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Enantioselective Addition of Et_2Zn to Benzaldehyde Catalyzed by *N*-(*S*)-α-Methylbenzyl-β-aminoalcohols

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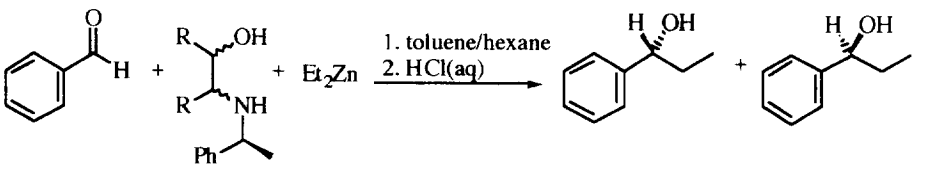
Abstract: The enantioselective alkylation of benzaldehyde by diethylzinc in the presence of catalytic amounts of *N*-(*S*)-α-methylbenzyl-β-aminoalcohols as the dilithium salts was studied. The extent of asymmetric induction was found to depend strongly upon the structure of catalyst used and also on the presence of lithium chloride. Copyright © 1996 Elsevier Science Ltd

Chiral metal catalysts are important tools for the synthesis of enantiopure organic compounds.[1] Chiral ligands containing nitrogen atom as donors are presently attracting much attention, since enantiopure ligands are increasingly accessible.[2] An easy to perform and well documented reaction for testing the catalytic reactivity and enantiodifferentiating ability of certain catalytic systems is the addition of diethylzinc to aromatic aldehydes such as benzaldehyde.[3] In particular, many chiral β-aminoalcohols, both natural and synthetic, have been tested in this addition with varying success. High enantioselectivity has been achieved by means of compounds such as 3-*exo*-(dimethylamino)isoborneol (DAIB) or derivatives of ephedrine and norephedrine.[4] Recent efforts directed toward the the synthesis of chiral β-aminoalcohols using (*R*)- and (*S*)-α-methylbenzylamine and the successful application of these compounds in enantioselective alkylation of aromatic aldehydes have been reported.[5]

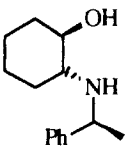
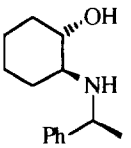
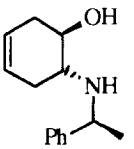
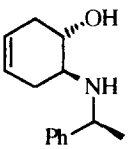
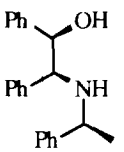
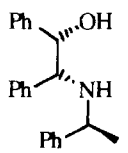


1 - 6 (*R*)- **7** (*S*)- **7** (1)

R = alkyl or phenyl

Recently, we have reported the rapid and efficient preparation of several enantiopure *N*-(*S*)-α-methylbenzyl-β-aminoalcohols from epoxides.[6] A recent report in the literature[7] on the synthesis of the *N*-(*S*)-α-methylbenzyl-β-aminoalcohols prepared from cyclohexene oxide has prompted us to disclose our preliminary results (eq. 1).

Table 1. Enantioselective Addition of Et_2Zn to Aldehydes (eq. 1).

Entry[a]	Chiral ligands	Yield (%)[b]	e.e. (%)[c]	Config.[d]
1		78	35	*S*
2		65	47	*R*
3		72	25	*R*
4		75	2	*R*
5		60	42	*R*
6		70	4	*S*

[a]All reactions were carried out in toluene : hexane (2 : 1) at 25 °C for 20 h. Molar ratio, Et_2Zn : benzaldehyde : chiral ligand : *n*-BuLi (2.03 : 1.00 : 0.06 : 0.12). [b]The final products were all purified by flash chromatography (petroleum ether : ethyl acetate, 15 : 1). [c]Determined by HPLC using a Chiralcel OD column. [d]The configuration of the main product was determined by the specific rotation and the order of elution in HPLC.

The addition of diethylzinc to benzaldehyde was carried out following a standard procedure reported in the literature.[8] The absolute configuration of the 1-phenyl-1-propanol has been obtained from the sign of the specific rotation[9] and from the elution order in HPLC on a Chiralcel OD stationary phase.[10] The results obtained are summarized in Table 1, finding low to moderate enantioselectivities with the *N*-(*S*)-α-methylbenzyl-β-aminoalcohols **1-6**. The best enantioselectivity was found with compound **2** (entry 2).

In order to gauge the potential of chiral ligand **2**, an additional experiment was carried out according to the same procedure, but using the hydrochloride salt derivative of **2**. Unexpectedly, (*S*)-1-phenyl-1-propanol was obtained as the major enantiomer (compare with entry 2 in Table 1). On the other hand, when the reaction was repeated with deliberate addition of LiCl,[11] (*S*)-**7** was again the main enantiomer (Table 2).

Table 2. Enantioselective Addition of Et_2Zn to Benzaldehyde in Presence of LiCl.

Entry[a]	Chiral ligand	LiCl (% mol)	Solvent	Yield[b] (%)	e.e.[c] (%)	Config. of main product[d]
1	**2** · HCl	6	$PhCH_3$:hexane:CH_2Cl_2 (10:5:1)	59	18	*S*
2	**2**	18	$PhCH_3$:hexane (2:1)	51	36	*S*
3	**2**	60	$PhCH_3$:hexane (2:1)	58	24	*S*

[a]All reactions were carried out at 25 °C for 20 h. Molar ratio, Et_2Zn : benzaldehyde : chiral ligand (2.03 : 1.00 : 0.06). [b]The final products were all purified by flash chromatography (petroleum ether : ethyl acetate, 15 : 1). [c]Determined by HPLC using a Chiralcel OD column. [d]Determined by the specific rotation and the order of elution in HPLC.

In conclusion, our results indicate that the enantioselectivity of Et_2Zn addition to benzaldehyde is modulated by the incorporation of the α-methylbenzyl group in the chiral aminoalcohol ligand. In addition, we present the first example of a salt effect that lithium chloride provokes on the enantioselectivity of the reaction. Further investigation of the mechanistic pathway of the reaction and the application of other *N*-(*S*)-α-methylbenzylated derivatives as chiral ligands is in progress.

Acknowledgment.

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