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A New Efficient Chiral Catalyst System. Combined Use of Tin(II) Oxide, Trimethylsilyl Triflate and Chiral Diamine in the Asymmetric Aldol Reaction

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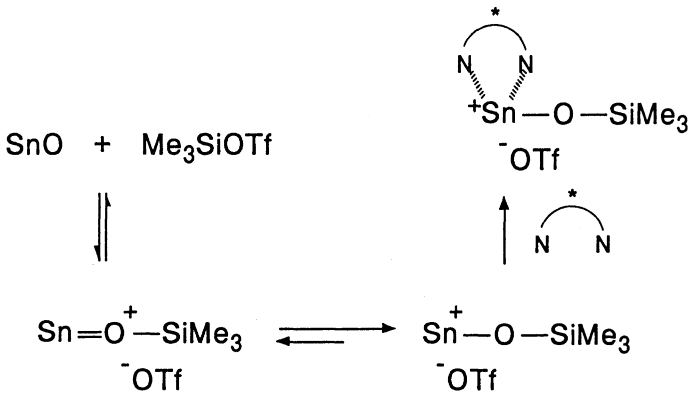
The asymmetric aldol reaction between both achiral silyl enol ethers of thioesters and aldehydes is efficiently catalyzed by the use of a new catalyst system consisted of tin(II) oxide, trimethylsilyl triflate and a chiral diamine, to give the corresponding adducts in high yields with high diastereo- and enantioselectivities .

The aldol reaction of silyl enol ethers with aldehydes is one of the most powerful methods for the stereoselective carbon-carbon bond formation,1) and several promoters and catalysts such as titanium tetrachloride2) and trityl salts3) have already been developed . We have lately found that new catalyst systems, such as TMSCl-$SnCl_2$,4) TrCl-$SnCl_2$,5) $SnCl_4$-$ZnCl_2$,6) $SbCl_5$-$Sn(OTf)_2$,7) and $SnCl_4$-$Sn(OTf)_2$,8) are effective for the aldol-type reactions of carbonyl and related compounds with silylated nucleophiles. These catalysts are supposed to behave as active cationic species generated by combination of a neutral molecule and a tin(II) compound or other Lewis acids. Quite recently, we have reported that the asymmetric version of this reaction is performed with perfect stereochemical control starting from both achiral silyl enol ethers and aldehydes by combined use of chiral diamine coordinated tin(II) triflate and tributyltin fluoride9) or dibutyltindiacetate.10) Further, we accomplished to develop this reaction into the first example of the catalytic asymmetric aldol reaction.11)

In the catalytic asymmetric aldol reaction by use of a catalytic amount of chiral diamine coordinated tin(II) triflate,11) the key step is the fast replacement reaction of the initially produced tin(II) alkoxide with trimethylsilyl triflate, which is formed in situ, to regenerate tin(II) triflate along with the trimethylsilyl ether. Otherwise, trimethylsilyl triflate promotes the undesirable achiral aldol reaction. Then we further considered to design a new chiral catalyst system consisted of metal oxide and trimethylsilyl triflate with a chiral ligand. Since trimethylsilyl triflate is known to activate the carbonyl and related compounds,12) we thought that there would be a possibility to use this reagent for activation of metal oxides or other oxygen containing metal compounds, leading to generation of a cationic catalyst shown in the following equation. In this communication, we would like to describe its first example, an efficient catalyst consisted of tin(II) oxide, trimethylsilyl triflate and chiral diamine in the asymmetric aldol reaction.

In the first place, aldol reaction of silyl enol ether of S-ethyl propanethioate with benzaldehyde was examined in the presence of tin(II) oxide (1.0 equiv.), trimethylsilyl triflate (1.1 equiv.) and (S)-1-methyl-2-[(N-1-naphthylamino)methyl]pyrrolidine (1.0 equiv.). The reaction smoothly proceeded at -78 °C to afford the



corresponding aldol adduct in 63% yield with good stereoselectivity (syn/anti=76/24, syn aldol=61%ee). It is noteworthy to point out that the reaction proceeded by the combination of three components, tin(II) oxide, trimethylsilyl triflate and the chiral diamine, while neither two components system of tin(II) oxide and the chiral diamine nor that of trimethylsilyl triflate and the chiral diamine catalyzed this reaction. Diastereo- and enantioselectivities were improved when the reaction was carried out according to the slow addition procedure.[11]

