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A convenient synthesis of piperidine-based β-amino alcohols from L-Phe and highly enantioselective addition of diethyl zinc to aldehydes

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Abstract—β-Amino alcohols **4a**–**e** were easily prepared from L-phenylalanine in three simple straightforward steps. The key intermediate compound (*S*)-**3** was achieved in high yield (up to 92%) with glutaraldehyde and $NaBH_4/H_2SO_4$ in THF at room temperature. These five ligands were applied to catalyze enantioselective addition of diethyl zinc to aldehydes, high asymmetric induction was observed with **4c** and **4e**, and the ee value was up to 98%. The effect of the substitutes on the nitrogen atom was also observed via comparing piperidine-based amino alcohols with pyrrolidine-based similar ligands.

1. Introduction

Among the numerous methods available for C–C bond formation, the enantioselective addition of organozinc to aldehydes appears to be one of the most useful methods and remains the focus of much research activity as evidenced by hundreds of research papers and several review articles.[1,2] Our group have continuously centered our interest on developing efficient chiral catalysts with cheap starting materials as well as easy and straightforward synthetic methods via short steps.[3] Natural amino acids form one of the best and the cheapest available chiral pools and many chiral ligands have been developed from them.[4] Herein we report our preparation of piperidine-based β-amino alcohols conveniently as well as efficiently from L-phenylalanine and its application to highly enantioselective addition of diethyl zinc to aldehydes.

2. Results and discussion

The azacyclo β-amino alcohols are among the most efficient chiral ligands reported in this catalytic asymmetric reaction,[5] and many of them were derived from amino acids.[3a,4a] The aza ring is usually synthesized with diiodoalkanes and potassium carbonate in MeCN.[6] By this method, however, the yields of the azacyclo products are always low. Furthermore, the diiodoalkanes are expensive and unstable.

In searching for a good substituent synthetic method, we observed that Vyskočil et al.[7] had reported an efficient way for the synthesis of C_2-chiral *N*-alkylated NOBIN, which used reductive alkylation with a series of ketones and $NaBH_4/H_2SO_4$ in THF at room temperature within only 15–30 min. But we could not find examples of this protocol employed to the alkylamine for azacircle synthesis. Although some results had been disclosed using similar reductive alkylation method to prepare the pyrrolidine or piperidine ring with sodium cynoborohydride under acidic circumstances, that reported process covered longer reaction time and did not achieve so high yield as this novel method.[8] In spite of this, we decided to make an effort to our designed amino alcohols with this process. If successful, this protocol would open a straightforward entry into many piperidine-based amino alcohols derived from amino acids. After several trials, this method proved to be very successful and efficient (Scheme 1). After the typical methyl esteration of L-phenylalanine, (*S*)-**2** in THF and solid $NaBH_4$ were simultaneously introduced into the reaction bottle containing 20% H_2SO_4 and glutaric dialdehyde at ambient temperature. This reductive alkylation afforded the desired piperiding-containing compound (*S*)-**3** in 92% yield within 30 min.[9] The successively reaction of the Grignard reagents with (*S*)-**3** achieved amino alcohols **4a**–**d**[10] in 60–92% yields.

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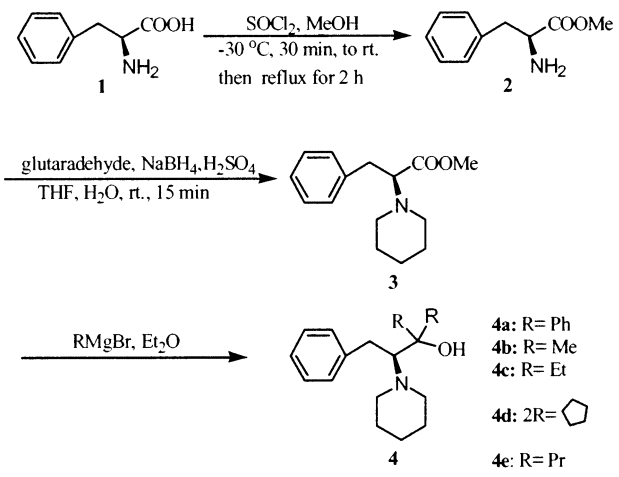


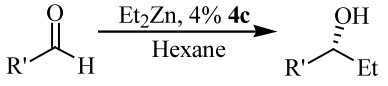
Scheme 1. Preparation of β-amino alcohols from L-Phe.

