

Tin Lewis acid

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1. Introduction

The element tin has played an increasingly important role in organic chemistry as well as organometallic chemistry, serving as a source of new reagents for selective transformations.¹⁻³ The main activity in these fields has been focused for a long time on tin(IV) compounds, and tin(II) compounds have been used primarily as reductants of aromatic nitro compounds to aromatic amines.⁴ During the last decade, asymmetric synthesis has been developed increasingly, and in this field tin(II) reagents have served main roles rather than tin(IV) reagents.

Electronegativity of tin(II) and tin(IV) is shown in Table 7.1.⁵ Tin(II) is more electropositive and hence cationic than tin(IV), and is expected to coordinate with nucleophilic ligands. On the other hand, covalent radius and ionic radius of tin(II) are longer than those of tin(IV) (Tables 7.2 and 7.3).⁶⁻¹³ This is due to electronic repulsion caused by unpaired electrons of tin(II), which weakens the δ -bond because tin(II) uses p-orbital for bonding. These

Table 7.1. Comparison of electronegativity

Oxidation state	Electronegativity (Pauling)	Electronegativity (Sanderson)
Sn(II)	1.80	1.58
Sn(IV)	1.96	2.02

Table 7.2. Sn-X bond distance (Å) in gas-phase

SnX ₂	Sn-X	SnX ₄	Sn-X	References
SnR ₂	2.28	SnR ₄	2.17	4
SnCl ₂	2.42~2.43	SnCl ₄	2.28~2.31	5-8
SnBr ₂	2.55	SnBr ₄	2.44	5,6,9
SnI ₂	2.73~2.78	SnI ₄	2.64	5,6,9

Table 7.3. Ionic radii (Å)

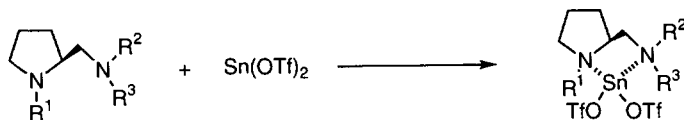
Oxidation state	Ionic radii
Sn(II)	1.02
Sn(IV)	0.71

characteristics are utilized in the following asymmetric reactions: to form a rigid complex with chiral diamines and to create an efficient asymmetric field, which has enough space to include several reactants. This chapter surveys use of tin(II) and tin(IV) Lewis acids, especially chiral Lewis acid, in organic synthesis.

2. Asymmetric aldol reaction

2.1 Preparation of chiral tin(II) Lewis acids

Chiral tin(II) Lewis acids are prepared *in situ* by mixing tin(II) triflate and chiral diamines, which are readily prepared from (*S*)-prolin in an appropriate solvent (Scheme 7.1). Tin(II) has three vacant orbitals, and after co-ordination of two nitrogen atoms one vacant orbital still remains.¹⁴ Therefore, chiral diamine-co-ordinated tin(II) has a rigid bicyclo[3.3.0]octane-like structure consisting of two fused five-membered rings, and can activate an aldehyde using the vacant orbital without changing the rigid structure.¹⁵

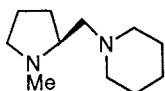
**Scheme 7.1**

2.2 Asymmetric aldol reactions of silyl enol ethers derived from acetic and propionic acid derivatives

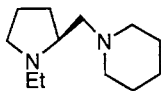
In the presence of a stoichiometric amount of tin(II) triflate, chiral diamine **1**, and tributyltin fluoride (Bu₃SnF), 1-*S*-ethyl-1-trimethylsiloxyethene or 1-*S*-*t*-butyl-1-trimethylsiloxyethene reacts with aldehydes to afford the corresponding adducts in high yields with high enantioselectivities.¹⁶ No chiral induction is observed without using Bu₃SnF. Although the precise function of Bu₃SnF is not yet clarified, it is believed that the fluoride connects the chiral tin(II) Lewis acid with the nucleophile, the silyl enol ether.^{17,18}

In the reactions with the propionate derivatives, which provide synthetically useful α-methyl-β-hydroxy ester derivatives, combination of tin(II) triflate, chiral diamine **5**, and Bu₂Sn(OAc)₂ gives better results.^{17,19} The asymmetric

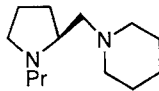
7: Tin Lewis acid



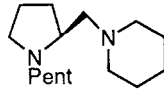
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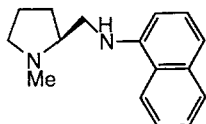
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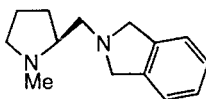
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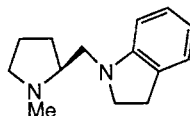
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aldol reactions proceed with higher enantioselectivity, and in addition, the reactions proceed faster using $\text{Bu}_2\text{Sn}(\text{OAc})_2$ than using Bu_3SnF as an additive.²⁰ A wide variety of aldehydes including aliphatic, aromatic, and α,β -unsaturated aldehydes are applicable to this reaction, and in all cases the aldol adducts are obtained in high yields with perfect *syn*-selectivities, and the enantiomeric excesses of these *syn*-adducts are more than 98%.

Protocol 1.

Asymmetric aldol reaction of (Z)-1-S-ethyl-1-trimethylsiloxypropene (8Z) with an aldehyde

Equipment

- Two-necked, round-bottomed flask (30 mL) fitted with a magnetic stirring bar. A three-way stopcock is fitted to the top of the flask and connected to a vacuum/argon source
- Vacuum/inert gas source (argon source may be an argon balloon)

Materials

- Tin(II) triflate (FW 416.82), 166.3 mg, 0.40 mmol
- Distilled chiral diamine **5** (FW 240.35), 115.4 mg, 0.48 mmol
- Distilled $\text{Bu}_2\text{Sn}(\text{OAc})_2$ (FW 351.03), 154.5 mg, 0.44 mmol
- Distilled benzaldehyde (FW 106.12), 38.2 mg, 0.36 mmol
- Distilled (Z)-1-S-ethyl-1-trimethylsiloxypropene (**8Z**) (FW 190.38), 76.2 mg, 0.40 mmol
- Dry, distilled dichloromethane

1. Flame dry the reaction vessel with a stirring bar under dry argon.
2. Add tin(II) triflate to the flask in dry box under argon atmosphere and dry at 100 °C for 1 h under reduced pressure (0.5 mmHg).

