Chirality Control by Substituents in the Asymmetric Addition of Et_2Zn to Aromatic Aldehydes Catalyzed by *cis*-(1*R*,2*S*)-2-Benzamidocyclohexanecarboxylic Acid Derived 1,3-Aminoalcohols

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A series of novel optically active 1,3-aminoalcohols based on *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid and *trans*-(1*R*,2*R*)-2-benzamidocyclohexanecarboxylic acid were synthesized and used in the asymmetric diethylzinc addition to aromatic aldehydes. Not only the enantioselectivity but also the stereochemistry of the product were controlled by the *N*-substituents and the substituents on the vicinity carbon to hydroxyl group of the *cis*-derivatives.

Keywords chirality control, asymmetric addition, aldehyde, *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid, 1,3-aminoalcohols

Introduction

Since the enantioselective addition of diethylzinc to aldehydes was first reported by Oguni and Omi in 1984,[1] various types of ligands, such as aminothiols,[2] sulfonamides,[3] aminophenols,[4] amides,[5] diamines[6] and diols[7] were synthesized and successfully applied.[8] Therefore, in return, the asymmetric addition of diethylzinc to aldehydes became one of the most common reactions for testing the effectiveness of newly developed chiral ligands.

Among the chiral ligands studied, aminoalcohols are particularly attractive due to their high catalytic activity and excellent enantioselectivity. In the past twenty years, a variety of chiral 1,2-aminoalcohols have been developed and showed excellent enantioselectivity.[9] Whereas, 1,3-aminoalcohols have been studied relatively too less and it is interesting and challenging to examine the chiral controllability.[10] Thus we decided to synthesize some new enantiopure 1,3-aminoalcohols derived from 2-benzamidocyclohexanecarboxylic acid, and studied their catalytic ability in the asymmetric addition of diethylzinc to aromatic aldehydes.

Results and discussion

Synthesis of enantiopure 1,3-aminoalcohols

In our synthetic routes, commercially available chiral ligand, *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid (**1**) and *trans*-(1*R*,2*R*)-2-benzamidocyclohexanecarboxylic acid (**2**) were chosen as the starting materials, which can be easily converted into appropriately substituted 1,3-aminoalcohols as follows (Scheme 1).

First, *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid was reduced with $LiAlH_4$ in tetrahydrofuran to give aminoalcohol **3**[11] in good yield. After debenzylation of **3** by catalytic hydrogenolysis under atmospheric pressure of H_2 over 10% Pd/C,[12] primary amine **4**[13] was obtained in high yield. Cycloalkylation reaction of **4** with 1,4-dibromobutane afforded **5** in 62.9% yield. In addition, **3** was treated with iodomethane and NaOH in methanol, then reduced with $LiAlH_4$ to give tertiary amine **6** (89.3% yield). Thus, four primary alcohols with different *N*-substituents (**3**—**6**) were easily prepared.

In order to introduce bulkiness to the vicinity of hydroxyl group, **1** was quantitatively esterified and subjected to Grignard reaction with PhMgBr, and then to reduction of amide group providing aminoalcohol **8** with two phenyl groups in high yield. Debenzylation of **8** gave the primary amine **9** as a white solid (87.5% yield) and cyclic tertiary amine **10** was obtained in 31.2% yield after cycloalkylation of **9**.[14]

On the other hand, **12**, the *trans*-isomer of **8**, was synthesized from **2** following the same procedure applied to **8** in 53.5% overall yield.

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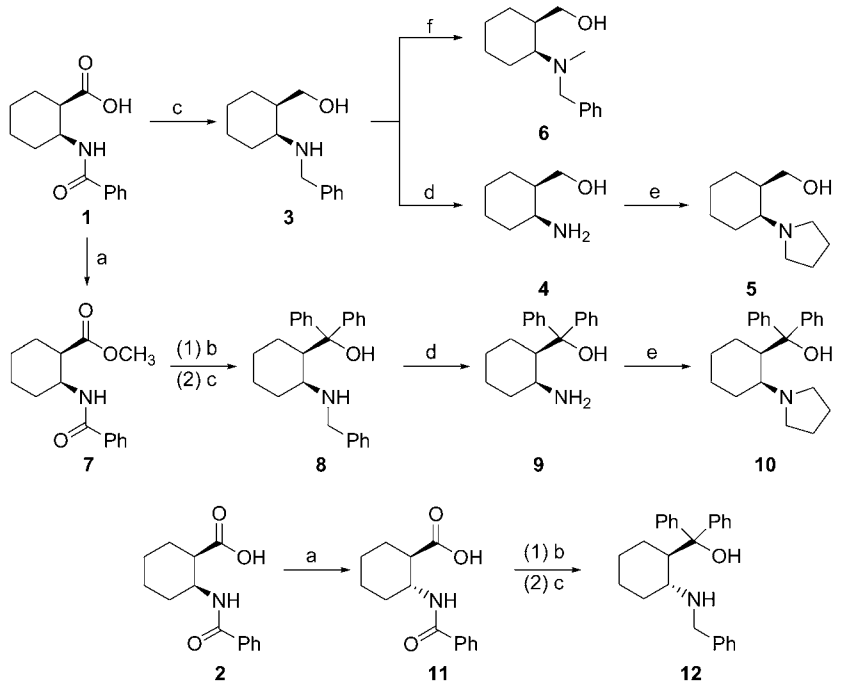
Scheme 1



