesters were prepared according to the present method from the same starting materials, by using similar types of chiral ligands, **3** and **5**.

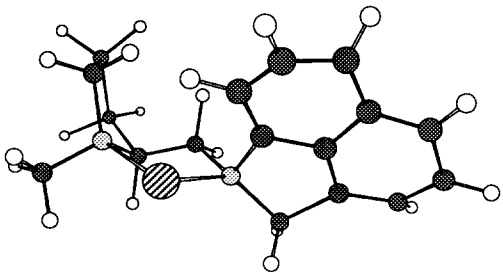
Table 2. Synthesis of Both Enantiomers of 2-Methyl-3-hydroxythioesters



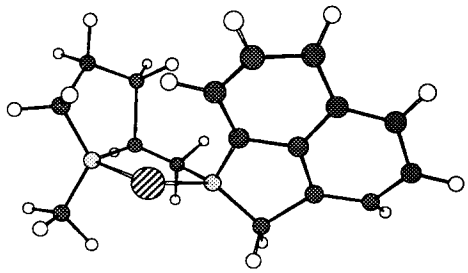
Aldehyde	Chiral diamine	Product	Yield/%	*syn*/*anti*	2*S*,3*S*/2*R*,3*R* (ee/%)	
Ph	**3**	**6**	80	>99/ 1	9.0/91.0	(82)
	5	**6**	85	>99/ 1	>99.5/<0.5	(>99)[a]
CH_3CH_2	**3**	**7**	67	>99/ 1	9.5/90.5	(91)[b]
	5	**7**	85	>99/ 1	>99.5/<0.5	(>99)[a,b]
$CH_3(CH_2)_6$	**3**	**8**	75	>99/ 1	9.5/90.5	(91)[b]
	5	**8**	90	>99/ 1	>99.5/<0.5	(>99)[a,b]
c-C_6H_{11}	**3**	**9**	75	>99/ 1	4.0/96.0	(92)[b]
	5	**9**	90	>99/ 1	>99.5/<0.5	(>99)[a,b]
CH_3CH=CH	**3**	**10**	69	>99/ 1	10.0/90.0	(80)[b]
	5	**10**	92	>99/ 1	>99.5/<0.5	(>99)[a,b]
PhCH=CH	**3**	**11**	79	>99/ 1	9.5/90.5	(81)[b]
	5	**11**	91	>99/ 1	>99.5/<0.5	(>99)[a,b]
2-furyl	**3**	**12**	83	>99/ 1	8.0/92.0	(84)
	5	**12**	93	>99/ 1	>99.5/<0.5	(>99)[a]

a) Ref. 6. b) 2*S*,3*R*/2*R*,3*S*

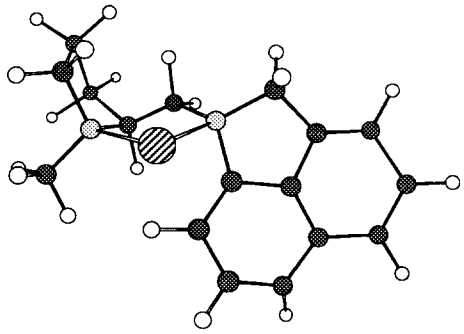
We now postulate the similar transition states as those in the reactions of *S*-ethyl 2-*t*-butyldimethylsiloxyethenethioate with aldehydes using tin(II) triflate, chiral diamine **2**, and $Bu_2Sn(OAc)_2$. Conformational analysis of tin(II)-chiral diamine **3** complex was made by using semi-empirical molecular orbital calculation (PM3).[10] The most stable structure is shown in Conformation I (Scheme 4). It should be noted that the conformation of the bicyclo[3.3.0]octane-like structure in Conformation I is very similar to that in the most stable conformation of tin(II)-chiral diamine **2** complex (Scheme 5). The high 2*R*, 3*R* selectivities