Ligands (*S*)-**4a–d** were initially tested in the asymmetric addition of diethyl zinc to benzaldehyde (Table 1). The results showed that ligands **4a** and **4d** possessing rigid substituents at the carbon of the hydroxyl group afforded low enantioselectivity (entries 1 and 4) than ligands **4b** and **4c** (entries 2 and 3). Ligand **4d** has the most rigid substitute and gave the lowest ee, but ligand **4c** possesses the most flexible substituent and gave the highest ee value. Another interesting phenomenon that could be observed was that the bulkier the substituents at the carbon of the hydroxyl groups, the more efficient the chemical catalytic activity obtained. The velocity of the reactions promoted by ligands **4a** and **4c** was much faster than ligands **4b** and **4d** (entries 1–4). The relative configurations of the resultant alcohols catalyzed by **4a–d**, all were R.

It could be obviously seen that ligand **4c** was the most efficient asymmetric catalyst among these four ligands. When 4% **4c** equivalent to benzaldehyde was used, the enantioselectivity was up to 96% (entry 5). Increasing the amount of the catalyst could not cause higher asymmetric induction (entries 5–7). For the promising solvent, hexane was the best (entry 5). Toluene obviously made the reaction sluggish and afforded lower enantioselectivity (entry 9). Under room temperature condition, the enantioselectivity did not change significantly (entry 10).

Under such optimized reaction conditions, ligand **4c** was subsequently employed to induce the enantioselective addition of diethyl zinc to a representative family of aromatic aldehydes. The results are shown in Table 2. Except for two examples, most aldehydes afforded

Table 2. Asymmetric addition of diethylzinc to aldehydes promoted by ligand **4c**



Entry	Aldehydes	Yield (%)[a]	Ee (%)[a]	Config.[b]
1	Benzaldehyde	98	96	*R*
2	4-Fluorobenzaldehyde	99	97	*R*
3[c]	2-Chlorobenzaldehyde	99	93	*R*
4	4-Chlorobenzaldehyde	99	97	*R*
5[d]	3-Bromobenzaldehyde	96	94	*R*
6	3-Tolualdehyde	96	95	*R*
7	4-Tolualdehyde	95	96	*R*
8	α-Naphthaldehyde	94	92	*R*
9	β-Naphthaldehyde	96	90	*R*
10	2-Anisaldehyde	98	83	*R*
11	3-Anisaldehyde	98	94	*R*
12	4-Anisdaldehyde	96	88	*R*
13[e]	Isobutyraldehyde	32	83	
14[e]	Lauraldehyde	30	54	
15[e]	Crotonaldehyde	37	74	

[a] The yield and ee value are determined by chiral HPLC with Chiracel OD column.
[b] Assigned by the retention time of the major peak of the isomers[11] and the direction of optical rotation with the literature.[7a]
[c] 12% ligand **4c** was used.
[d] 10% **4c** was used.
[e] 15% **4c** was used and the ee was measured by analyzing the benzoate of the alcohol by HPLC with Daicel chiracel OD column.[3b] The yield was isolated yield of the benzoate of the alcohol.

Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by ligands **4a–d**

Entry	Ligand[a]	Solvent	Time (h)	Yield (%)[b]	Ee (%)[b]	Config.[c]
1	**4a** (2%)	Hexane	4	99	62	*R*
2	**4b** (2%)	Hexane	20	95	64	*R*
3	**4c** (2%)	Hexane	6	99	89	*R*
4	**4d** (2%)	Hexane	20	86	46	*R*
5	**4c** (4%)	Hexane	5	98	96	*R*
6	**4c** (7%)	Hexane	5	96	95	*R*
7	**4c** (10%)	Hexane	5	98	95	*R*
8	**4c** (4%)	Benzene	10	93	93	*R*
9	**4c** (4%)	Toluene	36	95	89	*R*
10[d]	**4c** (4%)	Hexane	4	96	93	*R*

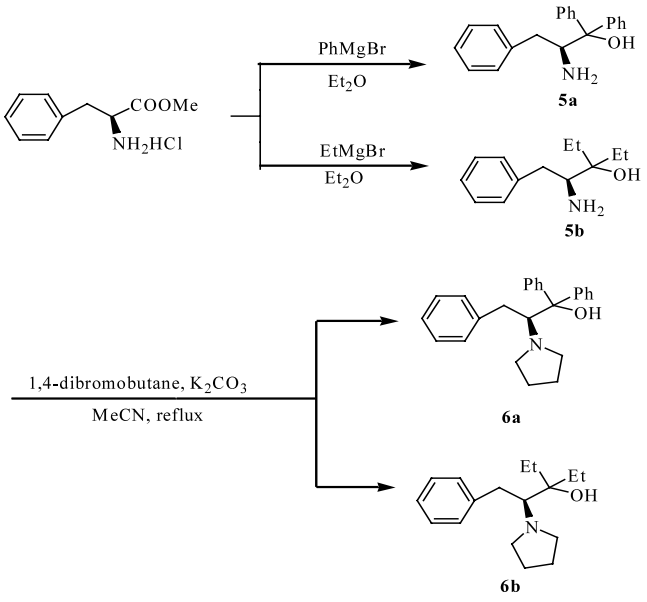
[a] The number in the bracket was the employed amount of the ligands.
[b] Determined by chiral HPLC with Chiracel OD column.
[c] Determined by the retention time of the major peak of the isomers[11] and the direction of optical rotation with the literature.[7a]
[d] The reaction was performed under room temperature.

high enantioselectivity and the ee value was up to 97%. When alkyl aldehydes were used as substrates, the ee value was also afforded as high as 84%. The α-branched alkyl aldehydes gave the highest ee among the three aldehydes. α,β-Unsaturated alkyl aldehydes afforded good enantioselectivity, but the linear alkyl aldehyde gave the poorest ee value (entries 13–15).

The efficient enantioselectivity of **4c** made us to like to prepare more bulky subsituents on the carbon of the hydroxy group and to discover their effects in this asymmetric reaction. **4e** which possessing two propyl substituents was readily synthesized as the same efficient course (Scheme 1) with 91% yield. But the more bulkier ligand with two isopropyl substituents could not be succeeded due to the isopropyl group too large to achieve the desired 1,2-amino alcohol but get the intermediate ketone product, and optical rotation value of the recovery (*S*)-**3** showed heavily racemization when it was exposed in this bulky strong base long time.

Ligand **4e** was successively applied to catalyze the enantioselective addition of diethyl zinc to aldehydes (Table 3). The results showed that ligand **4e** also had high asymmetric catalytic activity. The reaction time with it was similar to ligand **4c**, and so the reaction also behaved fast reactive velocity (Table 3, entry 1). For some aldehydes compared to ligand **4c**, higher enantioselectivity had been succeeded, and the ee up to 98% was achieved (entry 5).

