Asymmetric Aldol Reaction between Achiral Silyl Enol Ethers and Achiral Aldehydes by Use of a Chiral Promoter System

Shū Kobayashi,* Hiromi Uchiro, Yuko Fujishita, Isamu Shiina, and Teruaki Mukaiyama*

Contribution from the Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162, Japan. *Received May 31, 1990*

Abstract: In the presence of a chiral promoter consisting of tin(II) triflate, a chiral diamine, and tributyltin fluoride, the silyl enol ether of *S*-ethyl ethanethioate or *S*-*tert*-butyl ethanethioate reacts with aldehydes to afford the corresponding aldol-type adducts in good yields with high enantioselectivities. In the reaction of silyl enol ether of *S*-ethyl propanethioate with aldehydes, perfect stereochemical control is attained by the combined use of tin(II) triflate, a chiral diamine, and dibutyltin diacetate. A wide variety of aldehydes, including aliphatic, α,β-unsaturated, and aromatic aldehydes, are applicable to this reaction. The chiral promoters are characterized by ^{119}Sn NMR spectra and proved to form the three-component complexes, which behave as chiral Lewis acids. The reaction proceeds directly from silyl enol ethers without any accompanying metal exchange on the enolates.

Introduction

The titanium tetrachloride ($TiCl_4$) mediated aldol reaction of silyl enol ethers with aldehydes was first reported from this laboratory in 1973.[1] After this report, several rather strong Lewis acids such as $BF_3 OEt_2$, $SnCl_4$, etc.,[2] or fluoride anions such as $^nBu_4NF$, etc.,[3] have been found to be effective as promoters or catalysts in this reaction. The reaction was notably distinguished from the conventional aldol reaction carried out under basic conditions; it proceeded in a highly regioselective manner to give cross-aldols in high yields and was widely applied to the syntheses of natural producuts as a general and versatile carbon–carbon bond forming reaction.

Due to the increasing importance of asymmetric synthesis, some efforts have been recently made on the asymmetric version of this reaction by employing a combination of either chiral silyl enol ethers (ketene silyl acetals) and achiral aldehydes or achiral silyl enol ethers (ketene silyl acetals) and chiral aldehydes. Gennari et al. reported the enantioselective aldol reaction of (*E*)-ketene silyl acetal derived from *N*-methylephedrine-*O*-propionate with achiral aldehydes.[4] Helmchen et al. reported almost the same reaction through the use of camphor derivatives as chiral sources.[5] Though these examples provided useful methods for the preparation of optically active β-hydroxy esters in high enantioselectivities, tedious procedures for attaching and removing the chiral sources were required. Hitherto, the asymmetric aldol reaction of achiral silyl enol ethers with achiral aldehydes by the use of a chiral promoter has never been developed to a practical level.[6]

In this paper,[7] we report the highly enantioselective aldol reaction of achiral silyl enol ethers with achiral aldehydes by the use of a novel chiral promoter system consisting of chiral diamine-coordinated tin(II) triflate and tributyltin fluoride (or dibutyltin diacetate). In addition, a mechanistic study on the behavior of the promoters is described.

Results and Discussion

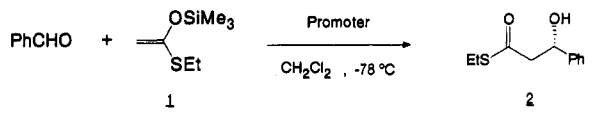
Reaction of Silyl Enol Ethers Derived from Acetic Acid Thioesters with Aldehydes. In 1985, we found that triphenylmethyl salts (trityl salts), which were represented by triphenylmethyl perchlorate (trityl perchlorate, $TrClO_4$), were excellent catalysts for the aldol reaction of silyl enol ethers with aldehydes.[8] This reaction has some characteristic features that can be compared with the original Lewis acid mediated one: the reaction proceeds in the presence of a catalytic amount of trityl salt, whereas the original Lewis acid promoted reaction requires a stoichiometric amount of promoter. Further, both the counteranions of trityl salts and the substituents on silicon of the silyl enol ethers play a significant role on the diastereoselectivities of the produced aldols, and syn or anti aldol is preferentially obtained by the appropriate choice of these substituents.

In 1987, the above aldol reaction was found to work by using a new catalyst system:[9] the combination of a neutral molecule (trityl chloride) and a weak Lewis acid (tin(II) chloride).[10] On the basis of the results that neither trityl chloride nor tin(II) chloride promotes the above-mentioned reaction, an active cationic species is assumed to be readily generated from the combination of trityl chloride and tin(II) chloride in this reaction. The most remarkable point is that this active promoter is generated by just mixing a neutral molecule and a weak Lewis acid; only 5–10 mol % each of these reagents is required to complete the reaction. As an extension of this reaction, we next examined the possibility of generating of a new active species by combining a Lewis acid and a tin(II) chloride. We subsequently found that some combinations of a neutral molecule and a tin(II) compound or Lewis acid, for example, tin(IV) chloride and zinc chloride,[11] antimony(V) chloride and tin(II) triflate,[12] tin(IV) chloride and tin(II) triflate,[13] etc.,[14] were effective catalysts for several carbon–carbon bond forming reactions. These catalysts are characterized as active cationic species that can promote these reactions when present in catalytic amounts, whereas the reactions are scarcely promoted when a neutral molecule or a Lewis acid is used alone. In the

(1) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
(2) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1981. Mukaiyama, T. *Org. React.* **1982**, *28*, 203.
(3) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265.
(4) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812.
(5) Helmchen, G.; Leikauf, U.; Knopfel, I. T. *Angew. Chem., Int Ed. Engl.* **1985**, *24*, 874.
(6) (a) Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *27*, 4721. (b) Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T. *Chem. Ind.* **1986**, 824. (c) Reetz, M. T.; Vougioukas, A. E. *Tetrahedron Lett.* **1987**, *28*, 793.
(7) For preliminary communications: Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 297. Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *Ibid.* **1989**, 1001, 1757.
(8) Mukaiyama, T.; Kobayashi, S.; Murakami, M.; *Chem. Lett.* **1985**, 447. Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Ibid.* **1985**, 1535.
(9) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1987**, 463.
(10) Mukaiyama, T.; Kobayashi, S.; Tamura, M.; Sagawa, Y. *Chem. Lett.* **1987**, 491.
(11) Hayashi, M.; Inubushi, A.; Mukaiyama, T. *Chem. Lett.* **1987**, 1975; *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4037.
(12) Kobayashi, S.; Tamura, M.; Mukaiyama, T. *Chem. Lett.* **1988**, 91.
(13) Mukaiyama, T.; Shimpuku, T.; Takashima, T.; Kobayashi, S. *Chem. Lett.* **1989**, 145.
(14) Mukaiyama, T.; Wariishi, K.; Saito, Y.; Hayashi, M.; Kobayashi, S. *Chem. Lett.* **1988**, 1011. Mukaiyama, T.; Sugumi, H.; Uchiro, H.; Kobayashi, S. *Ibid.* **1988**, 1291. Mukaiyama, T.; Wariishi, K.; Furuya, M.; Kobayashi, S. *Ibid.* **1989**, 1277.