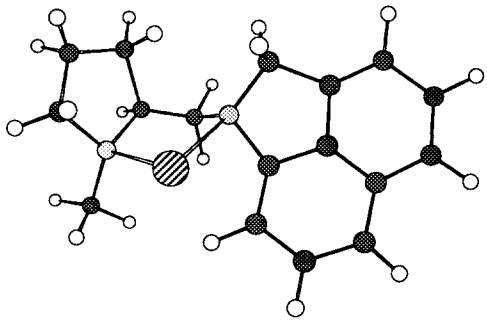
Conformation I: 449.03 kcal



Conformation II: 450.96 kcal

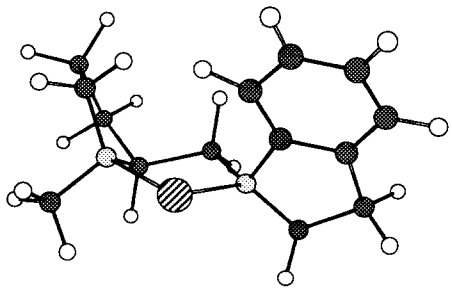


Conformation III: 450.29 kcal



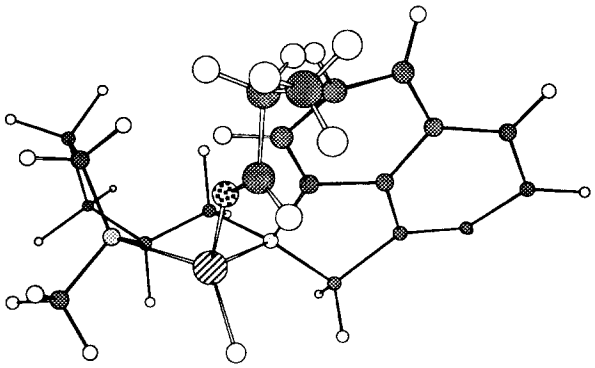
Conformation IV: 450.36 kcal

Scheme 4. Conformational Analysis of Sn^{2+}-Chiral Diamine **3** Complex (PM3)



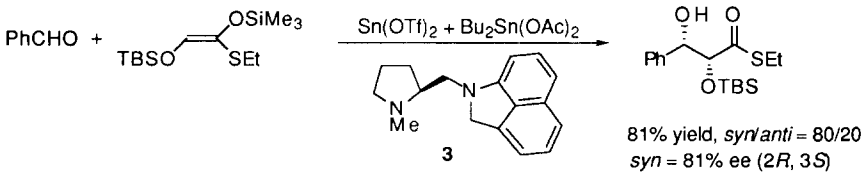
Scheme 5. The Most Stable Conformation of Sn^{2+}-Chiral Diamine **2** Complex (PM3)

shown in Table 2 can be explained by the assumed transition state (Scheme 6). An aldehyde approaches from the top side of the tin(II)-diamine complex, and the *si* face of the aldehyde is shielded by the amine part. Silyl enol ether **4** attacks this aldehyde from the *re* face via the acyclic transition state to form the *syn*-(2*R*, 3*S*)-aldol adduct.

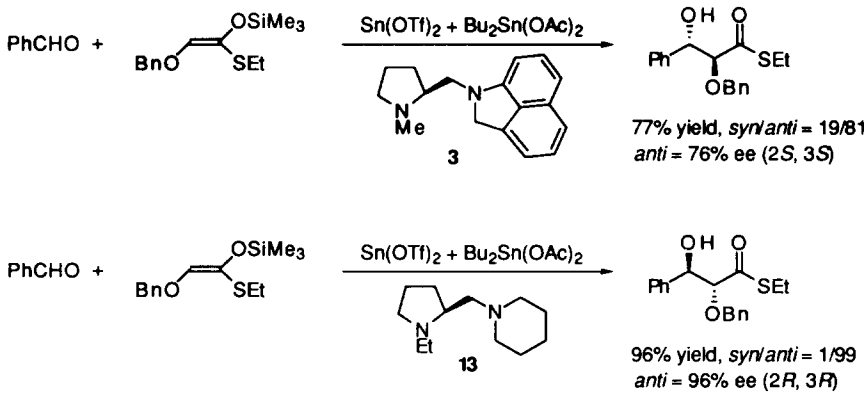


Scheme 6. Assumed Transition State

We then evaluated new chiral ligand **3** in asymmetric aldol reactions using silyl enolates other than **4**. When *S*-ethyl 2-*t*-butyldimethylsiloxyethenethioate was treated with benzaldehyde, the aldol adduct was obtained in an 81% yield with good diastereoselectivity (*syn*/*anti* = 80/20). The enantiomeric excess of the *syn*-adduct was 81% with a 2*R*, 3*S* absolute configuration (cf. Scheme 1).[2,11]



On the other hand, in the reaction of *S*-ethyl 2-benzyloxyethenethioate with benzaldehyde, the *anti*-adduct with a 2*S*, 3*S* configuration was obtained preferentially (*syn*/*anti* = 12/88, *anti*-aldol = 76% ee (2*S*, 3*S*)). While it was found that chiral diamine **1** was effective for the preparation of the enantiomer,[12] excellent diastereo- and enantioselectivities were obtained by using chiral diamine **13**.[13] Although the selectivities were not high enough, these reactions provide a route for the preparation of both enantiomers of optically active *anti*-2,3-dihydroxythioester derivatives based on CLAC synthesis (by choosing similar types of chiral diamines, **3** and **13**).



