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Synthesis of new chiral 1,2,3,4-tertrahydroisoquinoline β-amino alcohol for asymmetric diethylzinc addition to aryl aldehydes (I)

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Abstract

Four new chiral 1,2,3,4-tetrahydroisoquinoline-derived β-amino alcohols were synthesized from commercially available L-DOPA. These ligands were evaluated in the asymmetric addition of diethylzinc to benzaldehydes and showed different catalytic activities (up to 86% ee). The solvent played an important role in the enantioselective process. The transition state models were proposed to explain the reversion of the product configuration.

Keywords: β-Amino alcohol; Tetrahydroisoquinoline; Diethylzinc; Asymmetric addition

The optically active β-amino alcohol functional motif is not only the important chiral building blocks but also the chiral auxiliaries or ligands in asymmetric synthesis [1] including the enantioselectively catalytic borane reduction of prochiral ketones [2], enantioselective addition of dialkylzinc to aldehydes [3], asymmetric hydrogen transfer from alcohols to ketones [4] and other asymmetric reactions [5].

The formation of C–C bonds has always been one of the most challenging tasks in organic synthesis. Among current methods, the catalytic enantioselective addition of dialkylzinc reagents to aldehydes has been studied extensively and has become a classical test in the design of new ligands for the catalytically enantioselective synthesis in recent years [3,6,7]. Amino alcohols constitute an important part of the chiral ligands developed for dialkylzinc addition to aldehydes [7]. β-Amino alcohol ligands with different ring system, such as azetidine [8], pyrrolidine [9], piperdine [10] and aziridine [11] had been used in the enantioselective addition of dialkylzinc to aldehydes. The rigidity of the chiral amino alcohol is an important factor influencing the catalytic activity, but less attention has been paid to the application of the rigid peperdine derivatives. Herein, we report the synthesis of four new chiral 1,2,3,4-tetrahydroisoquinoline-derived β-amino alcohols and the catalytic efficiency of these ligands were examined in the enantioselective addition of diethylzinc to benzaldehydes (Fig. 1).

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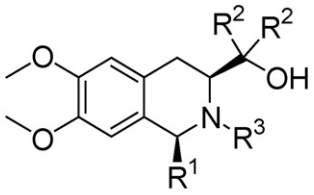
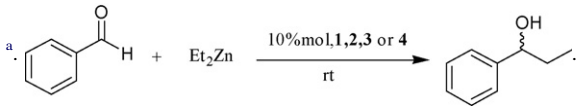


1: R^1=Ph R^2=Ph R^3=Me
2: R^1=Ph R^2=H R^3=Me
3: R^1=H R^2=Ph R^3=Me
4: R^1=Ph R^2=Ph R^3=H

Fig. 1. New chiral β-amino alcohol ligands.

Table 1
Asymmetric addition of diethylzinc to benzaldehyde by using amino alcohol ligands 1–4



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)	Config[d]
1	**2**	Toluene	24	59	22	*S*
2	**3**	Toluene	24	33	8	*S*
3	**4**	Toluene	24	59	47	*R*
4	**1**	Toluene	5	69	84	*R*
5	**1**	Hexane	5	76	85	*R*
6	**1**	CH_2Cl_2	24	33	38	*R*
7	**1**	Ether	10	93	86	*R*
8	**1**	THF	24	51	74	*R*

[a] The reaction was carried out with 10 mol.% amino alcohol ligand at room temperature. The molar ratio of benzaldehyde–Et_2Zn was 1:2.6.
[b] Isolated yields.
[c] Determined by HPLC using a chiral column: Chiralcel OB-H.
[d] The configurations were determined by comparing the signs of specific rotations with the known compounds [13].

The synthesis of compounds **4**, **5** and **6** starting from commercially available L-DOPA was performed as already described [12]. N-methylation of amino alcohols **4**, **5** and **6** with HCHO and $NaBH_3CN$ in CH_3OH at room temperature afforded **1**, **2** and **3** respectively in good yields (**1**: 60%, **2**: 77%, **3**: 85%) after recrystallization [15].

Ligands **1**, **2**, **3** and **4** were tested for the asymmetric diethylzinc reaction with benzaldehyde as the substrate. The results from these experiments are shown in Table 1. The reaction was carried out in different solvents with 10 mol.% amino alcohol ligand at room temperature. The diethylzinc addition to benzaldehyde proceeded with **4** as the chiral ligand to give (*R*)-1-phenylpropanol in 59% yield and 47% ee (entry 3). Methylation of the amino group (ligand **1**) provided the product in a higher yield (69%) and enantioselectivity (84%) (entry 4). However, it was interesting to find that the absolute configuration of the product was (*S*)- and the enantioselectivity was much lower for amino alcohols **2** and **3** (entries 1 and 2). This could be due to the steric influence of the geminal diphenyl groups and the phenyl group at C1 position of the tetrahydroisoquinoline moiety. Therefore, ligand **1** was the best among the four ligands and was further tested in various solvents. Toluene, hexane or ether gave satisfactory results of 69%, 76%, 93% yield and 84%, 85%, 86% ee respectively (entries 4, 5 and 7). However, CH_2Cl_2 or THF gave relatively lower yield and ee value (entries 6 and 8).