Reagents and conditions: (a) conc. H_2SO_4, MeOH, reflux; (b) 5 equiv. PhMgBr/dry THF, reflux; (c) $LiAlH_4$, dry THF, reflux; (d) 10% Pd/C, H_2, EtOH, 70 ℃; (e) $Br(CH_2)_4Br$, Et_3N, DMF, 60 ℃; (f) i) MeI, NaOH, MeOH, r.t.; ii) $LiAlH_4$, dry THF, reflux

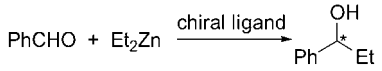
Enantioselective addition of diethylzinc to benzaldehydes and enantioselecitiviy using chiral 1,3-aminoalcohols

In order to examine the chiral induction abilities of chiral 1,3-aminoalcohols (**3**—**6**, **8**—**10**, **12**), we explored the enantioselective addition reaction of diethylzinc to benzaldehydes in the presence of 10 mol% of these ligands and the results are summarized in Table 1. The structural study has revealed that the enantiomeric excess changed with the number and the size of *N*-substituents; that is, secondary amines (**3** and **8**) worked as better ligands than primary amines (**4** and **9**), respectively, and **8** yielded better chemical yield than tertiary amines (**5** and **6**). However tertiary amine with a cyclic structure, **5**, showed the best chiral induction ability (71.2% *ee*) in the ligands studied.

On the other hand, increasing the steric bulkiness at the *α*-position of hydroxyl group also improved the enantioselectivity, that is, when two phenyl groups were introduced to the vicinity of hydroxyl group (**3** vs. **8**, **4** vs. **9**), the enantiomeric excess increased from 33.0% to 65.5% *ee* and 9.8% to 58.9% *ee* (Table 1, Entries 1 vs. 5, 2 vs. 6). However, *trans*-derivative **12** showed the lowest enantioselectivity due to its *trans*-configuration, which will be discussed later.

The most interesting feature of the present system is that both (*R*)- and (*S*)-1-phenyl-1-propanol were provided depending on the substituents in spite of the same chirality of the ligand, (1*R*,2*S*), derived from **1**: primary alcohols with tertiary amino groups, **5** and **6**, gave (*R*)-isomer (Table 1, Entries 3 and 4) while primary and secondary amines, **3**, **4**, and **9**, and tertiary alcohols, **8**—**10**, afforded (*S*)-isomer (Table 1, Entries 1, 2, and 5—7).

Table 1 Enantioselective addition of diethylzinc to benzaldehyde catalyzed by various chiral ligands[a]



Entry	Ligand	Time/h	Yield[b]/%	*ee*[c]/%	Config.[c]
1	**3**	60	11.5	33.0	*S*
2	**4**	70	13.0	9.8	*S*
3	**5**	40	30.1	71.2	*R*
4	**6**	40	13.2	58.1	*R*
5	**8**	20	68.5	65.5	*S*
6	**9**	60	46.0	58.9	*S*
7	**10**	18	63.6	27.2	*S*
8	**12**	30	46.5	7.7	*S*

[a] All reactions were carried out in dry *n*-hexane-toluene (2∶3, *V*/*V*) at 0 ℃. Aldehyde/Et_2Zn/chiral ligand=1/3/0.1 (molar ratio); Et_2Zn (1 mol•L^{-1} solution in *n*-hexane). [b] Isolated yield. [c] See the experimental.

The substituent effect and chirality inversion can be explained by the transition state model proposed by some researchers for 1,3-aminoalcohols,[10b,10g,10h] which also corresponds to that by Noyori *et al.*[15] for 1,2-aminoalcohols (Figures 1 — 4). Supposing the *anti*-6/4/4 tricyclic transition state, the cyclohexane ring plays an important role in primary and secondary amine ligands. As an example, *anti*-(*Si*) and *anti*-(*Re*) transi-

tion states for the alkylation using **3** are compared in Figure 1. In the *anti*-(*Re*) form, large steric repulsion between the cyclohexane ring and the Et group is expected due to the 1,3-diaxial relationship in the six-membered Zn-chelate ring while the *anti*-(*Si*) form avoids such repulsion to afford (*S*)-1-phenyl-1-propanol (33.0% *ee*, Table 1, Entry 1).

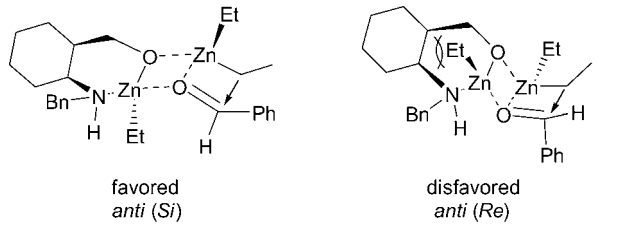


Figure 1 Proposed transition states for the alkylation using **3**.

In addition, it was shown that secondary amines, **3** and **8**, provided better *ee* values than the corresponding primary amines, **4** and **9**, (**3** [33.0% *ee*] vs. **4** [9.8% *ee*] and **8** [65.5% *ee*] vs. **9** [58.9% *ee*]). The result seems to suggest one *N*-substituent favours the pseudo-equatorial position stabilizing the *anti*-(*Si*) form.