In summary, we have developed an efficient method for the preparation of both enantiomers of optically active *syn*-2-methyl-3-hydroxythioesters, based on CLAC synthesis. According to this method, both enantiomers can be prepared from the same materials by simply choosing chiral ligands, **3** and **5**, which are prepared from *L*-proline. In addition to the synthetic utility of the present method, the similarity of the chiral ligands having naphthalene rings is noteworthy. We have also found that new chiral ligand **3** was effective in other asymmetric aldol reactions, affording adducts with the reverse absolute configurations.

Further studies to clarify the origin of the unique selectivities in the transition states as well as to develop more efficient ligands are now in progress.

Experimental

General. IR spectra were recorded on a Horiba FT-300 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Hitachi R-1100 or a JEOL JNR-EX270L spectrometer, and tetramethylsilane (TMS) served as the internal standard. HPLC was carried out using a Hitachi LC-Organizer, L-4000 UV Detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator. Mass Spectra were recorded on JEOL AX-505HA mass spectrometer. Optical rotations were recorded on a Jasco DIP-360 digital polarimeter. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. All reactions were carried out under argon atmosphere in dried glassware.

Dichloromethane was distilled from P_2O_5, then CaH_2, and dried over MS4A.

Tin(II) trifluoromethanesulfonate (tin(II) triflate)[14,15] and chiral diamines[15-17] were prepared according to the literature procedures. All handlings of tin(II) triflate were carried out under argon atmosphere. Borane-THF complex (1.0 mol/dm^{-3} THF solution) was purchased from Aldrich Chemical Co., Inc.

(*S*)-1-Methyl-2-[(1-benz[*cd*]indolinyl)methyl]pyrrolidine (3) To a dichloromethane (30 ml) solution of dicyclohexylcarbodiimide (7.10g, 34.0 mmol) was added Boc-(*S*)-proline (7.30 g, 34.0 mmol) at 0 °C. After stirring for 15 min, a dichloromethane solution of benz[*cd*]indoline[18] (5.89 g, 38.0 mmol) was slowly added to the mixture at 0 °C. The mixture was warmed to room temperature and stirred for 10 h. The solvent was then evaporated *in vacuo*, ethyl acetate (100 ml) was added, and the precipitate was removed by filtration. The organic

layer was washed with 10% citric acid solution, 4% sodium hydrogen carbonate solution and brine, and dried (Na_2SO_4). After removal of the solvents, the crude product was chromatographed on silica gel to give (*S*)-1-(*N*-*t*-Butoxycarbonylprolyl)benz[*cd*]indoline (8.38 g, 70%). Benz[*cd*]indoline was recovered (1.53 g, 26%).

A THF (20 ml) solution of the amide (7.04 g, 20.0 mmol) was added slowly to borane-THF complex (1 mol/dm^{-3} THF solution, 34 ml) at 0 °C, and the mixture was refluxed for 2 h. One mol/dm^{-3} HCl was added carefully at 0 °C to quench the reaction. Water was then added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with water, saturated sodium hydrogen carbonate and brine, and dried (Na_2SO_4). After removal of the solvents, the crude product was chromatographed on silica gel to give (*S*)-1-*t*-butoxycarbonyl-2-[(1-benz[*cd*]indolinyl)methyl]pyrrolidine (4.12 g, 61%).