0002-7863/91/1513-4247$02.50/0

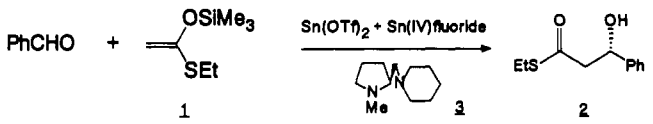
Table I. Effect of Chiral Promoeters



1 2

entry	promoter	yield/%	ee/%
1	$Sn(OTf)_2$ + chiral diamine **3**	74	0
2	$Sn(OTf)_2$ + chiral diamine **3** + AlF_3	76	0
3	$Sn(OTf)_2$ + chiral diamine **3** + MgF_2	72	0
4	$Sn(OTf)_2$ + chiral diamine **3** + $^nBu_3SnCl$	80	0
5	$Sn(OTf)_2$ + chiral diamine **3** + $^nBu_3SnF$	78	82

Table II. Effect of Tin(IV) Fluorides



1 **3** 2

entry	tin(IV) fluoride	yield/%	ee/%
1	$^nBu_3SnF$	78	82
2	Me_3SnF	64	76
3	Ph_3SnF	74	12

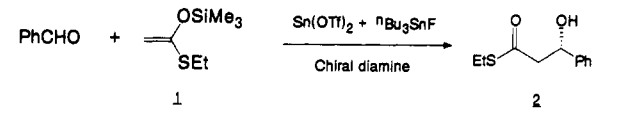
course of our investigations based on this concept, we have examined the suitable combination of these compounds including chiral sources, in order to develop a new chiral catalyst.

We focused on chiral diamine-coordinated tin(II) triflate as a potential chiral Lewis acid. The asymmetric aldol[15] and Michael reactions[16] of tin(II) enolates with aldehydes and α,β-unsaturated ketones by the use of a chiral diamine as a ligand have already been reported from this laboratory. In these reactions, a chiral diamine coordinated to the tin atom of a tin(II) enolate forms an excellent asymmetric environment, where relative and absolute stereochemistry can be controlled. On the other hand, the allylation reaction of allylaluminum reagents with aldehydes was found to be promoted by chiral diamine-coordinated tin(II) triflate.[17] However, our preliminary experiments demonstrated that no chiral induction was observed in the aldol reaction of silyl enol ethers with aldehydes by using chiral diamine-coordinated tin(II) triflate. On the basis of the experience that was obtained through the experiments to develop several new catalyst systems (combined use of a neutral molecule and a tin(II) compound or a Lewis acid and a tin(II) compound), we examined the possibility of the combination of chiral diamine-coordinated tin(II) triflate and other metal salts.

When the silyl enol ether of *S*-ethyl ethanethioate (**1**) was treated with benzaldehyde in the presence of stoichiometric amounts of tin(II) triflate, (*S*)-1-methyl-2-[(piperidin-1-yl)-methyl]pyrrolidine (**3**), and tributyltin fluoride, the aldol reaction proceeded at −78 °C to afford the corresponding adduct (**2**) in 78% yield with 82% ee. The importance of the combination of chiral diamine-coordinated tin(II) triflate and tributyltin fluoride is obvious from the result that no enantiomeric selection was observed by just using chiral diamine-coordinated tin(II) triflate or the combination of other metal salts (Table I). Tributyltin fluoride was found to be the most effective after other tin(IV) fluorides were screened (Table II).

Next, several chiral diamines were examined in order to improve the enantioselectivity. The 1-alkyl groups of pyrrolidine ring systems were found to have a strong influence on the enantiomeric excesses, and when (*S*)-1-*n*-pentyl-2-[(piperidin-1-yl)methyl]-pyrrolidine (**9**) was employed, the enantiomeric excess could be improved up to 88%. The maximum ee was obtained (92% ee) when (*S*)-1-methyl-2-[(*N*-1-naphthylamino)methyl]pyrrolidine

Table III. Effect of Chiral Diamines in the Reaction of **1** with Benzaldehyde



1 2

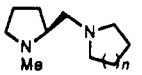
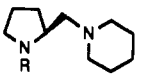
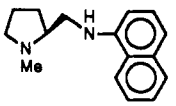
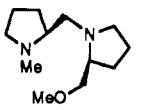
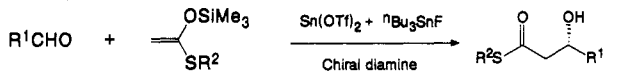
entry	chiral diamine		no.	yield/%	ee/%
1		n = 1	**4**	58	62
2		n = 2	**3**	78	82
3		n = 3	**5**	65	69
4		R = Me	**3**	78	82
5		R = Et	**6**	67	83
6		R = ^{n}Pr	**7**	58	83
7		R = ^{n}Bu	**8**	61	81
8		R = ^{n}Pent	**9**	75	88
9		R = ^{n}Hex	**10**	68	78
10			**11**	52	92
11			**12**	74	78

Table IV. Asymmetric Aldol Reaction of Silyl Enol Ethers of *S*-Ethyl or *S*-*tert*-Butyl Ethanethioate with Aldehydes



entry	R^1	R^2	chiral diamine	product	yield/%	ee/% (confign)
1	Ph	Et	**3**	**2**	78	82 (*S*)
2	Ph	Et	**11**	**2**	52	92 (*S*)
3	Ph	Et	**9**	**2**	75	88 (*S*)
4	Ph	^{t}Bu	**3**	**13**	73	86 (*S*)
5	$Ph(CH_2)_2$	Et	**3**	**14**	70	78
6	$Ph(CH_2)_2$	Et	**11**	**14**	50	81
7	$Ph(CH_2)_2$	^{t}Bu	**3**	**15**	71	85
8	^{i}Pr	Et	**3**	**16**	77	95
9	^{t}Bu	Et	**3**	**17**	90	>98

(**11**) was employed as a chiral diamine (Table III).

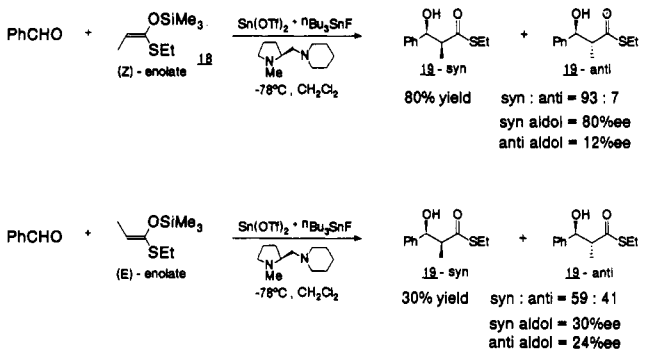
Several examples of this asymmetric aldol reaction are summarized in Table IV. In every case, the corresponding aldols are obtained in high yields with high enantioselectivities.

In some previously reported asymmetric aldol reactions using chiral enolate molecules, the enantioselectivities observed have been extremely low when acetic acid derivatives were employed as donors.[18] It should be noted that the present aldol reaction makes it possible to obtain the adducts between acetic acid derivatives and aldehydes from both achiral substrates in high enantiomeric excesses by this simple procedure. Further, the chiral diamine was easily recovered (>90%) without loss of any optical purity by usual workup.

