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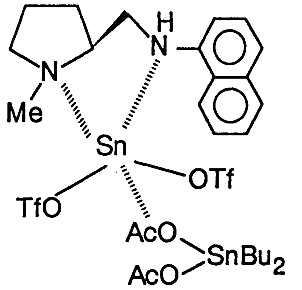
The Efficient Catalytic Asymmetric Aldol-type Reaction

Shu KOBAYASHI, Yuko FUJISHITA, and Teruaki MUKAIYAMA
Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

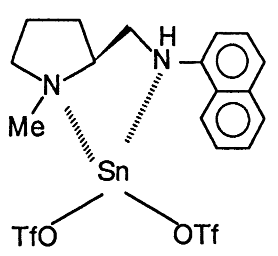
A wide variety of aldehydes including aromatic, aliphatic and α,β-unsaturated aldehydes react with silyl enol ether of S-ethyl propanethioate in propionitrile to afford the corresponding aldol-type adducts with high relative and absolute stereochemical control by use of chiral diamine coordinated tin(II) triflate as a catalyst.

Recently some chiral Lewis acids have been developed in the Diels-Alder and related reactions and fruitful results have been reported.$^{1)}$ Although the aldol reaction of silyl enol ethers with aldehydes is also one of the most important carbon-carbon bond forming reactions promoted by Lewis acids, less progress has been made in the asymmetric version of this reaction by use of a catalytic amount of chiral Lewis acid.$^{2)}$

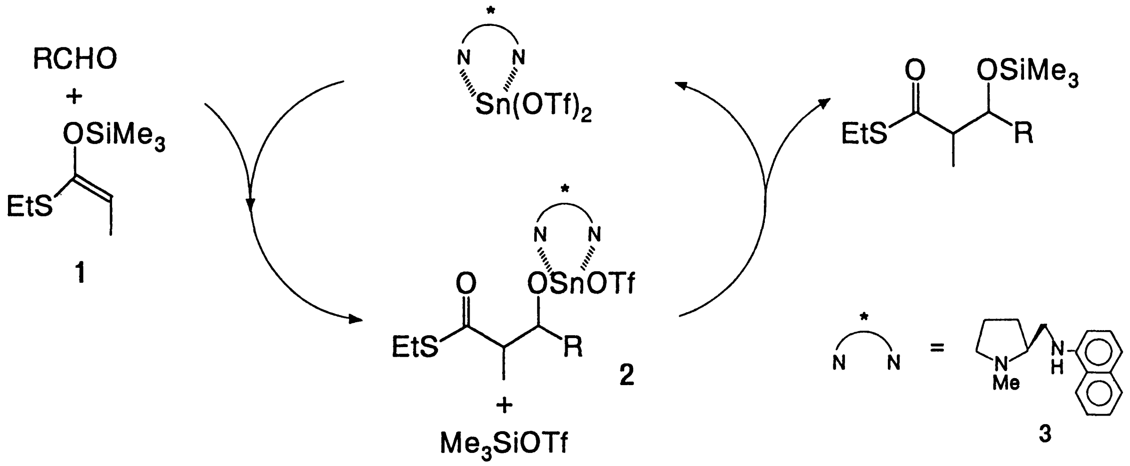
In the previous papers,$^{3)}$ we have demonstrated that almost perfect stereochemical control is achieved in the aldol-type reaction of silyl enol ethers of thioesters or esters with aldehydes by use of a stoichiometric amount of novel chiral promoter consisted of tin(II) triflate, a chiral diamine and tributyltin fluoride (dibutyltindiacetate) (Chiral Tin(II)-Tin(IV) Promoter). This reaction has been developed into the asymmetric aldol-type reaction by use of chiral diamine coordinated tin(II) triflate (Chiral Tin(II) Catalyst) as a chiral Lewis acid.$^{4)}$ We supposed the following catalytic cycle (Scheme 1) and the reaction could be successfully carried out according to a slow addition procedure. As shown in the preliminary communication, this procedure is applied to the reaction of silyl enol ether of S-ethyl propanethioate (1) with benzaldehyde (syn/anti=93/7, syn aldol=91%ee), octyl aldehyde (100/0, >98%ee), cyclohexanecarboxaldehyde (>99/1, 92%ee), or 4-chlorobenzaldehyde (93/ 7, 93%ee). After that, it was observed that, in some cases, selectivities were not so high; p-tolualdehyde (78/22, 80%ee), (E)-crotonaldehyde (84/16, 77%ee). Further, yield, diastereo- and enantioselectivities were lowered in the reaction of cyclohexanecarboxaldehyde when a smaller amount of the catalyst was used.



Chiral Tin(II)-Tin(IV) Promoter



Chirai Tin(II) Catalyst



Scheme 1.