Protocol 1. Continued

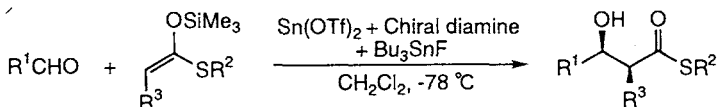
3. Add 1 ml of dry dichloromethane to the flask with stirring. Add chiral diamine **5** in 0.5 mL of dichloromethane and then $\text{Bu}_2\text{Sn}(\text{OAc})_2$ in 0.5 mL of dichloromethane.
 4. After stirring the mixture for 5 min at room temperature, cool to -78°C .
 5. Add (Z)-1-S-ethyl-1-trimethylsiloxypropene (**82**) in 0.5 mL of dichloromethane and benzaldehyde in 0.5 mL of dichloromethane successively.
 6. After stirring for 20 h, add saturated sodium hydrogen carbonate. Warm the mixture to the room temperature, filter the suspension through a pad of Celite, and wash the filter cake three times with dichloromethane. Extract the aqueous layer three times with dichloromethane and wash the combined extracts with brine.
 7. Concentrate the crude product under reduced pressure and apply to preparative TLC (silica gel). Elute with a mixed solvent of hexane–ethyl acetate (4:1) to obtain the product. Only *syn* isomer is produced and the optical purity is determined by HPLC analysis using a chiral column.
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

2.3 Asymmetric synthesis of 2-substituted malate derivatives

2-Substituted malic acids and their esters are widely distributed in nature as a variety of natural sources produced by plants or micro-organisms. Of more interest is their common inclusion as carboxylic acid components in biologically active alkaloids, and intense efforts have been made to prepare their carboxylic acid residues as optically active forms. Concerning asymmetric synthesis of 2-substituted malates, asymmetric aldol reactions of acetic acid derivatives with α -ketoesters are one of the most prospective methods.^{21–23}

In the presence of tin(II) triflate, (S)-1-pentyl-2-[(piperidin-1-yl)methyl]-pyrrolidine (**4**), and Bu_3SnF , 1-S-ethyl-1-trimethylsiloxyethene reacts with methyl pyruvate to give the desired adduct in 92% ee. Methyl isopropylglyoxylate and methyl phenylglyoxylate also react with 1-S-ethyl-1-trimethylsiloxyethene to give the corresponding 2-substituted malates in good yields with excellent enantioselectivities.²⁴

Recently, a series of pyrrolizidine alkaloids has attracted much attention due to their potent hepatotoxic, carcinogenic, and mutagenic properties.^{25–30} These alkaloids, especially 11- or 12-membered pyrrolizidine dilactones such as integerrimine, senecionine, fulvine, crispatine, etc., possess unique common structures of the α -methyl- β -hydroxy- β -alkyl units, and rather complicated multistage transformations have often been required for the stereoselective construction of these successive asymmetric centres including quaternary carbons.

Table 7.4. Asymmetric aldol reactions of silyl enolates with aldehydes

Entry	R ¹	R ²	R ³	Chiral diamine	Yield(%)	syn/anti	ee (%)
1	Ph	Et	H	1	78	—	82
2	Ph	Et	H	5	52	—	92
3	Ph	t-Bu	H	1	73	—	86
4	Ph(CH ₂) ₂	Et	H	1	70	—	78
5	Ph(CH ₂) ₂	Et	H	5	50	—	81
6	Ph(CH ₂) ₂	t-Bu	H	1	71	—	85
7	<i>i</i> -Pr	Et	H	1	77	—	95
8	<i>t</i> -Bu	Et	H	1	90	—	>98
9	Ph	Et	Me	5	85	100/0	>98
10	<i>p</i> -Cl Ph	Et	Me	5	96	100/0	>98
11	<i>p</i> -Me ₃ Ph	Et	Me	5	92	100/0	>98
12	<i>p</i> -MeO ₃ Ph	Et	Me	5	95	100/0	>98
13	CH ₃ (CH ₂) ₆	Et	Me	5	90	100/0	>98
14	<i>c</i> -C ₆ H ₁₁	Et	Me	5	90	100/0	>98
15	<i>i</i> -Pr	Et	Me	5	70	100/0	>98
16	<i>i</i> -Bu	Et	Me	5	86	100/0	>98
17	(<i>E</i>)-CH ₃ CH=CH	Et	Me	5	92	100/0	>98
18	(<i>E</i>)-PhCH=CH	Et	Me	5	91	100/0	>98
19	(<i>E</i>)- <i>n</i> -PrCH=CH	Et	Me	5	91	100/0	>98
20		Et	Me	5	93	100/0	>98
21		Et	Me	5	92	100/0	>98

Protocol 2.**Asymmetric aldol reaction of 1-*S*-ethyl-1-trimethylsiloxyethene with an α -ketoester***Equipment*

- Two-necked, round bottomed flask (30 mL) fitted with a magnetic stirring bar. A three-way stopcock is fitted to the top of the flask and connected to a vacuum/argon source
- Vacuum/inert gas source (argon source may be an argon balloon)

Materials

- Tin(II) triflate (FW 416.82), 166.7 mg, 0.40 mmol
- Distilled chiral diamine **4** (FW 238.42), 114.4 mg, 0.48 mmol
- Bu₃SnF (FW 309.05), 136.0 mg, 0.44 mmol

Protocol 2. Continued

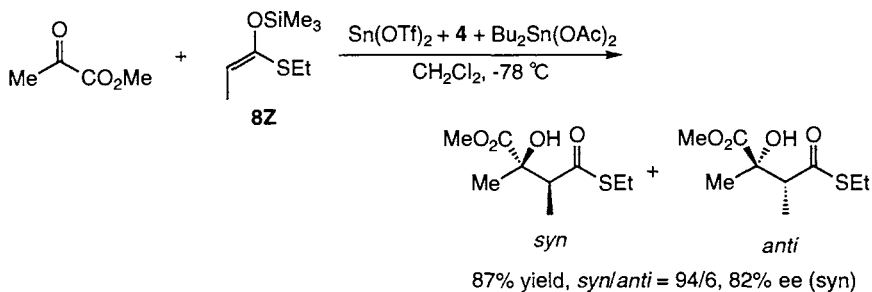
- Distilled methylpyruvate (FW 102.09), 36.8 mg, 0.36 mmol
- Distilled 1-*S*-ethyl-1-trimethylsiloxyethene (FW 176.35), 70.5 mg, 0.40 mmol
- Dry, distilled dichloromethane

