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An Efficient Asymmetric Aldol Reaction Promoted by a Chiral Tin(II) Lewis Acid Consisting of Tin(II) Triflate, (R)-2-[(N-1-Naphthylamino)methyl]tetrahydrothiophene and a Tin(IV) Compound

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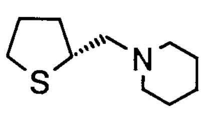
The title chiral Lewis acid is successfully employed in the enantioselective aldol reactions of silyl enol ether of S-ethyl propanethioate with achiral aldehydes to afford the corresponding aldol-type adducts in a highly stereoselective manner.

Recently we have reported a quite efficient asymmetric aldol reaction of silyl enol ethers with aldehydes using a chiral tin(II) Lewis acid consisting of tin(II) triflate, a chiral diamine and a tin(IV) compound.[1] While efficient asymmetric environment including bicyclo[3,3,0]octene structure was constructed by way of coordination of the chiral diamine to tin(II) triflate, Lewis acidity of this chiral acid is weakened by the coordination of the diamine. In the course of our investigations to search for more efficient ligands in asymmetric synthesis, the following chiral ligands **1**-**3** including tetrahydrothiophene ring instead of pyrrolidine ring in the above diamines was designed. These ligands are expected to form more acidic complexes with tin(II) triflate than the chiral diamines (for example, **4**), and the complexes would still have a possibility to construct a rigid bicyclo[3,3,0]octene structure based on strong coordination of sulfur atom towards tin(II) atom. In this communication, we would like to describe the



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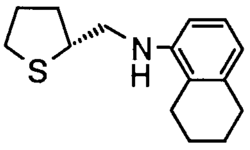

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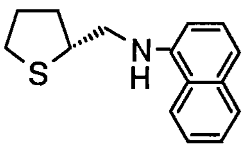

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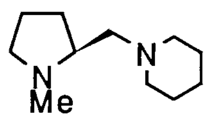

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highly enantioselective aldol reactions of achiral silyl enol ethers with achiral aldehydes promoted by the chiral Lewis acids consisting of tin(II) triflate, (R)-2-[(N-1-naphthylamino)methyl]tetrahydrothiophene and dibutyltin diacetate.

The chiral ligands **1**-**3** were prepared from (R)-tetrahydrothiophene carboxylic acid[2] via two steps; coupling with the corresponding amine using DCC as a coupling reagent and reduction using lithium aluminum hydride (LAH).[3]

Firstly, silyl enol ether of S-ethyl propanethioate was treated with benzaldehyde for 4 h in the coexistence of tin(II) triflate, **1**, and ^{n}Bu$_2$Sn(OAc)$_2$ in dichloromethane at -78 °C.[4] The reaction smoothly proceeded to afford the corresponding aldol adduct in 72% yield with syn/anti=90/10, and the optical purity of the syn aldol was proved to be 72%ee. On the other hand, when the corresponding chiral diamine ligand **4** was employed under the same reaction conditions, the corresponding aldol was obtained in rather low yield (42%) with almost same selectivities (syn/anti=92/ 8, syn aldol=72%ee). These results support our preliminary hypothesis that Lewis acidity of the present chiral Lewis acid is increased by changing nitrogen atom to sulfur atom involved in the bidentate ligands, with maintaining the efficient asymmetric environment.

Next, in order to improve the optical purity, chiral ligands **2** and **3** were examined by serving the above model system and the maximum ee (92%) was obtained when **3** was employed as a chiral ligand (Table 1).

