

Enantioselective addition of Et₂Zn to aldehydes catalyzed by chiral aliphatic β-amino alcohols

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This paper describes the preparation of two new optically active aliphatic β-amino alcohols (*R*)-5,5-dimethyl-2-(dimethylamino)-1,1-diphenyl-1-hexanol (**1a**) and (*S*)-8,8-dimethyl-2-(dimethylamino)-1,1-diphenyl-1-nonanol (**1b**). They were synthesized by methylation of the corresponding β-amino alcohols **2a** and **2b**. Compounds **1a** and **1b** catalyze the addition of diethylzinc to various aldehydes enantioselectively. The catalyst structure-enantioselectivity relationships were discussed.

Keywords Enantioselective addition, β-amino alcohol, enantioselectivity

Introduction

Enantioselective addition of Et₂Zn to aldehydes catalyzed by chiral β-amino alcohols affords optically active secondary alcohols. The reaction is one of the most important and fundamental asymmetric reactions.¹ It has been known that many tertiary β-amino alcohols, for instance, proline derivatives,^{2,3} camphor derivatives,^{4,5} ephedrine derivatives,⁶⁻⁹ and norephedrine derivatives^{10,11} promoted the enantioselective addition reaction in high enantiomeric excess. However, to our knowledge, the use of unnatural aliphatic β-amino alcohols as catalysts in this reaction has rarely been reported.

In our previous work,¹² the research on the structure-activity relationships of the chiral 1,3,2-oxazaborolidines in the enantioselective borane reduction of prochiral ketones, a series of chiral β-amino alcohols, including **2a—b**, were prepared. It was shown that **2b**, in which the bulky *t*-butyl group attached to the chiral center by a longer pentamethylene chain (compared to an ethylene chain in **2a**), gave better results than **2a** did.

As a continuation of this work, we prepared optically active amino alcohols **1a** and **1b**, by methylation of **2a** and **2b** with formaldehyde-formic acid, respectively (Scheme 1). Then catalytic asymmetric addition of diethylzinc to aromatic aldehyde using **1a** or **1b** was conducted (Scheme 2). These will be described in this paper.

Results and discussion

In a typical procedure, the addition reactions were run in toluene at 50—55°C, using a 2:1 molar ratio of diethylzinc to aldehyde in the presence of catalytic amount of **1a** or **1b**. The results obtained are summarized in Table 1.

The absolute configuration of 1-phenylpropanol and 1-(*m*-chlorophenyl)-propanol was assigned by comparison of the sign of the optical rotation detected with that reported in literatures.^{13,6} Although *R* and *S* 1-(*o*-chlorophenyl)propanols appeared in several papers,^{14,15} no optical rotation was reported. The absolute configuration of (+)-1-(*o*-chlorophenyl)propanol was assigned to be *R* based on the following facts: 1) 1-phenylpropanol and its simple ring-substituted derivatives including 1-(*m*-chlorophenyl)propanol and 1-(*p*-chlorophenyl)propanol have the same sign of optical rotation (“+” for *R* isomer and “-” for *S* isomer); 2) Running GC on a chiral cyclodextrin capillary column β-DEX120, *R* enantiomer always has a shorter retention time than the other enantiomer for all tested secondary alcohols obtained by asymmetric reduction of aryl alkyl ketones in our laboratory, and so was (+)-1-(*o*-chlorophenyl)propanol.

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It is obvious that catalyst **1b** showed higher enantioselective catalytic activity than **1a** did in this asymmetric addition. We come to the conclusion that a hindered catalytic center site decreases the activity and selectivity of the catalyst giving less satisfactory results. The addition of diethylzinc to benzaldehyde catalyzed by both **1a** and **1b** gave optically active secondary alcohol in

good yields with the enantiomeric excess ranged from moderate to high. The reaction of 3-chlorobenzaldehyde gave a product with much lower enantiomeric excess, and the lowest *ee*% was found in the addition of 2-chlorobenzaldehyde. This hints that the reaction is sensitive to steric effects.

Scheme 1 Synthesis of **1a** and **1b**

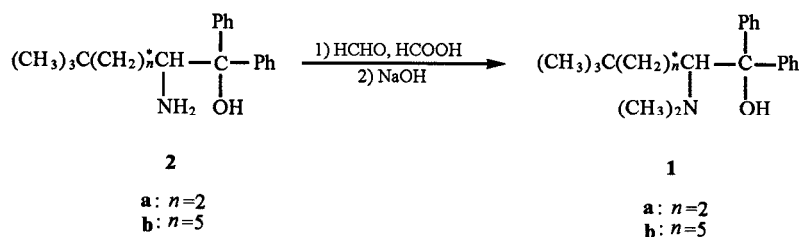
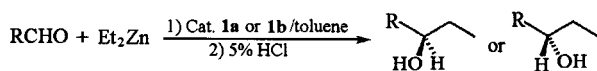


Table 1 Enantioselective addition of diethylzinc to aldehydes in the presence of catalyst (*R*)-**1a** or (*S*)-**1b** (8% mol)

