Highly Enantioselective Synthesis of Enantiomeric 2,3-Dihydroxy Thioesters by Using Similar Types of Chiral Sources Derived from L-Proline

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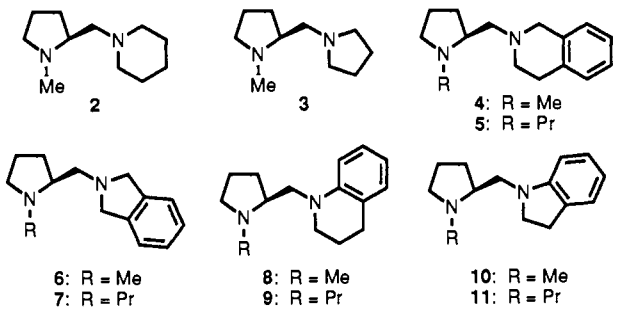
Received April 6, 1994

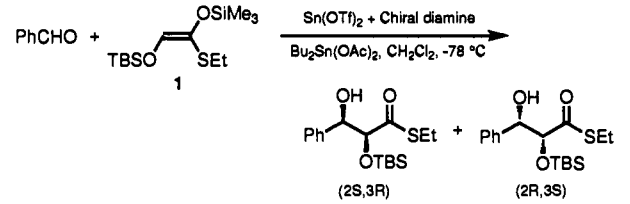
Synthesis of both enantiomers of a chiral compound is a very important task in asymmetric synthesis. In order to attain this goal, traditional methods have required sources of enantiomeric precursors, auxiliaries, or catalysts;[1] however, both enantiomers of the sources are often hard to obtain (for example, alkaloids, amino acids, sugars, etc.). In this paper, we report the preparation of both enantiomers including 1,2-diol units with almost perfect selectivities by using similar types of chiral sources derived from L-proline.

We have already reported the asymmetric aldol reactions of silyl enol ethers with aldehydes using chiral tin(II) Lewis acids consisting of tin(II) triflate and a chiral diamine.[2,3] Optically active 2,3-dihydroxy thioesters were prepared from silyl enol ethers derived from α-alkoxy thioesters with aldehydes by use of these reactions.[4] Quite recently, we developed a new type of chiral diamine, **5**, which was prepared from L-proline and tetrahydroisoquinoline.[5] Diamine **5** was effective in the chiral tin(II)



Lewis acid-mediated asymmetric aldol reactions of (*Z*)-1-(ethylthio)-1-(trimethylsiloxy)-2-(*tert*-butyldimethylsiloxy)-ethene (**1**) with α-keto esters for constructing α-alkoxy-β-hydroxy-β-methyl units. In the course of our investigations to develop efficient asymmetric catalysts, we first evaluated chiral diamine **5** in the reaction of **1** with benzaldehyde. The reaction was carried out in the presence of tin(II) triflate, chiral diamine **5**, and dibutyltin diacetate in dichloromethane at −78 °C. The aldol adduct with a 2*S*,3*R* configuration was obtained in 88% yield with a *syn*/*anti* ratio of 97/3, and the enantiomeric excess of the *syn* adduct was 96%.[6] When a similar chiral diamine, **9**, was used, the reaction also proceeded smoothly to afford the aldol adduct in a high yield with high *syn* selectivity. The enantiomeric excess of the *syn* aldol was also high (87%ee), *but the absolute configuration of the adduct was the reverse (2R,3S)*. Both diamines **5** and **9** were prepared from L-proline, and the absolute configuration of the 2-position is *S* in both cases. The difference is the fusion point of the benzene ring connected to the piperidine moiety. It was surprising that the slight difference in the structure of the chiral sources completely reversed the enantiofacial selectivity.[7] We further examined the effect of chiral diamines, and the results are summarized in Table 1. Almost perfect diastereo- and enantioselectivities with reverse absolute configurations were obtained when chiral diamines **6** and **10** were employed.