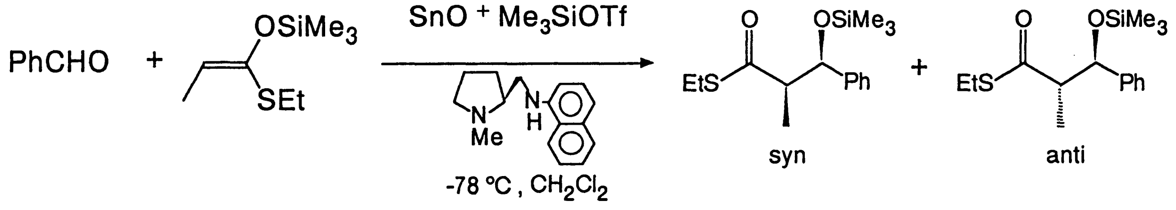


Table 1. Effect of Molar Ratio and Addition Time

Molar Ratio SnO	 Me$_3$SiOTf	 chiral diamine	Addition time/h	Yield / %	syn : anti	ee / %
1.0	1.1	1.0	6	84	91 : 9	87
0.5	0.6	0.5	6	85	88 : 12	79
0.5	0.65	0.5	6	85	93 : 7	83
0.5	0.70	0.5	6	87	89 : 11	78
1.0	0.65	0.5	6	85	94 : 6	89
1.0	0.65	0.5	9	82	94 : 6	91
0.25	0.33	0.25	6	80	88 : 12	21

Further, the molar ratio of the three compounds was found to strongly influence the stereoselectivities(Table 1). The best result was attained when a stoichiometric amount of tin(II) oxide, 50 mol% of trimethylsilyl triflate and chiral diamine were employed. Since tin(II) oxide is sparingly soluble in dichloromethane, this aldol reaction would be actually catalyzed by a quite small amount of chiral active species, however, use of 25 mol% of the reagents lowered the selectivities.

Several aldehydes are applicable to this asymmetric aldol reaction as shown in Table 2. In every case, aldols were obtained in good yields with high diastereo- and enantioselectivities.

A typical experimental procedure is described for the reaction of silyl enol ether of S-ethyl propanethioate with benzaldehyde; to a stirred suspension of tin(II) oxide (0.4 mmol) in dichloromethane (0.75 ml) was added trimethylsilyl triflate (0.24 mmol) in dichloromethane (0.5 ml). The mixture was stirred for 0.5 h, then (S)-1-methyl-2-[(N-1-naphthylamino)methyl] pyrrolidine (0.2 mmol) in dichloromethane (0.5 ml) was added to this solution. The mixture was cooled to -78 °C, then a mixture of silyl enol ether of S-ethyl propanethioate (0.4 mmol) and benzaldehyde (0.4 mmol) in dichloromethane (1.5 ml) was slowly added to this solution over 9h. The mixture was further stirred for 12 h, and quenched with saturated aqueous sodium hydrogen carbonate. After usual work up, the aldol was isolated as the corresponding trimethylsilyl ether. The enantiomeric excess of syn isomer was determined by HPLC analysis of the corresponding acetyl derivatives (DAICEL CHIRALCEL OD).

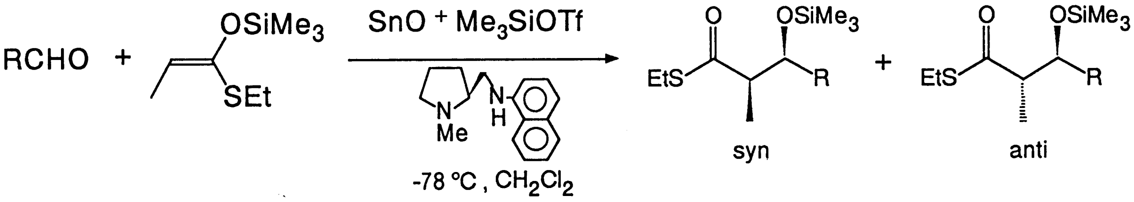


Table 2. The Asymmetric Aldol Reaction [a)]

Aldehyde	Yield / %	syn : anti	ee / %
PhCHO	82	94 : 6	91
i-BuCHO	70	98 : 2	94
$CH_3(CH_2)_6CHO$	65	98 : 2	85
CH_3CH_2CHO	65	96 : 4	67
c-$C_6H_{11}CHO$	58	91 : 9	68

a) SnO (100 mol%), Me_3SiOTf (65 mol%), chiral diamine (50 mol%).

Thus, the catalytic asymmetric aldol reaction between both achiral silyl enol ethers of thioesters and aldehydes was performed in high enantio- and diastereoselectivities by combined use of tin(II) oxide, chiral diamine and trimethylsilyl triflate. It should be noted that this catalyst system is classified into a new category of asymmetric catalyst because it consists of a chiral ligand coordinated neutral molecule (SnO) which can behave as an efficient catalyst via activation by a Lewis acid.

Further investigations to clarify the precise active species and the reaction mechanism is now in progress.

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