A THF (20 ml) solution of the Boc-protected amine (4.12 g, 12.2 mmol) was slowly added to a THF suspension (20 ml) of $LiAlH_4$ (6.97 g, 14.6 mmol) at 0 °C, and the mixture was refluxed for 2 h. Saturated sodium sulfate solution was then added carefully to the mixture at 0 °C, and the organic materials were collected by decantation. The organic layer was dried (Na_2SO_4-K_2CO_3) and the solvent was removed under reduced pressure. After removal of the solvents, the crude product was chromatographed on alumina and then distilled to give **3** (2.67 g, 87%): Bp 236 °C/0.1 mmHg (bath temp.); $[\alpha]_D^{28}$ -59.6 ° (c 3.0, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.60-1.87 (m, 3H), 1.89-2.02 (m, 1H), 2.15-2.26 (m, 1H), 2.41-2.54 (m, 4H), 3.07 (dd, 1H, *J* = 6.8, 8.4 Hz), 3.27 (dd, 1H, *J* = 6.9, 14.1 Hz), 3.53 (dd, 1H, *J* = 4.6, 14.2 Hz), 4.80 (m, 2H), 6.15 (d, 1H, *J* = 7.3 Hz), 6.85 (d, 1H, *J* = 8.3 Hz), 7.08 (d, 1H, *J* = 6.9 Hz), 7.19-7.24 (m, 1H), 7.32-7.37 (m, 1H), 7.45 (d, 1H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 22.3, 29.9, 41.2, 51.4, 57.6, 58.6, 64.8, 95.7, 110.9, 115.4, 122.1, 127.7, 129.8, 130.8, 132.0, 139.1, 152.8; precise mass for $C_{17}H_{20}N_2$, calcd m/z 252.1628, found 252.1631.

A Typical Procedure of the Asymmetric Aldol Reaction. A typical experimental procedure is described for the reaction of **4** with benzaldehyde. To a suspension of tin(II) triflate (0.4 mmol) in dichloromethane (0.5 ml) were added chiral diamine **3** (0.48 mmol) in dichloromethane (0.5 ml) and dibutyltin diacetate (0.44 mmol) in dichloromethane (0.5 ml) successively at room temperature. The mixture was then cooled to -78 °C and dichloromethane solutions (0.5 ml each) of **4** (0.4 mmol) and benzaldehyde (0.27 mmol) were successively added. The mixture was stirred for 20 h, and saturated sodium hydrogen carbonate was added to quench the reaction. After a usual work up, the crude product was chromatographed on silica gel to give *S*-ethyl 3-hydroxy-2-methyl-3-phenylpropanethioate. The diastereomers were separated and the optical purity was determined by HPLC using a chiral column (see below).

***S*-Ethyl (2*R*,3*R*)-3-hydroxy-2-methyl-3-phenylpropanethioate (6):** (82% ee) $[\alpha]_D^{25}$ -66.7 ° (c 1.2, PhH); IR (neat) 3450, 1675 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.10 (d, 3H, *J* = 7.0 Hz), 1.20 (t, 3H, *J* = 7.0 Hz), 2.65 (br s, 1H), 2.55-2.95 (m, 1H), 2.80 (q, 2H, *J* = 7.0 Hz), 5.00 (d, 1H, *J* = 4.0 Hz), 7.20 (m, 5H); precise mass for $C_{12}H_{16}O_2S$, calcd m/z 224.0889, found 224.0880. HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 19/1, flow rate = 1.0 mL / min): t_R = 7.3 min (major enantiomer), t_R = 9.3 min (minor enantiomer).

***S*-Ethyl (2*R*,3*S*)-3-hydroxy-2-methylpentanethioate (7):** (91% ee) $[\alpha]_D^{25}$ -16.4 ° (c 2.1, PhH); IR (neat) 3400, 1675 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.80-1.70 (m, 9H), 2.30 (br s, 1H), 2.35-2.65 (m, 1H), 2.85 (q, 2H, *J* = 7.0 Hz), 3.50-3.90 (m, 1H). Anal. ($C_8H_{16}O_2S$) C, H. Optical purity was determined after derivation to the corresponding acetate: HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 200/1, flow rate = 0.5 mL / min): t_R = 14.1 min (major enantiomer), t_R = 21.2 min (minor enantiomer).

***S*-Ethyl (2*R*,3*S*)-3-hydroxy-2-methyldecanethioate (8):** (91% ee) $[\alpha]_D^{27}$ -25.9 ° (c 3.1, PhH); IR (neat) 3450, 1680 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.80-1.70 (m, 21H), 2.25 (br s, 1H), 2.35-2.65 (m, 1H), 2.85 (q, 2H, *J* = 7.0

Hz), 3.45-3.95 (m, 1H). Anal. ($C_{13}H_{26}O_2S$) C, H, S. HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 1000/1, flow rate = 1.0 mL / min): t_R = 13.8 min (major enantiomer), t_R = 16.6 min (minor enantiomer).

