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ASYMMETRIC ALDOL-TYPE REACTION BETWEEN BOTH ACHIRAL KETENE SILYL ACETALS OF ACETIC ACID ESTERS AND ALDEHYDES BY THE USE OF A CHIRAL PROMOTER#

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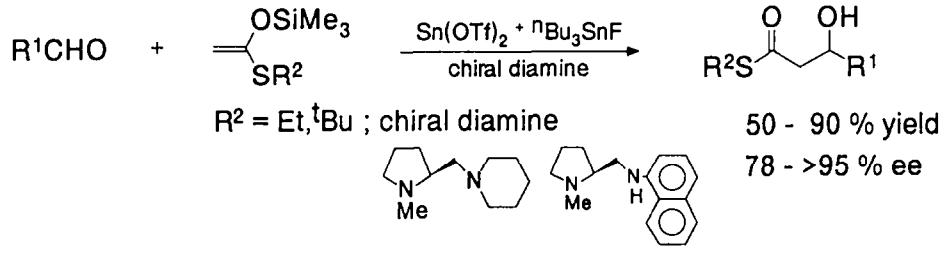
Abstract: Highly enantioselective aldol-type reaction between achiral ketene silyl acetals of acetic acid esters and achiral aldehydes is successfully carried out by the use of a chiral promoter, a combined use of chiral diamine coordinated tin(II) trifluoromethanesulfonate (tin(II) triflate) and tributyltin fluoride. The structure of this new promoter and the mechanism of the present asymmetric aldol-type reaction are discussed.

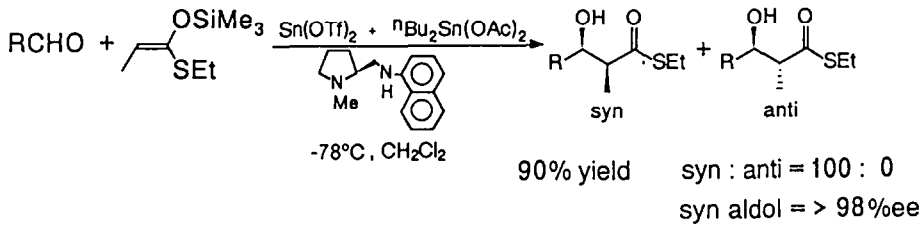
Ketene silyl acetals are useful reagents in organic synthesis and are frequently employed as isolable ester enolate equivalents because of their readiness in preparation and higher reactivities toward electrophiles compared with silyl enol ethers derived from ketones or thioesters.[1] Aldol-type reaction of ketene silyl acetals with aldehydes is one of the most important methods for carbon-carbon bond formations, however, control of stereochemistry is generally difficult. After the first report on the $TiCl_4$-mediated aldol-type reaction of ketene silyl acetals with aldehydes from this laboratory,[2] Chan[3] and Heathcock[4] examined the relative stereochemistry of this reaction and reported that the diastereoselectivities were not controlled so well except for a few examples. Recently, due to the added importance of asymmetric synthesis, some efforts have been made on the asymmetric version of this reaction. Gennari reported the enantioselective aldol reaction of (E)-ketene silyl acetal derived from N-methylephedrin-O-propionate with achiral aldehydes.[5] Helmchen also reported almost the same reaction by the use of camphor derivatives as chiral sources. Though these two examples provided useful methods for the preparation of optically active β-hydroxy esters with high enantioselecti-

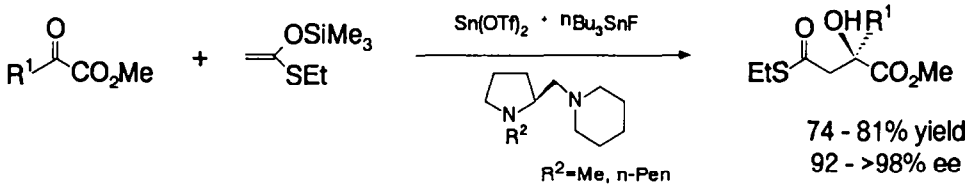
This paper is dedicated to Professor David Ollis on the occasion of his 65th birthday.

vities, tedious procedures for the attachment and removal of the chiral sources are inevitable.