More rigid and bulky cyclic tertiary amine **5**, however, should have much larger steric repulsion with the Et group on Zn in 1,2-relationship of the *anti*-(*Si*) form than that with the cyclohexane ring in 1,3-relationship of the *anti*-(*Re*) (Figure 2). As a result, (*R*)-1-phenyl-1-propanol was obtained in a high enantiomeric excess, 71.2% *ee* (Table 1, Entry 3). Similarly another tertiary amine **6** gave the same stereoselectivity but more flexible structure (benzyl methylamine) seemed to lead to lower enantioselectivity of 58.1% *ee* (Table 1, Entry 4).

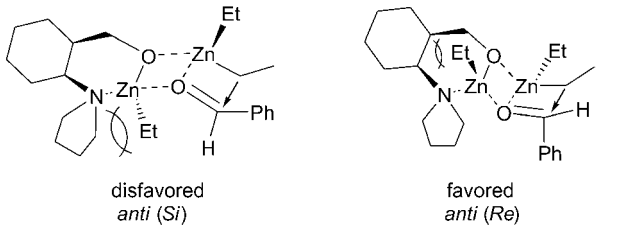


Figure 2 Proposed transition states for the alkylation using **5**.

Similar and interesting chirality inversion by *N*-substituent-effect has been observed for 1,3-aminoalcohols derived from α-pinene by Szakonyi *et al.*[10i] Their primary and tertiary amines gave 1-phenyl-1-propanol of the same chirality (40% & 62% *ee*) with those obtained by **4**, **5**, and **6** (9.8%—71% *ee*). On the other hand, their secondary amine gave the opposite chirality (13% *ee*) to that obtained by **3** (33% *ee*). While the cyclohexyl ring is the common structural feature, the bridging methylene might cause the difference due to its effect on the transition state geometry for the α-pinene derived ligands.[10i]

On the other hand, the bulkiness of the hydroxyl group also affected the stereochemistry of alkylation. When tertiary alcohol **8** was used as a chiral ligand, additional repulsion between the Ph group and the Et group on Et_2Zn for alkylation further destabilized the *anti*-(*Re*) form (Figure 3). As a result, **8** gave higher (*S*)-selectivity (65.5% *ee*, Table 1, Entry 5) than **3** (33.0% *ee*).

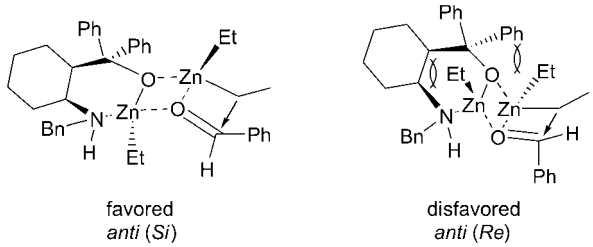


Figure 3 Proposed transition states for the alkylation using **8**.

Chirality change by the substitution on the α-carbon of hydroxyl group of 1,3-aminoalcohols has been reported by Cicchi *et al.*[10e] In their system, diphenyl methanol and 9-hydroxy fluorene moieties caused opposite chirality in the product. Although similar substitution effect on the α-carbon of hydroxyl group has been also observed for chiral 1,2-aminoalcohol ligands,[9c] there are only limited systems reported for the chirality inversion by this kind of substituent-effect. Considering the diversity of structural modification, chiral 1,3-aminoalcohols would be interesting scaffolds for asymmetric reactions.[4,10e,10f,10i]

In the case of **12**, the *trans*-(1*R*,2*R*)-configuration allows much less strained transition states than the *cis*-derivatives; that is, the steric repulsion of the substituents on the six-membered chelate ring is largely relieved and the cyclohexane ring has little effect on stereocontrol (Figure 4). Consequently, both *anti*-(*Si*) and *anti*-(*Re*) transition states have similar stability showing the least enantioselectivity (7.7% *ee*, Table 1 Entry 8).

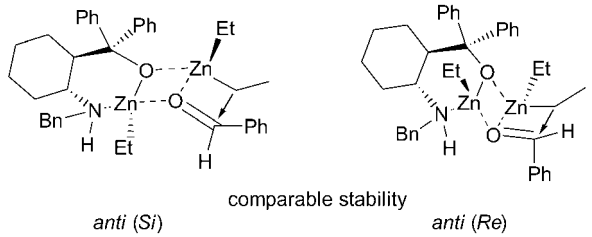


Figure 4 Proposed transition states for the alkylation using **12**.

Enantioselective addition of diethylzinc to various aldehydes

In order to optimize the reaction, the solvent, temperature and ligand loading effects were examined and the results are shown in Table 2. Apparently less-polar solvents (Entries 1 & 2) gave better chemical yield and enantiomeric excess than polar ethers (Entries 3 & 4),

especially in THF (26.8% *ee*). Many studies have shown that toluene or *n*-hexane-toluene mixture is a proper solvent system to provide higher enantioselectivity[9c-e,9j,9k] so that the ratio of this mixed solvent system was changed in our study as well. Although the ratio of *n*-hexane to toluene had less effect on the chiral control, the yield was observably enhanced when only *n*-hexane was used (Entries 5 vs. 7, 9 vs. 10). At the same time, the effect of the amount of chiral ligand on the enantioselectivity was investigated by the use of **5**. Although the reaction proceeded with 10 mol% ligand loading, the enantioselectivity and the yield were gradually improved by increasing the amount of **5** from 10 to 20 and 30 mol% (Entries 1, 5 & 9).