The different optical signs of the products of ligand **1** and **2** imply that the diethylzinc addition reactions proceed through different transition states. Fig. 2 shows a proposed mechanism for the reaction catalyzed by **1** and **2** [14]. In the first step, diethylzinc is chelated to form a five-membered ring with the nitrogen and oxygen atoms of the amino

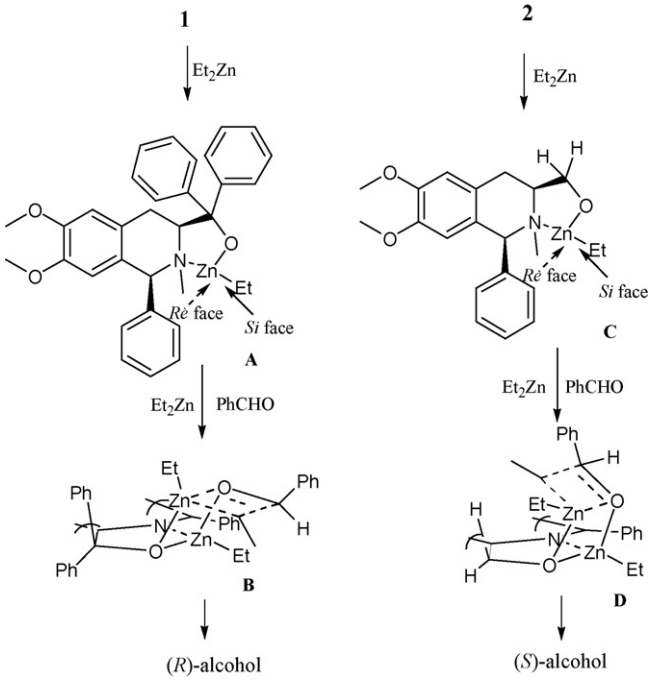
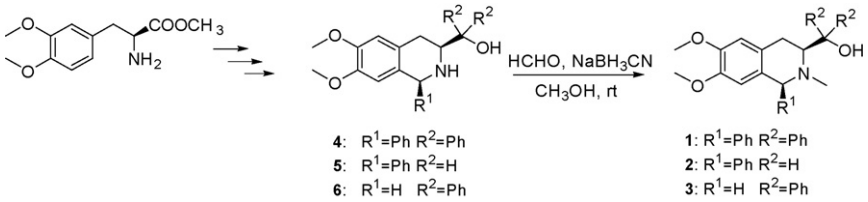


Fig. 2. Proposed model transition states.



Scheme 1. Synthesis of β-amino alcohols **1**, **2**, **3**, **4**.

alcohols to generate the zinc complexes A and C. Then the corresponding tricyclic transition state structure is formed by a fused 5/4/4 ring system. The Re-face is more accessible because the Si-face is more sterically hindered by the geminal phenyl groups and the phenyl group at C1 position of the tetrahydroisoquinoline. In the case of ligand **1**, transition state B is energetically favorable, in which the aromatic ring of the benzaldehyde is oriented far from the two hindered groups of the ligand, and (*R*)-alcohol is preferentially formed. On the other hand, transition state D is energetically favorable in the case of ligand **2** because of the absence of the geminal phenyl groups, and thus the (*S*)-alcohol is afforded (Scheme 1).

In summary, a novel class of chiral 1,2,3,4-tetrahydroisoquinoline β-amino alcohol ligands was synthesized from commercially available L-DOPA. The four ligands were evaluated in the asymmetric addition of diethylzinc to benzaldehydes and they showed different enantiomerically catalytic activities. The transition state models were proposed to explain the reversion of the product configurations. The best ligand **1** will be further investigated and the result will be reported later.