1. Flame dry the reaction vessel with a stirring bar under dry argon.
2. Add tin(II) triflate to the flask in dry box under argon atmosphere and dry at 100°C for 1 h under reduced pressure (0.5 mmHg).
3. Add 1 ml of dry dichloromethane to the flask with stirring. Add chiral diamine **4** in 1 mL of dichloromethane and then Bu₃SnF.
4. After stirring the mixture for 5 min at room temperature, cool to -78°C.
5. Add 1-*S*-ethyl-1-trimethylsiloxyethene in 0.5 mL of dichloromethane and methylpyruvate in 0.5 mL of dichloromethane successively.
6. After stirring for 20 h, add saturated sodium hydrogen carbonate. Warm the mixture to the room temperature and filter the suspension through a pad of Celite, and wash the filter cake three times with dichloromethane. Extract the aqueous layer three times with dichloromethane and wash the combined extracts with brine.
7. Concentrate the crude product under reduced pressure and apply to preparative TLC (silica gel). Elute with a mixed solvent of hexane-ethyl acetate (4:1) to obtain the product. The optical purity is determined by HPLC analysis using a chiral column.

When (*Z*)-1-*S*-ethyl-1-trimethylsiloxypropene (**8Z**) is treated with methylpyruvate in the presence of tin(II) triflate, (*S*)-1-pentyl-2-[(piperidin-1-yl)methyl]pyrrolidine (**4**), and Bu₃SnF, the reaction proceeds smoothly to give the *syn* isomer in high yield with high diastereo- and enantioselectivities (Scheme 7.2).³¹ Similarly, (*Z*)-1-*S*-ethyl-1-trimethylsiloxypropene (**8Z**) reacts

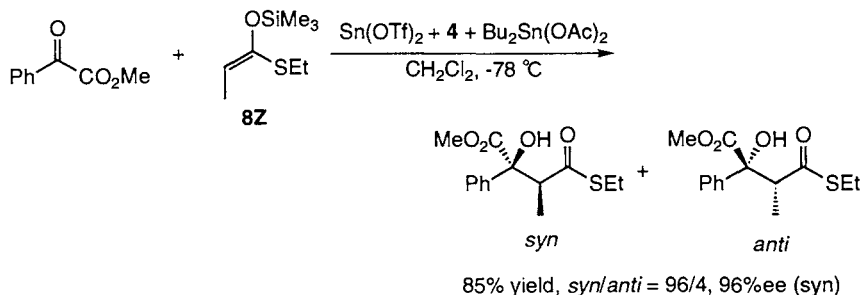
Table 7.5. Asymmetric aldol reactions of α-Ketoesters

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{CO}_2\text{Me} \end{array} + \begin{array}{c} \text{OSiMe}_3 \\ \parallel \\ \text{C}=\text{C} \\ \text{SEt} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, -78^\circ\text{C}]{\text{Sn(OTf)}_2 + \text{Chiral diamine} + \text{Bu}_3\text{SnF}} \begin{array}{c} \text{MeO}_2\text{C} \quad \text{OH} \quad \text{O} \\ \quad \quad \quad \parallel \\ \text{R}-\text{C}-\text{CH}_2-\text{C}-\text{SEt} \end{array} $				
Entry	R	Chiral diamine	Yield (%)	ee (%)
1	Me	1	73	83
2	Me	4	78	92
3	<i>i</i> -Pr	1	76	>98
4	<i>i</i> -Pr	4	81	>98
5	Ph	1	74	>98
6	Ph	4	74	>98



Scheme 7.2

with methyl phenylglyoxylate smoothly to give the corresponding *syn* adduct in a high enantiomeric excess (Scheme 7.3). The successive asymmetric centres including quarternary carbons are constructed efficiently with high selectivities by using this methodology.³² On the other hand, (*E*)-1-*S*-ethyl-1-trimethylsiloxypropene reacts with methyl phenylglyoxylate or methyl pyruvate very slowly under the same reaction conditions.

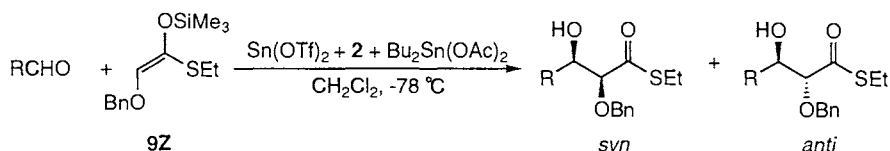


Scheme 7.3

2.4 Asymmetric synthesis of *syn*- and *anti*-1,2diol derivatives

Optically active 1,2-diol units are often observed in nature such as carbohydrates, macrolides, polyethers, etc. Recently several excellent asymmetric oxidation reactions of olefins using osmium tetroxide with a chiral ligand has been developed to achieve high enantiomeric excesses.^{33–36}

Asymmetric synthesis of 1,2-diol derivatives based on asymmetric aldol reactions of α -alkoxy silyl enol ethers with aldehydes has been developed. The reaction of (*Z*)-2-benzyloxy-1-*S*-ethyl-1-trimethylsiloxyethene (**9Z**) with benzaldehyde is carried out in dichloromethane at -78°C by using a chiral promoter consisting of tin(II) triflate, (*S*)-1-methyl-2-[(*N*-1-naphthylamino)methyl]pyrrolidine (**5**), and Bu_3SnF , to afford the corresponding aldol adduct

Table 7.6. Asymmetric synthesis of *anti*-1,2-diol derivatives


Entry	R	Yield (%)	syn/anti	ee (%) (<i>anti</i>)
1	Ph	83	1/99	96
2	CH ₃ CH ₂	72	2/98	97
3	c-C ₆ H ₁₁	59	9/91	96
4	(<i>E</i>)-PhCH=CH	88	2/98	98
5	(<i>E</i>)-CH ₃ CH=CH	85	2/98	97
6	(<i>E,E</i>)-CH ₃ CH=CHCH=CH	83	2/98	95

in a 69% yield with *anti* preference. The enantiomeric excesses of *syn* and *anti* aldols are 30% and 97%, respectively. Examination of several chiral diamines improves the diastereoselectivity, and when (*S*)-1-ethyl-2-[(piperidin-1-yl)-methyl]pyrrolidine (**2**) is employed, the aldol adduct is obtained in a 54% yield with excellent diastereo- and enantioselectivities. Furthermore, the yield is improved without any loss of the stereoselectivity by the combination of tin(II) triflate, **2**, and Bu₂Sn(OAc)₂.