For checking the effects of the substituents of the nitrogen atom on the asymmetric induction, we prepared two pyrrolidine-based 1,2-amino alcohols. Although these two ligands may be succeeded according to this novel efficient method, we synthesized them using the traditional course with dihaloalkane[6] (Scheme 2) due to 1,4-butanedialdehyde was not commercial available. Salt of (*S*)-**2** with hydrogen chloride was introduced with freshly prepared PhMgBr or EtMgBr to afford the Grignard products **5a** and **5b** with 70% and 63% yield. Then the two compounds were allowed to react with 1,4-dibromobutane and K_2CO_3 in dry MeCN. This process afforded two pyrrolidine-based β-amino alcohols **6a** and **6b**. But to our surprised, the diethyl product had too lower yield compared to the biphenyl ligand. Although we repeated the diethyl ligand's preparation, no obvious increase of it was achieved. This might be the flexible diethyl group blocking formation of the pyrrolidinyl ring. Of cause the dibromo substituted alkane might be the one main cause of the low yield.



Scheme 2. Synthesis of pyrrlidine-based 1,2-amino alcohols.

Ligands **6a** and **6b** were applied to induct this asymmetric reaction. Out of our good expectation on them, these two ligands showed both of poor chemical and enantioselective catalytic activity (Table 4). Compared with **4c** and **4a**, the reaction changed much more sluggish, and the enantioselectivity was drastically low. Low reaction temperature could only increase the ee value slightly. Another interesting results could be observed that ligand **6b** which possessed diethyl substituents did not had much higher superiority in asymmetric induction to **6a** having biphenyl groups, although **6b** afforded higher ee than **6a** similarly.

Table 3. Enantioselective addition of diethyl zinc to aldehydes promoted by ligand **4e**[a]

Entry	Aldehydes	Ee (%)[b]	Yield (%)[b]	Config.[c]
1[d]	Benzaldehyde	97	98	*R*
2[e]	2-Chlorobenzaldehyde	95	99	*R*
3	α-Naphthaldehyde	90	99	*R*
4[f]	β-Naphthaldehyde	97	98	*R*
5	3-Bromobenzaldehyde	98	95	*R*
6	*m*-Tolualdehyde	96	99	*R*
7	*p*-Anisaldehyde	47	96	*R*

[a] 4% ligand **4e** used.
[b] The yield and ee value are determined by chiral HPLC with Chiracel OD column.
[c] Assigned by the retention time of the major peak of the isomers and the direction of optical rotation with the literature.
[d] The reaction lasted for 5 h.
[e] 12% ligand **5e** was used.
[f] 8% ligand **6e** was used.

3. Conclusion

We have conveniently synthesized five piperidine-based chiral amino alcohols from natural phenylalanine in three steps. Compared with reported methods, the preparative protocol of the compound (*S*)-**3** made the synthesis of piperidine ring quite efficient. Ligand **4c** and **4e** proved to be efficient chiral catalysts in the highly enantioselective addition of diethyl zinc to aldehydes. And the piperidine-based 1,2-amino alcohols showed much superior in both of chemical catalytic activity and asymmetric induction to the pyrrolidinyl-based ligands derived from the same chiral resource.

Table 4. Catalytic addition of diethyl zinc to benzaldehyde catalyzed by ligands **6a** and **6b**

Entry	Ligand (4%)	Time (h)	Ee (%)[c]	Yield (%)[c]	Config.[d]
1	**6a**[a]	24	31	96	*R*
2	**6a**[b]	21	42	95	*R*
3	**6b**[a]	24	50	96	*R*
4	**6b**[b]	22	49	98	*R*

[a] The reaction was performed under ambient temperature after stirring for 0.5 h at 0°C.
[b] The reaction was performed at 0°C.
[c] Determined by chiral HPLC with Chiracel OD column.
[d] Assigned by the retention time of the major peak of the isomers and the direction of optical rotation with the literature.

4. Experimental

4.1. General methods

All reactions were carried out under an argon atmosphere condition and solvents were dried according to 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. Diethyl zinc was prepared from EtI with Zn and then was diluted with hexane to 1.0 M. Melting points was uncorrected and recorded on X-4 melting point apparatus. ^{1}H NMR spectra were measured on Bruker Am 400 MHz and DRX-200 MHz spectrometers (NMR in $CDCl_3$ with TMS as an internal standard). IR spectra were obtained on a Nicolet AVATAR 360 FT-IR. Optical rotations were recorded on a Perkin–Elmer 341 polarimeter. HR-MS were measured with an APEX II 47e mass spectrometer and the ESI-MS was recorded on a Mariner® biospectrometer. The ee value determination was carried out using chiral HPLC with a Daicel Chiracel® OD column on Waters® with a 996 UV-detector.

