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Enantioselective addition of diethylzinc to aldehydes in the presence of chiral aprotic ligands

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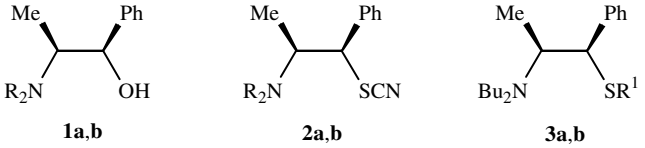
Abstract—Optically active amino thiocyanate derivatives of (−)-norephedrine were found to act as effective aprotic ligands for enantioselective addition of diethylzinc to aldehydes. This reaction provided optically active secondary alcohols with ee up to 96%.

Enantioselective addition of organozinc reagent to aldehyde in the presence of a catalytic amount of chiral ligand has emerged as an attractive method for the synthesis of optically active secondary alcohols.[1] The enantioselectivity of this process is mainly dependent on the chiral ligand, and therefore the search of new ligands for the asymmetric catalysis is a field of continuous interest. The catalysts used for the reaction have been based on chiral protic ligands such as amino alcohols,[2] diols,[3] diamines[4] and their derivatives,[5] whereas aprotic ligands have been scarcely studied in this area.[6a] Thus, it should be of interest to explore the catalytic ability of aprotic ligands. Herein, we present new chiral *N*,*S*-chelate aprotic ligands **2** and **3**, together with their catalytic applicability in the diethylzinc–aldehyde addition.



1a,**b** **2a**,**b** **3a**,**b**

a: R = C_4H_9 **b**: $R_2 = (CH_2)_5$

a: R^1 = Ph **b**: R^1 = CH_3

The amino thiocyanates **2a** and **b**[7] were readily prepared in 80% yields by treatment of the corresponding (−)-*N*,*N*-dialkylnorephedrines **1a** and **b**[2a] with methanesulfonyl chloride (1.0 equiv) and triethylamine (1.0 equiv) in methylene chloride at −20 °C, followed by subsequent displacement with sodium thiocyanate (2.4 equiv) in H_2O at 30 °C, respectively. This substitution proceeds with retention of configuration.[6] The presence of thiocyanate group in the compound **2** was confirmed by a strong sharp infrared band at ~2090 cm^{-1}. In contrast, isothiocyanate group shows a very broad band over the region from 2200 cm^{-1} to 2000 cm^{-1}.[8] The synthesis of **3a** was also achieved by treatment of sodium thiomethoxide in THF instead of sodium thiocyanate in H_2O. At first, the catalytic behaviour of the aprotic ligands **2** were examined in the addition of diethylzinc to benzaldehyde.[9] Gratifyingly enough, the initial trial of the addition with 5 mol% of ligand **2a** took place in excellent enantioselectivity of 96% with remarkable reactivity (Table 1, entry 1). The reaction was carried out in hexane at rt for 3 h. Toluene or hexane–toluene gave rise to slightly lower selectivity but with high conversions (entries 2 and 3). Other aromatic aldehydes were also converted to the corresponding (*R*)-secondary alcohols with high optical purity in high yields. For an aliphatic aldehyde, heptanal, good enantioselectivity was recorded (entry 12). Similar results were obtained from ligand **2b**. It is noteworthy that amino thiocyanates **2** give higher reaction rate and better or comparable asymmetric induction than previously reported amino alcohols **1**.[2a] This catalytic system involving aprotic ligands **2** would not match with the general mechanistic model[1] of the diethylzinc–aldehyde addition because the aprotic ligands do not possess an acidic hydrogen atom. An unusual mechanism may be operative in the addition. We assume that simple coordination of nitrogen and sulfur atoms to the zinc of diethylzinc generate an efficient chiral catalyst **4**. Next we examined the use of amino sulfides **3** in the addition of diethylzinc to benzaldehyde (entries 13 and

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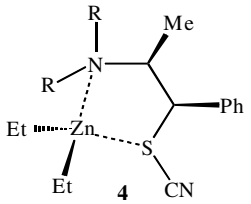

