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Novel non-azacyclo 1,2-aminoalcohols derived from L-Phe and highly enantioselective addition of diethylzinc to aryl aldehydes

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Abstract

A series of non-azacyclo β-aminoalcohols derived from natural L-phenylalanine were readily synthesized in three steps. They were used as chiral ligands in the catalytic asymmetric addition of diethylzinc to aldehydes. The results showed that ligands with diethyl or dipropyl substituents on the carbinol carbons of the aminoalcohols favored higher enantioselectivities, and ligands with *N*,*N*-dimethyl groups gave better asymmetric induction than other *N*,*N*-dialkyl substituted ligands. Compound **5b** was the most optimal ligand among these aminoalcohols, allowing to obtain a 96% ee. The results showed that high enantioselection should be determined by the subtle combination of the carbinol parts and amino parts of the aminoalcohols.

Keywords: Non-azacyclo aminoalcohols; Asymmetric catalysis; L-Phe; Diethylzinc; Aryl aldehyde

1. Introduction

Enantioselective addition of diethylzinc to aldehydes is one of the most important catalytic asymmetric C–C bond formation reactions which continues to be the interested center to many groups in the world [1,2]. Even though 1,2-aminoalcohols are among the most versatile and successful chiral ligands in this area, design and synthesis of highly enantioselective optically active 1,2-aminoalcohols continue to be the aim of many research groups on account of the necessary for highly effective, easily obtained and economical chiral catalysts [3]. In addition, researches on relationship between asymmetric catalytic activity and structural information of chiral ligand are very important and interesting in order to search for optimized asymmetric catalysts.

Naturally occurring amino acids are among the available and low-cost chiral pool, and have been extensively used as the source of cheap chiral ligands. Many natural amino acids have been derivatized directly to highly efficient chiral ligands or catalysts [4]. We have previously reported some novel piperidine- and pyrrolidine-based 1,2-aminoalcohols chiefly and efficiently derivatized from naturally occurring L-phenylalanine [5]. Researches by other groups have shown that the structurally flexible [6] but not rigid [3a,7] groups on the carbon atoms of the hydroxyl group served to high enantioselectivity. Greatly out of our expectation, piperidine-based ligands **1a** and **1b** (Fig. 1) gave higher enantioselectivity than pyrrolidine-based aminoalcohols **2a** and **2b** in the asymmetric addition of diethylzinc to aldehydes. This phenomenon seemed to show that the conformational flexibility or their structural bulkiness of the alkyl substituted groups of the nitrogen atoms of the ligands could also make great effect on their enantioselectivity in this asymmetric reaction. All those chiral ligands disclosed by us were aza-containing cycle chiral ligands and those two ligands **1a** and **1b** achieved very high enantioselectivity. However, how about the similar non-azacyclo aminoalcohols derivatized from L-phenylalanine? Could the flexible substituted alkyl groups of the hydroxyl groups of the novel chiral ligands make the same or similar effect on high asymmetric induction? How would different alkylated groups of the nitrogen atoms of the ligands influence their asymmetric catalytic activity? These are very interested questions to us. Considering the designed synthetic procedure and the prices of starting materials (alkyl dialdehydes are more expensive than alkyl monoaldehyde), non-azacyclo chiral aminoalcohols

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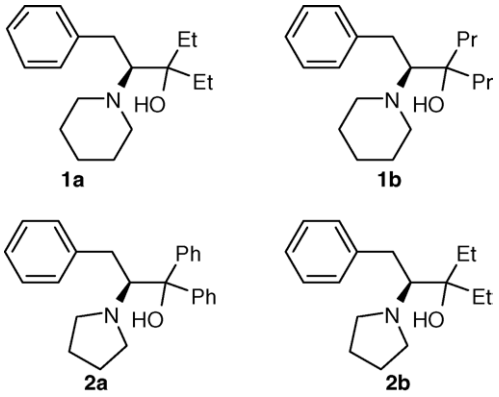


Fig. 1. Azacircle-containing aminoalcohols.

