CHEMISTRY LETTERS, pp. 1319-1322, 1989.

Asymmetric Aldol-type Reaction between Both Achiral Ketene Silyl Acetals and Aldehydes by the Use of a Chiral Promoter[1)]

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Highly enantioselective aldol-type reaction of achiral ketene silyl acetals with achiral aldehydes is carried out by the use of a chiral promoter, a combined use of chiral diamine coordinated tin(II) triflate and tributyltin fluoride.

Ketene silyl acetals are useful reagents in organic synthesis 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.[2)] 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 from this laboratory,[3)] Chan[4)] and Heathcock[5)] examined the stereochemistry of the aldol-type reaction of ketene silyl acetals with aldehydes respectively, and reported that the diastereoselectivities were not so good except for a few examples. Recently, Gennari reported the enantioselective aldol reaction of (E)-ketene silyl acetal derived form N-methylephedrine-O-propionate with achiral aldehydes.[6)] Helmchen also reported almost the same reaction by the use of camphor derivatives as a chiral source.[7)] Though these two examples provided useful methods for the preparation of optically active β-hydroxy esters with high enantioselectivities, tedious procedures for the attachment and removal of the chiral sources are inevitable.

We have already reported that, 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.[8)] This is a first practical example for the asymmetric aldol-type reaction employing both achiral enolates and aldehydes by the use of a chiral promoter. In the course of our investigations to develop more practical enantioselective reactions using this chiral promoter, we planned to apply to the aldol-type reaction of ketene silyl acetals with aldehydes. In this communication, we would like to describe on highly enantioselective aldol-type reaction between both achiral ketene silyl acetals and aldehydes with the above promoter system.

In the first place, the reaction of benzaldehyde with 1-t-butyldimethylsiloxy-1-benzyloxyethylene was carried out in dichloromethane at -78 °C in the presence of stoichiometric amounts of tin(II) triflate, (S)-1-methyl-2-[(piperidin-1-yl)-

methyl]-pyrrolidine, and tributyltin fluoride. This is the optimum condition for the aldol-type reaction of silyl enol ethers of thioesters with aldehydes, however, in the present experiment using ketene silyl acetal, the aldol-type adduct was obtained in 64% yield with rather low enantioselectivity (51% ee). Several reaction conditions were examined to improve the enantioselectivity and it was found that the optical yield was improved when the reaction was carried out in a mixed solvent of 1,3,5-trimethylbenzene and dichloromethane (2:1, Table 1). Further, it was shown that chiral diamines also effected the enantiomeric excess (Table 2). The best result was obtained when the reaction was carried out in a mixture of 1,3,5-trimethylbenzene and dichloromethane(2:1) at -95 °C by the use of (S)-1-ethyl-2-[(piperidin-1-yl)methyl]-pyrrolidine as a chiral diamine.

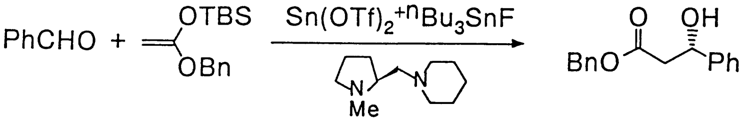
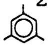


Table 1. The Effect of Solvent[a)]

Solvent	Yield/%	ee/%
DME[b)]	39	2
toluene	52	39
CH_2Cl_2	64	51
 :CH_2Cl_2(2:1)	60	65

a) The reaction was carried out at -78 °C.
b) 1,2-Dimethoxyethane.

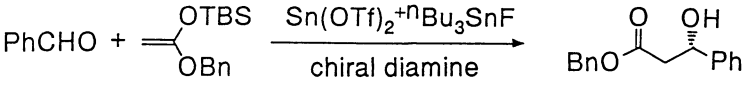
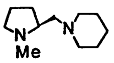


Table 2. The Effect of Chiral Diamines

Chiral diamine[a)]	Temp/°C	Yield/%	ee/%[b)]
A	-78	60	65
B	-78	41	5
A	-95	81	82
C	-95	76	89

a) Chiral diamine

A


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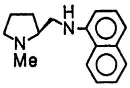

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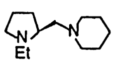

b) Determined by measurement of the ^{1}H NMR spectrum of the corresponding acetyl derivatives using $Pr(hfc)_3$ as a chiral shift reagent.

Several aldehydes are applicable to this asymmetric aldol-type reaction as shown in Table 3. 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.

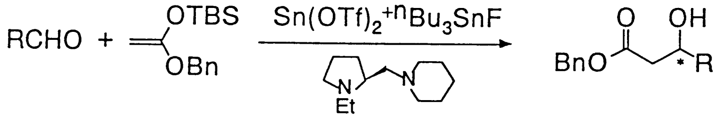

Table 3. Asymmetric Aldol Reaction of the Ketene Silyl Acetal with Aldehydes[a)]

R	Yield/%	ee/%(config.)
Ph	76	89 [b)](S)
p-CH_3-Ph	62	89 [b)]
p-Cl-Ph	73	95 [b)]
$CH_3(CH_2)_4$	79	91 [c)]
^{i}Pr	61	>98 [d)]
c-C_6H_{11}	60	97 [d)]
(E)-$CH_3CH=CH_2$	51	91 [c)]

a) The reaction was carried out in a mixture of 1,3,5-trimethylbenzene and dichloromethane(2:1) at -95 °C.
b) Determined by measurement of the ^{1}H NMR spectrum of the corresponding acetyl derivatives using $Pr(hfc)_3$ as a chiral shift reagent.
c) Determined by HPLC analysis of the corresponding MTPA esters.
d) Determined by measurement of the ^{1}H NMR spectrum of the corresponding acetyl derivatives using $Eu(hfc)_3$ as a chiral shift reagent.

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 6 h at -95 °C, then quenched with saturated aqueous sodium hydrogen carbonate. After usual work-up, the desired aldol, 3-hydroxy-3-phenylpropionic acid benzyl ester, was obtained in 76% yield. The enantiomeric excess was determined to be 89% by measurement of the ^{1}H-NMR spectrum of the corresponding acetyl derivatives using $Pr(hfc)_3$ as a chiral shift reagent.

Concerning the asymmetric aldol-type reaction of ester enolates with aldehydes, several reactions were reported by using chiral ester enolates and/or chiral aldehydes as reactants.9) However, there have been few examples on the reaction between both achiral ester enolates and aldehydes by the use of chiral promoters.10) It should be noted that highly enantioselective aldol-type reaction between easily available reagents as achiral ketene silyl acetals and achiral aldehydes was realized by the use of a chiral promoter, chiral diamine coordinated tin(II) triflate and tributyltin fluoride.

References

1) This paper is dedicated to Prof. Günther Ohloff on the occasion of his 65th birthday.
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(Received May 22, 1989)