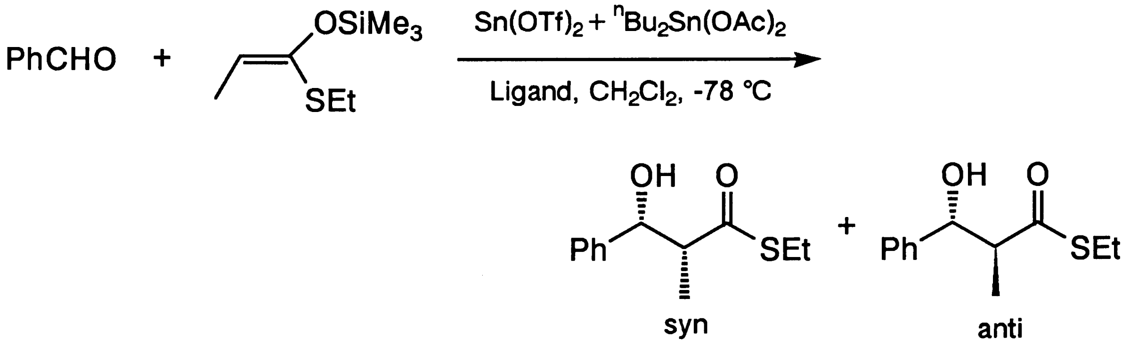

Table 1. Effect of Ligands

Ligand	Yield/%	syn/anti	ee/%
1	72	90/10	72
2	85	84/16	60
3	85	96/ 4	92

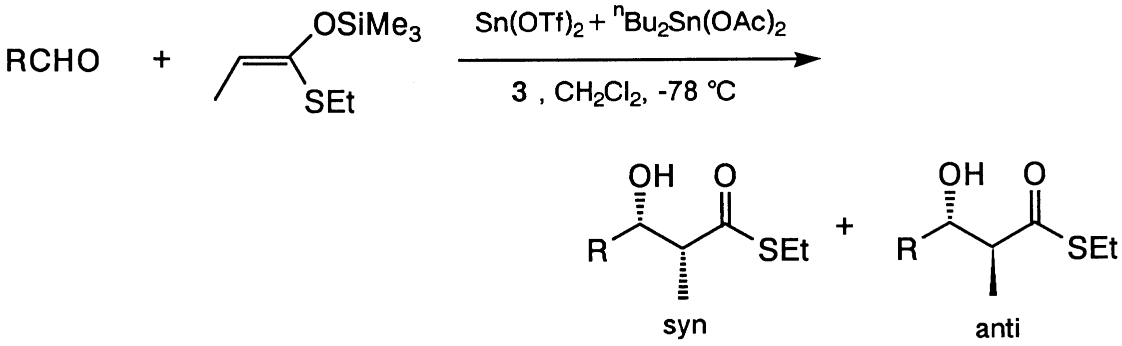

Table 2. Asymmetric Aldol Reaction of Various Aldehydes

Entry	R	Yield/%	syn/anti	ee/%
1	Ph	86	94/ 6	92
2	p-Cl Ph	98	92/ 8	90
3	p-Me Ph	89	96/ 4	93
4	$CH_3CH{=}CH$	78	100/ 0	92
5	$CH_3(CH_2)_2CH{=}CH$	85	100/ 0	93
6	$^{n}BuC{\equiv}C$	72	91/ 9	90
7	$CH_3C{\equiv}C$	63	89/11	91
8	CH_3	48	86/14	63

Several examples of this asymmetric aldol reaction using 3 as a chiral ligand are demonstrated in Table 2. In most cases, the corresponding aldol adducts are obtained in high yields with high diastereo- and enantioselectivities.5) It should be noted that the aldol adducts with more than 90%ee are prepared starting from both achiral silyl enol ethers and aldehydes using this novel chiral ligand.

A typical experimental procedure is described for the reaction of silyl enol ether derived from S-ethyl propanethioate (5) with 2-hexenal; to a suspension of tin(II) triflate (0.4 mmol) and (R)-2-[(N-1-naphthylamino)methyl]tetrahydrothiophene (0.48 mmol) in dichloromethane (1 ml) was added dibutyltin diacetate (0.44 mmol) at room temperature. The suspension became clear immediately. The mixture was further stirred for 30 min at this temperature and then cooled to -78 °C. Dichloromethane solutions (0.5 ml each) of 5 (0.4 mmol) and 2-hexenal (0.36 mmol) were successively added. The reaction mixture was further stirred for 20 h, and quenched with aqueous sodium hydrogen carbonate. After usual work up, S-ethyl 2-methyl-3-hydroxy-4-octenethioate was obtained in 93% yield (syn/anti=100/ 0, syn aldol=93%ee).

Further investigations to apply these chiral ligands to other asymmetric reactions are now in progress.

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References

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3) (R)-Tetrahydrothiophene carboxylic acid was coupled with 1-naphthylamine by a procedure similar to that of ref. 6 to afford the corresponding amide. A THF solution (30 ml) of this amide (30 mmol) was slowly added to a THF suspension (30 ml) of $LiAlH_4$ (75 mmol) at 0 °C, and the mixture was refluxed for 2 h. Then, saturated Na_2SO_4 (aq) was added to the mixture at 0 °C, and organic materials were collected by decantation. The organic layer was dried over K_2CO_3. After removal of the solvent, the crude product was purified by silica gel column chromatography and then distilled to afford **3**. 62% yield; bp 220 °C / 0.5 mmHg (bath temp.); $[\alpha]_D^{30}$ -95.2 ° (c 1.34, $CHCl_3$); IR (neat) 2942, 1581, 1527, 1407, 769 cm-1; ^1H NMR ($CDCl_3$) δ 1.80-2.17 (m, 4H), 2.84-2.99 (m, 2H), 3.30 (dd, 1H, J=7.1, 12.3 Hz), 3.45 (dd, 1H, J=5.9, 12.1 Hz), 3.76-3.86 (m, 1H), 4.70 (s, 1H), 6.60 (d, 1H, J=7.2 Hz), 7.21-7.32 (m, 2H), 7.41-7.44 (m, 2H), 7.75-7.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.3, 32.5, 34.8, 48.0, 49.29, 104.6, 117.6, 119.9, 123.6, 124.7, 125.7, 126.5, 128.6, 134.3, 143.1. The optical purities of the ligands **2** and **3** were proved to be more than 99%ee by means of HPLC analysis using the chiral column (Daicel Chiralcel). The optical purity of the ligand **1** was not determined, however, we assumed that no racemization was occured in its preparation. See ref. 6 .

4) While the two components mixture of tin(II) triflate and the ligand **1**, **2**,or **3** was only sparingly soluble in dichloromethane at rt., addition of dibutyltin diacetate to the mixture make the suspension clear immediately. These observations strongly indicate the formation of an active complex consisting of three components, tin(II) triflate, the ligand and dibutyltin diacetate.

5) Relative and absolute configuration assignments were made by comparison with the authentic samples. See ref. 1 .

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