We have already reported that the asymmetric aldol reaction of silyl enol ethers of thioesters with aldehydes is performed with excellent diastereo- and enantioselectivities by the use of a new chiral promoter, a combined use of chiral diamine coordinated tin(II) triflate and tributyltin fluoride[7] or dibutyltindiacetate.[8] This reaction is a first practical example for the asymmetric aldol-type reaction starting from both achiral enolates and aldehydes by the use of a chiral promoter, and has successfully been applied to the enantioselective synthesis of 2-substituted malates.[9]







In the course of our investigations to develop practical enantioselective reactions using this chiral promoter, the application to the asymmetric aldol-type reaction of ketene silyl acetal of acetic acid ester with aldehydes was planned. It is generally known that the aldol-type reaction of acetic acid ester enolate with aldehydes is hard to control the stereochemistry.[10] In spite of the usefulness of the product,

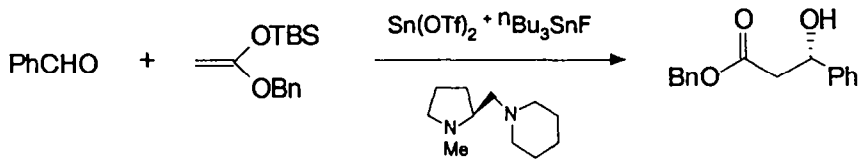


Table 1. The Effect of Solvents[a)]

Solvent	Yield/%	ee/%
DME[b)]	39	2
toluene	52	39
CH_2Cl_2	64	51
1,3,5-TMB[c)]-CH_2Cl_2(2:1)	60	65
1,3,5-TMB-CH_2Cl_2(4:1)	65	44
1,2,5-TMB[d)]-CH_2Cl_2(2:1)	52	30
cumene-CH_2Cl_2(2:1)	58	41

a) The reaction was carried out at -78 °C.
b) 1,2-Dimethoxyethane
c) 1,3,5-Trimethylbenzene
d) 1,2,5-Trimethylbenzene

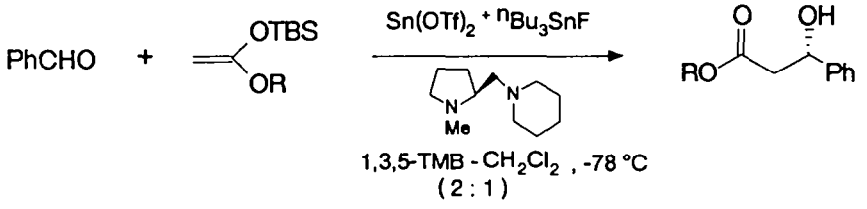


Table 2. The Effect of Ester Groups

R	Yield/%	ee/%
Et	63	60
^{i}Pr	60	41
^{t}Bu	14	64
c-C_6H_{11}	48	10
CH_2Ph	60	65

there have been a few examples of this type of reactions with high stereoselectivities.[11] In this article, we would like to describe on highly enantioselective aldol-type reaction between both achiral ketene silyl acetals of acetic acid esters and aldehydes by the use of the chiral promoter system.[12]

In the first place, the reaction of benzaldehyde with 1-t-butyldimethylsiloxy-1-benzyloxyethylene was chosen as a model and the effect of solvents was examined in the presence of stoichiometric amounts of tin(II) triflate, (S)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine and tributyltin fluoride. When the above reaction was carried out in dichloromethane, which was the best solvent in the aldol-type reaction of silyl enol ethers of thioesters with aldehydes,[7,8] the aldol-type adduct was obtained in 64%

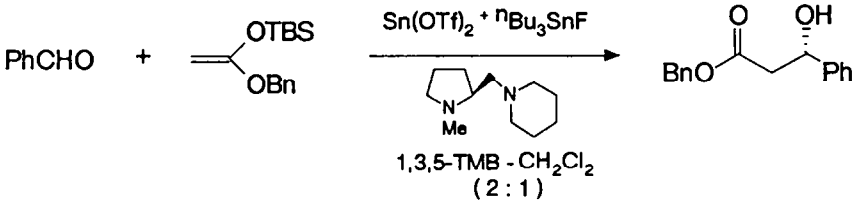
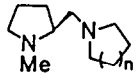
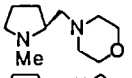
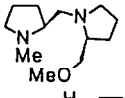
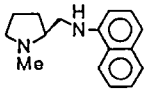
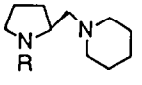


