

Asymmetric Addition of Diethylzinc to Aldehydes Catalyzed by Chiral γ -Amino Alcohols

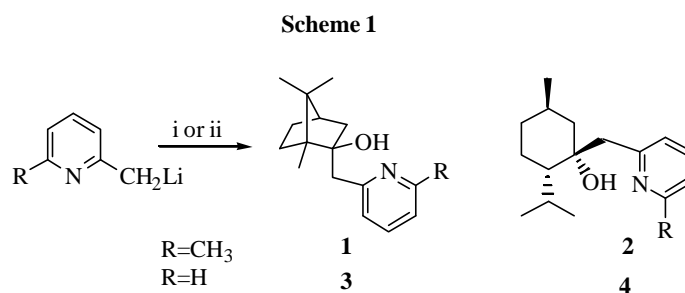
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Abstract: New chiral γ -amino alcohols **1-4** were synthesized and applied in the asymmetric addition of diethylzinc to aldehydes to give *sec*-alcohol with up to 94.0% enantiomeric excess.

Keywords: Asymmetric addition, γ -amino alcohols, diethylzinc.

Although the asymmetric additions of diethylzinc to aldehydes have been extensively studied in the presence of chiral catalyst, most of the chiral ligands tested are β -amino alcohols¹. In this report, the synthesis of chiral γ -amino alcohols **1-4** from the reaction of (+)-camphor and (-)-menthone with 2-lithiomethyl-6-methyl-pyridine or 2-picollylithium², which give a single diastereomer as determined by ¹H NMR with high yields (**Scheme 1**)³, and their application in the enantioselective addition of diethylzinc to aldehydes are described (**Table 1**).



Reagents and conditions: i. (+)-Camphor, ether; 0°C, ii. (-)-Menthone, ether, 0°C.

The results show that ligand **4** is the best catalyst when the enantioselective addition of diethylzinc to benzaldehyde was carried out in toluene/hexane (v:v, 1:1) at 0°C by using 20 mol% of catalyst (entry 4). For ligands **1** and **3**, (*R*)-1-phenyl-propanol was produced (entries 1 and 3). While for ligands **2** and **4**, (*S*)-1-phenyl-propanol was obtained (entries 2 and 4). The ligand **4** was further examined in the enantioselective addition of diethylzinc to various aldehydes. For aromatic aldehydes, moderate to good

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enantioselectivities (76.5-94.0%) were observed with high yields (entries 5-11). However, for aliphatic aldehydes, the enantioselectivities were moderate with good yields (entries 12-15).

Table 1 Enantioselective addition of diethylzinc to aldehydes catalyzed by ligand **1-4**^a



Entry	Substrate	Ligand	Yield (%) ^b	ee (%) (Config.) ^c
1	Benzaldehyde	1	91	74.8 (<i>R</i>)
2	Benzaldehyde	2	86	68.8 (<i>S</i>)
3	Benzaldehyde	3	93	38.1 (<i>R</i>)
4	Benzaldehyde	4	94	92.3 (<i>S</i>)
5	<i>o</i> -Anisaldehyde	4	92	84.1 (<i>S</i>)
6	<i>p</i> -Anisaldehyde	4	90	89.7 (<i>S</i>)
7	<i>p</i> -Tolualdehyde	4	91	88.6 (<i>S</i>)
8	<i>o</i> -Chlorobenzaldehyde	4	82	83.2 (<i>S</i>)
9	<i>p</i> -Chlorobenzaldehyde	4	87	88.4 (<i>S</i>)
10	3,4-Dimethoxybenzaldehyde	4	97	88.7 (<i>S</i>) ^d
11	4-(Dimethylamino)benzaldehyde	4	98	76.5 (<i>S</i>) ^d
12	1-Naphthaldehyde	4	92	94.0 (<i>S</i>) ^d
11	2-Naphthaldehyde	4	90	82.7 (<i>S</i>) ^d
12	<i>trans</i> -Cinnamaldehyde	4	87	76.3 (<i>S</i>) ^d
13	Dodecylaldehyde	4	83	59.6 (<i>S</i>) ^e
14	Nonylaldehyde	4	86	54.2 (<i>S</i>) ^e
15	Cyclohexanecarboxaldehyde	4	80	61.3 (<i>S</i>) ^e

a) Ligand/aldehyde/Et₂Zn = 1.0/5.0/10.0 (mmol); b) Based on isolated product; c) Except as note, the e.e. values were determined by GC with Chrompack CP-Chirasil-DEX CB capillary column and the configurations were determined by comparison the sign of the specific rotation with the known compounds; d) Determined by HPLC with a Chiralcel-OD column from Daicel; e) Determined by GC with Chrompack CP-Chirasil-DEX CB capillary column after acetylation.

Acknowledgment

The authors acknowledge Hong Kong Polytechnic University for the financial support.

References and notes

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- Selected spectra for compound **4**: mp 73-74°C; $[\alpha]_D^{20} = -62.9$ (c 1.03, CHCl₃); IR (KBr, cm⁻¹): 3324-3366, 1566, 1520; ¹H NMR (CDCl₃, δ ppm): 0.72 (d, 3H, *J*=6.3 Hz, CH₃), 0.95 (d, 3H, *J*=6.8 Hz, CH₃), 1.01 (d, 3H, *J*=6.8 Hz, CH₃), 1.05-1.13 (m, 1H, 4-H_{ax}), 1.15-1.21 (m, 1H, 6-H_{ax}), 1.26-1.41 (m, 1H, 4-H_{eq}), 1.48-1.65 (m, 3H, 2-H_{ax}, 3-H_{eq}, 6-H_{eq}), 1.72-1.77 (m, 2H, 3-H_{ax}, 5-H_{ax}), 2.26-2.29 (m, 1H, CHMe₂), 2.53 (d, 1H, *J*=13.8 Hz, PyCH₂), 3.43 (d, 1H, *J*=13.8 Hz, PyCH₂), 4.91 (br, 1H, OH), 7.14-7.27 (m, 2H, PyH³, PyH⁵), 7.63 (m, 1H, PyH⁴), 8.50 (m, 1H, PyH⁶).

Received 23 April, 2001