Table 1. Effect of Chiral Diamines



chiral diamine	yield (%)	*syn*/*anti*	2*S*,3*R*/2*R*,3*S*	ee (%)[a]
2	83	91/9	74.5/25.5	49
3	86	97/3	90.5/9.5	81
4	85	95/5	90.0/10.0	80
5	88	97/3	98.0/2.0	96
5[b]	77	98/2	98.0/2.0	96
6	86	98/2	99.0/1.0	98
7	73	>99/1	99.0/1.0	98
8	71	94/6	4.0/96.0	92
8[b]	76	97/3	4.0/96.0	92
9	90	94/6	6.5/93.5	87
10	82	99/1	1.0/99.0	98
11	79	97/3	7.0/93.0	86

[a] Enantiomeric excesses of *syn* adducts. [b] Tributyltin fluoride (Bu_3SnF) was used instead of $Bu_2Sn(OAc)_2$.

In addition to the unique selectivities, the present reaction provides convenient methods for the preparation of both enantiomers of *syn*-2,3-dihydroxy thioesters.[8] As shown in Table 2, adducts with the 2*S*,3*R* configuration were obtained from chiral diamine **6**, while adducts with the 2*R*,3*S* configuration were produced from chiral diamine **10** in all six typical aldehydes including aromatic, aliphatic, unsaturated, heterocyclic, and diene aldehydes. In every case, the selectivities were very high; almost perfect *syn* selectivities and more than 98% enantiomeric excesses of the *syn* adducts were obtained.[9] It should be noted that the

(1) (a) Stinson, S. C. *Chem. Eng. News* **1993**, Sept 27, 38. (b) Narasaka, K. *Synthesis* **1991**, 1. (c) Quite recently, we developed a new method for preparation of both enantiomers by using a single chiral source and a choice of achiral ligands in chiral lanthanide(III)-catalyzed Diels–Alder reactions. Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083.

(2) (a) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247. (b) Kobayashi, S.; Harada, T.; Han, J. S. *Chem. Express* **1991**, *6*, 563. (c) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761 and references cited therein.

(3) For chiral Lewis acid-promoted aldol reactions of silyl enolates with aldehydes, see: Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417.

(4) (a) Mukaiyama, T.; Uchiro, H.; Shiina, I.; Kobayashi, S. *Chem. Lett.* **1990**, 1019. (b) Mukaiyama, T.; Shiina, I.; Kobayashi, S. *Ibid.* **1991**, 1901.

(5) Kobayashi, S.; Horibe, M. *Synlett* **1994**, 147.

(6) The reaction of (*E*)-1-(ethylthio)-1-(trimethylsiloxy)-2-(*tert*-butyldimethylsiloxy)ethene with benzaldehyde was sluggish under the same reaction conditions. Cf. ref 2.

(7) In some cycloaddition or cross coupling reactions, it was reported that the stereochemical course changed when chiral sources with same configurations and slightly different structures were used, but the selectivities were moderate. (a) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412. (b) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *Ibid.* **1982**, *104*, 180. Cf.: (c) Suzuki, H.; Mochizuki, K.; Hattori, T.; Takahashi, N.; Tajima, O.; Takiguchi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1999.

(8) For preparation of optically active 1,2-diols using the osmium-catalyzed asymmetric oxidation, see: Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, Germany, 1993; pp 227–272.