Table 3. The Effect of Chiral Diamines

Chiral diamine		Temp./°C	Yield/%	ee/%
	n=1	-78	43	20
	n=2	-78	60	65
	n=3	-78	41	43
		-78	50	17
		-78	62	27
		-78	41	5
	R=Me	-95	81	82
	R=Et	-95	76	89
	R=^{n}Pr	-95	74	58
	R=^{n}Bu	-95	87	74

yield with moderate enantioselectivity (51% ee). After screening various solvents, the optical yield was found to be improved when a mixed solvent of 1,3,5-trimethylbenzene and dichloromethane (2:1) was employed (see Table 1). Next, the effect of ester groups was examined, and benzyloxy group gave the best result (see Table 2). When 1-t-butyldimethylsiloxy-1-t-butoxyethylene was employed, good enantioselectivity was obtained, however, the yield was low. Further, in order to improve the chemical and optical yields, the effect of chiral diamines was examined. Ring number of amino group moiety in 1-alkyl-2-aminopyrrolidine strongly influenced on the enantioselectivity; the use of [(2-piperidin-1-yl)methyl]pyrrolidine gave higher ee, however, the use of morpholine instead of piperidin gave lower selectivity. The use of (S)-1-methyl-2-[(N-1-naphthylamino)methyl]pyrrolidine, which is the best diamine in several asymmetric aldol reactions of

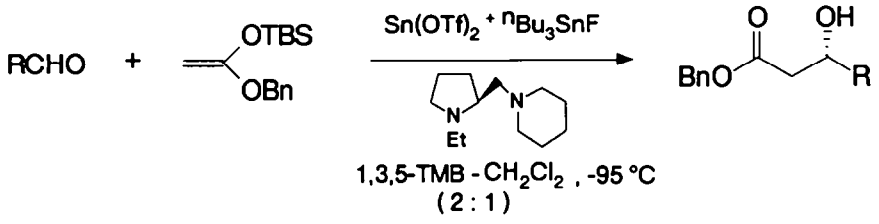


Table 4. The Asymmetric Aldol Reaction of Ketene Silyl Acetals with Aldehydes

Entry	R	Yield/%	ee/%
1	Ph	76	89
2	p-CH_3-Ph	62	89
3	p-Cl-Ph	73	95
4	$CH_3(CH)_4$	79	91
5	i-Pr	61	>98
6	c-C_6H_{11}	60	97
7	(E)-$CH_3CH{=}CH_2$	51	91

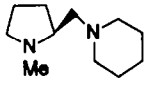
silyl enol ethers derived from thioesters with aldehydes, also gave lower enantioselectivity. Finally, the best result was obtained when the reaction was carried out at -95 °C by the use of (S)-1-ethyl-2-[(piperidin-1-yl)methyl]pyrrolidine as a chiral diamine.

Under the optimum conditions, several aldehydes were employed for this asymmetric aldol-type reaction as shown in Table 4. Not only aromatic and aliphatic aldehydes but also crotonaldehyde, as a representative of α,β-unsaturated aldehydes, react with 1-t-butyldimethylsiloxy-1-benzyloxy-ethylene to afford the corresponding aldols in excellent ees.

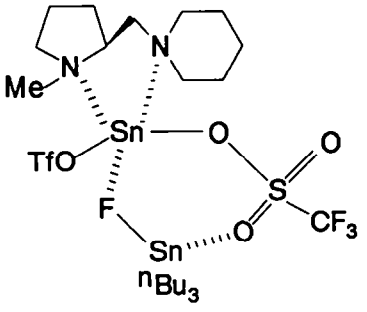
In this aldol-type reaction, the formation of an active complex consisting of three components, tin(II) triflate, chiral diamine and tributyltinfluoride was assumed. This assumption was supported by the observation that the mixture of three components was completely soluble in dichloromethane, while either tin(II) triflate or tributyltin fluoride was sparingly soluble under the conditions. ^{119}Sn NMR spectrum of this chiral promoter A in dichloromethane indicates a formation of three components complex without accompanying any metal exchange.

Table 5. ^{119}Sn Chemical Shifts

Chiral promoter	Sn(II)	Sn(IV)
A ($Sn(OTf)_2$+chiral diamine+$^{n}BuSn_3F$)	-505.5	+106.4
B ($Sn(OTf)_2$+chiral diamine)	-625.5	____

chiral diamine: 

The comparison of values of chemical shift of tin(II) of three components and two components systems indicates that electron density on tin(II) of the three components complex A is higher than that of the two components complex B consisting of tin(II) triflate and chiral diamine. This observation can be explained by the electron donation from fluorine atom of tributyltin fluoride to tin(II) atom, which supports a formation of six membered ring complex as shown below.



In the transition state, tin(II) triflate activates an aldehyde and, at the same time, the electronegative fluorine atom which was pulled apart by the approaching aldehyde from tin(II) center interacts with a silicon atom of a silyl enol ether. This double activation makes the aldehyde and the enol ether more reactive in addition to the acceleration by the formation of the entropically advantageous five components intermediate.