4.2. Preparation of (*S*)-phenylalanine methylester, (*S*)-(+)-2

To a mixture of 9.7 g (58.8 mmol) L-phe in 300 ml methanol was given dropwise at −30°C $SOCl_2$ 21.53 ml (294.95 mmol). After warming up to room temperature the reaction mixture was refluxed for 2 h. The organic solvent was concentrated in vacuum, and then the residue was introduced with $NH_3{\cdot}H_2O$ into pH 9.0 or so. 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 in vacuum, then obtained 10.0 g (*S*)-**2**, 95%; $[\alpha]_D^{23}=+25.0$ (*c* 4.04, C_2H_5OH); ^{1}H NMR (200 MHz): 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 $(M+H)^+$: 180.

4.3. General procedure for preparation of (*S*)-3-phenyl-2-piperidinopropionic acid methyl ester, (*S*)-(−)-3

A solution of 1.0 g (5.58 mmol) (*S*)-(+)-**2** in 56 ml THF and solid $NaBH_4$ 1.477 g (39.05 mmol) were slowly added (simultaneously) to a solution of 50% glutaraldehyde 11.9 ml (66.95 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 chromatography on silica gel to give the piperidine-based α-amino ester (*S*)-**3** as a yellow oil 1.27 g, 92%; $[\alpha]_D^{19}=-30.2$ (*c* 4.11, $CH_3COOC_2H_5$); ^{1}H NMR (400 MHz): δ 7.18–7.27 (m, 5H, Ph-H), 3.58 (s, 3H, CH_3), 3.39–3.43 (dd, 1H, CHCO, $J=5.2$ Hz, $J=9.8$ Hz), 3.04–3.10 (dd, 1H, PhCH, $J=13.2$ Hz), 2.93–2.97 (dd, 1H, PhCH), 2.62–2.67 (m, 2H, NCH_2), 2.50–2.55 (m, 2H, NCH_2), 1.55–1.61 (m, 4H, CH_2), 1.43–1.46 (m, 2H, CH_2); IR (KBr): 3062, 3027, 2933, 2852, 2808, 1733, 1652, 1603, 1495, 1451, 1348, 1195, 1155, 1113, 1054, 1033, 1005, 748, 699 cm^{-1}; HR-MS calcd for $(M+H)^+$: 248.1645, found: 248.1641.

4.4. General procedure for preparation of (*S*)-4 via the reaction of (*S*)-(−)-3 with Grignard reagents

A solution of 497 mg (2 mmol) (*S*)-**3** 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 dropped 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 in vacuum and the crude amino alcohol was purified by column Chromatography with petroleum ether and ethyl acetate as mobile phase.

[†] The Grignard reagents used for (*S*)-**4b** and (*S*)-**4d** were CH_3MgI and $BrMg(CH_2)_4MgBr$, respectively.

4.4.1. (*S*)-1,1,3-Tripheny-2-piperidinopropan-1-ol, (*S*)-(+)-4a. A pale yellow oil, 610 mg, 82%; $[\alpha]_D^{20}=+39.0$ (*c* 1.0, $CH_3COOC_2H_5$); ^{1}H NMR (400 MHz): δ 7.57 (d, 2H, Ph-H, $J=7.6$ Hz), 7.51 (d, 2H, Ph-H, $J=7.4$ Hz), 7.21–7.37 (m, 11H, Ph-H), 6.42 (br., 1H, OH), 3.69–3.92 (dd, 1H, CHN, $J=1.9$ Hz, $J=12.1$ Hz), 3.14–3.17 (dd, 1H, PhCH, $J=14.7$ Hz), 2.70–2.77 (dd, 1H, PhCH), 2.39 (br., 2H, NCH_2), 1.99–2.05 (m, 2H, NCH_2), 1.33–1.41 (m, 4H, CH_2), 1.23–1.28 (m, 2H, CH_2); IR (KBr): 3268 (br.), 3058, 3026, 2931, 2849, 2822, 1600, 1493, 1445, 1276, 1159, 1109, 1050, 1029, 758, 727, 699, 662, 635 cm^{-1}; HR-MS calcd for $(M+H)^+$: 372.2322, found: 372.2323.