The results employing several kinds of aldehydes such as aromatic, aliphatic, α,β-unsaturated aldehydes and a dienal of the present asymmetric aldol reaction are shown in Table 7.6.³⁷ In all cases, *anti*-α,β-dihydroxy thioesters are obtained in high yields with excellent diastereo- and enantioselectivities. The aldol adducts thus obtained, optically active *anti*-α,β-dihydroxy ester derivatives, are generally difficult to prepare by the conventional asymmetric oxidative procedure because starting materials, *cis*-α,β-unsaturated ester equivalents, are sometimes difficult to obtain. Moreover, a consideration of the mechanistic model of the asymmetric dioxyosmylation was recently reported and it was shown that preparation of *anti*-1,2-diols in high enantiomeric excesses is difficult.³⁸ According to the present aldol methodology, two hydroxyl groups can be introduced in 1,2-*trans* position stereoselectively during new carbon-carbon bond formation.

In contrast to the fact the aldol reactions of the silyl enol ether derived from *S*-ethyl propanethioate (**8Z**) with aldehydes using the above chiral promoter proceed with *syn* preference in excellent diastereo- and enantioselectivities (see Table 7.4), excellent *anti* selectivities have been achieved in reactions of (*Z*)-2-benzyloxy-1-*S*-ethyl-1-trimethylsiloxyethene (**9Z**) with aldehydes. The consideration of the transition states of these aldol reactions has led to the assumption that (i) co-ordination of the oxygen atom of the α-benzyloxy group of silyl enol ether **9Z** to the tin(II) atom of tin(II) triflate is essential in

Table 7.7. Asymmetric synthesis of *syn*-1,2-diol derivatives

$\text{RCHO} + \begin{array}{c} \text{OSiMe}_3 \\ \\ \text{C}=\text{C} \\ \quad \\ \text{TBSO} \quad \text{SEt} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, -78^\circ\text{C}]{\text{Sn}(\text{OTf})_2 + \mathbf{3} + \text{Bu}_2\text{Sn}(\text{OAc})_2} \begin{array}{c} \text{HO} \quad \text{O} \\ \quad \\ \text{R} \quad \text{C} \\ \quad \\ \text{OTBS} \quad \text{SEt} \end{array} + \begin{array}{c} \text{HO} \quad \text{O} \\ \quad \\ \text{R} \quad \text{C} \\ \quad \\ \text{OTBS} \quad \text{SEt} \end{array}$				
Entry	R	Yield (%)	<i>syn/anti</i>	ee (%) (<i>anti</i>)
1	Ph	86	88/12	90
2	CH ₃ CH ₂	46	92/8	82
3		93	94/6	93
4	(<i>E</i>)-PhCH=CH	76	90/10	92
5	(<i>E</i>)-CH ₃ CH=CH	75	97/3	94
6	(<i>E,E</i>)-CH ₃ CH=CHCH=CH	83	93/7	94

the *anti* selective transition state, leading to the different course in the diastereofacial selectivity compared with that of the *syn* selective reaction of **8Z**, (ii) *syn* α,β -dihydroxy thioesters would be formed when this co-ordination is restrained.

According to this hypothesis, the *t*-butyldimethylsilyl group has been chosen as a sterically hindered functional group, which would forbid the co-ordination of the oxygen atom to tin(II) atom, and (*Z*)-2-*t*-butyldimethylsiloxy-1-*S*-ethyl-1-trimethylsiloxyethene (**10Z**) has been prepared. As expected, the *syn* aldol adduct has been obtained under the same reaction conditions. In the presence of tin(II) triflate, chiral diamine (*S*)-1-propyl-2-[(piperidin-1-yl)methyl]pyrrolidine (**3**), and Bu₂Sn(OAc)₂, the reaction of **9Z** with benzaldehyde proceeds smoothly to give the corresponding aldol adduct in high yield with high *syn* selectivity.

Several examples of the *syn* selective aldol reactions are shown in Table 7.7. In all cases, the reactions proceed smoothly to afford the aldol adducts in good yields with very high *syn* selectivities, and the enantiomeric excesses of these *syn* isomers are more than 90% in most cases.^{31,39}

Now it becomes possible to control the enantiofacial selectivity of the silyl enol ethers derived from α -alkoxy thioesters **9Z** and **10Z** by choosing the appropriate protective groups of the alkoxy parts of the silyl enol ethers, and both diastereomers of optically active α,β -dihydroxy thioesters can be synthesized.

It is also possible to synthesize both enantiomers including 1,2-diol units with perfect stereochemical control by using similar types of chiral sources, based on Chiral Lewis Acid-Controlled Synthesis (CLAC Synthesis).⁴⁰⁻⁴³ The key is to use two new types of chiral diamines, **6** and **7**. In the presence of tin(II) triflate, chiral diamine **6**, and Bu₂Sn(OAc)₂, (*Z*)-2-(*t*-butyldimethylsiloxy)-1-ethylthio-1-trimethylsiloxyethene (**10Z**) reacts with aldehydes to

afford the desired aldol adducts with a *2S*, *3R* configuration. On the other hand, when a similar chiral diamine, **7**, is used, the reaction also proceeds smoothly, but the absolute configuration of the adducts is the reverse (*2R*, *3S*). In both cases, the selectivities are very high; almost perfect *syn*-selectivities and more than 98% enantiomeric excesses are obtained. Diamines **6** and **7** are readily prepared from *S*-proline and the absolute configurations of the 2-position were *S* in both cases. The difference is the position of the benzene ring connected to the pyrrolidine moiety. It is exciting that the slight difference in the structure of the chiral sources completely reverses the enantiofacial selectivities.

Protocol 3.