Reaction of Silyl Enol Ethers of Propionic Acid Thioesters with Aldehydes. The enantioselective synthesis of α-methyl-β-hydroxy ester equivalents is one of the most challenging tasks in organic synthesis. The aldol reaction is a prospective tool for this purpose, and recently several metal enolates, such as boron,[6a,19] silicon,[1,4,5] lithium,[20] zirconium,[21] or tin(II),[15,22] etc.,[23] have been developed

(15) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381, and references cited therein.
(16) Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* **1988**, 1023. Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1988**, 1025.
(17) Mukaiyama, T.; Minowa, N.; Oriyama, T.; Narasaka, K. *Chem. Lett.* **1986**, 97. Minowa, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1988**, *60*, 3697.
(18) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24.
(19) (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. (b) Masamune, S.; Sato, T.; Kim, B.; Wollman, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (c) Evans, D. A.; Bantroli, J.; Shi, T. L. *Ibid.* **1981**, *103*, 2127. (d) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309. (e) Paterson, I.; Lister, M. A.; McClure,, C. K. *Ibid.* **1986**, *27*, 4787.
(20) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077.
(21) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876.

Scheme I



to realize high diastereofacial selectivities. Most of the above-mentioned approaches depend on substrate-based asymmetric induction by employing chiral enolates (including metal enolates that have chiral substituents on the metal) or chiral aldehydes. There are few examples of asymmetric aldol reactions for the preparation of syn or anti α-methyl-β-hydroxy carboxylic acid derivatives, starting from two prochiral reactants by the use of a chiral promoter that activates the carbonyl compounds.

In the previous section, we showed that high enantiomeric excesses were realized in the aldol reaction of achiral silyl enol ether derived from *S*-ethyl ethanethioate or *S*-*tert*-butyl ethanethioate with achiral aldehydes by use of a new chiral promoter (combined use of chiral diamine-coordinated tin(II) triflate and tributyltin fluoride). We next studied the further possible extension of this enantioselective reaction for the synthesis of syn-α-methyl-β-hydroxy thioesters.

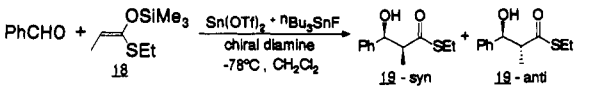
First, the reaction of benzaldehyde with 1-(trimethylsiloxy)-1-(ethylthio)propene was chosen as a model, and several reaction conditions were examined in the presence of stoichiometric amounts of tin(II) triflate, (*S*)-1-methyl-2-[(piperidin-1-yl)-methyl]pyrrolidine (**3**), and tributyltin fluoride. The geometry of the silyl enol ether was found to influence both reactivity and selectivity strongly; namely, (*Z*)-1-(trimethylsiloxy)-1-(ethylthio)propene (**18**) smoothly reacted with benzaldehyde to afford the corresponding aldol adduct with high syn selectivity (80% yield, syn:anti = 93:7, syn aldol 80% ee), while the reaction of the corresponding (*E*)-enolate proceeded more slowly and the aldol adduct was obtained with lower selectivity (30% yield, syn:anti = 59:41; syn aldol 30% ee) (Scheme I).

Next, we examined the effect of chiral diamines on the diastereo- and enantioselectivities in this reaction (Table V). When (*S*)-1-ethyl-2-[(piperidin-1-yl)methyl]pyrrolidine (**6**) was employed, the syn:anti ratio was slightly lowered, while ee was rather improved. Dramatic improvement in both diastereo- and enantioselectivity was observed when (*S*)-1-methyl-2-[(*N*-1-naphthylamino)methyl]pyrrolidine (**11**) was used; only the syn aldol was obtained with excellent enantioselectivity (syn:anti = 100:0, syn aldol >98% ee). It is noteworthy to point out that the reaction proceeded faster by employing chiral diamine **11**, since the coordination of the nitrogen atom of the naphthylamino group to tin atom is expected to be weaker, thus enhancing the Lewis acidity of chiral diamine **11** coordinated tin(II) triflate compared with that of the other more basic 2-[(trialkylamino)methyl]-pyrrolidine-coordinated tin(II) triflates.

Several aldehydes were successfully employed in the present asymmetric aldol reaction (Table VI). In every case, syn α-methyl-β-hydroxy thioesters were prepared in good yields with almost perfect diastereo- and enantioselectivities (syn:anti = 100:0, syn aldol >98% ee).

At this stage, the asymmetric aldol reaction between both achiral silyl enol ethers and aldehydes by use of a chiral promoter system was achieved with perfect stereochemical control. Our next interests were in the possible structure of this unique chiral promoter as well as the mechanism of this reaction. In order to clarify these points, we first examined the effect of various tin(IV) compounds other than tributyltin fluoride. A similar reaction was postulated to proceed by use of a tin(IV) compound that had oxygen atoms, since they were also expected to show strong affinity toward silicon atoms of silylated nucleophiles. Various tin(IV) compounds such as tin(IV) alkoxides and tin(IV) carboxylates were examined by taking the reaction of benzaldehyde with (*Z*)-1-(trimethylsiloxy)-1-(ethylthio)propene (**18**) as a model. The results are shown in Table VII. In most cases, the aldol-type products were obtained by the combined use of chiral diamine-coordinated tin(II) triflate and the above tin(IV) compounds in good to high yields with good to excellent diastereo- and enantioselectivities. With regard to the chemical yields and stereoselectivities, the following general tendencies were observed: (1) use of tin(IV) carboxylates gave better chemical yields than that

Table V. Effect of Chiral Diamine in the Reaction of **18** with Benzaldehyde



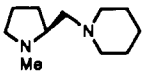
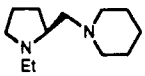
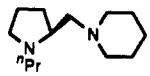
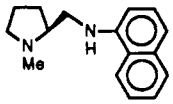
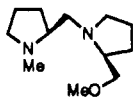
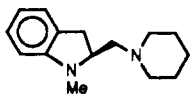
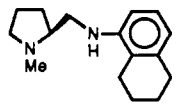
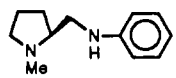
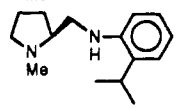
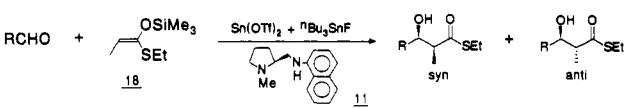
chiral diamine	no.	time/h	yield/%	syn:anti	ee/%
	**3**	20	80	93:7	80
	**6**	20	85	91:9	96
	**7**	20	85	93:7	96
	**11**	3	86	100:0	>98
	**12**	20	77	88:12	44
	**20**	20	60	90:10	60
	**21**	3	79	100:0	84
	**22**	3	58	88:12	42
	**23**	3	59	98:2	64