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[15] Compound **1**: mp 166–168 °C $[\alpha]_D^{15}$ + 9.2 (*c* 0.50, $CHCl_3$); IR (KBr): 3081, 3005, 2945, 2861, 2803, 1612, 1512, 1463, 1447, 1412, 1338, 1289, 1273, 1215, 1179, 1134, 1096, 1036, 1011, 988, 919, 880, 864, 761, 753, 742, 708, 700, 651, 632. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.12 (s, 3H, N–CH_3), 2.47–2.50 (m, 2H, Ar–CH_2–C), 3.72–3.77 (m, 1H, C–CH–N), 3.74 (s, 3H, –OCH_3), 3.84 (s, 3H, –OCH_3), 4.21 (s, 1H, –OH), 4.62 (s, 1H, Ar–CH–Ar), 6.45 (s, 1H, Ar–H), 6.54 (s, 1H, Ar–H), 7.16–7.67 (m, 10H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 29.27, 47.42, 55.49, 68.82, 69.30, 77.45, 110.50, 110.69, 125.66, 125.77, 125.82, 126.90, 127.40, 127.45, 128.14, 128.42, 128.47, 143.45, 144.72, 146.75, 147.63, 147.73. ESI-MS: 466 (*m*/*z* + 1); HRMS (ESI) calcd. For $C_{31}H_{32}NO_3$ 466.2382, found 466.2386. **2**: mp 66–68 °C $[\alpha]_D^{15}$ + 56.9 (*c* 0.55, $CHCl_3$); IR (KBr): 3204, 3057, 3015, 2932, 2893, 2809, 2779, 1610, 1515, 1465, 1451, 1369, 1310, 1256, 1222, 1191, 1148, 1110, 1044, 1020, 1006, 976, 915, 866, 840, 803, 745, 702, 593, 566. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.32 (s, 3H, N–CH_3), 2.51 (br, 1H, –OH), 2.70–2.82 (m, 2H, Ar–CH_2–C), 3.06–3.14 (dd, 1H, *J* = 14.1, 5.7 N–CH–C), 3.48–3.52 (dd, 1H, *J* = 10.5, 2.4, O–CH_2–C), 3.59 (s, 3H, –OCH_3), 3.85 (s, 3H, –OCH_3), 3.85–3.89 (m, 1H, O–CH_2–C), 4.41 (s, 1H, Ar–CH–Ar), 6.14 (s, 1H, Ar–H), 6.62 (s, 1H, Ar–H), 7.20–7.36 (m, 5H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 30.58, 40.13, 55.33, 55.38, 60.09, 63.15, 69.78, 110.08, 110.76 125.96, 126.87, 127.94, 128.63, 129.05, 144.09, 146.66, 147.13. ESI-MS: 314 (*m*/*z* + 1); HRMS (ESI) calcd. For $C_{19}H_{24}NO_3$ 314.1756, found 314.1757. **3**: mp 177–179 °C $[\alpha]_D^{15}$ − 28.2 (*c* 0.86, $CHCl_3$); IR (KBr): 3300, 3058, 2998, 2958, 2931, 2831, 2796, 1594, 1504, 1447, 1407, 1315, 1298, 1268, 1219, 1178, 1151, 1112, 1056, 1028, 1021, 987, 979, 962, 937, 888, 860, 780, 767, 754, 712, 700, 664, 632, 560. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.02 (s, 3H, N–CH_3), 2.47–2.50 (m, 2H, Ar–CH_2–C), 3.45–3.57 (m, 2H, Ar–CH_2–N), 3.82 (s, 3H, –OCH_3), 3.85 (s, 3H, –OCH_3), 3.85–3.89 (m, 1H, C–CH–N), 4.76 (s, 1H, –OH), 6.60 (s, 1H, Ar–H), 6.65 (s, 1H, Ar–H), 7.17–7.70 (m, 10H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 29.03, 45.52, 55.83, 55.93, 56.02, 67.62, 79.06, 109.92, 110.98, 126.04, 126.20, 126.33, 126.46, 127.94, 128.55, 144.61, 147.07, 147.72, 147.86. ESI-MS: 390 (*m*/*z* + 1); HRMS (ESI) calcd. For $C_{25}H_{28}NO_3$ 390.2069, found 390.2060. **4**: mp 169–171 °C $[\alpha]_D^{15}$ − 29.2 (*c* 0.96, $CHCl_3$); IR (KBr): 3373, 3054, 2964, 2902, 2832, 1610, 1512, 1450, 1348, 1279, 1251, 1232, 1168, 1117, 1074, 1058, 1003, 957, 897, 848, 766, 733, 707, 627, 578, 537. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.07 (s, 1H, –NH–), 2.26–2.32 (dd, 1H, *J* = 16.5, 2.7, Ar–CH_2–C), 3.05–3.14 (dd, 1H, *J* = 15, Ar–CH_2–C), 3.57 (s, 3H, –OCH_3), 3.77 (s, 3H, –OCH_3), 4.06 (s, 1H, –OH), 4.18–4.23 (dd, 1H, *J* = 3.0, 10.5 C–CH–N), 5.18 (s, 1H, Ar–CH–Ar), 6.12 (s, 1H, Ar–H), 6.50 (s, 1H, Ar–H), 7.17–7.70 (m, 15H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 29.04, 55.74, 55.81, 58.62, 62.36, 78.40, 110.30, 111.36, 125.46, 125.87, 126.59, 126.84, 127.20, 127.72, 128.14, 128.43, 128.75, 128.87, 129.34, 144.02, 146.60, 145.62, 146.99, 147.67. ESI-MS: 452 (*m*/*z* + 1); HRMS (ESI) calcd. For $C_{30}H_{30}NO_3$ 452.2226, found 452.2227.