Synthesis of both enantiomers of 1,2-diol units by choosing similar chiral ligands in asymmetric aldol reactions of the silyl enol ethers with aldehydes (chiral Lewis acid-controlled synthesis)

Equipment

- Two-necked, round-bottomed flask (30 mL) fitted with a magnetic stirring bar. A three-way stopcock is fitted to the top of the flask and connected to a vacuum/argon source
- Vacuum/inert gas source (argon source may be an argon balloon)

Materials

- Tin(II) triflate (FW 416.82), 166.7 mg, 0.40 mmol
- Distilled chiral diamine **6** (FW 216.33), 103.8 mg, 0.48 mmol
- Distilled chiral diamine **7** (FW 216.33), 103.8 mg, 0.48 mmol
- Distilled Bu₂Sn(OAc)₂ (FW 351.03), 154.5 mg, 0.44 mmol
- Distilled benzaldehyde (FW 106.12), 38.2 mg, 0.36 mmol
- Distilled (*Z*)-2-(*t*-butyldimethylsiloxy)-1-ethylthio-1-trimethylsiloxyethene (**10Z**) (FW 278.53), 111.4 mg, 0.40 mmol
- Dry, distilled dichloromethane

1. Flame dry the reaction vessel with a stirring bar under dry argon.
2. Add tin(II) triflate to the flask in dry box under argon atmosphere and dry at 100°C for 1 h under reduced pressure (0.5 mmHg).
3. Add 1 mL of dry dichloromethane to the flask with stirring. Add chiral diamine **6** or **7** in 0.5 mL of dichloromethane and then Bu₂Sn(OAc)₂ in 0.5 mL of dichloromethane.
4. After stirring the mixture for 5 min at room temperature, cool to –78°C.
5. Add (*Z*)-2-(*t*-butyldimethylsiloxy)-1-ethylthio-1-trimethylsiloxyethene (**10Z**) in 0.5 mL of dichloromethane and benzaldehyde in 0.5 mL of dichloromethane successively.
6. After stirring for 20 h, add saturated sodium hydrogencarbonate. Warm the mixture to the room temperature and filter the suspension through a pad of

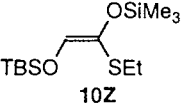
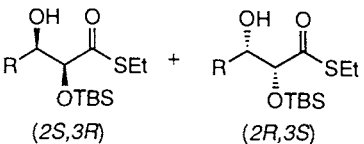



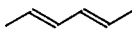



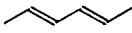
Celite, and wash the filter cake three times with dichloromethane. Extract the aqueous layer three times with dichloromethane and wash the combined extracts with brine.

- Concentrate the crude product under reduced pressure and apply to preparative TLC (silica gel). Elute with a mixed solvent of hexane–ethyl acetate (4:1) to obtain the product. Only *syn* isomer is produced and the optical purity is determined by HPLC analysis using a chiral column.

2.5 Catalytic asymmetric aldol reactions

As shown in the previous sections, highly diastereo- and enantioselective aldol reactions of silyl enol ethers with aldehydes using the novel promoter

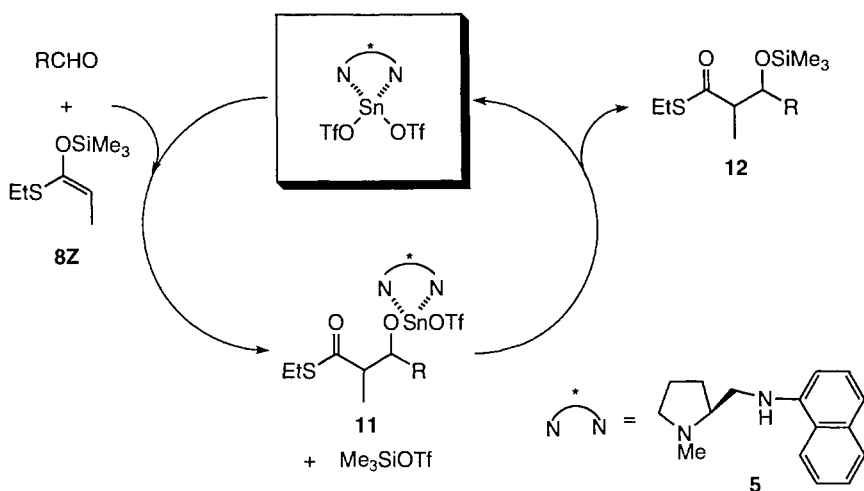
Table 7.8. Synthesis of both enantiomers

$\text{RCHO} + \text{10Z} \xrightarrow[\text{Bu}_2\text{Sn}(\text{OAc})_2, \text{CH}_2\text{Cl}_2, -78^\circ\text{C}]{\text{Sn}(\text{OTf})_2 + \text{Chiral diamine}}$ <div style="text-align: center;">  <p>10Z</p> </div>					
<div style="text-align: center;">  <p>(2<i>S</i>,3<i>R</i>) (2<i>R</i>,3<i>S</i>)</p> </div>					
R	Chiral diamine	Yield (%)	2 <i>S</i> ,3 <i>R</i> /2 <i>R</i> ,3 <i>S</i>	<i>syn/anti</i>	ee (%) ^a
Ph	6	86	98/2	99.0/1.0	(98)
C ₂ H ₅	6	61	>99/1	99.0/1.0	(98)
	6	86	>99/1	99.0/1.0	(98)
Ph 	6	84	>99/1	99.5/0.5	(99)
	6	94	>99/1	98.5/1.5 ^b	(97)
	6	86	98/2	98.0/2.0	(96)
Ph	7	82	99/1	1.0/99.0	(98)
C ₂ H ₅	7	63	>99/1	1.0/99.0	(98)
	7	81	>99/1	1.0/99.0	(98)
Ph 	7	80	99/1	1.0/99.0	(98)
	7	86	>99/1	<0.5/>99.5 ^b	(>99)
	7	78	>99/1	<0.5/>99.5	(>99)

^a Enantiomeric excesses of *syn*-adducts.

^b 2*S*,3*S*/2*R*,3*R*.

system, combined use of stoichiometric amounts of tin(II) triflate, a chiral diamine, and a tin(IV) compound (Bu_3SnF or $\text{Bu}_2\text{Sn}(\text{OAc})_2$), have been developed. According to these reactions, optically active aldol adducts are easily prepared from both achiral aldehydes and silyl enol ethers, but stoichiometric use of the chiral source still remains a problem in terms of practical use. Based on the investigations to characterize the above promoter system as well as to clarify the mechanism of these reactions toward a truly catalytic aldol process,⁴⁴ the following catalytic cycle is postulated (Scheme 7.4).



