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The Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by 2-Methylquinoline Derived Chiral Ligands

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Abstract: Readily available 2-methylquinoline derived chiral ligands **1** and **2** have been applied in the enantioselective addition of diethylzinc to aldehydes with up to 91.4% ee being recorded.

Keywords: 2-Methylquinoline, enantioselective addition, diethylzinc.

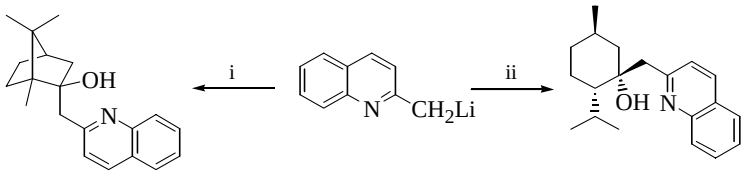
One of the most important and fundamental synthetic procedures for the establishment of a carbon-carbon bond stereoselectively is the enantioselective addition of organometallic reagents to aldehydes affording chiral secondary alcohols[1]. In this process, a frequently used method is to perform the reaction in the presence of a chiral ligand such as amino alcohol[2]. Here, we first report that two new chiral ligands[3], which were readily available by the reaction of chiral ketone with lithiated 2-methylquinoline as single diastereomer as shown by ^{1}H NMR analysis of the product mixtures (**Scheme 1**), were applied to catalyze the enantioselective addition of diethylzinc to aldehydes (**Table 1**).

Table1 Enantioselective addition of diethylzinc to aldehydes [a]

Entry	Substrate	Ligand (mol %)	Yield (%)[b]	ee% (config.) [c]
1	Benzaldehyde	**1** (20)	96	3.1 (R)
2	Benzaldehyde	**2** (5)	93	4.5 (S)
3	Benzaldehyde	**2** (20)	92	4.4 (S)
4	*p*-Chlorobenzaldehyde	**1** (20)	90	6.5 (R)
5	*o*-Anisaldehyde	**1** (20)	95	0.2 (R)
6	*p*-Anisaldehyde	**1** (20)	89	1.4 (R)
7	*p*-Tolualdehyde	**1** (20)	93	3.5 (R)
8	4-(Dimethylamino)benzaldehyde	**1** (20)	97	8.5 (R) [d]
9	3,4-Dimethoxybenzaldehyde	**1** (20)	93	6.8 (R) [d]
10	1-Naphthaldehyde	**1** (20)	91	9.3 (R) [d]
11	2-Naphthaldehyde	**1** (20)	87	8.6 (R) [d]
12	*trans*-Cinnamaldehyde	**1** (20)	93	4.5 (R) [d]
13	Nonylaldehyde	**1** (20)	70	8.5 (R) [e]
14	Dodecylaldehyde	**1** (20)	78	9.7 (R) [e]
15	Cyclohexanecarboxaldehyde	**1** (20)	83	2.7 (R) [e]

a) The reaction was run in toluene/hexane (1:1 v/v) at 0℃, aldehyde/ Et_2Zn = 1.0/2.0 (mmol);
b) Based on isolated product;
c) Except as note, the ee values were determined by GLC;
d) Determined by HPLC; e) Determined by GLC after acetylation.

Scheme 1



1 **2**

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

It can be seen from the results that compound **1** is a better ligand than compound **2** (entry 1, 2, 3). The enantioselectivity of the catalytic addition of diethylzinc to an aldehyde with an electron-donating group in the *para* position of the aromatic ring is higher than to an aldehyde with an electron-withdrawing group (entry 4, 6, 7, 8, 9). For aliphatic aldehyde, the enantioselectivity of the reaction is generally low.

References and notes

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3. Compound **1**: mp 88-89℃; $[\alpha]_D^{20}$ = -37.8 (c 1.01, $CHCl_3$); IR (KBr, cm^{-1}): 3320-3447, 1582, 1553; ^1H NMR ($CDCl_3$, δ_{ppm}): 0.56 (s, 3H, CH_3), 0.64 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.10- 1.15 (m, 1H, H-4), 1.41-1.49 (m, 2H, H-5, H-6), 1.52-1.58 (m, 1H, H-3), 1.71-1.78 (m, 2H, H-5', H-6'), 2.14 (m, 1H, H-3'), 3.17 (s, 2H, $ArCH_2$), 6.75 (br, 1H, OH), 7.33 (d, 1H, *J* = 8.4 Hz, ArH^3), 7.51 (m, 1H, ArH^7), 7.69 (m, 1H, ArH^6), 7.80 (d, 1H, *J* = 8.4 Hz, ArH^5), 8.01 (d, 1H, *J* = 8.2 Hz, ArH^8), 8.12 (d, 1H, *J* = 8.4 Hz, ArH^4); ^{13}C NMR ($CDCl_3$, δ_{ppm}): 11.27, 21.04, 21.48, 22.23, 30.97, 45.07, 45.57, 47.53, 49.47, 52.50, 81.45, 122.91, 126.08, 126.67, 127.50, 128.71, 129.75, 136.71, 146.68, 161.27; MS (*m/z*) (EI): 295 (M^+, 6), 280 (4), 185 (29), 143 (100); Anal. calcd. for $C_{20}H_{25}NO$: C 81.31, H 8.53, N 4.7s4, Found: C 81.23, H 8.44, N 4.89. Compound **2**: mp 137-138℃; $[\alpha]_D^{20}$ = -61.6 (c 1.14, $CHCl_3$); IR (KBr, cm^{-1}): 3330-3456, 1578, 1550; ^1H NMR ($CDCl_3$, δ_{ppm}): 0.66 (d, 3H, *J* = 6.5 Hz, CH_3), 0.95 (d, 3H, *J* = 6.5 Hz, CH_3), 1.02 (d, 3H, *J* = 6.5 Hz, CH_3), 0.87-0.91 (m, 1H, $CHMe_2$), 1.10-1.12 (m, 1H, H-5), 1.24-1.27 (m, 1H, H-6), 1.44-1.48 (m, 1H, H-2), 1.61-1.70 (m, 4H, 2×CH_2), 2.36 (m, 1H, H-6'), 3.14 (d, 1H, *J* = 13.8 Hz, $ArCH_2$), 3.47 (d, 1H, *J* = 13.8 Hz, $ArCH_2$), 5.30 (br, 1H, OH), 7.43 (d, 1H, *J* = 8.4 Hz, ArH^3), 7.53 (m, 1H, ArH^7), 7.71 (m, 1H, ArH^6), 7.91 (d, 1H, *J* = 8.4 Hz, ArH^5), 7.99 (d, 1H, *J* = 8.4 Hz, ArH^8), 8.24 (d, 1H, *J* = 8.4 Hz, ArH^4). ^{13}C NMR ($CDCl_3$, δ_{ppm}): 18.47, 21.40, 22.69, 24.00, 28.31, 26.98, 36.08, 47.89, 48.22, 51.33, 75.60, 124.29, 126.67, 127.49, 128.53, 129.22, 130.36, 137.24, 147.84, 162.53. MS (*m/z*) (EI): 297 (M^+, 2), 282 (1), 254 (1), 240 (1), 212 (11), 143 (100); Anal. calcd. for $C_{20}H_{27}NO$: C 80.76, H 9.15, N 4.71, Found: C 80.67, H 9.24, N 4.93.

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