When the reaction was carried out at different temperatures, we found a large effect on the conversion and the enantioselectivity. The best result was obtained at 0 ℃ and either lower or higher temperature decreased both the chemical yields and *ee* values (Table 2, Entries 6—8). Similar results on the temperature effect were observed by other researchers.[4c,5b,7c,16].

Considering the results shown in Table 2, we investigated the ligand effect on the chiral induction in the presence of 20 mol% of **5** and **8** for not only various aromatic aldehydes having an electron donating or withdrawing group but also heteroaromatic and aliphatic aldehydes. The results are summarized in Table 3. The enantioselectivity observed in Table 1 was confirmed for all aromatic aldehydes: **5** gave (*R*)-1-aryl-1-propanol while **8** afforded (*S*)-enantiomer in good yields. In addition, little substituent effect was observed for the *meta*- or *para*-substituted benzaldehydes on both chemical yield and enantioselectivity. However, the *ortho*substituent, especially an *ortho*-bromo substituent, decreased the enantioselectivity. The substituent effect on the substrate needs to be further investigated since the present result is in accordance with the results reported by Yang *et al*.,[4a,4b] Sun *et al*.,[17a] and Jaworska *et al*.,[17b] but is opposite to the results reported by Joshi *et al*.[9i]

Among the heteroaromatic aldehydes, a similar result was obtained for furan-2-carboxaldehyde (Entry 8) but lower enantioselectivity was obtained for thiophene-2-carboxaldehyde (Entries 9 and 17). The heteroatom might be the cause as commented by Noyori *et al*.[15a] On the other hand, the present system was not effective for aliphatic aldehydes as complex product mixtures were obtained for three aliphatic aldehydes examined (Entries 10—12). Comparing 1,2-aminoalcohol ligands, a more flexible 6/4/4 tricyclic transition state might be the cause of this limitation. Further control of molecular design is necessary to the present ligand structure.

Conclusion

We have synthesized a series of novel optically active 1,3-aminoalcohols from *cis*-(1*R*,2*S*)-2-benzamidocyclohexanecarboxylic acid **1**. The structural characteristics of the chiral ligands were explored in asymmetric diethylzinc addition to various aldehydes. The results demonstrated that the cyclohexane ring, *N*-substituents and the substituents to the vicinity of hydroxyl group have crucial effect on chirality control. Providing the rigid and bulky cyclic tertiary amine **5** showed the best promoting ability to aromatic aldehydes with (*R*)-selectivity (79.4% *ee*) in the ligands studied in this article. With two phenyl groups to provide the proper steric bulkiness, the tertiary alcohol **8** showed the opposite (*S*)-selectivity (66.0% *ee*). Further studies on chiral control and versatility are currently underway by 1,3-aminoalcohol ligands derived from **1**.

Experimental

General

All the asymmetric addition reactions of diethylzinc to aldehydes were carried out under nitrogen in anhydrous solvents. NMR spectra were obtained at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) on a Bruker DPX400 spectrometer (Molecular Analysis and Life Science Center, Saitama University) using $CDCl_3$ as the solvent. Optical rotations were measured with a JASCO

Table 2 Optimization of the reaction conditions[a]

Entry	**5**/mol%	Solvent	Time/h	*T*/℃	Yield[b]/%	*ee*[c]/%	Config.[c]
1	20	*n*-Hexane	40	0	69.3	71.0	*R*
2	20	CH_2Cl_2	40	0	49.2	51.0	*R*
3	20	Et_2O	40	0	28.0	30.2	*R*
4	20	THF	40	0	19.8	26.8	*R*
5	10	*n*-Hexane	40	0	40.8	63.3	*R*
6	10	H/T,[d] 2∶3	60	r.t.	26.9	33.5	*R*
7	10	H/T, 2∶3	40	0	30.1	71.2	*R*
8	10	H/T, 2∶3	25	−18	2.5	—	—
9	30	*n*-Hexane	40	0	72.1	79.4	*R*
10	30	H/T, 2∶3	20	0	45.5	76.1	*R*

[a] Aldehyde/Et_2Zn=1∶3 (molar ratio); Et_2Zn (1 mol•L^{-1} solution in *n*-hexane). [b] Isolated yield. [c] See the experimental. [d] The volume ratio of *n*-hexane to toluene.

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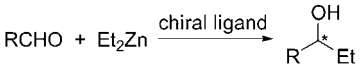
Table 3 Asymmetric addition of diethylzinc to aldehydes in the presence of **5** or **8**[a]