***S*-Ethyl (2*R*,3*S*)-3-cyclohexyl-3-hydroxy-2-methylpropanethioate (9):** (92% ee) $[\alpha]_D^{27}$ -35.5 ° (c 2.0, PhH); IR (neat) 3475, 1680 cm^{-1}; ^1H NMR (CCl_4) δ 0.50-2.10 (m, 11H), 1.15 (d, 3H, *J* = 7.0 Hz), 1.25 (t, 3H, *J* = 7.0 Hz), 2.25 (br s, 1H), 2.75 (m, 1H), 2.90 (q, 2H, *J* = 7.0 Hz), 3.40-3.70 (m, 1H). Anal. ($C_{12}H_{22}O_2S$) C, H, S. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 200/1, flow rate = 1.0 mL / min): t_R = 29.0 min (minor enantiomer), t_R = 39.6 min (major enantiomer).

***S*-Ethyl (2*R*,3*S*,4*E*)-3-hydroxy-2-methyl-4-hexenethioate (10):** (80% ee) $[\alpha]_D^{27}$ -37.6 ° (c 2.2, PhH); IR (neat) 3400, 1665 cm^{-1}; ^1H NMR (CCl_4) δ 1.20 (d, 3H, *J* = 7.0 Hz), 1.25 (t, 3H, *J* = 7.0 Hz), 1.70 (d, 3H, *J* = 5.0 Hz), 2.35-2.75 (m, 1H), 2.55 (br s, 1H), 2.80 (q, 2H, *J* = 7.0 Hz), 4.05-4.35 (m, 1H), 5.05-5.95 (m, 2H). Anal ($C_9H_{16}O_2S$) C, H, S. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 50/1, flow rate = 1.0 mL / min): t_R = 7.8 min (major enantiomer), t_R = 14.5 min (minor enantiomer).

***S*-Ethyl (2*R*,3*S*,4*E*)-3-hydroxy-2-methyl-5-phenyl-4-pentenethioate (11):** (81% ee) $[\alpha]_D^{28}$ -67.7 ° (c 3.2, PhH); IR (neat) 3400, 1665 cm^{-1}; ^1H NMR (CCl_4) δ 1.20 (t, 3H, *J* = 7.0 Hz), 1.25 (d, 3H, *J* = 7.0 Hz), 2.55 (br s, 1H), 2.55-2.95 (m, 1H), 2.80 (q, 2H, *J* = 7.0 Hz), 4.30-4.65 (m, 1H), 6.05 (dd, 1H, *J* = 5.0, 16.0 Hz), 6.60 (d, 1H, *J* = 16.0 Hz), 7.05-7.45 (m, 5H). Anal. ($C_{14}H_{18}O_2S$) C, H, S. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 9/1, flow rate = 0.6 mL / min): t_R = 14.1 min (major enantiomer), t_R = 21.2 min (minor enantiomer).

***S*-Ethyl (2*R*,3*R*)-3-(2-furyl)-3-hydroxy-2-methylpropanethioate (12):** (84% ee) $[\alpha]_D^{27}$ -30.4 ° (c 2.8, PhH); IR (neat) 3475, 1675 cm^{-1}; ^1H NMR (CCl_4) δ 1.15 (d, 3H, *J* = 7.0 Hz), 1.20 (t, 3H, *J* = 7.0 Hz), 2.75 (br s, 1H), 2.75 (q, 2H, *J* = 7.0 Hz), 2.90 (m, 1H), 4.85 (d, 1H, *J* = 5.0 Hz), 6.10 (m, 2H), 7.15 (m, 1H) Anal. ($C_{10}H_{14}O_3S$) C, H, S. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 19/1, flow rate = 1.0 mL / min): t_R = 11.2 min (major enantiomer), t_R = 13.2 min (minor enantiomer).

***S*-Ethyl (2*R*,3*S*)-2-(*t*-butyldimethylsiloxy)-3-hydroxy-3-phenylpropanethioate:** (81% ee) $[\alpha]_D^{28}$ 93.5 ° (c 2.4, PhH); IR (neat) 3490, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.42 (s, 3H), 0.03 (s, 3H), 0.95 (s, 9H), 1.29 (t, 3H, *J* = 7.4 Hz), 2.93 (q, 2H, *J* = 7.4 Hz), 3.08 (d, 1H, *J* = 8.6 Hz), 4.34 (d, 1H, *J* = 2.7 Hz), 5.16 (dd, 1H, *J* = 2.7, 8.6 Hz), 7.28-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ –5.7, 14.4, 18.1, 22.8, 25.7, 75.3, 82.3, 126.1, 127.7, 128.1, 140.5, 203.4. Anal. ($C_{17}H_{28}O_3SSi$) C, H, S. HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 50/1, flow rate = 1.0 mL / min): t_R = 7.6 min (minor enantiomer), t_R = 9.4 min (major enantiomer).