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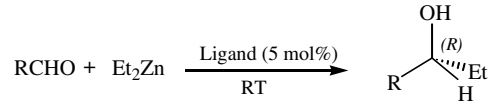
Table 1. Enantioselective addition of diethylzinc to aldehydes with chiral aprotic ligands **2** and **3**[a]



Entry	R	Ligand	Time (h)	Yield[b] (%)	ee (%)[c]
1	Ph	**2a**	3	98	96
2[d]	Ph	**2a**	3	96	92
3[e]	Ph	**2a**	3	94	90
4	Ph	**2b**	3	95	95
5	*p*-Cl-C_6H_4	**2a**	3	97	95
6	*p*-Cl-C_6H_4	**2b**	3	96	93
7	*o*-MeO-C_6H_4	**2a**	9	96	90
8	*o*-MeO-C_6H_4	**2b**	9	91	90
9	*p*-MeO-C_6H_4	**2a**	9	95	91
10	*p*-MeO-C_6H_4	**2b**	9	92	90
11	2-Naphthyl	**2a**	6	95	93
12	C_6H_{13}	**2a**	6	82	75
13	Ph	**3a**	12	85	41
14	Ph	**3b**	18	70	3

[a] Reactions were carried out in hexane using 2.0 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 product by GC.
[c] Determined by HPLC analysis (chiralcel OD column) or GC analysis (DEX chiral column).
[d] Reaction in toluene.
[e] Reaction in hexane–toluene, 1:1.

14). The reaction proceeded smoothly and poor ee was observed. Interestingly, the amino thiocyanates led to fast reaction with high ee, whereas the amino sulfides dramatically decrease the enantioselectivity. This fact suggests that the enantioselectivity strongly depends on the electronic environment around the sulfur atom. In conclusion, we have demonstrated that new chiral aprotic amino thiocyanates catalyze efficiently the enantioselective addition of dialkylzinc to aldehydes. Our study may open the way to the use of aprotic ligands in the dialkylzinc–aldehyde addition.

Acknowledgments

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7. For compound **2a**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.40–7.20 (m, 5H), 4.81 (d, J = 5.7 Hz, 1H), 3.05 (m, 1H), 2.52–2.34 (m, 4H), 1.40–1.06 (m, 8H), 1.08 (d, J = 6.7 Hz, 3H), 0.84 (t, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 10.7, 14.0, 20.3, 30.9, 49.9, 62.0, 63.9, 128.3, 129.0, 126.3, 131.5, 138.5; IR ν_{SCN} 2091 cm^{-1}; $[\alpha]_D^{20}$ −13.8 (c 1.0, $CHCl_3$); MS (CI) m/z 305 (MH^+).
For compound **2b**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.35–7.19 (m, 5H), 4.92 (d, J = 3.8 Hz, 1H), 2.83 (m, 1H), 2.51 (m, 4H), 1.51 (m, 4H), 1.40 (m, 2H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 10.6, 24.7, 26.5, 50.6, 62.4, 67.0, 126.1, 127.7, 128.4, 132.5, 138.2; IR ν_{SCN} 2089 cm^{-1}; $[\alpha]_D^{20}$ −42.5 (c 1.0, $CHCl_3$); MS (CI) m/z 261 (MH^+).
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9. A typical procedure for the present catalytic reaction is described as follows: benzaldehyde (106 mg, 1.0 mmol) was added to a solution of amino thiocyanate **2a** (15 mg, 0.05 mmol) in hexane (1.6 mL) at 0 °C. Diethylzinc (2 mL, 1.0 M in hexane) was then added dropwise. The mixture was allowed to warm to room temperature. The mixture was stirred for an additional 3 h, observing the progress of the reaction by GC. The reaction was quenched by the addition of dilute aqueous NH_4Cl and the resulting mixture was extracted with CH_2Cl_2. The organic extract was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel. The ee was determined by HPLC with a Daicel OD-H column.