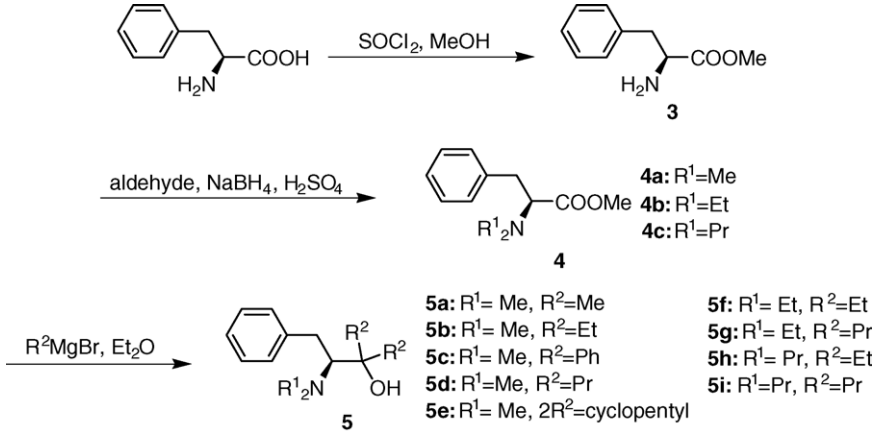
should deserve to be given more attention. So, we designed and prepared a series of novel 1,2-aminoalcohols once more directly from L-phenylalanine which featured non-azacyclo but chain alkyl substituted groups on the nitrogen atom of them. Herein, we disclosed the synthesis of these series novel aminoalcohols and their catalytic enantioselectivity in the asymmetric addition of diethylzinc to aryl aldehydes.

2. Results and discussion

As to the synthetic procedure, the key step was how to alkylate the nitrogen atom. In general, the alkylation of the nitrogen atom was accomplished via reaction of varieties of iodoalkanes with amines typically under a basic condition, which was usually promoted by potassium carbonate in an organic solvent system. But this typical procedure was often long time-consuming. Furthermore, the iodoalkanes were not cheap and unstable. These characteristics would make the synthesis of the ligands inefficient. They were also disadvantageous for preparation of low-cost chiral ligands. So, it was very important to find a novel efficient protocol to synthesis these aminoalcohols. The reductive alkylation procedure to synthesis azacycles reported by Vyskočil et al. [8] and our group [5] was more efficient and low-cost, which accomplished the reaction within only 15–30 min and used the inexpensive simple alkylaldehyde. Thus, we decided to adopt this low-cost and fast protocol to prepare these aminoalcohols. According to the previous procedure, the 1,2-aminoalcohols **5a–5i** could be readily synthesized. The typical methyl esterification of L-phenylalanine with methanol afforded the compound (*S*)-**3** (Scheme 1). Then, (*S*)-**3** was dissolved in THF. Simultaneously, with solid $NaBH_4$, it was slowly added into the mixture of 20% H_2SO_4 and the corresponding aldehydes (formaldehyde, acetaldehyde or propionaldehyde) at ambient temperature. This reductive alkyl protocol allowed to obtain the *N*,*N*-dialkylamino methyl esters (*S*)-**4**. The successive Grignard reactions of (*S*)-**4** with freshly prepared Grignard reagents gave aminoalcohols (*S*)-**5a–5i** (Scheme 1).

With these series of aminoalcohols in hand, we began to study the relation between their asymmetric catalytic activities and structural features in the addition of diethylzinc to benzaldehyde (Table 1). We also chose hexane as the optimal solvent. The results showed that the asymmetric induction directions of these non-azacyclo aminoalcohols were identical to the reported azacyclo aminoalcohols in this reaction, the configurations of the resulted secondary alcohols were all *R*. Compared with ligands **1a–1b** and **2a–2b**, the enantioselecivities of the new ligands (entries 1–11) were superior to the pyrrolidine-based ligands **2a–2b** (entries 14–15). Only *N*,*N*-dimethylaminoalcohols showed similar enantioselectivities to the piperidine-based ligands **1a–1b**. The ligands **5b** and **5d**'s enantioselection were up to 95 and 94%, respectively (entries 2 and 4, Table 1). As for aminoalcohols with diethyl or dipropyl substituted nitrogen atoms, their enantioselectivity could not be heightened up to 90% (entries 6, 8, 10 and 11), even if higher catalyst loading were used to promote the reaction (entries 7 and 9).

Next, we studied the effect of the substituents on the carbinol atom. If similar results to those reported with piperidine-based ligands were observed, it should be concluded that the flexible substituted groups on this carbon atom favored high enantioselectivity in this asymmetric reaction. This phenomenon had been also observed by Kawanami and co-workers in the course of the same catalytic enantioselective reaction [6]. They suggested that



Scheme 1. Preparation of chiral ligands **5a–5i**. The aldehyde was formaldehyde, acetaldehyde or propionaldehyde, respectively.