In summary, the asymmetric aldol-type reaction of both achiral ketene silyl acetals of acetic acid esters and aldehydes is performed in good yields with excellent ees by the use of the chiral promoter system consisting of chiral diamine coordinated tin(II) triflate and tributyltin fluoride. The present interesting results encourage us to develop the asymmetric aldol-type reaction of ketene silyl acetals of propionic acid esters or 2-methylpropionic acid esters.[13] Further development of the above asymmetric aldol reaction by using a catalytic amount of chiral promoter, successfully performed in the case of using silyl enol ethers of thioesters and aldehydes[14], is also a promising topic.

Experimental

IR spectra were recorded on Hitachi 260-30 or JASCO IRA-2 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Hitachi R-24B, R-1100 or Bruker AM 500 spectrometer and ^{119}Sn-NMR on a Hitachi R-1900 spectrometer. 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 was dried in vacuo at 100 ^{o}C for 6h[15]. Tin(II) trifluoromethanesulfonate (tin(II) triflate) was prepared by the method of

the literature[16]. 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 correspponding acetyl derivatives using $Pr(hfc)_3$ (Table 4, entries 1, 2, 3) or $Eu(hfc)_3$ (Table 4, entries 5,6) as chiral shift reagent or HPLC analysis of the corresponding MTPA esters[17] (Table 4, entries 4,7).

Preparation of Chiral Diamine

(S)-N-(N-Benzyloxycarbonylprolyl)piperidin(1). This amide was prepared from Z-(S)-proline by a procedure similar to that of Ref. 16). 67% yield. IR(neat) 1690, 1635, 1450, 1345 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.1-2.4 (m,10H), 3.0-3.9 (m,6H), 4.4-4.8 (m,1H), 5.0 (S,2H), 7.4 (S,5H).

(S)-2-[(Piperidin-1-yl)methyl]pyrrolidine(2). To a methanol (100 ml) solution of the amide 1 (21.0 g, 66 mmol) was added 10% Pd-C (1g), and the mixture was stirred for 1h at room temperature under hydrogen atmosphere. After filtration, the solvent was removed under reduced pressure and the crude (S)-N-prolylpiperidin (12.6 g) was obtained.

A THF solution (50 ml) of this crude oil (12.6 g) was slowly added to a THF suspension (50 ml) of $LiAlH_4$ (3.8 g, 100 mmol) at 0 °C, and the mixture was refluxed for 3h. Then, sat.Na_2SO_4aq. was added to the mixture at 0 °C and the organic materials were collected by decantation. The organic layer was dried over Na_2SO_4-K_2CO_3, and the solvent was removed under reduced pressure. The resultant oil was distilled to afford 2 (9.52 g, 86%). IR (neat) 2920, 1440, 1300 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.1-2.0 (m,10H), 2.0-3.0 (m,9H), 3.17 (t,1H,J=7H_z), $[\alpha]_D^{17}$ + 15.8 ° (C 0.50, EtOH).

(S)-1-Acetyl-2-[(piperidin-1-yl)methyl]pyrrolidine(3). To a CH_2Cl_2 solution (5 ml) of 2 (1.68 g, 10 mmol) was added pyridine (2.0 g, 25 mmol) and acetic anhydride (2.0 g, 20 mmol) successively at 0 °C, and the mixture was stirred overnight at room temperature. The solvent and the excess reagents were removed under reduced pressure and the residue was chromatographed on alumina to afford 3 (1.82 g, 87%). IR (neat) 2900, 1630, 1410 cm^{-1}, ^1H NMR (CCl_4) δ 1.2-1.8 (m,6H), 1.2-2.6(m, 7H), 1.75 (s,3H), 3.0-3.5 (m,2H), 3.5-4.2 (m,1H).

(S)-1-Ethyl-2-[(piperidin-1-yl)methyl]pyrrolidine(4). The acetoamide 3 was reduced by $LiAlH_4$ (1.2 eq.) according to a procedure similar to that of the preparation of 2 to afford 4 (80%). IR (neat) 2930, 2780, 1450 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0.88 (t,3H,J=6.5H_z), 1.1-1.8(m,10H), 1.8-2.5 (m,8H), 2.5-3.1(m,3H), bp 110 °C/8 mmHg, $[\alpha]_D$-97.1° (C 0.52, EtOH).

The asymmetric aldol-type reaction of ketene silyl acetal derived from acetic acid esters with aldehydes in the presence of tin(II) triflate,

chiral diamine and tributyltin fluoride.