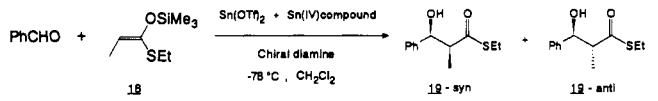
Table VI. Synthesis of Syn α-Methyl-β-hydroxy Thioesters by Use of $Sn(OTf)_2$, **11**, and $^nBu_3SnF$



entry	aldehyde	product	yield/%	syn:anti	ee/%
1	PhCHO	**19**	86	100:0	>98
2	*p*-ClPhCHO	**24**	86	100:0	>98
3	*p*-CH_3PhCHO	**25**	91	100:0	>98
4	*p*-MeOPhCHO	**26**	80	100:0	>98
5	$^nC_7H_{15}CHO$	**27**	48	99:1	>98
6	c-$C_6H_{11}CHO$	**28**	54	100:0	>98
7	^{i}PrCHO	**29**	52	100:0	>98

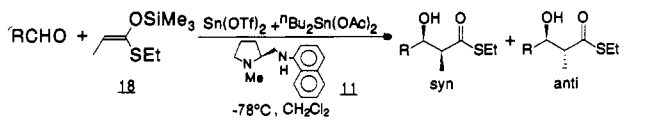
(22) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, *161*, 467.
(23) Eichenauer, H.; Friedrich, E.; Lutz, W.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 206. Davis, S. G.; Hedgecock, I. M. D.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 2125. Narasaka, K.; Miwa, T. *Chem. Lett.* **1985**, 1217.

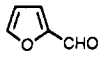
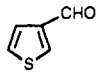
Table VII. Effect of Additives: Tin(IV) Compounds



tin(IV) compd	chiral diamine	yield/%	syn:anti	ee/%
^{n}Bu$_3$SnF	**3**	80	93:7	80
	11	86	100:0	>98
^{n}Bu$_2$SnF$_2$	**3**	NR		
	11	90	100:0	88
^{n}Bu$_3$SnOAc	**3**	65	63:37	55
	11	81	98:2	90
^{n}Bu$_2$Sn(OAc)$_2$	**3**	86	89:11	77
	11	85	100:0	>98
^{n}BuSn(OAc)$_3$	**3**	90	94:6	82
	11	93	100:0	75
^{n}Bu$_3$SnOMe	**3**	74	80:20	65
	11	NR		
^{n}Bu$_2$Sn(OMe)$_2$	**3**	54	95:5	75
	11	NR		
^{n}Bu$_2$Sn(OCOPh)$_2$	**11**	65	100:0	>98
^{n}Bu$_2$Sn(OCOCH$_2$Cl)$_2$	**11**	91	97:3	92

Table VIII. Synthesis of Syn α-Methyl-β-hydroxy Thioesters by Use of Sn(OTf)$_2$, **11**, and ^{n}Bu$_2$Sn(OAc)$_2$



entry	aldehyde	product	yield/%	syn:anti	ee/%
1	PhCHO	**19**	85	100:0	>98
2	*p*-ClPhCHO	**24**	96	100:0	>98
3	*p*-CH$_3$PhCHO	**25**	92	100:0	>98
4	*p*-OMePhCHO	**26**	95	100:0	>98
5	CH$_3$(CH$_2$)$_6$CHO	**27**	90	100:0	>98
6	c-C$_6$H$_{11}$CHO	**28**	90	100:0	>98
7	^{i}PrCHO	**29**	70	100:0	>98
8	^{t}BuCHO	**30**	86	100:0	>98
9	(*E*)-CH$_3$CH=CHCHO	**31**	92	100:0	>98
10	(*E*)-PhCH=CHCHO	**32**	91	100:0	>98
11	(*E*)-^{n}PrCH=CHCHO	**33**	91	100:0	>98
12		**34**	93	100:0	>98
13		**35**	92	100:0	>98

of tin(IV) alkoxides; (2) higher stereoselectivities were obtained when tin(IV) dicarboxylates were employed compared with tin(IV) monocarboxylates; (3) use of tin(IV) carboxylates, which had electron-withdrawing groups, lowered stereoselectivities. In particular, high yield and perfect stereochemical control were achieved by the combination of tin(II) triflate, (*S*)-1-methyl-2-[(*N*-1-naphthylamino)methyl]pyrrolidine (**11**) and dibutyltin diacetate.

Various aldehydes were employed under the present conditions (Table VIII). In every case, aldol-type adducts were obtained in high yields with almost perfect stereochemical control. It is noteworthy that a wide variety of aldehydes including aliphatic or α,β-unsaturated aldehydes as well as aromatic aldehydes are applicable in this reaction. The reactions proceeded smoothly with high yields by the use of this novel promoter system, which indicated that tin(IV) diacetate was superior to the other tin(IV) compounds such as tributyltin fluoride.

In the above aldol reaction, we assumed the formation of an active complex consisting of three components, tin(II) triflate, a chiral diamine, and tributyltin fluoride (or dibutyltin diacetate) (Chart I). This assumption was supported by the observation that the mixture of three components was completely soluble in dichloromethane, while either tin(II) triflate or tributyltin fluoride was only sparingly soluble under these conditions. The ^{119}Sn NMR

Chart I

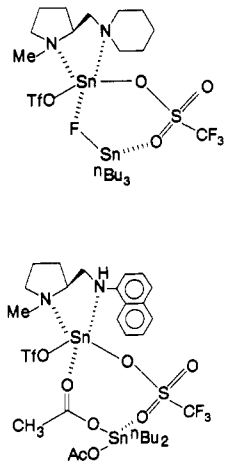
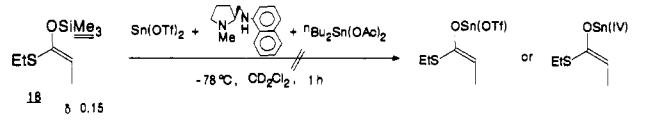


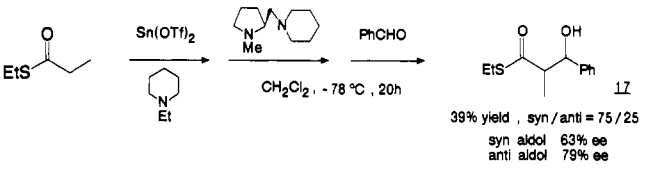
Table IX. ^{119}Sn NMR Chemical Shifts

chiral promoter	Sn(II)	Sn(IV)
Sn(OTf)$_2$ + **3** + ^{n}Bu$_3$SnF	−505.5	+106.4
Sn(OTf)$_2$ + **3**	−625.5	
Sn(OTf)$_2$ + **11** + ^{n}Bu$_3$SnF	−633.0	+122.7
Sn(OTf)$_2$ + **11** + ^{n}Bu$_2$Sn(OAc)$_2$	−632.2	−155.1
cf. ^{n}Bu$_2$Sn(OAc)$_2$		−149.2

Scheme II



Scheme III



spectrum of these chiral promoters in dichloromethane indicates the formation of three-component complexes without any accompanying metal exchange (Table IX).