Table 1
Enantioselective addition of diethylzinc to benzaldehyde catalyzed by β-aminoalcohols **5a–5i**

Entry	Ligand[a]	Yields (%)[b]	Ee (%)[b]	Configuration[c]
1	**5a** (4)	97	84	*R*
2	**5b** (4)	98	95	*R*
3	**5c** (4)	92	79	*R*
4	**5d** (4)	98	94	*R*
5	**5e** (4)	93	90	*R*
6	**5f** (4)	98	82	*R*
7	**5f** (10)	99	88	*R*
8	**5g** (4)	98	84	*R*
9	**5g** (10)	99	89	*R*
10	**5h** (4)	99	85	*R*
11	**5i** (4)	99	87	*R*
12	**1a** (4)	98	96	*R*
13	**1b** (4)	98	97	*R*
14	**2a** (4)	96	42	*R*
15	**2b** (4)	98	49	*R*
16	**5b** (2)	98	79	*R*
17	**5b** (10)	99	94	*R*

Values in parentheses are in percent.
[a] Hexane was used as solvent. The number in the bracket was the used amount of the ligand.
[b] Determined by chiral HPLC with Daicel Chiracel OD column.
[c] Determined by the retention time of the major peak of the enantiomers on HPLC [5].

Table 2
Catalytic asymmetric addition of diethylzinc to aryl aldehydes promoted by ligand **5b**[a]

Entry	Aldehydes	Yields (%)[b]	Ee (%)[b]	Configuration[c]
1	Benzaldehyde	98	95	*R*
2	2-Anisaldehyde	97	76	*R*
3[d]	3-Anisaldehyde	98	96	*R*
4[d]	4-Anisaldehyde	98	91	*R*
5	3-Tolualdehyde	99	93	*R*
6	4-Tolualdehyde	98	84	*R*
7	α-Naphthaldehyde	98	83	*R*
8[d]	α-Naphthaldehyde	97	94	*R*
9	β-Naphthaldehyde	98	94	*R*
10	4-Chlorobenzaldehyde	98	94	*R*
11	4-Fluorobenzaldehyde	99	91	*R*
12[d]	4-Fluorobenzaldehyde	97	93	*R*

[a] Hexane was used as solvent and 4 mmol% **5b** was used as chiral catalyst.
[b] Determined by chiral HPLC with Daicel Chiracel OD column.
[c] Determined by the retention time of the major peak of the enantiomers on HPLC [5].
[d] 10% **5b** equivalent to aldehyde was used.

the flexibility of the substituents at the carbinol carbon atom could play a critical role in the enantioselection of the addition reaction. This suggestion was obviously important to the design and preparation of efficient chiral ligands. But similarly, the substituents on the nitrogen atoms were also vital to get high enantioselection. High enantioselection should owe to the subtle cooperation of the different parties of the ligands.

Among ligands **5a–5e** with dimethylamino group moieties (entries 1–5), both **5b** and **5d** which featured diethyl or dipropyl flexible groups on the α-carbon atoms of the hydroxyl group behaved with very high enantioselectivity. Ligand **5c** with diphenyl groups gave the lowest ee, while **5a** with dimethyl substitutents achieved the middle ee which was higher than **5c** but lower than **5b**, **5d** and **5e**. The distinct phenomenon was that the ligand **5e** which possessed cyclopentyl substituted group on the α-carbon atom of the hydroxyl group gave a good enantioselectivity up to 90% (entry 5). The high enantioselectivity should be the cooperative result of substituted groups of *N* atoms and α-carbon atoms of the hydroxyl groups. From the experimental data in Table 1, we could also find that ligands featured with diethyl or dipropyl groups on the α-carbon of the hydroxyl groups with the same *N*,*N*-dialkyl substituted groups behaved nearly the same enantioselectivity, whatever the amino group parts were piperidine cycle, *N*,*N*-dimethylamino, diethylamino or dipropylamino (entries 2 and 4, 6 and 8, 10 and 11 versus 12 and 13). Maybe these structure–activity relationships were related to the structure of L-phenylalanine itself own. When comparing to piperidine-based ligands **1a** and **1b**, **5b** and **5d** could be found a trifle decreases in ee value. This result maybe gave us an apocalypse that only subtle and elaborate and felicitous cooperation of many parts of one chiral ligand could contribute to the highest enantioselective outcome. Maybe combination of the piperidine cycle with diethyl or dipropyl groups was more optimal than *N*,*N*-dimethyl group with the same diethyl or dipropyl groups. In spite of such a trifle decreases in ee value, ligands **5b** and **5d** were among the most efficient, low-cost and easy obtained chiral ligands, if it was considerated that formaldehyde is a much cheaper starting material than glutaric dialdehyde, and that the actual high asymmetric induction outcome achieved by these two ligands, together with the straightforward synthetic protocol.

