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New Chiral Catalysts for the Highly Enantioselective Addition of Diethylzinc to Aldehydes

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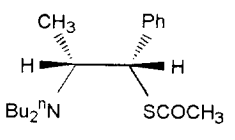
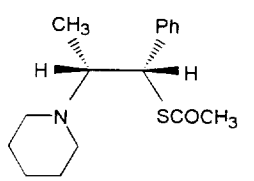
Abstract: Optically active amino thioacetate derivatives of (+)-norephedrine were found to act as effective catalysts for enantioselective addition of diethylzinc to aldehydes. This reaction provided optically active secondary alcohols with e.e. of up to >99%.

Asymmetric catalysis is a topic of increasing interest and is one of the most important focal area in organic synthesis. Among several methods, catalytic enantioselective addition of dialkylzinc reagent to aldehydes has proved to be convenient for the synthesis of optically active secondary alcohols.[1] Most of successful results have been mainly obtained by using chiral amino alcohols which cause catalytic asymmetric induction in the formation of the corresponding alcohols.[2] It has recently been reported that chiral amino thiols and amino disulfides can coordinate dialkylzinc more favorably than chiral amino alcohols to give enhanced asymmetric induction.[3,4] However, to the best of our knowledge, chiral amino thiocarboxylates have never been employed in the reaction. In the context of our research directed towards the development of new chiral ligands, we now report that optically active amino thioacetates **1** can act as highly efficient catalysts for the enantioselective dialkylzinc-aldehyde addition.

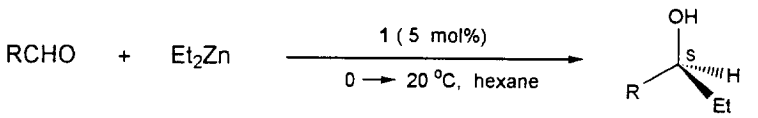


1a



1b

Table 1. Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of **1**.



Entry	R	Et_2Zn (eq)	1	Time (h)	Yield (%)[a]	%e.e.[b](config.[c])
1	Ph	2.0	**1a**	6	100 (98)	>99 (S)
2	Ph	1.1	**1a**	10	95	98 (S)
3	Ph	2.0	**1b**	6	100	>99 (S)
4	Ph	1.1	**1b**	10	97	97 (S)
5	*p*-ClC_6H_4	2.0	**1a**	6	100 (98)	>99 (S)
6	*p*-ClC_6H_4	1.1	**1a**	10	95	>99 (S)
7	*p*-ClC_6H_4	2.0	**1b**	6	100	>99 (S)
8	*o*-$MeOC_6H_4$	2.0	**1a**	6	100 (97)	99 (S)
9	*o*-$MeOC_6H_4$	1.1	**1a**	10	98	98 (S)
10	*o*-$MeOC_6H_4$	2.0	**1b**	6	99	98 (S)
11	*p*-$MeOC_6H_4$	2.0	**1a**	6	99	>99 (S)
12	*p*-$MeOC_6H_4$	2.0	**1b**	6	99 (92)	>99 (S)
13	2-naphthyl	2.0	**1a**	6	99 (94)	98 (S)
14	2-naphthyl	2.0	**1b**	6	99	98 (S)
15	*cyclo*-C_6H_{11}	2.0	**1b**	10	95 (90)	>99 (S)

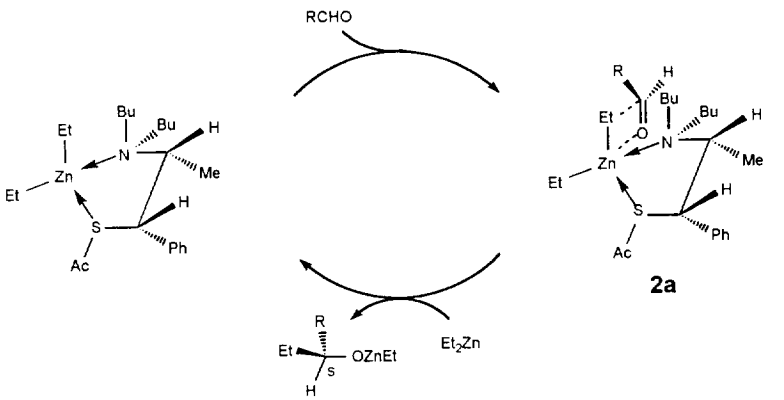
a) Determined by GC analysis using naphthalene as a internal standard. GC response factors were determined by averaging three separate runs of authentic samples and naphthalene. Figures in parentheses are isolated yields of pure product. Isolated yields were slightly lower.