The ^{1}H NMR spectra of the mixture of the chiral promoter and the silyl enol ether at −78 °C showed that no metal exchange took place from silicon to tin(II) or from silicon to tin(IV). To a dichloromethane-d_2 solution of tin(II) triflate, (*S*)-1-methyl-2-[(*N*-1-naphthylamino)methyl]pyrrolidine (**11**), and dibutyltin diacetate was added (*Z*)-1-(trimethylsiloxy)-1-(ethylthio)propene (**18**) in dichloromethane-d_2 at −78 °C. The singlet at δ 0.15 corresponding to the trimethylsiloxy group of **18** did not change within 1 h under the reaction conditions (Scheme II).

These observations support the hypothesis that the reaction does not proceed via tin(II) or tin(IV) enolates formed by metal exchange and that aldehydes are directly attacked by silyl enol ethers.[24] The complex would be able to activate both an aldehyde and a silyl enol ether (double activation); chiral diamine-coordinated tin(II) triflate activates an aldehyde as a Lewis acid and, at the same time, the electronegative fluoride or oxygen of acetoxy group derived from tin(IV) compounds interacts with a silicon atom of a silyl enol ether.

Conclusion

The asymmetric aldol reaction of silyl enol ethers of thioesters with aldehydes is performed by the combination of tin(II) triflate,

(24) The tin(II) enolate mediated aldol reaction of *S*-ethyl propanethioate with benzaldehyde was carried out at −78 °C in dichloromethane to afford the corresponding aldol-type adduct in 39% yield (syn:anti = 75:25, syn aldol 63% ee, anti aldol 79% ee) (Scheme III).

a chiral diamine, and tributyltin fluoride (or dibutyltin diacetate). This reaction has several characteristic points, some of which are advantageous over hitherto reported asymmetric aldol reactions.

(1) This is the first practical example of the asymmetric aldol reaction of isolable enolates (silyl enol ethers) with aldehydes, starting from both achiral substrates.

(2) This asymmetric reaction is employed by using both achiral substrates in the presence of a chiral promoter. The chiral promoters were characterized by ^{119}Sn NMR and proved to behave as chiral Lewis acids,[25] and they mainly activate an aldehyde. Therefore, the present reaction is markedly distinguished from conventional asymmetric aldol reactions that employ chiral aldehydes and/or enolates.

(3) In this aldol reaction, the products are directly isolated as desired β-hydroxy ester equivalents without the tedious procedures for attaching and removing the chiral sources.

(4) This asymmetric aldol reaction is successfully applicable to silyl enol ethers of acetic acid and propionic acid derivatives. Particularly, it is noted that perfect stereochemical control is attained in the reaction of silyl enol ether of *S*-ethyl propanethioate with various kinds of aldehydes (aromatic, aliphatic, and α,β-unsaturated aldehydes, syn:anti = 100:0, syn aldol >98% ee).

Experimental Section

IR spectra were recorded on a Hitachi 260-30 or a Jasco IRA-2 infrared spectrophotometer. ^1H NMR spectra were recorded on a Hitachi R-24B or R-1100 or a Bruker AM 500 spectrometer, and ^{119}Sn NMR spectra were recorded on a Hitachi R-1900 spectrometer. Tetramethylsilane (TMS) and tetramethyltin (Me_4Sn) served as internal and external standard, respectively. Low- and high-resolution mass spectra were recorded on JEOL DX-303HF mass spectrometer. Optical rotations were measured with a Jasco DIP-360 digital polarimeter. Column chromatography was performed on silica gel 60 (Merck) or Wakogel B5F. All reactions were carried out under an argon atmosphere in dried glassware.

Tributyltin fluoride (Tokyo Kasei Co., Ltd.) was dried in vacuo at 100 °C for 6 h.[26] Tin(II) trifluoromethanesulfonate (tin(II) triflate) was prepared by the literature method.[15] All handling of tin(II) triflate was carried out under argon atmosphere.

Optical purity was determined by measurement of the ^1H NMR spectrum of the corresponding acetyl derivatives with $Pr(hfc)_3$ (Table IV, entries 1–9) or $Eu(hfc)_3$ (Table VI, entries 1–7; Table VIII, entries 1–13) as a chiral shift reagent. The methoxy peaks cleanly separated in all cases for racemic forms. No separation could be detected at all by ^1H NMR analysis in cases of Table VI, entries 1–7, and Table VIII, entries 1–13. Absolute configurations of the aldol-type adducts **2** and **17** were determined by optical rotation of the corresponding methyl ester.[19c] The stereochemical course of this reaction is thought to be the same in all examples.

Chiral diamines **3–5**,[15] **6–10**,[27] **12**,[15] and **20**[15] were prepared by a literature method.

(*S*)-1-Methyl-2-[(pyrrolidin-1-yl)methyl]pyrrolidine (4): bp 111 °C/34 mmHg; $[\alpha]^{21}_D$ −84.5° (*c* 0.53, EtOH); IR (neat) 2960, 2780, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27–2.70 (m, 16 H), 2.27 (s, 3 H), 2.83 (m, 1 H).

(*S*)-1-Methyl-2-[(hexamethyleneimino)methyl]pyrrolidine (5): bp 90.8 °C/3 mmHg; $[\alpha]^{30}_D$ −68.4° (*c* 1.03, EtOH); IR (neat) 2950, 2810, 1480 cm^{-1}; ^1H NMR (CCl_4) δ 1.37–2.73 (m, 20 H), 2.24 (s, 3 H), 2.74–3.03 (m, 1 H).

(*S*)-1-Ethyl-2-[(piperidin-1-yl)methyl]pyrrolidine (6): bp 110 °C/8 mmHg; $[\alpha]^{20}_D$ −97.1° (*c* 0.52, EtOH); IR (neat) 2930, 2780, 1450, 1300, 1160, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, *J* = 6.5 Hz), 1.10–1.80 (m, 10 H), 1.80–2.50 (m, 8 H), 2.50–3.20 (m, 3 H); precise mass for $C_{12}H_{24}N_2$, calcd *m/z* 196.1939, found 196.1912.

(*S*)-1-Propyl-2-[(piperidin-1-yl)methyl]pyrrolidine (7): bp 69 °C/0.5 mmHg; $[\alpha]^{25}_D$ −107.4° (*c* 2.18, EtOH); IR (neat) 2920, 2770, 1440 cm^{-1}; ^1H NMR (CCl_4) δ 0.65–1.15 (m, 3 H), 1.15–2.65 (m, 21 H), 2.65–3.20 (m, 2 H).

(*S*)-1-*n*-Butyl-2-[(piperidin-1-yl)methyl]pyrrolidine (8): bp 85 °C/0.6 mmHg; $[\alpha]^{31}D$ −94.9° (*c* 0.91, EtOH); IR (neat) 2950, 2810, 1490, 1340, 1200, 1160 cm^{-1}; ^1H NMR (CCl_4) δ 0.72–1.11 (m, 3 H), 1.11–2.01 (m, 14 H), 2.01–2.56 (m, 8 H), 2.56–3.20 (m, 3 H).