Entry	Ligand	Aldehyde	Yield[b]/%	*ee*[c]/%	Config.[c]
1	**5**	*p*-ClC_6H_4CHO	62.0	65.6	*R*
2	**5**	*p*-MeC_6H_4CHO	56.0	63.6	*R*
3	**5**	*m*-ClC_6H_4CHO	72.5	75.4	*R*
4	**5**	*m*-MeC_6H_4CHO	68.8	75.0	*R*
5	**5**	*o*-BrC_6H_4CHO	58.6	32.6	*R*
6	**5**	*o*-ClC_6H_4CHO	51.1	38.1	*R*
7	**5**	*o*-MeC_6H_4CHO	64.8	53.4	*R*
8	**5**	Furan-2-carboxaldehyde	70.4	52.0	*R*
9	**5**	Thiophene-2-carboxaldehyde	57.1	47.5	*R*
10	**5**	Isobutyraldehyde	Trace	—	—
11	**5**	Hexanal	Trace	—	—
12	**5**	Cyclohexanecarbaldehyde	Trace	—	—
13	**8**	*p*-ClC_6H_4CHO	77.3	60.1	*S*
14	**8**	*p*-MeC_6H_4CHO	81.0	55.8	*S*
15	**8**	*m*-ClC_6H_4CHO	78.3	66.0	*S*
16	**8**	*m*-MeC_6H_4CHO	82.5	61.1	*S*
17	**8**	Thiophene-2-carboxaldehyde	60.6	27.3	*S*

[a] All reactions were carried out in dry *n*-hexane at 0 ℃ for 72 h. Aldehyde/Et_2Zn/chiral ligand＝1/3/0.2 (molar ratio); Et_2Zn (1 mol•L^{-1} solution in *n*-hexane). [b] Isolated yield. [c] See the experimental.

DIP-370 polarimeter. Melting points were obtained using a Mitamura Riken Kogyo MEL-TEMP instrument and uncorrected. IR spectra were recorded on a JASCO FT/IR 400. Enantiomeric excess was determined using a set of JASCO LC 900 series with Chiralcel OB-H or OJ columns (Daicel Chemical Industries, Ltd.). The starting material **1** is commercially available while **2** was prepared according to the literature.[18]

Synthesis of (1*R*,2*S*)-2-benzylaminocyclohexylmethanol (3)

To a suspension of $LiAlH_4$ (1.2 g, 31.62 mmol) in dry THF (20 mL) was added slowly a solution of **1** (2.49 g, 10.07 mmol) in THF (30 mL). After refluxing for 24 h, the reaction was cautiously quenched with water and the mixture was further treated with 20% NaOH aq. solution. The precipitate was filtered off and washed with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. After purification by column chromatography (silica gel, *n*-hexane/ethyl acetate＝1/1—0/1, *V*/*V*), **3** was obtained as a white solid (2.01 g, 91.0%). m.p. 68—68.5 ℃, $[\alpha]_D^{25}$ −24.0 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.35—7.14 (m, 5H), 6.25—5.65 (br, 1H), 3.94—3.87 (m, 1H), 3.82 (d, *J*＝8.90 Hz, 2H), 3.73—3.71 (m, 1H), 3.00—2.98 (m, 1H), 1.91—1.90 (m, 2H), 1.65—1.36 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 149.7, 128.6, 128.3, 127.2, 66.4, 58.7, 51.7, 39.0, 27.8, 25.9, 23.5, 22.6; IR (KBr) *v*: 3297, 3198, 3065, 3027, 2925, 2844, 1499, 1483, 1462, 1448, 1370, 1348, 1333, 1251, 1228, 1203, 1188, 1143, 1105, 1080, 1065, 1033, 966, 914, 899, 864, 840, 805, 748, 696, 628, 607, 475 cm^{-1}; HRMS (ESI^+) calcd for $C_{14}H_{21}NOH^+$ 220.1696, found 220.1615.

Synthesis of (1*R*,2*S*)-2-aminocyclohexylmethanol (4)

The mixture of **3** (1.80 g, 8.22 mmol) and 10% Pd/C (0.18 g) in ethanol (40 mL) was stirred under hydrogen (1×10^5 Pa) at 70 ℃ or 24 h. After cooling to room temperature, Pd/C was filtered off and the solvent was removed under reduced pressure to afford **4** as a white solid (1.06 g, 94.4%), which could be used directly in the next step without further purification. m.p. 60—62 ℃, $[\alpha]_D^{19}$ +16.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 3.81—3.70 (m, 2H), 3.27—3.25 (m, 1H), 3.21—2.85 (br, 3H), 1.73—1.70 (m, 1H), 1.60—1.44 (m, 7H), 1.36—1.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 66.3, 51.0, 41.1, 33.0, 24.6, 24.2, 21.3; IR (KBr) *v*: 3445, 3335, 2934, 2846, 2175, 1630, 1556, 1489, 1464, 1386, 1355, 1335, 1303, 1256, 1217, 1196, 1140, 1105, 1092, 1059, 1047, 1026, 975, 960, 937, 904, 882, 815, 802, 783, 718, 644, 586, 539, 498 cm^{-1}; HRMS (ESI^+) calcd for $C_7H_{15}NOH^+$ 130.1226, found 130.1278.

Synthesis of (1*R*,2*S*)-2-pyrrolidin-1'-ylcyclohexylmethanol (5)

Chiral aminoalcohol **4** (0.49 g, 3.90 mmol), Et_3N (0.79 g, 7.80 mmol) and 1,4-dibromobutane (0.84 g, 3.90 mmol) were dissolved in DMF (5 mL), and stirred at 60 ℃ for 36 h. After chloroform (30 mL) was added,

the mixture was washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude product was purified by column chromatography (Al_2O_3, *n*-hexane/ethyl acetate = 1/1, *V*/*V*) to afford **5** (0.45 g, 62.9%) as a light yellow liquid. $[\alpha]_D^{26}$ +21.4 (*c* 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.20—4.10 (m, 1H), 3.48—3.44 (m, 1H), 2.87—2.58 (m, 2H), 2.57—2.39 (m, 2H), 2.38—2.31 (m, 2H), 1.76—1.59 (m, 7H), 1.49—1.46 (m, 1H), 1.38—1.15 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 67.9, 64.0, 52.2, 36.2, 28.1, 25.8, 25.7, 23.0, 20.7; IR (KBr) *v*: 3437, 3393, 3318, 2934, 2856, 2778, 2708, 1654, 1445, 1408, 1126, 1107, 1036, 953, 915, 888 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{11}H_{21}NOH^+$ 184.1696, found 184.1673.

