Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Chiral Amino Thioacetate Derived from L-Prolinol

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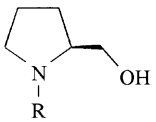
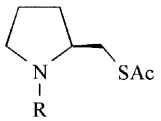
Received October 25, 1999

Catalytic enantioselective addition of organozinc reagent to aldehyde has been extensively studied as a valuable method for the synthesis of optically active secondary alcohols.[1] Most of the studies have focused on the use of chiral protic ligands such as amino alcohols,[2] amino thiols,[3] diols,[4] diamines[5] and their derivatives.[6] However, chiral aprotic ligands have scarcely been investigated in this area, although there is no doubt about their catalytic potential. Recently, we have found that chiral norephedrine-derived amino thioacetate can be effectively used as an aprotic ligand in the enantioselective reaction.[7] As an extension of this work, we here present new chiral amino thioacetates derived from L-prolinol, together with their applicability in the catalytic diethylzinc addition to aldehydes.

Similarly to the reported procedure,[3] the amino thioacetates **2** were readily prepared by mesylation of *N*-substituted prolinols **1**, followed by treatment with potassium thioacetate.[8] The addition of diethylzinc to aldehydes was perfomed in the presence of 5 mol% of **1** or **2**.

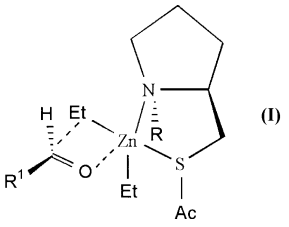


1a: R = Me
1b: R = Bn
1c: R = Bu



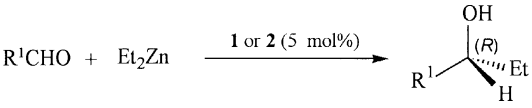
2a: R = Me
2b: R = Bn
2c: R = Bu

As can be seen from Table 1, high levels of enantiomeric excess up to 97% were obtained along with nearly quantitative conversion in the presence of the thioacetate catalyst **2b** or **2c**. The results obtained are very superior to those for the corresponding pyrrolidinylmethanols. (*R*)-Alcohols were preferentially formed in all the examined cases. Among the ligands employed, thioacetate **2c** provided the highest enantioselectivity. As the thioacetate was inert to the present reaction condition, no change giving thiol was observed.



(I)

Table 1. Enantioselective Addition of Diethylzinc to Aldehydes[a]



Entry	R^1	Ligand	Time (h)	Yield[b] (%)	e.e.[c] (%)
1[d]	Ph	**1a**	12	79	2
2	Ph	**1b**	12	80	59
3	Ph	**1c**	12	80(76)	59
4[d]	Ph	**2a**	8	90	26
5	Ph	**2b**	6	97	92
6	Ph	**2c**	6	95(91)	95
7	*p*-ClC_6H_4	**2b**	6	99(95)	91
8	*p*-ClC_6H_4	**2c**	6	98(95)	96
9	*o*-$MeOC_6H_4$	**2b**	8	95	90
10	*o*-$MeOC_6H_4$	**2c**	8	94	94
11	*p*-$MeOC_6H_4$	**2b**	8	97	93
12	*p*-$MeOC_6H_4$	**2c**	8	95	97
13	2-naphthyl	**2b**	6	93	90
14	2-naphthyl	**2c**	6	91	91
15	*cyclo*-C_6H_{11}	**2b**	8	98	90
16	*cyclo*-C_6H_{11}	**2c**	8	98(94)	95

[a]Reactions were carried out in hexane at 0 °C → 20 °C using 2 equiv. of Et_2Zn unless otherwise noted. Absolute configuration was assigned by the sign of the optical rotation and elution order from a chiral OD column. [b]Measured as %-conversion into the product by GC. Figures in parentheses are isolated yields. [c]Entries 1-14: determined by HPLC analysis (chiralcel OD column). Entries 15-16: determined GC analysis (β-DEX chiral column). [d]Ether was used as solvent.

This catalytic system would not match with the general mechanistic model[9] involving protic ligand. In the present reaction, the addition of Et_2Zn may be related to a chiral complex (**I**). The aldehyde is attacked on its *Re* face to afford (*R*)-alcohol in accordance with the experimental results. The *N*-alkyl substituent affected the ee result and a bulkier group gave a better ee. Some steric property of the ligand plays a role on the enantioselectivity. However, the origin of asymmetric induction by the ligand will require more detailed mechanistic studies.

In summary, chiral prolinol-derived amino thioacetate could be served as an effective aprotic ligand in the enantioselective diethylzinc-aldehyde addition. This result clearly indicates that the S-acyl moiety in the N,S-chelating ligand has a beneficial effect in enhancing the degree of chirality induction and reaction rate. The bulkiness of the N substituent on pyrrolidine ring was essential in maximizing the stereodifferentiating ability of the catalyst.

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

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8. **2a**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.05 (dd, J = 13.5, 3.2 Hz, 1H), 2.90 (m, 1H), 2.64 (dd, J = 13.4, 7.4 Hz, 1H), 2.17 (s, 3H), 2.12 (s, 3H), 2.04 (m, 2H), 1.75 (m, 1H), 1.53 (m, 2H), 1.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 21.6, 29.6, 30.1, 31.6, 39.9, 56.7, 64.4, 195.1; IR (neat) $\upsilon_{C=O}$ 1692 cm^{-1}; $[\alpha]_D^{20}$ -118.6 (c 1.15, $CHCl_3$); MS (CI) *m/z* 174 (MH^+, 100%).
2b: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.40-7.20 (m, 5H), 4.07 (d, J = 13.0 Hz, 1H), 3.31 (d, J = 13.0 Hz, 1H) 3.30 (d, J = 13.0 Hz, 1H), 2.92 (m, 2H), 2.72 (m, 1H), 2.35 (s, 3H), 2.19 (m, 1H), 1.92 (m, 1H), 1.80-1.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 22.3, 29.8, 30.6, 33.0, 54.1, 58.4, 62.5, 126.8, 128.1, 128.7, 139.2, 196.0; IR (neat) $\upsilon_{C=O}$ 1691 cm^{-1}; $[\alpha]_D^{20}$ -78.4 (c 1.0, $CHCl_3$); MS (CI) *m/z* 250 (MH^+, 100%).
2c: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.22 (dd, J = 13.3, 3.0 Hz, 1H), 3.12 (m, 1H), 2.77 (m, 2H), 2.51 (m, 1H), 2.31 (s, 3H), 2.13 (m, 2H), 1.95-1.60 (m, 3H), 1.55-1.20 (m, 5H), 0.89 (t, J = 7.3, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.0, 20.7, 22.3, 29.8, 30.5, 30.9, 33.0, 54.1, 54.3, 63.3, 196.0; IR (neat) $\upsilon_{C=O}$ 1693 cm^{-1}; $[\alpha]_D^{20}$ -100.9 (c 0.41, $CHCl_3$); MS (CI) *m/z* 216 (MH^+, 100%).
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