(*S*)-1-*n*-Pentyl-2-[(piperidin-1-yl)methyl]pyrrolidine (9): bp 93 °C/0.64 mmHg; $[\alpha]^{29}_D$ −93.1° (*c* 2.47, EtOH); IR (neat) 2920, 2760, 1460, 1150, 1115 cm^{-1}; ^1H NMR (CCl_4) δ 0.65–1.10 (m, 3 H), 1.10–2.55 (m, 25 H), 2.55–3.20 (m, 2 H); precise mass for $C_{15}H_{30}N_2$, calcd *m/z* 238.2399, found 238.2389.

(*S*)-1-*n*-Hexyl-2-[(piperidin-1-yl)methyl]pyrrolidine (10): bp 122 °C/3 mmHg; $[\alpha]^{32}_D$ −84.9° (*c* 0.94, EtOH); IR (neat) 2970, 2830, 1500, 1330, 1190, 1160 cm^{-1}; ^1H NMR (CCl_4) δ 0.60–1.09 (m, 3 H), 1.09–2.00 (m, 18 H), 2.00–2.72 (m, 8 H), 2.72–3.19 (m, 3 H).

(*S*)-1-Methyl-2-[(piperidin-1-yl)methyl]-2,3-dihydroindole (20): bp 126 °C/0.7 mmHg; $[\alpha]^{25}_D$ −44.9° (*c* 2.98, EtOH); IR (neat) 3030, 2925,, 2840, 2790, 1610, 1485, 1465, 1320, 1270 cm^{-1}; ^1H NMR (CCl_4) 1.25–2.85 (m, 6 H), 2.05–3.20 (m, 9 H), 2.75 (s, 3 H), 3.25–3.65 (m, 1 H), 6.15–6.65 (m, 2 H), 6.65–7.10 (m, 1 H).

Chiral diamine **11** was prepared as follows.

(*S*)-*N*-[*N*-(*tert*-Butoxycarbonyl)prolyl]-1-naphthylamine (36). This amide was prepared from Boc-(*S*)-proline and 1-naphthylamine by a procedure similar to that of ref 15: 87% yield; $[\alpha]^{21}_D$ −68.0° (*c* 1.77, EtOH); IR (neat) 3400, 1700, 1665, 1400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 9 H), 1.70–2.20 (m, 4 H), 3.30–3.60 (m, 2 H), 4.40–4.60 (m, 1 H), 7.00–8.20 (m, 7 H), 9.40 (br s, 1 H).

(*S*)-1-Methyl-2-[(*N*-1-napththylamino)methyl]pyrrolidine (11). A THF solution (30 mL) of the amide **34** (10.3 g, 30 mmol) was slowly added to a THF suspension (30 mL) of $LiAlH_4$ (2.85 g, 75 mmol) at 0 °C, and the mixture was refluxed for 4 h. Then, saturated Na_2SO_4(aq) was added to the mixture at 0 °C, and the organic materials were collected by decantation. The organic layer was dried over K_2CO_3. After removal of the solvent, the crude product was purified by alumina column chromatography and then distilled to afford **10**: 9.8 g, 83%; mp 66 °C; bp 151 °C/0.5 mmHg; $[\alpha]^{30}_D$ −35.6° (*c* 1.05, EtOH); $[\alpha]^{30}_D$ −2.9° (*c* 1.50, $CHCl_3$); IR (neat) 3400, 2950, 1470 cm^{-1}; ^1H NMR (CCl_4) δ 1.30–2.10 (m, 4 H), 2.10–2.70 (m, 2 H), 2.25 (s, 3 H), 2.85–3.35 (m, 3 H), 4.95 (br s, 1 H), 6.15–6.60 (m, 1 H), 6.80–7.95 (m, 1 H); precise mass for $C_{16}H_{20}N_2$, calcd *m/z* 240.1626, found 240.1621.

Chiral diamines **21-23** were prepared by a similar procedure.

(*S*)-1-Methyl-2-[[*N*-(5,6,7,8-tetrahydronaphth-1-yl)amino]methyl]pyrrolidine (21): bp 144 °C/0.7 mmHg; $[\alpha]^{22}_D$ −27.1° (*c* 0.88, EtOH); IR (neat) 3375, 2920, 1590, 1500, 1465 cm^{-1}; ^1H NMR (CCl_4) δ 1.40–2.20 (m, 8 H), 2.20–2.90 (m, 6 H), 2.25 (s, 3 H), 2.90–3.25 (m, 3 H), 3.95 (br s, 1 H), 6.10–6.45 (m, 2 H), 6.65–7.00 (m, 1 H); precise mass for $C_{16}H_{24}N_2$, calcd *m/z* 244.1939, found 244.1921.

(*S*)-1-Methyl-2-(anilinomethyl)pyrrolidine (22): bp 93 °C/0.5 mmHg; $[\alpha]^{30}_D$ −68.9° (*c* 1.37, EtOH); IR (neat) 3390, 2960, 2840, 1600 cm^{-1}; ^1H NMR (CCl_4) δ 1.20–2.70 (m, 6 H), 2.35 (s, 3 H), 2.75–3.45 (m, 3 H), 4.10 (br s, 1 H) 6.20–6.85 (m, 3 H), 6.85–7.45 (m, 2 H); precise mass for $C_{12}H_{18}N_2$, calcd *m/z* 190.1470, found 190.1440.

(*S*)-1-Methyl-2-[(2-isopropylanilino)methyl]pyrrolidine (23): bp 110 °C/0.7 mmHg; $[\alpha]^{25}_D$ −25.0° (*c* 2.00, EtOH); IR (neat) 3375, 2945, 2775, 1600, 1505, 1450 cm^{-1}; ^1H NMR (CCl_4) δ 1.25 (d, 2 H, *J* = 7 Hz), 1.55–3.05 (m, 8 H), 2.30 (s, 3 H), 2.95–3.30 (m, 3 H), 4.25 (br s, 1 H), 6.25–6.70 (m, 2 H), 6.70–7.10 (m, 2 H); precise mass for $C_{15}H_{24}N_2$, calcd *m/z* 232.1939, found 232.1935.

Typical Procedure of the Asymmetric Aldol Reaction. To a solution of tin(II) triflate (0.4 mmol) and a chiral diamine (0.48 mmol) in dichloromethane was added tributyltin fluoride (0.44 mmol, solid, without solvent) or dibutyltin diacetate (0.44 mmol, in 0.5 mL of dichloromethane) at room temperature. After the mixture was cooled to −78 °C, a silyl enol ether (0.4 mmol) in dichloromethane (0.5 mL) and an aldehyde (0.36 mmol) in dichloromethane (0.5 mL) were added successively. The reaction mixture was stirred for an appropriate time and then quenched with aqueous sodium hydrogen carbonate. After the aqueous layer was extracted with dichloromethane, the organic layer was dried and the solvent was removed under reduced pressure. The crude product was purified by thin-layer chromatography (silica gel).