4.4.2. (*S*)-2-Methyl-4-phenyl-3-piperidinobutan-2-ol, (*S*)-(−)-4b. 479 mg, 97%. Needles, mp 58–59°C; $[\alpha]_D^{20}=-49.0$ (*c* 1.0, $CH_3COOC_2H_5$); ^{1}H NMR (400 MHz): δ 7.21–7.30 (m, 5H, Ph-H), 5.14 (s, 1H, OH), 2.89–2.95 (dd, 1H, PhCH, $J=9.6$ Hz, $J=13.8$ Hz), 2.72–2.83 (dq, 2H, CHN, PhCH, $J=-3.8$ Hz), 2.48–2.57 (m, 4H, NCH_2), 1.40–1.56 (m, 4H, CH_2), 1.31 (br., 2H, CH_2), 1.20 (s, 3H, CH_3), 1.19 (s, 3H, CH_3); IR (KBr): 3418 (br.), 3061, 3026, 2968, 2929, 2851, 2815, 1602, 1494, 1453, 1383, 1363, 1159, 1103, 1034, 1012, 966, 756, 731, 698 cm^{-1}; HR-MS calcd for $(M+H)^+$: 248.2009, found: 248.2005.

4.4.3. (*S*)-3-Ethyl-1-phenyl-2-piperidinopentan-3-ol, (*S*)-(−)-4c. Pale yellow oil, 506 mg, 92%; $[\alpha]_D^{20}=-26.0$ (*c* 1.0, $CH_3COOC_2H_5$); ^{1}H NMR (400 MHz): δ 7.18–7.30 (m, 5H, Ph-H), 3.00–3.05 (dd, 1H, CHN, $J=3.2$ Hz, $J=10.7$ Hz), 2.87–2.93 (q, 1H, PhCH, $J=14.4$ Hz), 2.73–2.77 (d, 1H, PhCH), 2.53 (br., 4H, NCH_2), 1.44–1.50 (m, 6H, CH_2), 1.26–1.30 (m, 4H, CH_2Me), 0.959 (t, 3H, CH_3, $J=7.3$ Hz), 0.952 (t, 3H, CH_3, $J=7.1$ Hz); IR (KBr): 3585, 3389 (br), 3066, 3026, 2931, 2852, 1715, 1656, 1494, 1455, 1397, 1374, 1157, 1105, 1033, 957, 727, 698 cm^{-1}; HR-MS calcd for $(M+H)^+$: 276.2322, found: 276.2327.

4.4.4. (*S*)-(−)-1-(2′-Phenyl-1′-piperidinoethyl)cyclopentanol, (*S*)-(−)-4d. Yield 60%, a pale yellow oil; $[\alpha]_D^{20}=-26.0$ (*c* 1.0, $CH_3COOC_2H_5$); ^{1}H NMR (400 MHz): δ 7.20–7.31 (m, 5H, Ph-H), 3.04–3.07 (dd, 1H, CHN, $J=3.6$ Hz, $J=9.6$ Hz), 2.90–2.96 (dd, 1H, PhCH, $J=14.4$ Hz), 2.62–2.66 (dd, 1H, PhCH), 2.44–2.51 (m, 4H, NCH_2), 1.63–1.70 (m, 6H, CH_2), 1.41–1.56 (m, 6H, CH_2), 1.31–1.34 (m, 2H, CH_2); IR (KBr): 3592, 3335 (br.), 3025, 2931, 2852, 1730, 1652, 1602, 1493, 1447, 1383, 1157, 1104, 1031, 998, 730, 698 cm^{-1}; HR-MS calcd for $(M+H)^+$: 274.2165, found: 274.2171.