(9) A typical experimental procedure is described for the reaction of **1** with benzaldehyde. To a suspension of tin(II) triflate (0.4 mmol) in dichloromethane (0.5 mL) were added chiral diamine **6** or **10** (0.48 mmol) in dichloromethane (0.5 mL) and dibutyltin diacetate (0.44 mmol) successively at room temperature. The mixture was then cooled to −78 °C, and dichloromethane solutions (0.5 mL each) of **1** (0.4 mol) and benzaldehyde (0.27 mmol) were successively added. The mixture was stirred for 21 h, and saturated $NaHCO_3$ was added to quench the reaction. After a usual workup, the crude product was chromatographed on silica gel to give 2-(*tert*-butyldimethylsiloxy)-3-hydroxy-3-phenylpropanethioate. The diastereomers were separated, and the optical purity was determined by HPLC using a chiral column (see supplementary material). We have tried to develop the truly catalytic version,[2b,c] but have not yet succeeded. This may be due to lower Lewis acidity of chiral diamine **6**-coordinated tin(II). Our final goal is to develop the truly catalytic process, and we are now in progress toward this goal.

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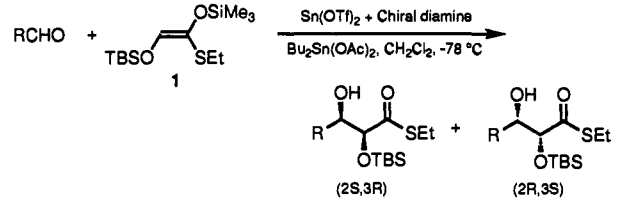
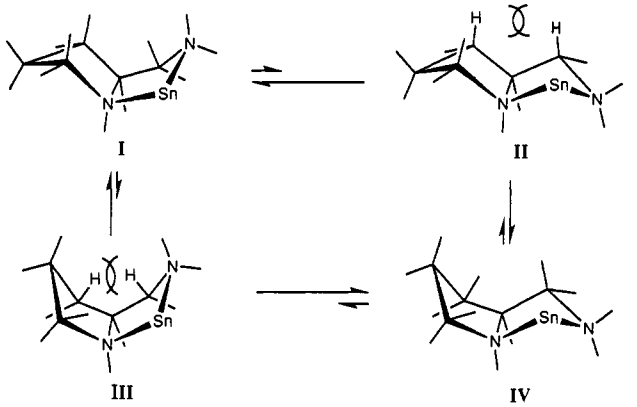
Table 2. Synthesis of Both Enantiomers



R	chiral diamine	yield (%)	*syn/anti*	2*S*,3*R*/2*R*,3*S*	(ee (%))[a]
Ph	**6**	86	98/2	99.0/1.0	(98)
C_2H_5	**6**	61	>99/1	99.0/1.0	(98)
CH_3CH=CH	**6**	74	>99/1	99.0/1.0	(98)
PhCH=CH	**6**	71	>99/1	99.5/0.5	(99)
2-furyl	**6**	86	>99/1	98.5/1.5[b]	(97)
CH_3CH=CHCH=CH	**6**	86	98/2	98.0/2.0	(96)
Ph	**10**	82	99/1	1.0/99.0	(98)
C_2H_5	**10**	63	>99/1	1.0/99.0	(98)
CH_3CH=CH	**10**	81	>99/1	1.0/99.0	(98)
PhCH=CH	**10**	80	99/1	1.0/99.0	(98)
2-furyl	**10**	86	>99/1	<0.5/>99.5[b]	(>99)
CH_3CH=CHCH=CH	**10**	78	>99/1	<0.5/>99.5	(>99)

[a] Enantiomeric excesses of *syn* adducts. [b] 2*S*,3*S*/2*R*,3*R*.

Scheme 1. Conformational Isomers of Bicyclo[3.3.0]octane-like Structure



benzene ring connected to the pyrrolidine moiety in the chiral diamines controlled the enantiofacial selectivities with high generality.[10]