(*S*)-*S*-Ethyl 3-hydroxy-3-phenylpropanethioate (2): $[\alpha]^{28}_D$ −56.3° (*c* 1.40, PhH) (92% ee); IR (neat) 1680 cm^{-1}; ^1H NMR (CCl_4) δ 1.15 (t, 3 H, *J* = 7.0 Hz), 2.70 (q, 2 H, *J* = 7.0 Hz), 2.70 (d, 2 H, *J* = 6.0 Hz), 3.10 (br s, 1 H), 4.85 (t, 1 H, *J* = 6.0 Hz), 7.00 (m, 5 H); precise mass for $C_{11}H_{14}O_2S$, calcd *m/z* 210.0714, found 210.0681.

(*S*)-*S*-*tert*-Butyl 3-hydroxy-3-phenylpropanethioate (13): $[\alpha]^{27}_D$ −41.4° (*c* 1.53, PhH) (86% ee); IR (neat) 1680 cm^{-1}; ^1H NMR (CCl_4) δ 1.45 (s, 9 H), 2.65 (d, 2 H, *J* = 6.0 Hz), 3.05 (br s, 1 H), 4.85 (t, 1 H, *J* = 6.0 Hz), 7.00 (m, 5 H). Anal. ($C_{13}H_{18}O_2S$) C, H, S.

(*S*)-*S*-Ethyl 3-hydroxy-5-phenylpentanethioate (14): $[\alpha]^{28}_D$ −10.4° (*c* 2.78, PhH) (81% ee); IR (neat) 1680 cm^{-1}; ^1H NMR (CCl_4) δ 1.25 (t, 3 H, *J* = 7.0 Hz), 1.50–1.90 (m, 2 H), 2.60–3.05 (m, 7 H), 3.75–4.10 (m, 1 H), 7.10 (m, 5 H); precise mass for $C_{13}H_{18}O_2S$, calcd *m/z* 238.1028, found 238.1023.

(25) Quite recently we have developed the catalytic asymmetric aldol reaction by the use of chiral diamine-coordinated tin(II) triflate as a catalyst: Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett.* **1990**, 129. Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455.

(26) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831.

(27) Mukaiyama, T.; Kobayashi, S.; Sano, T. *Tetrahedron* **1990**, *46*, 4653.

(S)-S-tert-Butyl 3-hydroxy-5-phenylpentanethioate (15): $[\alpha]^{28}_D$ -7.5° (c 4.27, PhH) (85% ee); IR (neat) 1680 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.45 (s, 9 H), 1.55-1.95 (m, 2 H), 2.45-2.95 (m, 7 H), 3.95 (m, 1 H), 7.15 (m, 5 H); precise mass for $C_{15}H_{22}O_2S$, calcd m/z 266.1340, found 266.1254.

(S)-S-Ethyl 3-hydroxy-4-methylpentanethioate (16): $[\alpha]^{22}_D$ -52.0° (c 3.16, PhH) (95% ee); IR (neat) 1680 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.90 (d, 6 H, J = 7.0 Hz), 1.25 (t, 3 H, J = 7.0 Hz), 1.40-1.80 (m, 1 H), 2.50-2.75 (m, 3 H), 2.85 (q, 2 H, J = 7.0 Hz), 3.70 (m, 1 H). Anal. ($C_8H_{16}O_2S$) C, H, S.

(S)-S-Ethyl 3-hydroxy-4,4-dimethylpentanethioate (17): $[\alpha]^{24}_D$ -60.9° (c 3.96, PhH) (>98% ee); IR (neat) 1680 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.90 (s, 3 H), 1.25 (t, 3 H, J = 7.0 Hz), 2.45-2.75 (m, 3 H), 2.85 (q, 2 H, J = 7.0 Hz), 3.65 (m, 1 H). Anal. ($C_9H_{18}O_2S$) C, H, S.

(2S,3S)-S-Ethyl 3-hydroxy-3-phenyl-2-methylpropanethioate (19): $[\alpha]^{24}_D$ -85.2° (c 2.70, PhH) (>98% ee); IR (neat) 3450, 1675 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.10 (d, 3 H, J = 7.0 Hz), 1.20 (t, 3 H, J = 7.0 Hz), 2.65 (br s, 1 H), 2.55-2.95 (m, 1 H), 2.80 (q, 2 H, J = 7.0 Hz), 5.00 (d, 1 H, J = 4.0 Hz), 7.20 (m, 5 H); precise mass for $C_{12}H_{16}O_2S$, calcd m/z 224.0889, found 224.0880.

(2S,3S)-S-Ethyl 3-hydroxy-3-(4-chlorophenyl)-2-methylpropanethioate (24): $[\alpha]^{29}_D$ +86.4° (c 2.47, PhH) (>98% ee); IR (neat) 3450, 1675 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.10 (d, 3 H, J = 7.0 Hz), 1.20 (t, 3 H, J = 7.0 Hz), 2.70 (m, 1 H), 2.80 (q, 2 H, J = 7.0 Hz), 3.00 (br s, 1 H), 4.95 (d, 1 H, J = 4.0 Hz), 7.20 (m, 4 H); precise mass for $C_{12}H_{15}O_2SCl$, calcd m/z 258.0482, found 258.0473.

(2S,3S)-S-Ethyl 3-hydroxy-3-p-tolyl-2-methylpropanethioate (25): $[\alpha]^{30}_D$ +93.4° (c 3.29, PhH) (>98% ee); IR (neat) 3450, 1675 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.10 (d, 3 H, J = 7.0 Hz), 1.20 (t, 3 H, J = 7.0 Hz), 2.30 (s, 3 H), 2.70 (br s, 1 H), 2.70 (m, 1 H), 2.80 (q, 2 H, J = 7.0 Hz), 4.95 (d, 1 H, J = 4.0 Hz), 7.10 (m, 4 H); precise mass for $C_{13}H_{18}O_2S$, calcd m/z 238.1028, found 238.1041.

(2S,3S)-S-Ethyl 3-hydroxy-3-(4-methoxyphenyl)-2-methylpropanethioate (26): $[\alpha]^{28}_D$ +99.7° (c 2.90, PhH) (>98% ee); IR (neat) 3475, 1675 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.10 (d, 3 H, J = 7.0 Hz), 1.20 (t, 3 H, J = 7.0 Hz), 2.50 (br s, 1 H), 2.65 (m, 1 H), 2.75 (q, 2 H, J = 7.0 Hz), 3.20 (s, 3 H), 4.80 (d, 1 H, J = 4.0 Hz), 6.60 (d, 2 H, J = 9.0 Hz), 7.00 (d, 2 H, J = 8.0 Hz); precise mass for $C_{13}H_{18}O_3S$, calcd m/z 254.0977, found 254.0973.

(2S,3R)-S-Ethyl 3-hydroxy-2-methyldecanethioate (27): $[\alpha]^{26}_D$ +32.1° (c 2.70, PhH) (>98% ee); IR (neat) 3450, 1680 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.80-1.70 (m, 21 H), 2.25 (br s, 1 H), 2.35-2.65 (m, 1 H), 2.85 (q, 2 H, J = 7.0 Hz), 3.45-3.95 (m, 1 H). Anal. ($C_{13}H_{26}O_2S$) C, H. S.

