

Communications

Highly Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Isoindolinyl Alcohol as a Chiral Ligand

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Enantioselective alkylation of carbonyl compounds is a challenged domain of asymmetric C-C bond formation.¹ Particularly, asymmetric addition of diethylzinc to aldehydes is one of the important synthetic methods for the preparation of optically active secondary alcohols, and numerous efforts have been made to find effective chiral ligands.² To date, most of the successful results were obtained by using sterically constrained β -amino alcohols such as *N,N*-dialkylated norephedrine derivatives.³ Extensive studies by Soai on the effect of ligand structure on enantioselectivity indicated that the chain length of the *N*-alkyl substituent is very important. Thus, the catalyst with *N*-alkyl substituents of a chain length of four carbons, **1** (DBNE), gave the best results in dialkylzinc addition to various aliphatic (87-93% ee) and aromatic (90-95% ee) aldehydes. It has been recently reported that some azacyclo β -amino alcohols (**2** and **3**) are among the most efficient chiral ligand in catalytic asymmetric reaction.⁴ Employment of conformationally rigid rings such as pyrrolidine and piperidine would provide beneficial on controlling precisely the stereochemical sense in asymmetric catalysis. Here we wish to report a new-type of amino alcohol (**4**) bearing isoindolinyl moiety as a face blocker and its catalytic efficiency in asymmetric addition of diethylzinc to various aldehydes. The isoindolinyl moiety may possess similar steric and electronic properties with substituted groups at nitrogen of the DBNE, but conformationally more rigid. Hence, compare to DBNE or pyrrolidine ligand **2**, it may block effectively the approach of the attacking species to one of the enantiotopic faces of aldehydes.

The (1*S*,2*R*)-1-phenyl-2-(2-isoindolinyl)-1-propanol[(1*S*,2*R*)-

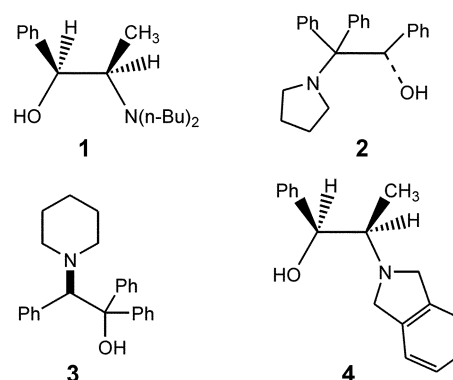
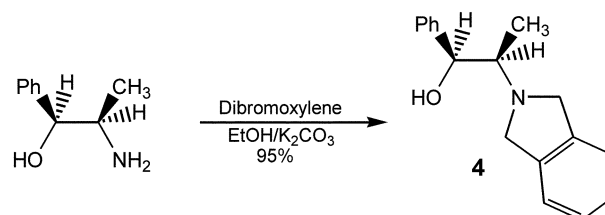


Figure 1. β -Aminoalcohols for diethylzinc addition.

4]⁵ was easily prepared in 95% yield by the reaction of (1*S*,2*R*)-norephedrine with α,α' -dibromoxylene in ethanol in the presence of potassium carbonate (Scheme 1).

In order to examine the catalytic ability of the ligand **4**, the enantioselective addition of diethylzinc to aldehydes⁶ was



Scheme 1. Synthesis of isoindolinyl alcohol (**4**).

Table 1. Addition of diethylzinc to aldehydes using ligand **4**

Entry	aldehyde	solvent	temp (°C)	time (hr)	% ee	yield (%) ^a
1	benzaldehyde	hexane	0	24	79 ^b	67
2	benzaldehyde	toluene	0	18	98 ^b	97
3	benzaldehyde	toluene	30	3	97 ^b	98
4	4-chlorobenzaldehyde	toluene	30	3	97 ^b	97
5	4-methoxybenzaldehyde	toluene	30	5	96 ^c	96
6	<i>trans</i> -cinnamaldehyde	toluene	30	3	95 ^b	89
7	hexanal	toluene	30	2	89 ^c	94

^aIsolated yield. ^bDetermined by HPLC analysis using Daicel Chiralcel OB column with 10% 2-propanol in hexane. ^cDetermined by ¹H NMR (CDCl₃) analysis of the corresponding (*S*)-(-)-MTPA ester derivatives. ^dBased on reported sign of optical rotation.

examined and the results are summarized in Table 1.

The reaction of diethylzinc (1.0 M solution in hexane) with benzaldehyde in hexane at 0 °C for 24 h in the presence of 10 mol% of catalyst (1*S*,2*R*)-**4** resulted in 67% yield of (*S*)-(-)-1-phenyl-1-propanol of 79% ee (entry 1). In hexane solvent, the reaction temperature did not largely effect on the enantioselectivity and reactivity. However, when the solvent was changed to toluene, enantioselectivity was increased, thus, the ethylation of benzaldehyde at 0 °C for 18 h afforded 97% yield of (*S*)-1-phenyl-1-propanol in 98% ee (entry 2). By increasing the reaction temperature to 30 °C, the reaction rate was dramatically increased without significant decreasing of optical purity (97% ee) and chemical yield (98%) (entry 3). The effect of solvent on the reaction rate and enantioselectivity may be due to the poor solubility of ligand **4** in hexane. Enantioselective alkylation of *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde using ligand **4** in toluene at 30 °C afforded the corresponding chiral secondary alcohols in 97 and 96% ee, respectively, and in almost quantitative chemical yields (entries 4 and 5). Moreover, aliphatic aldehydes, hexanal (89% ee) and *trans*-cinnamaldehyde (95% ee), are also alkylated with enantioselectivities. These results are quite comparable or superior to those obtained from any other chiral ligand used for asymmetric diethylzinc addition to aldehydes.

In conclusion, highly enantioselective addition of diethylzinc to various aldehydes using chiral isoindolylpropanol **4** as a ligand has been achieved at relatively high temperature within few hours. These results suggest that conformationally rigid isoindolyl ring of the catalyst **4** effectively block the approaching of the carbanion to one of the enantiotopic faces of the aldehyde in the reaction condition.

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References and Notes

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- mp 90–91 °C; [α]_D²⁵ = -54.63 (c 0.9, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 0.90 (d, *J* = 6.6 Hz, 3H), 2.84 (m, 1H), 3.35 (bs, 1H), 4.1 (Abq, *J* = 11.1 Hz, 4H), 5.1 (d, *J* = 2.7 Hz, 1H), 7.27–7.43 (m, 9H).
- General procedure for the enantioselective addition of diethylzinc to aldehydes: To a solution of chiral ligand **4** in toluene, diethylzinc (1 M solution in hexane or 1 M solution in toluene) was added at room temperature. After the mixture had been stirred at room temperature for 1 hr under argon atmosphere, aldehyde was introduced at 0 °C or 30 °C. After completion of the reaction (by TLC), 10% aqueous HCl solution was added and extracted with ether. The combined organic layer was dried (MgSO₄) and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography or preparative thin layer chromatography with *n*-hexane/ethyl acetate (8/1, v/v) to afford the corresponding chiral alcohols. Enantiomeric excesses (% ee) were determined by HPLC analysis of the resulting secondary alcohols or ¹H NMR analysis of the corresponding (*S*)-MTPA ester derivatives.