b) Entries 1-14: determined by HPLC analysis (chiralcel OD column; flow rate, 0.5 mL/min; detection, 254 nm). For 1-phenylpropan-1-ol: eluent, 3% 2-propanol in hexane; t_R(min), 29.3 (S), 25.9 (R). For 1-(*p*-chlorophenyl)propan-1-ol: 3% 2-propanol in hexane; 22.4 (S), 24.3 (R). For 1-(*o*-methoxy-phenyl)propan-1-ol: 3% 2-propanol in hexane; 27.5 (S), 29.6 (R). For 1-(*p*-methoxyphenyl) propan-1-ol: 3% 2-propanol in hexane; 38.1 (S), 33.6 (R). For 1-(2-naphthyl)propan-1-ol: 20% 2-propanol in hexane; 12.8 (S), 19.5 (R). Entry 15: determined by GC analysis of the menthyloxy-carbonyl derivatives [β-DEX 60m capillary column; oven temp., 90℃; column flow, 0.85 mL/min; t_R(min), 76.5 (S), 77.7 (R)]. Racemic comparison samples were prepared by reactions of the corresponding aldehydes with EtMgBr.

c) Configurations were assigned by comparison with the sign of the optical rotation[2c] and known elution order from a chiralcel OD column[2g].

Chiral amino thioacetates (+)-**1** were easily prepared in three steps from (+)-norephedrine as follows. Reaction of (+)-norephedrine with 2.4 equiv of iodobutane in refluxing EtOH in the presence of K_2CO_3 gave *N,N*-dibutylnorephedine in good yield.[2f] Mesylation of *N,N*-dibutylnorephedine (2 g, 7.6 mmol) with methanesulfonyl chloride (0.96 g, 8.4 mmol) and triethylamine (0.85 g, 8.4 mmol) was carried out in dry CH_2Cl_2 (20 mL) at -20 ℃. Successively, after removal of solvent the residue was dissolved in H_2O/DMF (1/1, 12 mL) and an excess (*ca.* 2 equiv) of potassium thioacetate was added to the solution. The reaction mixture was stirred for 8 h at 40 ℃. Usual extractive work-up, followed by silica gel chromatography afforded (+)-**1a**[5] in 70% overall yield without racemization.[3,4] The synthesis of (+)-**1b**[6] was also achieved in a similar manner to the described above. To examine their catalytic activity in the asymmetric alkylation of aldehydes, the addition of diethylzinc (1 *M* in hexane, 6.0 mmol) to aldehydes (3.0 mmol) in hexane (12 mL) at 0→20℃ was performed in the presence of 5 mol% of **1**. As shown in Table 1, (+)-**1**-catalyzed ethylation led to striking success, generating (*S*)-(-)-alcohols with 97~>99% enantiomeric excess (e.e.) within ±1% error. The results are comparable to those of amino thiols corresponding to **1** which have afforded very high enantioselectivity in this reaction.[4] Decreasing of the amount of zinc reagent from 2.0 to 1.1 equiv has only a small effect on both synthetic yield and enantioselectivity. General enantioselective diethylzinc-aldehyde addition has been explained in terms of six-membered cyclic transition.[2d] A catalytic system in the presence of the aprotic ligand **1**, however, does not match with the general mechanism. In this case, a special mechanism that accelerates the reaction may be operative. We assume that the asymmetric reaction using **1a** proceeds via the following catalytic cycle (Scheme 1). Since no change of the amino thioacetate was observed under the reaction condition, a possible four-center transition state giving zinc alkoxide product can be described by the structure **2a**. The ligand coordinates with zinc atom of Et_2Zn, in

Scheme 1



which the aldehyde is attacked on its *Si* face to afford chiral ethylzinc alkoxide. The alternative approach of aldehyde is clearly less favorable for steric reasons. Aprotic ligand such as tertiary diamine has been known to catalyze the addition effectively.[7] The high stereoselectivity may be due to strong influence of such asymmetric environment as well as different electronic properties of N and polarizable S chelate. On the basis of the results, it was established that chiral amino thiocarboxylate is an efficient asymmetric catalyst for the addition of dialkylzinc to aldehydes. We are studying further synthesis of this N,S-chelate system through modification of chiral amino alcohols and their application to other asymmetric catalysis.

Acknowledgment: We appreciate the financial support of this work by Inha University.

References and Notes

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5. **1a**: light yellow oil; $[\alpha]_D^{20}$ = +210 (c = 1.0, $CHCl_3$), ^1H NMR ($CDCl_3$, 250 MHz) δ 7.26-7.19 (m, 5H), 4.63 (d, J = 9.6 Hz, 1H), 3.15 (m, 1H), 2.40-2.20 (m, 4H), 2.30 (s, 3H), 1.20-0.95 (m, 8H), 1.10 (d, J = 6.6 Hz, 3H), 0.79 (t, J = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 9.53, 12.39, 18.65, 28.77, 29.20, 48.05, 50.54, 57.55, 124.99, 126.22, 126.78, 140.67, 192.83.
6. **1b**: light yellow oil; $[\alpha]_D^{20}$ = +207 (c = 1.0, $CHCl_3$), ^1H NMR ($CDCl_3$, 250 MHz) δ 7.25-7.17 (m, 5H), 4.70 (d, J = 8.1 Hz, 1H), 2.95 (m, 1H), 2.51-2.25 (m, 4H), 2.28 (s, 3H), 1.29 (m, 6H), 1.09 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 10.01, 23.04, 24.64, 28.84, 48.51, 50.17, 62.09, 124.99, 126.28, 126.60, 140.42, 192.76.
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