Entry	R	Catalyst	<i>T</i> (°C)	Yield (%) ^a	<i>ee</i> % ^b	Configuration
1	Ph	(<i>R</i>)- 1a	rt	76.6	70.8	<i>R</i>
2	Ph	(<i>S</i>)- 1b	rt	84.5	85.2	<i>S</i>
3	Ph	(<i>R</i>)- 1a	55/rt	88.1	76.2	<i>R</i>
4	Ph	(<i>S</i>)- 1b	55/rt	89.7	94.0	<i>S</i>
5	2-Cl-Ph	(<i>R</i>)- 1a	55/rt	62.7	12.2	<i>R</i>
6	2-Cl-Ph	(<i>S</i>)- 1b	55/rt	70.3	24.1	<i>S</i>
7	3-Cl-Ph	(<i>R</i>)- 1a	55/rt	68.7	19.7	<i>R</i>
8	3-Cl-Ph	(<i>S</i>)- 1b	55/rt	72.5	36.8	<i>S</i>

^a Isolated yield. ^b Enantiomeric excess values were determined by GC on a chiral cyclodextrin capillary column β-DEX120.

Scheme 2 Enantioselective addition of Et₂Zn to aldehydes



Experimental

Melting points were measured in capillary tubes and uncorrected. Elemental analyses were performed with a Carlo Erba Model 1106 instrument. ¹H NMR spectra were recorded in CDCl₃ with a Bruker AR-400 and optical rotations were measured with a WZZ-115 automatic polarimeter. The enantiomeric excess values were determined by GC analyses using a β-DEX120 chiral stationary phase fused quartz capillary column.

Syntheses of *N,N*-dimethyl-β-amino alcohols

(*R*)-5,5-Dimethyl-2-dimethylamino-1,1-diphenyl-1-hexanol (**1a**) 0.53 g of 88% formic acid (10 mmol) was slowly added followed by 0.87 g of 35% formaldehyde (10 mmol) to 1.0 g (3.4 mmol) of (*R*)-**1a** while cooling with an ice bath. After 10 min stirring, the reaction temperature was constant to reflux for 9 h. Then the mixture was cooled and the solid NaOH was added to alkali. The organic layer was separated, and the water layer was extracted twice with 5 mL of benzene, and the combined organic extracts were washed with 5 mL of water and then dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave a yellow oil. The crude product was purified by column chromatography (silica gel, eluate: chloroform/petroleum ether = 3:1) to give **1a** as a colorless oil (0.

98 g), yield 89.6%, $[\alpha] = -58.3$ ($c = 1$ in CHCl_3). Enantiomeric excess 95.8% (by HPLC, chiral stationary phase) δ_{H} : 0.84(s, 9H, $(\text{CH}_3)_3\text{C}$), 1.27–1.76 (m, 4H, CH_2CH_2), 2.24(s, 6H, $(\text{CH}_3)_2\text{N}$), 3.38 (d, $J = 9.7$ Hz, 1H, CH), 5.76(bs, 1H, OH), 7.18–7.40(m, 10H, ArH). Anal. $\text{C}_{22}\text{H}_{31}\text{ON}$. Calcd: C, 81.18; H, 9.60; N, 4.30. Found: C, 81.34; H, 9.74; N, 4.05.

(*S*)-8, 8-Dimethyl-2-dimethylamino-1, 1-diphenyl-1-nonanol (**1b**) The procedure employed was the same as used in preparation of **1a**. Yield 92.4%, $[\alpha]_{\text{D}}^{25} + 34.5$ ($c = 1$ in CHCl_3). Enantiomeric excess 98.0% (by HPLC, chiral stationary phase). δ_{H} : 0.85(s, 9H, $(\text{CH}_3)_3\text{C}$), 1.13–1.70(m, 10H, $(\text{CH}_2)_5$), 2.26(s, 6H, $(\text{CH}_3)_2\text{N}$), 3.41(d, $J = 10$ Hz, 1H, CH), 5.96 (bs, 1H, OH), 7.21–7.41(m, 10H, ArH). Anal. $\text{C}_{25}\text{H}_{37}\text{ON}$. Calcd: C, 81.69; H, 10.12; N, 3.81. Found: C, 81.36; H, 10.15; N, 3.84.

General procedure for the enantioselective addition of diethylzinc to aldehydes using 1a or 1b as chiral catalyst

The reaction was carried out in flame-dried glasswares under nitrogen atmosphere.

To a solution of chiral catalyst (0.4 mmol) in 5 mL of toluene, diethylzinc (5 mL of 2 mol/L toluene solution, 10 mmol) was added by syringe at 0°C. The reaction mixture was heated to 50–55°C and kept for 15 min, then aldehyde (5 mmol) was added by syringe during a period of about 30 min. The mixture was stirred for 9 h at room temperature. The completion of the reaction was checked by thin layer chromatography. The reaction was quenched by adding 1 mol/L HCl to pH 3–4 while cooled with an ice bath, extracted with methylene chloride and washed successively with brine, saturated

sodium bicarbonate aqueous solution, and brine, dried over anhydrous sodium sulfate. The solvent was evaporated and the optically active alcohols were obtained by distillation under reduced pressure. The catalyst can be recovered by dissolving the residue with chloroform, purified by column chromatography.

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