Scheme 7.4. The catalytic cycle of the asymmetric aldol reaction

A chiral diamine co-ordinated tin(II) triflate (chiral tin(II) Lewis acid) interacts with an aldehyde, and tin(II) alkoxide **11** and trimethylsilyl triflate (TMSOTf) are initially produced by the attack of silyl enol ether **8Z** to the activated aldehyde. When the metal exchange between tin(II) and silicon of the above product **11** takes place smoothly, the corresponding aldol adduct can be obtained as its trimethylsilyl ether **12** together with the regeneration of the catalyst. If the above-mentioned metal exchange step is slow, undesirable TMSOTf-promoted reaction^{45,46} (to afford the achiral aldol adduct) proceeds to result in lowering the selectivity.

On the basis of these considerations, a slow addition of the substrates to the solution of the catalyst has been performed to keep the concentration of TMSOTf as low as possible during the reaction. A dichloromethane solution of silyl enol ether **8Z** and an aldehyde is added for over 9 h to a dichloromethane solution of the catalyst (20 mol%) (Table 7.9).⁴⁷ As expected, aldol adducts are obtained in good yields with excellent enantiomeric excesses and high diastereoselectivities in some cases, but the selectivities are not so high

Table 7.9. Catalytic asymmetric aldol reactions (1) (solvent : CH₂Cl₂)

Entry	R	Yield (%)	syn/anti	ee (%) (anti)
1	Ph	86	93/7	91
2	<i>p</i> -Cl Ph	80	93/7	93
3	<i>p</i> -CH ₃ Ph	82	78/22	80
4	CH ₃ (CH ₂) ₆	75	100/0	>98
5	<i>c</i> -C ₅ H ₁₁	31	>99/1	74
6	(<i>E</i>)-CH ₃ CH=CH	51	84/16	77
7	(<i>E</i>)-CH ₃ (CH ₂) ₂ CH=CH	62	81/19	74

when *p*-tolualdehyde, α,β -unsaturated aldehydes, and cyclohexanecarboxaldehyde are used.

The lower selectivities are considered to be ascribed to the incompleteness of the above catalytic cycle, especially the metal exchange reaction of the initially formed aldol adduct **11** with TMSOTf (metal exchange between tin(II) and silicon). In order to accelerate this metal exchange step, various polar solvents with low melting points (below -78°C) have been carefully examined by taking the reaction of **8Z** with benzaldehyde as a model, and finally propionitrile (C₂H₅CN) has been found to be an excellent solvent.⁴⁸ The examination of the addition time (addition of the reactants to the solution of the catalyst) reveals that the rate of the metal exchange in propionitrile is faster than that in dichloromethane. Although 9 h (addition time) is necessary to attain the best result in dichloromethane, comparable selectivities are achieved when the substrates are added to the catalyst for 3 h in propionitrile. It is noted that a tin(II) triflate is more soluble in propionitrile than in dichloromethane indicating that the co-ordination of the nitrile group to tin(II) is expected to be rather strong, but that the ligand exchange of the nitrile for the diamine takes place smoothly to form the desired chiral Lewis acid when the chiral diamine is added to this propionitrile solution of tin(II) triflate. Although tin(II) triflate is also soluble in tetrahydrofuran (THF) or 1,2-dimethoxyethane (DME), the above aldol reaction does not proceed at -78°C after the addition of chiral diamine **5** in these solvents.

Several aldehydes including aromatic, aliphatic, and α,β -unsaturated aldehydes, are applicable to this reaction, and the desired products are obtained in good yields with high selectivities (>90% ee, Table 7.10). In particular, the lower yields or selectivities observed in the reaction of *p*-tolualdehyde, (*E*)-crotonaldehyde, (*E*)-2-hexenal, and cyclohexanecarboxaldehyde, are remarkably improved by using propionitrile as a solvent. High selectivities are also achieved even when 10 mol% of the catalyst was used.⁴⁹

The key step in the asymmetric aldol reactions using the chiral tin(II) Lewis acid is believed to be the metal exchange process from tin(II) to silicon on the initially produced aldol adduct **11**. If this step is slow, the TMSOTf-promoted aldol reaction of aldehydes with silyl enol ethers proceed to result in lower

Table 7.10. Catalytic asymmetric aldol reactions (2) (solvent : C₂H₅CN)

Entry	R	Addition time (h)	Yield (%)	syn/anti	ee (%) (syn)
1	Ph	3	77	92/8	90
2	<i>p</i> -Cl Ph	4.5	83	87/13	90
3	<i>p</i> -CH ₃ Ph	3	75	89/11	91
4	CH ₃ (CH ₂) ₆	4.5	80	100/0	>98
5	<i>c</i> -C ₈ H ₁₁	3	71	100.0	>98
6	(<i>E</i>)-CH ₃ CH=CH	3	76	96/4	93
7	(<i>E</i>)-CH ₃ (CH ₂) ₂ CH=CH	3	73	97/3	93

selectivities. Slow addition of the substrates to the catalyst in propionitrile has been successfully performed to suppress the undesirable reaction. It is also expected that higher stereoselectivities would be obtained when the Lewis acidity of TMSOTf is reduced by using an additive. This idea has been obtained from the recent report on the catalytic asymmetric aldol reaction using TMSOTf, a chiral diamine, and tin(II) oxide.⁵⁰ In this reaction, the lone-pair electrons of tin(II) oxide interact with TMSOTf to weaken the Lewis acidity of TMSOTf, and as a result high selectivities have been obtained. It would be possible to reduce the Lewis acidity of various triflates by using this interaction. On the basis of this idea, it has been found that in the presence of a novel chiral catalyst system consisting of tin(II) triflate, a chiral diamine, and tin(II) oxide, highly enantioselective aldol reactions of the silyl enol ether of *S*-ethyl ethanethioate or *S*-ethyl propanethioate with aldehydes proceed smoothly to afford the aldol adducts in high yields.

Protocol 4.