A typical experimental procedure is described for the reaction of 1-t-butyldimethylsiloxy-1-benzyloxyethylene with benzaldehyde; to a solution of tin(II) triflate (0.4 mmol) and (S)-1-ethyl-2-[(piperidin-1-yl)methyl]-pyrrolidine (0.48 mmol) in a mixture of 1,3,5-trimethylbenzene and dichloromethane (2:1, 1.6 ml) was added tributyltin fluoride (0.44 mmol) at room temperature. The mixture was stirred for 30 min and then cooled to -78 °C. After 1-t-butyldimethylsiloxy-1-benzyloxyethylene (0.4 mmol) in 1,3,5-trimethylbenzene-dichloromethane (2:1, 0.8 ml) was added, the mixture was further stirred for 30 min at the same temperature, then cooled to -95 °C. Benzaldehyde (0.27 mmol) in 1,3,5-trimethylbenzene-dichloromethane (2:1, 0.6 ml) was added and the reaction mixture was further stirred for 6h at -95 °C, then quenched with saturated aqueous sodium hydrogen carbonate. After usual work-up, the desired aldol, benzyl 3-hydroxy-3-phenyl-propionate, was obtained in 76% yield. IR (neat) 3450, 1725 cm^{-1}, ^1H NMR (CCl_4) δ 2.63(d,2H,J=7.0Hz), 3.30(brs,1H), 5.03(s,2H), 4.83-5.19(m,1H),7.24(m,10H). Precise mass calc for $C_{16}H_{16}O_3$ m/z 256.1099. Found 256.1099.

Other spectral data are presented:

Benzyl 3-hydroxy-3-tolylpropionate(Table 4, entry 2). IR (neat) 3450, 1725 cm^{-1}, ^1H NMR (CCl_4) δ 2.60(d,2H,J=7.0Hz), 2.87-3.16(brs,1H), 3.76(s,3H), 5.07(s,2H), 4.80-5.13(m,1H), 6.60-7.35(m,9H). Precise mass calc for $C_{17}H_{18}O_3$ m/z 270.1222. Found 270.1188.

Benzyl 3-(p-chlorophenyl)-3-hydroxypropionate(Table 4, entry 3). IR (neat) 3450, 1725 cm^{-1}, ^1H NMR (CCl_4) δ 2.59(d,2H,J=7.0Hz), 3.35-3.59(brs,1H), 5.03(s,2H), 4.77-5.12(m,1H), 7.14(m,4H), 7.23(m,5H). Precise mass calc for $C_{16}H_{15}O_3Cl$ m/z 290.0691. Found 290.0672.

Benzyl 3-hydroxyoctanate(Table 4, entry 4). IR (neat) 3450, 1725 cm^{-1}, ^1H NMR (CCl_4) δ 0.85(t,3H,J=5.0Hz), 1.09-1.53(m,8H), 2.27-2.46(m,2H), 2.81(brs,1H), 3.88(brs,1H), 5.03(s,2H), 7.23(m,5H). Precise mass calc for $C_{15}H_{22}O_3$ m/z 250.1585. Found 250.1601.

Benzyl 3-hydroxy-4-methylpentanate(Table 4, entry 5). IR (neat) 3450, 1725 cm^{-1}, ^1H NMR (CCl_4) δ 0.91(d,6H,J=5.0Hz), 1.60(m,1H), 2.41(d,1H,J=7.0Hz), 2.43(d,1H,J=5.0Hz), 2.72-2.93(m,1H), 3.43-3.86(brs,1H), 5.02(s,2H), 7.23(m,5H). Precise mass calc for $C_{13}H_{18}O_3$ m/z 222.1289. Found 222.1322.

Benzyl 3-cyclohexyl-3-hydroxypropionate(Table 4, entry 6). IR (neat) 3450, 1725 cm^{-1}, ^1H NMR (CCl_4) δ 0.68-2.18(m,11H), 2,40(d,1H,J=7.0Hz), 2.42(d,1H,J=5.0Hz), 2.60-2.93(m,1H), 3.44-3.90(brs,1H), 5.07(m,2H), 7.24(m,5H). Precise mass calc for $C_{16}H_{22}O_3$ m/z 262.1576. Found 262.1583.

Benzyl 3-hydroxy-4-hexenate(Table 4, entry 7). IR (neat) 3450, 1725 cm-1, ^{1}H NMR (CCl_4) δ 1.67(d,3H,J=5.0Hz), 2.45(d,2H,J=7.0Hz), 2.57-2.77(brs,1H), 4.12-4.57(m,1H), 5.07(s,2H), 5.32-5.66(m,2H), 7.24(m,5H). Precise mass calc for $C_{13}H_{16}O_3$ m/z 220.1113. Found 220.1127.

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