***S*-Ethyl (2*S*,3*S*)-2-benzyloxy-3-hydroxy-3-phenylpropanethioate:** (76% ee) The diastereomers were not separated in the aldol form. IR (neat) 3450, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3H, *J* = 7.6 Hz), 2.85 (q, 2H, *J* = 7.6 Hz), 3.19 (d, 1H, *J* = 3.6 Hz), 4.02 (d, 1H, *J* = 6.9 Hz), 4.20 (d, 1H, *J* = 11.2 Hz), 4.59 (d, 1H, *J* = 11.2 Hz), 4.87 (dd, 1H, *J* = 3.6, 6.9 Hz), 7.11-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.4, 22.7, 74.23, 74.9, 87.2, 127.2, 128.0, 128.3, 128.3, 128.4, 128.4, 136.5, 139.3, 203.0. Anal. ($C_{18}H_{20}O_3S$) C, H, S. Optical purity was determined after derivation to the corresponding acetate. *S*-Ethyl (2*R*,3*R*)-3-acetoxy-2-benzyloxy-3-phenylpropanethioate: $[\alpha]_D^{28}$ -35.0 ° (c 2.3, PhH); ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, *J* = 7.3 Hz), 1.54 (s, 3H), 2.82 (q, 2H, *J* = 7.3 Hz), 4.25 (d, 1H, *J* = 5.8 Hz), 4.42 (d, 1H, *J* = 11.9 Hz), 4.76 (d, 1H, *J* = 11.9 Hz), 6.02 (d, 1H, *J* = 5.8 Hz), 7.17-7.36 (m, 5H). HPLC (Daicel Chiralcel OD, hexane/*i*-PrOH = 19/1, flow rate = 0.8 mL/min): t_R = 8.5 min (major enantiomer), t_R = 11.0 min (minor enantiomer).

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References and Notes

(1) Stinson, S. C. *Chem. Eng. News* **1993**, Sept 27, 38, and references cited therein.
(2) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805.
(3) Cf. Kobayashi, S.; Hayashi, T. *J. Org. Chem.* **1995**, *60*, 1098; Kobayashi, S.; Horibe, M.; Matsumura, M. *Synlett* **1995**, 675.
(4) Kobayashi, S.; Horibe, M. *Chem. Lett.* **1995**, 1029.
(5) For recent example, Smith, III, A. B.; Condon, S. M.; McCauley, J. A.; Leazer, Jr., J. L.; Leahy, J. M.; Maleczka, Jr., R. E. *J. Am. Chem. Soc.* **1995**, *117*, 5407; Paterson, I.; Yeung, K.-S.; Ward, R. A.; Cumming, J. G.; Smith, J. D. *ibid.* **1994**, *116*, 9391; Mori, Y.; Asai, M.; Kawade, J.; Okumura, A.; Furukawa, H. *Tetrahedron Lett.* **1994**, *35*, 6503.
(6) Mukaiyama, T.; Kobayashi, S. "Organic Reactions," ed by Paquetee, L. A. et al., John Wiley & Sons, New York (1994), Vol. 46, p. 1; Gennari, C. "Asymmetric Synthesis with Enol Ethers," in "Comprehensive Organic Synthesis," ed by Trost, B. M.; Fleming, I. Pergamon Press, Oxford (1991), Vol. 2, p. 629.
(7) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247.
(8) 2*S*, 3*R* in some cases. See Table 2.
(9) 2*R*, 3*S* in some cases. See Table 2.
(10) Calculated with MOPAC 93 (by Stewart, J. J. P.) using the PM3 Hamiltonian.
(11) Kobatashi, S.; Horibe, M.; Saito, Y. *Tetrahedron* **1994**, *50*, 9629.
(12) 79% yield, *syn*/*anti* = 14/86, *anti* aldol = 81% ee (2*R*, 3*R*).
(13) Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1708.
(14) Batchelor, R. J.; Ruddick, J. N. R.; Sams, J. R.; Aubke, F. *Inorg. Chem.* **1977**, *16*, 1414.
(15) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381.
(16) Mukaiyama, T.; Kobayashi, S.; Sano, T. *Tetrahedron* **1990**, *46*, 4653.
(17) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761.
(18) (a) Stoll, A.; Petrzilka, T.; Rutschmann, J. *Helv. Chim. Acta* **1950**, *33*, 2256. (b) Smith, D. C. C.; Berry, D. *J. Chem. Soc., Perkin 1* **1972**, 699.

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