For the achievement of more higher ee, we then tried to optimize the appropriate amount of the ligand (Table 1, entries 2 and 16–17). The results showed that the amount of 4% equivalent to benzaldehyde was optimal to the ligand. When decreasing the amount of **5b**, the ee was also dropped down. However, the ee could not be risen while increasing the quantity of **5b**.

Since ligand **5b** showed the highest enantioselectivity, we chose some typical aromatic aldehydes as reaction substrates and observed the scope of the method (Table 2). The results showed that ligand **5b** was a good chiral ligand in this asymmetric reaction. Many substrates could achieve high enantioselectivity, and the ee value could be up to 96% (entry 3). Only 2-anisaldehyde got a lower enantioselectivity, correspondingly (entry 2).

Ligands **5a–5i** possessed *S* configuration but gave *R* configurational secondary alcohols. We presumed the probable mechanism as Fig. 2 according to the proposed transition state of this asymmetric reaction by Noyori and co-workers [9]. Therefore, the transition state with the lowest energy should be **6** with an anti conformation (Fig. 2). The phenyl group of benzaldehyde would adopt the direction far away from the amino groups of the ligands. Within the tricycle system **7**, ethyl group would attack the benzaldehyde plane from the upper side, i.e. the lower energy transition state would make for the 'Re-attack' of the benzaldehyde. Thus, the *R* dominant configurational products were obtained.

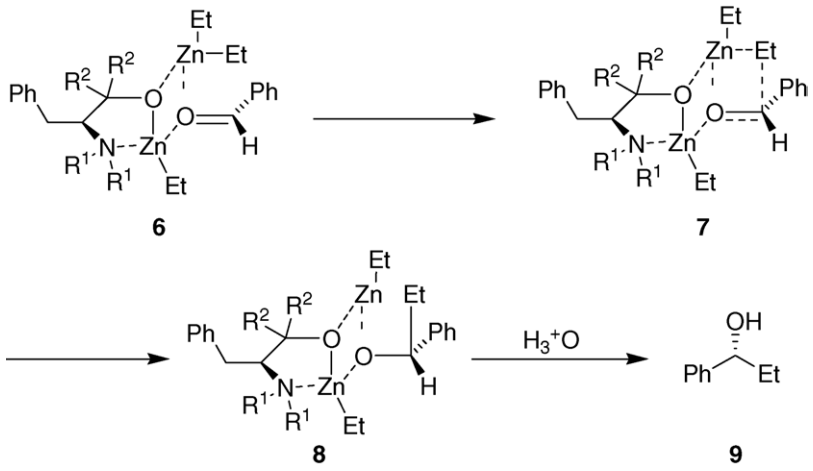


Fig. 2. Probable mechanism of the catalytic asymmetric addition of diethylzinc to benzaldehyde, which would make for the sec-alcohol with *R* configuration.

3. Conclusion

In conclusion, we have designed and readily prepared nine novel aminoalcohols in three straightforward steps derivatized from naturally occurring L-phenylalanine. The results showed that ligands with diethyl or dipropyl substituents on the carbinol carbons of the aminoalcohols served to higher enantioselectivity. As for the amino parts of these novel aminoalcohols, ligands with dimethyl groups substituted on the nitrogen atom behaved with higher enantioselectivity than the others. This phenomenon would hint that the high enantioselective outcome should be owing to the subtle combination of the every part of the ligand. The ligand **5b** gave the highest asymmetric induction, its enantioselectivity was up to 96%. Considering the prices of the starting synthetic materials, synthetic protocol and enantioselectivity, ligand **5b** should be among the optimal chiral ligands in this asymmetric reaction.

4. Experimental

4.1. General

All reactions were carried out under argon and solvents were dried according to the established procedures. Reactions were monitored by thin layer chromatography (TLC), column chromatography purifications were carried out using silica gel. All aldehydes and L-phenylalanine were purchased from Acros or Fluka. Diethylzinc was prepared from EtI with Zn and then was diluted with hexane to 1.0 M. Melting points were uncorrected and recorded on X-4 melting point apparatus. ^{1}H NMR spectra were measured on Bruker Am 400M and DRX-200 (NMR in $CDCl_3$ with TMS as an internal standard). IR spectra were obtained on Nicolet AVATAR 360 FT-IR. Optical rotations were recorded on Perkin-Elmer 341 polarimeter. HR-MS were measured with APEX II 47e mass spectrometer and the ESI-MS was recorded on Mariner® biospectrometer. The ee value determination was carried out using chiral HPLC with Daicel Chiracel® OD column on Waters® with 996 UV-detector.