4.4.5. (*S*)-3-Propyl-1-phenyl-2-piperidinohexan-3-ol, (*S*)-(−)-4e. 91% (551 mg), a pale yellow oil; $[\alpha]_D^{22}=-29.0$ (*c* 1.7, $CH_3COOC_2H_5$); ^{1}H NMR (200 M): δ 7.20–7.30 (m, 5H, Ph-H), 4.47 (br., 1H, OH), 2.96–3.03 (dd, 1H, CHN, $J=10.4$ Hz, $J=2.8$ Hz), 2.84–2.89 (d, 1H, PhCH, $J=12.6$ Hz), 2.72–2.78 (dd, 1H, PhCH), 2.49–2.54 (m, 4H, NCH_2), 1.41–1.51 (m, 8H, CH_2), 1.26–1.36 (m, 6H, CH_2), 0.93 (t, 3H, CH_3), 0.91 (t, 3H, CH_3, $J=7.0$ Hz); IR (KBr): 3443 (br.), 3062, 3026, 2956, 2928, 2853, 1602, 1494, 1457, 1398, 1375, 1344, 1311, 1159, 1107, 1076, 1034, 1005, 912, 859, 763, 729, 698 cm^{-1}; HR-MS cacld. For $(M+H)^+$: 304.2635, found: 304.2635.

4.5. General procedure for preparation of pyrrolidine-containing ligands 6a and 6b

4.5.1. Preparation of (*S*)-1,1,3-tripheny-2-aminopropan-1-ol, (*S*)-(−)-5a. The hydrogen chloride salt of (*S*)-**2** (the work-up of preparation of (*S*)-**2** was not introduced with diluted base but directly concentrated and then afforded the salt) 1.0775 g (5 mmol) was introduced with freshly prepared Grignard reagent PhMgBr (50 mmol) in the usual way under 0°C and argon atmosphere in diethyl ether. Then the mixture was stirred at ambient temperature overnight, and cold saturated NH_4Cl was dropped into it under vigorous stirring. The mixture was extracted with ethyl acetate three times. The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4, concentrated in vacuum. This residue was recrystallized with ethyl acetate and petroleum ether and gave **5a** as a colorless crystal, 70% yield (1.06 g); mp 134–136°C; $[\alpha]_D^{21}=-86.0$ (*c* 1.53, CH_2Cl_2); ^{1}H NMR (400 M): δ 7.66 (d, 2H, Ph-H, $J=7.4$ Hz), 7.62 (d, 2H, Ph-H, $J=7.9$ Hz), 4.52 (br, 1H, OH), 4.18–4.21 (q, 1H, CHN, $J=2.5$ Hz, $J=10.9$ Hz), 2.64–2.68 (dd, 1H, PhCH, $J=13.9$ Hz), 2.43–2.49 (dd, 1H, PhCH), 1.21 (s, 2H, NH_2); IR (KBr): 3396 (br.), 3243, 3082, 3057, 3023, 2919, 2850, 1594, 1491, 1445, 1364, 1321, 1273, 1168, 1105, 1056, 1028, 958, 900, 857, 749, 700 cm^{-1}; HR-MS calcd For (M+H)+: 304.1696, found: 304.1696.