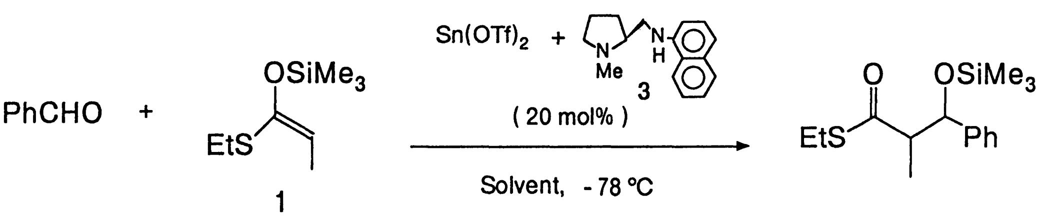


Table 1. Effect of Addition Time

Solvent : CH_2Cl_2

Addition time / h	Yield / %	syn / anti	ee / %
0	88	53/47	48
2	85	54/46	52
4	84	88/12	85
6	86	89/11	87
9	**86**	**93 / 7**	**91**
12	72	92/ 8	86

Solvent : C_2H_5CN

Addition time / h	Yield / %	syn / anti	ee / %
0	81	70/30	69
2	79	79/21	82
3	**77**	**92 / 8**	**90**
4	80	90/10	89
6	74	90/10	89
9	77	92/ 8	89

The lower selectivities were supposed to be ascribed to the incompleteness of the catalytic cycle. The key step is a metal exchange reaction of initially produced aldol-type adduct **2** with trimethylsilyl triflate (TMSOTf) (metal exchange from tin(II) to silicon). When this step is slow, undesirable TMSOTf promoted achiral aldol-type reaction proceeds to result in lowering the selectivities. In order to accelerate this metal exchange step, several polar solvents were screened. After careful examination of more polar solvents than dichloromethane by taking the reaction of **1** with benzaldehyde as a model, propionitrile was found to be a comparable solvent to dichloromethane. The examination of the addition time (addition of the reactants to the solution of the catalyst) revealed that the reaction rate of the metal exchange in propionitrile is faster than that in dichloromethane(Table 1). While 9 h (addition time) was necessary to attain the best result in dichloromethane, comparable selectivities were obtained when substrates were added to the catalyst for 3 h in propionitrile. It is noted that tin(II) triflate is readily dissolved in propionitrile different from dichloromethane indicating that the coordination of nitrile group to tin(II) is expected to be rather strong(^{119}Sn NMR; Sn(OTf)$_2$ in C_2H_5CN, δ -334.6; Me_4Sn served as external standard). When chiral diamine was added to the propionitrile solution of tin(II) triflate, ligand exchange took place (^{119}Sn NMR; Sn(OTf)$_2$ + chiral diamine **3** in C_2H_5CN; δ -712.0). Tin(II) triflate is also dissolved in tetrahydrofuran(THF) or 1,2-dimethoxyethane (DME), however, the above reaction did not proceed at -78 °C after the addition of chiral diamine **3** in these solvents.

Several aldehydes including aromatic, aliphatic and α,β-unsaturated aldehydes, are applicable in good yields with high selectivities in this reaction (Table 2). In particular, the lower selectivities in the reaction of p-

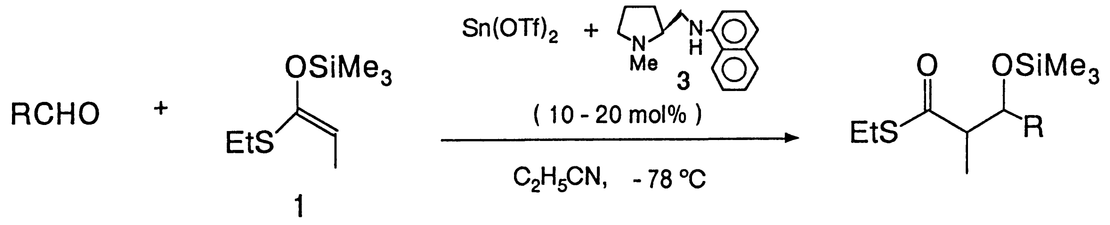


Table 2. Synthesis of syn-α-Methyl-β-hydroxythioesters

R	Cat./mol%	Yield / %	syn / anti	ee / %
Ph	20	77	93/ 7	90
p-Me Ph	20	75	89/11	91
(E)-CH_3CH=CH	20	76	96/ 4	93
(E)-$CH_3(CH_2)_2CH$=CH (4)	20	73	97/ 3	93
4	15	67	96/ 4	92
4	10	65	95/ 5	89
$CH_3(CH_2)_6CHO$	20	80	100/ 0	>98
c-$C_6H_{11}CHO$	20	71	100/ 0	>98

tolualdehyde and (E)-crotonaldehyde in dichloromethane were remarkably improved by use of propionitrile as a solvent. The present reaction is also applied to the reaction of (E)-2-hexenal, and further, the selectivities were improved in the case of cyclohexanecarboxaldehyde. In the reactions of six aldehydes listed in Table 2, the aldol-type adducts were obtained with high optical purities (>90%ee). High selectivities were also attained when even 10 mol% of the catalyst was employed.

A typical experimental procedure is described for the reaction of **1** with an aldehyde; to a solution of tin(II) triflate (0.08 mmol, 20 mol%) in propionitrile (1 ml) was added (S)-1-methyl-2-[(N-1-naphthylamino)methyl]-pyrrolidine (**3**, 0.088 mmol) in propionitrile (1 ml). The mixture was cooled to -78 °C, then a mixture of **1** (0.44 mmol) and an aldehyde (0.4 mmol) was slowly added to this solution over 3 h. The mixture was further stirred for 2 h, then quenched with saturated aqueous sodium hydrogencarbonate. After usual work up, the aldol-type adduct was isolated as the corresponding trimethylsilyl ether.

Thus, the catalytic asymmetric aldol reaction of **1** with several aldehydes including aromatic, aliphatic and α,β-unsaturated aldehydes by use of chiral diamine coordinated tin(II) triflate, is successfully attained when propionitrile was employed as a solvent. Several synthetically valuable syn-α-methyl-β-hydroxythioesters are prepared in high optical purities (>90%ee) according to the present procedure.

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