*4.2. Preparation of (S)-phenylalanine methyl ester, (**S**)-(+)-**3***

To a mixture of 9.7 g (58.8 mmol) L-Phe in 300 ml methanol was added dropwise $SOCl_2$ 21.53 ml (294.95 mmol) at −30 °C. After warming up to room temperature, the reaction mixture was refluxed for 2 h. The organic solvent was concentrated under reduced pressure, and then the residue was treated with $NH_3{\cdot}H_2O$ into ca. pH 9.0. The mixture was extracted three times with Et_2O. The combined organic layers were washed with little brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, to obtain 10.0 g (*S*)-**2**, 95%. $[\alpha]_D^{23}$ = +25.0 (*c* 4.04, C_2H_5OH). ^{1}H NMR (200 M) δ 7.11–7.30 (m, 5H, Ph-H), 3.65–3.71 (m, 4H, CHN, CH_3, J = 5.2 Hz, J = 8.0 Hz), 2.99–3.08 (dd, 1H, PhCH, J = 13.4 Hz), 2.74–2.85 (dd, 1H, PhCH), 1.44 (s, 2H, NH_2). IR (KBr) 3380, 3314, 3061, 3028, 2950, 2852, 1738, 1602, 1495, 1438, 1276, 1198, 1174, 1112, 1076, 1010, 839, 747, 701 cm^{-1}; ESI-MS for $(C_{10}H_{13}NO_2 + H)^+$: 180.

*4.3. Preparation of 3-phenyl-2-(N,N-dialkylamino)-propionic acid methyl ester, (**S**)-**4***

4.3.1. General procedure for preparation of (S)-4, typical with (S)-(+)-4a, (S)-(+)-3-phenyl-2-(N,N-dimethylamino)-propionic acid methyl ester

A solution of 1.0 g (5.579 mmol) (*S*)-(+)-**3** in 56 ml THF and solid $NaBH_4$ 1.477 g (39.05 mmol) were slowly added (simultaneously) to a solution of 37% formaldehyde 6.0 ml (208 mmol) and 20% H_2SO_4 5.6 ml in 28 ml THF over a period of 15 min at room temperature. The reaction mixture was stirred for additional 15 min and then was introduced with diluted aqueous KOH to pH 9.0. The resulting suspension was extracted with ethyl acetate three times, and the combined organic layer was washed with brine and dried with anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel to give the dimethyl substituted α-amino ester (*S*)-**4a** as a yellow oil, 754 mg (65%). $[\alpha]_D^{20}$ = +4.7 (*c* 2.84,

$CH_3COOC_2H_5$). ^{1}H NMR (200 M) δ 7.12–7.26 (m, 5H, Ph-H), 3.55 (s, 3H, OCH_3), 3.34–3.41 (dd, 1H, CHN, J = 9.1 Hz, J = 5.9 Hz), 2.95–3.06 (dd, 1H, $PhCH_2$, J = 13.4 Hz), 2.83–2.92 (dd, 1H, $PhCH_2$), 2.34 (s, 6H, NCH_3). IR (KBr) 3085, 3062, 3028, 2946, 2866, 2831, 2786, 1948, 1732, 1603, 1495, 1453, 1355, 1291, 1265, 1211, 1164, 1067, 1030, 979, 749, 699 cm^{-1}. HR-MS for $(C_{12}H_{17}NO_2 + H)^+$, *calcd*.: 208.1332, found: 208.1335.

*4.3.2. (S)-(−)-3-Phenyl-2-(N,N-diethylamino)-propionic acid methyl ester, (**S**)-(−)-**4b***

A pale yellow oil, 62% yield. $[\alpha]_D^{20} = -70.0$ (*c* 2.84, $CH_3COOC_2H_5$). ^{1}H NMR (200 M) δ 7.19–7.28 (m, 5H, Ph-H), 3.61 (s, 3H, CH_3), 3.03–3.14 (dd, 1H, $PhCH_2$, J = 13.4 Hz, J = 8.8 Hz), 2.73–2.94 (m, 4H, $PhCH_2$, CHN, NCH_2, J = 6.2 Hz), 2.54 (dt, 2H, NCH_2, J = 20 Hz, J = 7.0 Hz), 1.035 (t, 6H, CH_3, J = 7.0 Hz). IR (KBr) 3085, 3062, 3027, 2970, 2870, 2837, 1733, 1603, 1495, 1451, 1382, 1283, 1204, 1161, 1113, 1070, 1005, 904, 831, 784, 747, 699, 546 cm^{-1}. HR-MS for $(C_{14}H_{21}NO_2 + H)^+$, *calcd*.: 236.1645, found: 236.1643.