Synthesis of (1*R*,2*S*)-2-[benzyl(methyl)amino]cyclohexylmethanol (6)

To a methanol solution (15 mL) of **3** (0.58 g, 2.64 mmol), iodomethane (3.75 g, 26.45 mmol) and NaOH (0.21 mg, 5.29 mmol) were added and the reaction mixture was stirred at room temperature for 48 h. After removal of the solvent, the residue was dissolved in 20 mL of chloroform, washed with water, dried over anhydrous Na_2SO_4, and then concentrated to dryness. Reduction of the white residue with $LiAlH_4$ followed the procedure similar to that for **3** gave **6** as a colorless liquid (0.55 g, 89.3%). $[\alpha]_D^{19}$ +23.0 (*c* 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33—7.25 (m, 5H), 4.33—4.27 (m, 1H), 3.75 (d, *J* = 12.58 Hz, 1H), 3.61—3.52 (m, 2H), 2.63—2.56 (m, 2H), 2.15 (s, 3H), 1.97—1.89 (m, 2H), 1.75—1.63 (m, 2H), 1.49—1.44 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.4, 129.2, 128.5 127.2, 67.1, 64.1, 59.3, 39.0, 35.4, 28.6, 26.2, 24.6, 20.8; IR (KBr) *v*: 3399, 2930, 2854, 2786, 1495, 1451, 1421, 1375, 1347, 1323, 1253, 1229, 1121, 1069, 1038, 995, 909, 882, 853, 745, 700 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{15}H_{23}NOH^+$ 234.1852, found 234.1352.

Synthesis of methyl (1*R*,2*S*)-2-benzamidocyclohexanecarboxylate (7)

To a dry methanol solution (10 mL) of **1** (0.99 g, 4 mmol), was added concentrated H_2SO_4 (32 mg, 0.32 mmol) and the reaction mixture was refluxed for 12 h. After concentration, the residue was dissolved in chloroform (30 mL), washed with water, and dried over anhydrous Na_2SO_4. Removal of the solvent afforded **7** as a white solid (1.04 g, 99.1%), which could be used directly in the next step. m.p. 80—81.5 ℃, $[\alpha]_D^{26}$ −45.0 (*c* 0.7, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.79—7.79 (m, 2H), 7.51—7.41 (m, 3H), 7.26 (s, 1H), 4.38—4.31 (m, 1H), 3.54 (s, 3H), 2.93—2.91 (m, 1H), 2.20—2.17 (m, 1H), 1.85—1.64 (m, 4H),1.58—1.47 (m, 2H), 1.32—1.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.9, 166.3, 134.8, 131.3, 128.5, 126.9, 51.8, 48.3, 44.4, 29.4, 27.5, 24.3, 22.5; IR (KBr) *v*: 3321, 3060, 3029, 1727, 1636, 1604 1579, 1534, 1490, 1449, 1396, 1337, 1313, 1277, 1261, 1203, 1132, 1120, 1079, 1028, 1004, 962, 924, 857, 818, 801, 727, 693, 679, 666, 583 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{15}H_{19}NO_3H^+$ 262.1438, found 262.1057.

Synthesis of (1*R*,2*S*)-2-benzylaminocyclohexyl-(diphenyl)methanol (8)

A THF (20 mL) solution of **7** (0.64 g, 16.7 mmol) in a dropping funnel was slowly added to a THF solution of phenyl magnesium bromide (90 mmol) at 0 ℃ for 20 min. The reaction mixture was stirred at room temperature for 0.5 h and then heated to reflux for 12 h. After cooling to room temperature, the reaction was quenched with saturated NH_4Cl aq. solution. The mixture was extracted with ether and the organic layer was dried over anhydrous Na_2SO_4. After the solvent was removed, the crude product was obtained as a light yellow solid, which was recrystallized from ethyl acetate to afford a white crystalline solid (0.49 g, 52.3%) for the use in the next step.