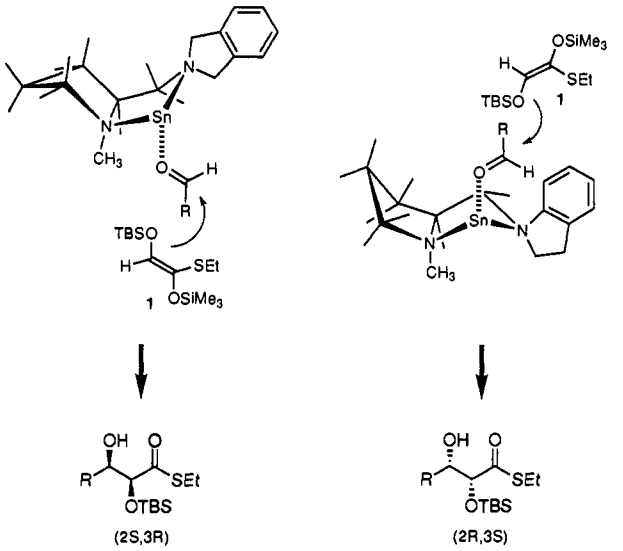
In order to clarify the origin of the selectivities, we examined the structures of the tin(II) triflate–chiral diamine complexes.[11] A possible explanation for the stereoselectivity is the formation of bicyclic tin(II) intermediates, which has been proposed previously[12] (the chiral diamines coordinate tin(II) to form bicyclo-[3.3.0]octane-like structures). If these are involved, then the differences might be accounted for by conformational isomers as shown in Scheme 1, and the following structures are consistent with the stereochemical outcome (Scheme 2). In chiral diamine **6**-coordinated tin(II), conformation I is favored and an aldehyde approaches from the bottom side. The *re* face of the aldehyde

(10) Enantioselectivities with reverse absolute configurations by chiral diamine **6** and **10** were observed in reactions of (*E*)-1-phenoxy-1-(trimethylsiloxy)-2-(*tert*-butyldimethylsiloxy)ethene or (*Z*)-1-(ethylthio)-1-(trimethylsiloxy)propene. Full details will be reported as a full paper.

(11) Cf.: (a) Shields, K. G.; Seccombe, R. C.; Kennard, C. H. L. *J. Chem. Soc., Dalton Trans.* **1973**, 741. (b) van Remoortere, F. P.; Flynn, J. J.; Boer, F. P.; North, P. P. *Inorg. Chem.* **1971**, *10*, 1511.

(12) (a) Mukaiyama, T.; Asami, M. *Top. Curr. Chem.* **1985**, *127*, 133. (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381. (c) Stevens, R. W.; Mukaiyama, T. *Chem. Lett.* **1983**, 1799.

Scheme 2. Assumed Transition States



is shielded by the amine part, and silyl enol ether **1** attacks this aldehyde from the *si* face via the acyclic transition state[13] to form the *syn*-(2*S*,3*R*)-aldol adduct. On the other hand, in chiral diamine **10**-coordinated tin(II), conformation IV is preferred. This is supported by NOE experiments.[14] The bottom side of the complex is crowded with nitrogen substituents and an aldehyde coordinated at the top side of the complex. At this time, the *si* face of the aldehyde is shielded and silyl enol ether **1** attacks this aldehyde from the *re* face via the acyclic transition state to form the *syn*-(2*R*,3*S*)-aldol adduct.

In summary, synthesis of both enantiomers including 1,2-diol units was attained with almost perfect stereochemical control by using chiral diamines **6** and **10** as chiral sources. It is noteworthy that the present report provides a new route to prepare both enantiomers by using similar types of chiral sources. Further investigations to develop new chiral catalysts according to this line are now actively in progress in our laboratory.

Acknowledgment. The authors are grateful to Mr. Takashi Kawasuji for helpful discussion and Miss Yumi Saito for her technical assistance. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

Supplementary Material Available: IR and NMR spectral data and HPLC data (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248.

(14) No NOE was observed in chiral diamine **10**-coordinated tin(II). The NOE experiments were carried out in CD_3CN at 20 °C. In CD_2Cl_2 enough NMR spectra with good resolution were not obtained probably due to the insolubility of the tin(II) complex. We confirmed that similar high selectivities were obtained in CH_3CN at −40 °C or in C_2H_5CN at −78 °C.