*4.3.3. (S)-(−)-3-Phenyl-2-(N,N-dipropylamino)-propionic acid methyl ester, (**S**)-(−)-**4c***

A pale yellow oil. Yield 68.3%. $[\alpha]_D^{20} = -66.5$ (*c* 12.54, $CH_3COOC_2H_5$). ^{1}H NMR (300 M) δ 7.18–7.28 (m, 5H, Ph-H), 3.61 (s, 3H, OCH_3), 3.56–3.61 (dd, 1H, CHCO, J = 6.3 Hz, J = 9.0 Hz), 3.03–3.10 (dd, 1H, $PhCH_2$, J = 13.5 Hz), 2.81–2.88 (dd, 1H, $PhCH_2$), 2.54–2.63 (m, 2H, NCH_2), 2.38–2.47 (m, 2H, NCH_2), 1.34–1.45 (m, 4H, CH_2), 0.82 (t, 6H, CH_3, J = 7.5 Hz). IR (KBr) 3062, 3027, 2959, 2871, 2822, 2740, 1945, 1734, 1603, 1495, 1459, 1380, 1348, 1280, 1193, 1160, 1090, 1014, 981, 839, 782, 747, 699, 674, 549 cm^{-1}. HR-MS for $(C_{16}H_{25}NO_2 + H)^+$, *calcd*.: 264.1958, found: 264.1957.

*4.4. General procedure for the synthesis of chiral aminoalcohols **5a–5i***

A solution of 414 mg (2 mmol) (*S*)-**4a** in 3 ml ether was added dropwise under argon atmosphere at 0 °C to a solution of RMgBr (10 mmol) in diethyl ether, which was freshly prepared in the usual way. The reaction was then stirred at room temperature over 4 h. When the reaction was complete checked by TLC, cold saturated aqueous NH_4Cl was added dropwise into the mixture under vigorous stirring. Then the mixture was extracted with ether three times. The combined solvent was washed with brine and dried with anhydrous Na_2SO_4, concentrated under reduced pressure and the crude aminoalcohol was purified by column chromatography with petroleum ether and ethyl acetate as mobile phase.

*4.4.1. (S)-(−)-2-Methyl-4-phenyl-3-(N,N-dimethylamino) butan-2-ol, (**S**)-(−)-**5a***

A pale yellow oil, 55.3% yield. $[\alpha]_D^{20} = -34.0$ (*c* 2.34, $CH_3COOC_2H_5$). ^{1}H NMR (300 M) δ 7.21–7.29 (m, 5H, Ph-H), 2.70–2.91 (m, 3H, $PhCH_2$, CHN), 2.32 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.17 (s, 3H, CH_3). IR (KBr) 3438 (br.), 3061, 3026, 2971, 2935, 2835, 2789, 1603, 1494, 1457, 1384, 1363, 1290, 1265, 1173, 1155, 1062, 1026, 974, 934, 893, 867, 842, 779, 730, 698, 566 cm^{-1}. HR-MS for $(C_{13}H_{21}NO + H)^+$, *calcd*.: 208.1696, found: 208.1691.

*4.4.2. (S)-(−)-3-Ethyl-1-phenyl-2-(N,N-dimethylamino) pentan-3-ol, (**S**)-(−)-**5b***

A pale yellow oil, 100% yield. $[\alpha]_D^{19} = -15.0$ (*c* 1.83, $CH_3COOC_2H_5$). ^{1}H NMR (200 M) δ 7.14–7.22 (m, 5H, Ph-H), 3.6 (br, 1H, OH), 2.95–3.02 (dd, 1H, CHN, J = 4.3 Hz, J = 9.6 Hz), 2.63–2.79 (dq, 2H, $PhCH_2$), 2.23 (s, 6H, CH_3), 1.15–1.76 (m, 4H, CH_2Me), 0.869 (t, 3H, CH_3, J = 7.2 Hz), 0.856 (t, 3H, CH_3, J = 7.2 Hz). IR (KBr) 3441 (br.), 3084, 3062, 3026, 2965, 2937, 2790, 1603, 1495, 1475, 1397, 1373, 1348, 1322, 1292, 1262, 1176, 1156, 1129, 1070, 1042, 1024, 979, 954, 767, 726, 699, 564 cm^{-1}. HR-MS for $(C_{15}H_{25}NO + H)^+$, *calcd*.: 236.2009, found: 236.2008.