To a suspension of $LiAlH_4$ (0.12 g, 3.16 mmol) in dry THF (15 mL) was added slowly a solution of the alcohol in THF (10 mL). After refluxing for 18 h, the reaction was cautiously quenched with water and the mixture was further treated with 20% NaOH aq. solution. The precipitate was filtered off and washed with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. After purification by column chromatography (silica gel, *n*-hexane/ethyl acetate = 3/1, *V*/*V*), **8** was obtained as a colorless viscous liquid (0.44 g, 93.1%). $[\alpha]_D^{26}$ +85.6 (*c* 2.6, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.54—8.25 (br, 1H), 7.67—7.65 (m, 2H), 7.55—7.52 (m, 2H), 7.34—7.24 (m, 9H), 7.16—7.09 (m, 2H), 3.59 (d, *J* = 12.21 Hz, 1H), 3.24 (d, *J* = 12.10 Hz, 1H), 3.15—2.94 (m, 1H), 2.48—2.44 (m, 1H), 1.92—1.89 (m, 1H), 1.76—1.68 (m, 1H), 1.67—1.46 (m, 4H), 1.44—1.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.1, 146.9, 139.3, 128.6, 128.3, 128.2, 128.0, 127.4, 125.9, 125.8, 125.5, 125.2, 80.6, 54.1, 52.0, 47.3, 28.5, 25.8, 21.6, 20.2; IR (KBr) *v*: 3317, 3075, 3060, 3029, 2926, 2852, 1597, 1491, 1468, 1450, 1432, 1381, 1313, 1242, 1210, 1176, 1136, 1067, 1032, 992, 969, 909, 881, 768, 747, 698, 648, 633, 552 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{26}H_{29}NOH^+$ 372.2322, found 372.2896.

Synthesis of (1*R*,2*S*)-2-aminocyclohexyl (diphenyl)-methanol (9)

The mixture of **8** (0.24 g, 0.65 mmol) and 10% Pd/C (24 mg) in ethanol (20 mL) was stirred under hydrogen (1×10^5 Pa) at 60 ℃ for 24 h. After cooling to room temperature, Pd/C was filtered off and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (Al_2O_3, *n*-hexane/ethyl acetate = 2/1, *V*/*V*) to afford **9** (0.16 g, 87.5%). m.p. 228—230 ℃, $[\alpha]_D^{25}$ −6.65 (*c* 0.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63—7.61 (m, 2H), 7.53—7.51 (m, 2H), 7.30—7.24 (m, 4H), 7.15—7.09 (m, 2H), 3.91—3.00 (br, 2H), 3.15—3.14 (m, 1H), 2.45—2.40 (m, 1H), 1.80—1.70 (m, 1H), 1.64—1.40 (m, 6H), 1.39—1.19 (m,

2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.0, 147.0, 128.1, 128.0, 125.9, 125.8, 125.7, 125.2, 80.5, 47.2, 46.5, 35.4, 26.1, 20.8, 19.5; IR (KBr) v: 3426, 3374, 3313, 3083, 3014, 3013, 2925, 2862, 1598, 1578, 1490, 1459, 1448, 1430, 1387, 1305, 1265, 1246, 1182, 1135, 1063, 1037, 994, 959, 912, 887, 864, 819, 793, 765, 745, 707, 695, 641, 549 cm^{-1}; HRMS (ESI^+) calcd for $C_{19}H_{23}NOH^+$ 282.1852, found 282.1457.

Synthesis of (1*R*,2*S*)-2-pyrrolidin-1'-ylcyclohexyl-(diphenyl)methanol (10)

Chiral aminoalcohol **10** was prepared by the procedure similar to that for the preparation of **5** as a white solid (31.2%). m.p. 143—145 ℃, $[\alpha]_D^{27}$ +4.4 (*c* 0.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.31—8.65 (br, 1H), 7.66—7.64 (m, 2H), 7.54—7.52 (m, 2H), 7.30—7.23 (m, 4H), 7.14—7.08 (m, 2H), 3.19 (s, 1H), 2.92—2.18 (m, 4H), 1.93—1.83 (m, 2H), 1.69—1.49 (m, 8H), 1.43—1.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.3, 147.1, 128.1, 128.0, 125.8, 125.7, 125.5, 125.0, 80.6, 63.7, 54.1, 51.9, 48.0, 29.7, 26.4, 24.4, 22.6; IR (KBr) v: 3426, 3055, 3032, 2952, 2916, 2840, 1596, 1489, 1460, 1447, 1434, 1399, 1343, 1253, 1179, 1143, 1066, 1032, 994, 908, 855, 768, 752, 707, 666, 638, 555 cm^{-1}; HRMS (ESI^+) calcd for $C_{23}H_{29}NOH^+$ 336.2322, found 336.2583.

Synthesis of methyl (1*R*,2*R*)-2-benzamidocyclohexanecarboxylate (11)

By the procedure similar to that for the preparation of **7**, **11** was quantitatively prepared as a white solid (99.0%) and could be used directly in the next step without further purification. m.p. 151—152.5 ℃, $[\alpha]_D^{19}$ −49.2 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.72—7.64 (m, 2H), 7.41—7.33 (m, 3H), 6.11 (s, 1H), 4.12—4.07 (m, 1H), 3.57 (s, 3H), 2.38—2.33 (m, 1H), 2.13—2.11 (m, 1H), 1.93—1.90 (m, 1H), 1.73—1.58 (m, 3H), 1.41—1.37 (m, 1H), 1.23—1.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.3, 166.8, 134.8, 131.4, 128.5, 126.9, 51.9, 50.7, 49.9, 32.8, 28.4, 24.7, 24.5; IR (KBr) v: 3301, 3060, 2948, 2862, 1721, 1637, 1603 1578, 1542, 1491, 1448, 1433, 1372, 1330, 1284, 1248, 1205, 1194, 1179, 1126, 1075, 1049, 1029, 1012, 963, 915, 873, 835, 800, 725, 697, 671, 583 cm^{-1}; HRMS (ESI^+) calcd for $C_{15}H_{19}NO_3H^+$ 262.1438, found 262.1081.