(2S,3R)-S-Ethyl 3-cyclohexyl-3-hydroxy-2-methylpentanethioate (28): $[\alpha]^{28}_D$ +33.8° (c 2.50, PhH) (>98% ee); IR (neat) 3475, 1680 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.50-2.10 (m, 11 H), 1.15 (d, 3 H, J = 7.0 Hz), 1.25 (t, 3 H, J = 7.0 Hz), 2.25 (br s, 1 H), 2.75 (m, 1 H), 2.90 (q, 2 H, J = 7.0 Hz), 3.40-3.70 (m, 1 H). Anal. ($C_{12}H_{22}O_2S$) C, H, S.

(2S,3R)-S-Ethyl 3-hydroxy-2,4-dimethylpentanethioate (29): $[\alpha]^{30}_D$ +14.4° (c 1.80, PhH) (>98% ee); IR (neat) 3450, 1680 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.70-1.45 (m, 9 H), 1.25-1.95 (m, 1 H), 2.25 (br s, 1 H), 2.45-2.80 (m, 1 H), 2.30 (q, 2 H, J = 7.0 Hz), 3.25-3.60 (m, 1 H). Anal. ($C_9H_{18}O_2S$) C, H, S.

(2S,3R)-S-Ethyl 3-hydroxy-2,5-dimethylhexanethioate (30): $[\alpha]^{30}_D$ + 39.9° (c 2.70, PhH) (>98% ee); IR (neat) 3425, 1680 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.95 (d, 6 H, J = 6.0 Hz), 1.20 (d, 3 H, J = 7.0 Hz), 1.25 (t, 3 H, J = 7.0 Hz), 1.55-2.00 (m, 2 H), 2.20 (br s, 1 H), 2.30-2.60 (m, 1 H), 3.65-4.10 (m, 1 H). Anal. ($C_{10}H_{20}O_2S$) C, H, S.

(2S,3R)-S-Ethyl 3-hydroxy-2-methyl-trans-4-hexenethioate (31): $[\alpha]^{26}_D$ +50.7° (c 2.10, PhH) (>98% ee); IR (neat) 3400, 1665 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.20 (d, 3 H, J = 7.0 Hz), 1.25 (t, 3 H, J = 7.0 Hz), 1.70 (d, 3 H, J = 5.0 Hz), 2.35-2.75 (m, 1 H), 2.55 (br s, 1 H), 2.80 (q, 2 H, J = 7.0 Hz), 4.05-4.35 (m, 1 H), 5.05-5.95 (m, 2 H). Anal. ($C_9H_{16}O_2S$) C, H, S.

(2S,3R)-S-Ethyl 3-hydroxy-2-methyl-5-phenyl-trans-4-pentenethioate (32): $[\alpha]^{29}_D$ +84.4° (c 3.50, PhH) (>98% ee); IR (neat) 3400, 1665 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.20 (t, 3 H, J = 7.0 Hz), 1.25 (d, 3 H, J = 7.0 Hz), 2.55 (br s, 1 H), 2.55-2.95 (m, 1 H), 2.80 (q, 2 H, J = 7.0 Hz), 4.30-4.65 (m, 1 H), 6.05 (dd, 1 H, J = 5.0, 16.0 Hz), 6.60 (d, 1 H, J = 16.0 Hz), 7.05-7.45 (m, 5 H). Anal. ($C_{14}H_{18}O_2S$) C, H, S.

(2S,3R)-S-Ethyl 3-hydroxy-2-methyl-trans-4-octenethioate (33): $[\alpha]^{25}_D$ +39.8° (c 2.70, PhH) (>98% ee); IR (neat) 3400, 1665 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.60-1.70 (m, 9 H), 1.80-2.45 (m, 4 H), 2.30 (br s, 1 H), 2.45-2.85 (m, 1 H), 2.80 (q, 2 H, J = 7.0 Hz), 4.10-4.35 (m, 1 H), 5.05-5.90 (m, 2 H). Anal. ($C_{11}H_{20}O_2S$) C, H, S.

(2S,3S)-S-Ethyl 3-(2-furyl)-3-hydroxy-2-methylpropanethioate (34): $[\alpha]^{25}_D$ +39.3° (c 3.00, PhH) (>98% ee); IR (neat) 3475, 1675 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.15 (d, 3 H, J = 7.0 Hz), 1.20 (t, 3 H, J = 7.0 Hz), 2.75 (br s, 1 H), 2.75 (q, 2 H, J = 7.0 Hz), 2.90 (m, 1 H), 4.85 (d, 1 H, J = 5.0 Hz), 6.10 (m, 2 H), 7.15 (m, 1 H). Anal. ($C_{10}H_{14}O_3S$) C, H, S.

(2S,3S)-S-Ethyl 3-(3-thienyl)-3-hydroxy-2-methylpropanethioate (35): $[\alpha]^{31}_D$ + 58.4° (c 3.30, PhH) (>98% ee); IR (neat) 3425, 1680 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.75-1.40 (m, 6 H), 2.45-3.20 (m, 3 H), 2.80 (br s, 1 H), 5.15 (d, 1 H, J = 5.0 Hz), 6.55-7.15 (m, 2 H), 7.15-7.40 (m, 1 H). Anal. ($C_{10}H_{14}O_2S$) C, H, S.

Acknowledgment. The present research was partially supported by a Grant-in-Aid for Scientific Research, No. 01649008, from the Ministry of Education, Science and Culture. We are also grateful to Miss Yasuko Tanaka (Hitachi Instrument Engineering Co., Ltd.) and Mr. Hitoshi Sasabuchi (Naka Works, Hitachi, Ltd.) for measuring the ^{119}Sn NMR spectrum.

Hyperbranched Macromolecules via a Novel Double-Stage Convergent Growth Approach

Karen L. Wooley, Craig J. Hawker, and J. M. J. Fréchet*

Contribution from the Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301. *Received December 10, 1990*

Abstract: A novel double-stage convergent growth approach for the preparation of dendritic macromolecules is described. In the first stage, convergent growth with 4,4-bis(4'-hydroxyphenyl)pentanol as the building block is used to create symmetrical dendritic structures containing a large number of phenolic "surface" functionalities. In the second stage of growth, these polyphenolic dendritic macromolecules are utilized as cores for the attachment of other dendritic macromolecules, derived from 3,5-dihydroxybenzyl alcohol, that contain a single benzylic bromide reactive group at their focal point. This two-stage process affords hyperbranched spherical macromolecules consisting of a flexible inner core surrounded by a more rigid outer layer. The double-stage convergent growth approach allows for the preparation of larger dendrimers in less time and with greater ease than the single-stage approach while retaining the advantages of near monodispersity and ease of purification and characterization.

Introduction

Spherical dendritic macromolecules have received considerable attention as a new class of polymers.[1] This interest is due to their novel highly branched structure, which may result in a variety of new and improved properties. Two fundamentally different approaches have been developed to synthesize these molecules. The first is a "divergent-growth" approach, best known for the preparation of "starburst"[2] and "arborol"[3] dendrimers. An ex-

(1) Bikales, N. M. *Polym. J.* **1989**, *19*, 11.

0002-7863/91/1513-4252$02.50/0