*4.4.3. (S)-(+)-1,1,3-Triphenyl-2-(N,N-dimethylamino) propan-1-ol, (**S**)-(+)-**5c***

A pale yellow oil, 81% yield. $[\alpha]_D^{20} = +32.0$ (*c* 0.85, $CH_3COOC_2H_5$). ^{1}H NMR (200 M) δ 7.45–7.52 (m, 5H, Ph-H), 7.20–7.32 (m, 10H, Ph-H), 3.86–3.92 (d, 1H, CHN, J = 11.8 Hz), 3.03–3.10 (d, 1H, $PhCH_2$, J = 14.6 Hz), 2.65–2.78 (dd, 1H, $PhCH_2$, J = 14.6 Hz), 1.98 (s, 6H, CH_3). IR (KBr) 3314 (br.), 3085, 3059, 3026, 2933, 2844, 2792, 1600, 1494, 1471, 1448, 1370, 1287, 1265, 1160, 1069, 1032, 946, 911, 758, 741, 725, 699 cm^{-1}. HR-MS for $(C_{23}H_{25}NO + H)^+$, *calcd*.: 332.2009, found: 332.2014.

*4.4.4. (S)-(−)-3-Propyl-1-phenyl-2-(N,N-dimethylamino) hexan-3-ol, (**S**)-(−)-**5d***

A pale yellow oil, 49% yield. $[\alpha]_D^{20} = -6.0$ (*c* 1.76, $CH_3COOC_2H_5$). ^{1}H NMR (200 M) δ 7.26–7.29 (m, 5H, Ph-H), 2.93–3.00 (dd, 1H, $PhCH_2$, J = 13.0 Hz), 2.81–2.86 (dd, 1H, $PhCH_2$, J = 9.6 Hz), 2.77–2.79 (dd, 1H, CHN, J = 4.4 Hz), 2.309 (s, 3H, CH_3), 2.300 (s, 3H, CH_3), 1.17–1.42 (m, 8H, CH_2), 0.85–0.92 (m, 6H, CH_3). IR (KBr) 3457, 3288, 3062, 3026, 2957, 2933, 2871, 2789, 1603, 1494, 1456, 1396, 1375, 1345, 1284, 1253, 1179, 1155, 1127, 1050, 1015, 976, 928, 908, 860, 776, 728, 698, 586 cm^{-1}. HR-MS for $(C_{17}H_{29}NO + H)^+$, *calcd*.: 264.2322, found: 264.2329.

*4.4.5. (S)-(−)-1-(2′-Phenyl-1′-(N,N-dimethylamino) ethyl)-cyclopentanol, (**S**)-(−)-**5e***

A pale yellow oil, 74% yield. $[\alpha]_D^{19} = -15.0$ (*c* 1.0, $CH_3COOC_2H_5$). ^{1}H NMR (200 M) δ 7.28–7.35 (br, 5H, Ph-H), 3.08–3.15 (dd, 1H, CHN, J = 3.8 Hz, J = 9.0 Hz), 2.87–2.99 (dd, 1H, $PhCH_2$, J = 14.2 Hz), 2.60–2.69 (dd, 1H, $PhCH_2$), 2.28 (s, 6H, CH_3), 1.27–1.94 (m, 8H, CH_2). IR (KBr) 3328 (br.), 3083, 3061, 3026, 2954, 2868, 2789, 1602, 1494, 1454, 1384, 1311, 1283, 1167, 1104, 1076, 1046, 1027, 1007, 952, 923, 847, 730, 699 cm^{-1}. HR-MS for $(C_{15}H_{23}NO + H)^+$, *calcd*.: 234.1852, found: 234.1852.

*4.4.6. (S)-(−)-3-Ethyl-1-phenyl-2-(N,N-diethylamino) pentan-3-ol, (**S**)-(−)-**5f***

A pale yellow oil, 92.4% yield. $[\alpha]_D^{19} = -17.1$ (*c* 3.66, $CH_3COOC_2H_5$). ^{1}H NMR (200 M) δ 7.26–7.33 (m, 5H, Ph-H), 3.20–3.27 (dd, 1H, CHN, *J* = 4.4 Hz, *J* = 9.8 Hz), 2.88–3.00 (dd, 1H, $PhCH_2$, *J* = 14.2 Hz), 2.73–2.82 (dd, 1H, $PhCH_2$), 2.73 (br, 2H, NCH_2), 2.37 (br, 2H, NCH_2), 1.52 (q, 2H, CH_2, *J* = 7.2 Hz), 1.26 (q, 2H, CH_2, *J* = 7.0 Hz), 0.94–1.05 (m, 12H, CH_3). IR (KBr) 3451, 3291, 3062, 3026, 2966, 2934, 2878, 1602, 1494, 1455, 1396, 1375, 1316, 1298, 1266, 1201, 1174, 1028, 957, 919, 744, 720, 699, 582 cm^{-1}. HR-MS for $(C_{17}H_{29}NO + H)^+$, *calcd*.: 264.2322, found: 264.2326.