Synthesis of (1*R*,2*R*)-2-benzylaminocyclohexyl-(diphenyl)methanol (12)

Chiral aminoalcohol **12** was prepared by the procedure similar to that for the preparation of **8** as a colorless viscous liquid (54.0%). $[\alpha]_D^{19}$ −102.8 (*c* 1.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.65—10.35 (br, 1H), 7.57—7.49 (m, 2H), 7.42—7.19 (m, 13H), 3.79 (d, J= 12.4 Hz, 1H), 3.54 (d, J=12.4 Hz, 1H), 2.49—2.24 (m, 3H), 1.92—1.62 (m, 3H), 1.35—0.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.3, 145.1, 139.0, 128.7, 128.2, 128.0, 127.7, 127.5, 127.1, 126.8, 126.5, 82.8, 59.2, 51.4, 51.3, 34.7, 30.0, 26.3, 25.8; IR (KBr) v: 3426, 3257, 3086, 3059, 3029, 2932, 2853, 1600, 1581, 1492, 1445, 1356, 1286, 1211, 1140, 1096, 1052, 1032, 1010, 951, 909, 860, 763, 744, 714, 700, 649, 626, 608 cm^{-1}; HRMS (ESI^+) calcd for $C_{26}H_{29}NOH^+$ 372.2322, found 372.2673.

General procedure for the asymmetric addition of diethylzinc to aldehydes[4a,4b]

The chiral 1,3-aminoalcohol (0.03 mmol) was dissolved in *n*-hexane (0.5 mL) at room temperature under nitrogen and diethylzinc (0.9 mmol, 1 mol•L^{-1} in *n*-hexane) was added to this solution. The mixture was cooled to 0 ℃ and stirred for 30 min. Aldehyde (0.3 mmol in 1 mL *n*-hexane) was added to the mixture. After stirring at 0 ℃ for 18—72 h, the reaction was quenched with saturated NH_4Cl aq. solution. The mixture was extracted with diethyl ether, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by thin layer chromatography (silica gel, *n*-hexane/ethyl acetate, V/V=4/1) to give the pure alcohol as a colorless oil. The absolute configuration and the *ee* values were determined by the chiral HPLC analysis[4] and the data are as follows: 1-phenyl-1-propanol; Daicel Chiralcel OB-H, V(*n*-hexane)/V(2-propanol)=90∶10, 0.5 mL/min, 254 nm, t_{R_1}= 11.9 min (*S*-isomer), t_{R_2}=13.5 min (*R*-isomer). 1-(4-Chlorophenyl)-1-propanol; Daicel Chiralcel OJ, V(*n*-hexane)/V(2-propanol)=97∶3, 0.5 mL/min, 254 nm, t_{R_1} = 32.36 min (*S*-isomer), t_{R_2} = 35.46 min (*R*-isomer). 1-(4-Tolyl)-1-propanol; Daicel Chiralcel OJ, V(*n*-hexane)/V(2-propanol)=97∶3, 0.5 mL/min, 254 nm, t_{R_1} = 32.29 min (*S*-isomer), t_{R_2} = 34.33 min (*R*-isomer). 1-(3-Chlorophenyl)-1-propanol; Daicel Chiralcel OB-H, V(*n*-hexane)/V(2-propanol)=90∶10, 0.5 mL/min, 254 nm, t_{R_1}=12.03 min (*S*-isomer), t_{R_2}= 13.69 min (*R*-isomer). 1-(3-Tolyl)-1-propanol; Daicel Chiralcel OB-H, V(*n*-hexane)/V(2-propanol) = 95∶5, 0.5 mL/min, 254 nm, t_{R_1}=12.68 min (*S*-isomer), t_{R_2}= 14.93 min (*R*-isomer). 1-(2-Bromophenyl)-1-propanol; Daicel Chiralcel OB-H, V(*n*-hexane)/V(2-propanol)= 97∶3, 0.5 mL/min, 254 nm, t_{R_1}=16.34 min (*S*-isomer), t_{R_2} = 17.97 min (*R*-isomer). 1-(2-Chlorophenyl)-1-propanol; Daicel Chiralcel OB-H, V(*n*-hexane)/V(2-propanol)=98∶2, 0.5 mL/min, 254 nm, t_{R_1}=18.46 min (*S*-isomer), t_{R_2}=21.00 min (*R*-isomer). 1-(2-Tolyl)-1-propanol; Daicel Chiralcel OB-H, V(*n*-hexane)/V(2-propanol)=98∶2, 0.5 mL/min, 254 nm, t_{R_1}=20.92 min (*S*-isomer), t_{R_2} = 24.41 min (*R*-isomer). 1-(2-Thienyl)-1-propanol; Daicel Chiralcel OD, V(*n*-hexane)/V(2-propanol) = 99.5∶0.5, 1.5 mL/min, 230 nm, t_{R1}=24.55 min (*R*-isomer), t_{R_2}=27.16 min (*S*-isomer). 1-(2-Furyl)-1-propanol; Daicel Chiralcel OD, V(*n*-hexane)/V(2-propanol) = 99.5∶0.5, 1.5 mL/min, 230 nm, t_{R1}=20.17 min (*R*-isomer), t_{R2}=23.55 min (*S*-isomer).

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