Catalytic asymmetric aldol reactions of the silyl enol ether derived from (*Z*)-1-*S*-ethyl-1-trimethylsiloxypropene with an aldehyde

Equipment

- Two-necked, round-bottomed flask (30 mL) fitted with a magnetic stirring bar. A three-way stopcock is fitted to the top of the flask and connected to a vacuum/argon source
- Vacuum/inert gas source (argon source may be an argon balloon)

Materials

- Tin(II) triflate (FW 416.82), 33.4 mg, 0.08 mmol
- Tin(II) oxide (FW 134.71), 21.6 mg, 0.16 mmol
- Distilled chiral diamine **5** (FW 240.35), 23.1 mg, 0.096 mmol
- Distilled benzaldehyde (FW 106.12), 42.5 mg, 0.40 mmol
- Distilled (*Z*)-1-*S*-ethyl-1-trimethylsiloxypropene (FW 190.38), 76.2 mg, 0.40 mmol
- Dry, distilled propionitrile

1. Flame dry the reaction vessel with a stirring bar under dry argon.

- Add tin(II) triflate and tin(II) oxide to the flask in dry box under argon atmosphere and dry at 100°C for 1 h under reduced pressure (0.5 mmHg).
- Add 1 mL of dry propionitrile to the flask with stirring. Add chiral diamine **4** in 0.5 mL of propionitrile.
- After stirring the mixture for 5 min at room temperature, cool to -78°C.
- Slowly add a mixture of (Z)-1-S-ethyl-1-trimethylsiloxyprene in 0.5 mL of propionitrile and benzaldehyde in 0.5 mL of propionitrile over 4 h (syringe pump).
- After stirring for 1 h (after addition), add saturated sodium hydrogen carbonate. Warm the mixture to the room temperature and filter the suspension through a pad of Celite, and wash the filter cake three times with dichloromethane. Extract the aqueous layer three times with dichloromethane and wash the combined extracts with brine. Dry the combined organic layer over (Na₂SO₄).
- Concentrate the crude product under reduced pressure and apply to preparative TLC (silica gel). Elute with a mixed solvent of hexane-ethyl acetate (6:1) to obtain the product. Only *syn* isomer is produced and the optical purity is determined by HPLC analysis using a chiral column. After a usual work-up, the aldol-type adduct was isolated as the corresponding trimethylsilyl ether. The enantiomeric excess of this aldol adduct was determined after converting it into the corresponding alcohol (tetrahydrofuran-1M HCl (20:1) at 0°C) to be 94% by HPLC analysis using a chiral stationary phase column.

3. Asymmetric cyanation reaction

Asymmetric cyanation reaction of aldehydes is an important process in organic synthesis and recently some excellent works have been made in this

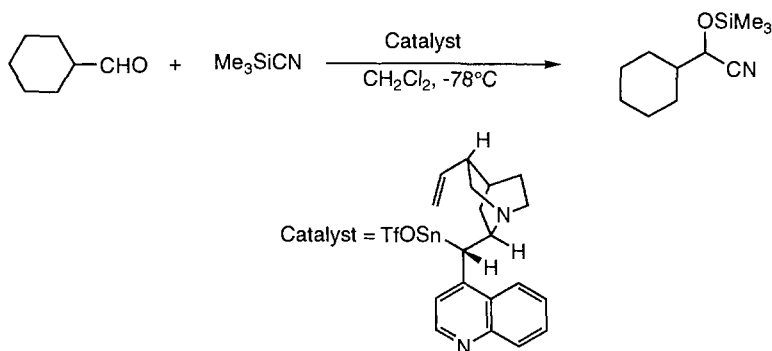
Table 7.11. Catalytic asymmetric aldol reactions using a novel catalyst system

$R^1CHO + \begin{array}{c} \text{OSiMe}_3 \\ \diagup \\ R^2 \\ \diagdown \\ \text{SEt} \end{array}$			$\xrightarrow[\text{C}_2\text{H}_5\text{CN, } -78^\circ\text{C, slow addition 4-6 h}]{20 \text{ mol\% Sn(OTf)}_2 + 5 + \text{SnO (20-40 mol\%)}}$			$\begin{array}{c} \text{Me}_3\text{SiO} \\ \\ R^1 - \text{C} - \text{C} - \text{C} = \text{O} \\ \quad \quad \\ R^2 \quad \text{SEt} \end{array}$ <p style="text-align: center;"><i>syn</i></p>		
Entry	R ¹	R ²	With SnO			Without SnO		
			Yield (%)	<i>syn/anti</i>	ee (%)	Yield (%)	<i>syn/anti</i>	ee (%)
1	Ph	Me	78	95/5	93	77	93/7	90
2	CH ₃ (CH ₂) ₆	Me	81	100/0	>98	80	100/0	>98
3	CH ₃ CH=CH	Me	85	99/1	95	76	96/4	93
4	CH ₃ (CH ₂) ₂ CH=CH	Me	81	100/0	94	73	97/3	93
5	CH ₃ (CH ₂) ₃	H	71	—	92	79	—	91
6	<i>i</i> -Pr	H	50	—	92	48	—	90
7	<i>c</i> -C ₆ H ₁₁	H	78	—	94	81	—	92
8	CH ₃ (CH ₂) ₂ CH=CH	H	83	—	84	65	—	72

area,^{51–55} however, some significant problems still remain such as stoichiometric use of chiral sources, lower enantioselectivities in the reaction with aliphatic aldehydes, etc.

For the synthesis of cyanohydrin trimethylsilyl ethers,^{56,57} one of the most convenient preparative methods is addition reactions of trimethylsilyl cyanide (TMS-CN) with aldehydes under the influence of Lewis acids such as zinc iodide (ZnI₂), aluminium chloride (AlCl₃), or under almost neutral conditions using anionic catalysis.^{58,59} It has been found that in the presence of a catalytic amount of Lewis base such as amine, phosphine, arsine, or antimony, TMS-CN smoothly reacts with aldehydes to afford the corresponding cyanohydrin trimethylsilyl ethers in excellent yields.