*4.4.7. (S)-(−)-3-Propyl-1-phenyl-2-(N,N-diethylamino) hexan-3-ol, (**S**)-(−)-**5g***

A pale yellow oil, 55% yield. $[\alpha]_D^{19} = -7.0$ (*c* 1.41, $CH_3COOC_2H_5$). ^{1}H NMR (200 M) δ 7.15–7.30 (m, 5H, Ph-H), 4.36 (br, 1H, OH), 3.09–3.16 (dd, 1H, CHN, *J* = 4.5 Hz, *J* = 9.8 Hz), 2.81–2.93 (dd, 1H, $PhCH_2$, *J* = 14.2 Hz), 2.66–2.76 (dd, 1H, $PhCH_2$), 2.66 (br, 2H, NCH_2), 2.28 (br, 2H, NCH_2), 1.14–1.69 (m, 8H, CH_2), 0.81–0.96 (m, 12H, CH_3). IR (KBr) 3304 (br.), 3062, 3026, 2960, 2930, 2870, 1602, 1494, 1455, 1387, 1299, 1257, 1202, 1105, 1063, 1029, 998, 910, 754, 724, 698, 597 cm^{-1}. HR-MS for $(C_{19}H_{33}NO + H)^+$, *calcd*.: 292.2635, found: 292.2644.

*4.4.8. (S)-(−)-3-Ethyl-1-phenyl-2-(N,N-dipropylamino) pentan-3-ol, (**S**)-(−)-**5h***

A pale yellow oil, 75% yield. $[\alpha]_D^{21} = -27.0$ (*c* 2.60, $CH_3COOC_2H_5$). ^{1}H NMR (300 M) δ 7.16–7.30 (m, 5H, Ph-H), 4.43 (br, 1H, OH), 3.12–3.16 (dd, 1H, CHN, *J* = 4.5 Hz, *J* = 9.6 Hz), 2.86–2.93 (dd, 1H, $PhCH_2$, *J* = 14.3 Hz), 2.69–2.75 (dd, 1H, $PhCH_2$), 2.24 (br, 2H, NCH_2), 1.15–1.51 (m, 10H, CH_2), 0.77–0.96 (m, 12H, CH_3, *J* = 7.2 Hz). IR (KBr) 3307 (br.), 3026, 2962, 2930, 2873, 1496, 1460, 1401, 1376, 1172, 1120, 1078, 1033, 956, 880, 726, 699, 668 cm^{-1}. HR-MS for $(C_{19}H_{33}NO + H)^+$, *calcd*.: 292.2635, found: 292.2642.

*4.4.9. (S)-(−)-3-Propyl-1-phenyl-2-(N,N-dipropylamino) hexan-3-ol, (**S**)-(−)-**5i***

A pale yellow oil, 75% yield. $[\alpha]_D^{21} = -3.0$ (*c* 0.68, $CH_3COOC_2H_5$). ^{1}H NMR (300 M) δ 7.17–7.30 (m, 5H, Ph-H), 4.45 (br, 1H, OH), 3.09–3.14 (dd, 1H, CHN, *J* = 4.5 Hz, *J* = 9.6 Hz), 2.87–2.95 (dd, 1H, $PhCH_2$, *J* = 14.1 Hz), 2.70–2.76 (dd, 1H, $PhCH_2$), 2.23 (br, 2H, NCH_2), 1.58–1.67 (m, 2H, NCH_2), 1.26–1.53 (m, 10H, CH_2), 1.17–1.23 (m, 2H, CH_2), 0.77–0.93 (m, 12H, CH_3). IR (KBr) 3307 (br.), 3062, 3026, 2959, 2931, 2871, 1602, 1494, 1459, 1401, 1382, 1342, 1284, 1173, 1068, 1011, 910, 861, 729, 699, 603 cm^{-1}. HR-MS for $(C_{21}H_{37}NO + H)^+$, *calcd*.: 320.2948, found: 320.2956.

4.5. Typical procedure of asymmetric addition of diethylzinc to aldehydes

To a solution of chiral β-aminoalcohol **5b** (4.7 mg, 0.02 mmol) in hexane (1.0 ml) was added dropwise a solution of diethylzinc (1.0 ml, 1.0 M in hexane) at 0 °C. After stirring for 30 min, benzaldehyde (53 mg, 0.50 mmol) was added at 0 °C, and the reaction was continued to stirred under the same condition until the reaction was complete checked by TLC. The reaction mixture was quenched by 5% cold aqueous HCl solution and extracted with ether. The combined organic extracts were washed with little brine, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure to give an oily residue. The residue was analyzed with HPLC to give the yield and ee value.

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