Asymmetric version of this reaction is investigated. In the presence of a catalytic amount of (+)-cinchonine (10 mol%), cyclohexanecarboxaldehyde reacts with TMS-CN smoothly at -78°C to give the corresponding cyanohydrin trimethylsilyl ether in a 94% yield with 25% ee. (+)-Cinchonine trimethylsilyl ether also works with the same level of ee (25%). The importance of the silyl ether is revealed as almost no chiral induction is observed when (+)-cinchonine acetate or benzoate is used as a catalyst. The proposed mechanism is that the tertiary amine part of (+)-cinchonine interacts with the silicon atoms of TMS-CN to form the pentavalent silicate and, at the same time, the Lewis acidic silicon atom of the silyl ether activates an aldehyde. This ‘double activation’ would provide a desirable transition state in the chiral induction using chiral catalysts. Based on this hypothesis, high levels of enantiomeric excesses are obtained when tin(II) ether is introduced instead of the silyl ether and a novel tin(II) Lewis acid, tin(II) monoalchoxymonotriflate containing (+)-cinchonine as a chiral source, has been designed. This chiral tin(II) Lewis acid is easily prepared from 1,1'-dimethylstannocene,⁶⁰ triflic acid, and (+)-cinchonine. In the presence of this Lewis acid, the reactions of TMS-CN with aldehydes proceed smoothly at -78°C in dichloromethane to give the corresponding cyanohydrin trimethylsilyl ether in high yields with good to excellent ees (Scheme 7.5). In the present reaction, the products are



Scheme 7.5

isolated as trimethylsilyl ether form and the reaction smoothly proceeds in the presence of 30 mol% of the tin(II) Lewis acid. The catalyst, tin(II) monoalkoxymonotriflate, is supposed to be regenerated from the initially produced tin(II) alkoxide and trimethylsilyl triflate.

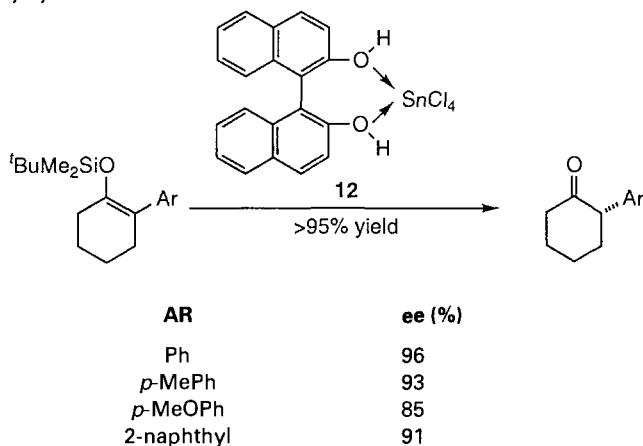
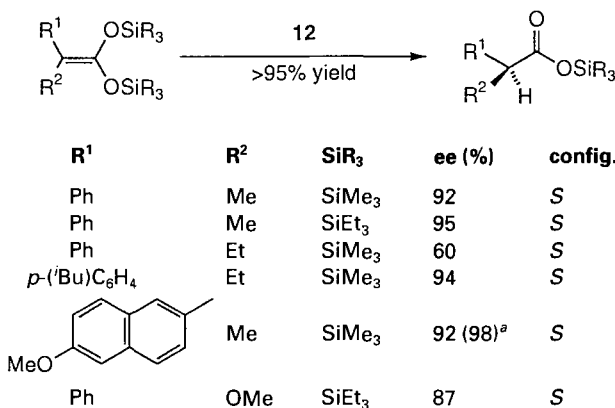
4. Asymmetric protonation

Enantioselective protonation of prochiral enol derivatives provides a convenient route for the preparation of optically active carbonyl compounds.^{61–89} Several examples of protonation of metal enolates by chiral proton sources^{64–79} and hydrolysis of enol esters catalysed by enzymes^{80,81} or antibodies⁸² under basic or neutral conditions, have been reported. The acid-promoted hydrolysis of enol ethers is an interesting alternative which has been little investigated for enantioselectivity.^{83–86} A new Lewis acid-assisted chiral Brønsted acid (LBA)^{87–89} for enantioselective protonation of prochiral silyl enol esters and ketene bis(trialkylsilyl) acetals is reported.⁹⁰

The LBA (**12**) is generated *in situ* from (*R*)-(+)-1,1'-binaphthol (BINOL) and tin tetrachloride (SnCl₄) in toluene or dichloromethane at -78°C . The protons in (*R*)-BINOL are activated by the co-ordination of tin tetrachloride. In the presence of a stoichiometric amount of **12** in dichloromethane, the C-protonation of the trimethylsilyl enol ether derived from 2-phenylcyclohexanone proceeds even at -78°C to form (*S*)-2-phenylcyclohexanone with good enantioselectivity (79% ee). The enantioselectivity of the reaction is dramatically increased by using sterically bulky *O*-substituents. The protonation of the *tert*-butyldimethylsilyl enol ether (Ar = Ph, SiR₃ = Si^tBuMe₂) occurs with excellent enantioselectivity (93% ee), and the best result (96% ee) is achieved by using toluene as solvent. (*R*)-BINOL is converted into a mixture of 2,2'-disiloxy-1,1'-binaphthyl and 2-siloxy-2'-hydroxy-1,1'-binaphthyl in dichloromethane solution, whereas it is only converted into the latter product in toluene. It is noted that the enantioselective protonation proceeded with a catalytic amount (10 mol %) of tin tetrachloride.

The enantioselective protonation of a variety of silyl enol ethers derived from 2-arylcyclohexanones with **12** under optimum conditions is summarized in Table 7.12. The reactions are generally complete after 1 h at -78°C . Excellent enantioselectivity was achieved in the reactions of the silyl enol ethers of 2-arylcyclohexanones, and both enantiomers can be obtained from racemic 2-arylcyclohexanones depending on the choice of optically active BINOL: (*S*)- and (*R*)-arylcyclohexanones are obtained using (*R*)- and (*S*)-**12**, respectively. Enantioselectivity is low in the case of the protonation of the silyl enol ether derived from 2-methylcyclohexanone (42% ee).

Representative results of application of **12** to enantioselective protonation of ketene bis(trialkylsilyl) acetals derived from 2-arylcarboxylic acids are summarized in Table 7.13. The crude carboxylic acids, which are formed with excellent enantiomeric excesses, are isolated as the corresponding methyl

Table 7.12. The enantioselective protonation of silyl enol ethers from 2-arylcyclohexanones with **12****Table 7.13.** Enantioselective protonation of ketene bis(trialkyl silyl) acetals derived from 2-arylcarboxylic acids^a After recrystallization from dichloromethane-hexane.

esters in quantitative yields. The enantioselectivity is independent of the steric features of trialkylsilyl substituents. Simple recrystallization of the (*S*)-methyl ester of naproxen can be used to upgrade the optical purity. It is noteworthy that the protonation of the ketene silyl acetal, diastereomer ratio (*E* and *Z*) = 63:37, derived from methyl 6-methoxy- α -methyl-2-naphthalene acetate and trimethylsilyl chloride by (*R*)-**12** gives the (*S*)-methyl ester of naproxen with decreased enantioselectivity (79% ee).

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