4.5.2. Preparation of (*S*)-3-ethyl-1-phenyl-2-aminopentan-3-ol, (*S*)-(−)-5b. Compound **5b** was prepared using the same procedure as **5a**. After the usual work-up, the residue was introduced with acetic acid 90% equivalent to the starting salt of (*S*)-**2**, recrystallized the ammonium salt with little THF and afforded a colorless crystal with mp: 92–94°C, $[\alpha]_D^{19}=-39.0$ (*c* 0.94, $CHCl_3$). After that, the crystals was treated with dilute NaOH and extracted with ethyl acetate, which was then dried and concentrated to afford (*S*)-**5b** as a pale yellow oil with 63% yield (652 mg); $[\alpha]_D^{21}=-41$ (*c* 1.83, CH_2Cl_2); ^{1}H NMR (400 MHz): δ 7.19–7.35 (m, 5H, Ph-H), 2.97–3.00 (q, 1H, CHN, $J=3.5$ Hz, $J=9.0$ Hz), 2.29–2.35 (q, 2H, $PhCH_2$, $J=12.0$ Hz), 1.44–1.57 (m, 4H, CH_2), 1.11 (s, 2H, NH_2), 0.97 (t, 3H, CH_3, $J=7.3$ Hz), 0.96 (t, 3H, CH_3); IR (KBr): 3391 (br.), 3059, 3026, 2964, 2926, 2851, 1595, 1494, 1457, 1397, 1376, 1316, 1260, 1153, 1076, 1028, 952, 750, 697 cm^{-1}; HR-MS calcd for (M+H)+: 208.1696, found: 208.1701.

4.5.3. (*S*)-1,1,3-Tripheny-2-pyrrolidinopropan-1-ol, (*S*)-(+)-6a. Typical procedure for the preparation of (*S*)-**6**: To a solution of 909 mg (3 mmol) (*S*)-**5a** in acetonitrile, 1,4-dibromobutane 0.36 ml (3 mmol), and anhydrous potassium carbonate 828 mg (6 mmol) were added, and the mixture was reflued for 24 h. After filtration of the reaction mixture and evaporation, the residue was dissolved in diethyl ether, washed with little water and dried over anhydrous Na_2SO_4. Then the residue was concentrated and purification via column chromatography to give (*S*)-**6a** as pale yellow oil with 48% yield

(514 mg); $[\alpha]_D^{19}=+14$ (c 1.07, $CH_3COOC_2H_5$); ^1H NMR (400 MHz): δ 7.61 (d, 2H, Ph-H, $J=7.5$ Hz), 7.56 (d, 2H, Ph-H, $J=7.5$ Hz), 7.18–7.37 (m, 11H, Ph-H), 4.25–4.27 (d, 1H, CHN, $J=11.2$ Hz), 3.07–3.11 (d, 1H, PhCH, $J=14.7$ Hz), 2.84–2.90 (dd, 1H, PHCH), 2.59–2.63 (m, 2H, NCH_2), 2.22–2.23 (m, 2H, NCH_2), 1.42–1.54 (m, 4H, CH_2); IR (KBr): 3377 (br.), 2924, 1595, 1486, 1445, 1375, 1312, 1164, 1124, 1027, 748, 702 cm^{-1}; HR-MS calcd For (M+H)+: 358.2165, found: 358.2161.

4.5.4. (*S*)-3-Ethyl-1-phenyl-2-pyrrolidinopentan-3-ol, (*S*)-(−)-6b. According to the same course of preparation of (*S*)-**6a**, (*S*)-**6b** was also synthesized with 12% yield; $[\alpha]_D^{21}=-35$ (c 1.01, $CH_3COOC_2H_5$); ^1H NMR (400 MHz): δ 7.17–7.30 (m, 5H, Ph-H), 3.33–3.36 (q, 1H, CHN, $J=3.9$ Hz, $J=9.8$ Hz), 2.86–2.92 (dd, 1H, PhCH, $J=14.4$ Hz), 2.72–2.76 (dd, 1H, PhCH), 2.55–2.56 (m, 4H, NCH_2), 1.53–1.60 (m, 4H, CH_2), 1.24–1.48 (m, 2H, CH_2), 1.23–1.30 (m, 2H, CH_2), 0.95 (t, 3H, CH_3, $J=7.4$ Hz), 0.92 (t, 3H. CH_3, $J=7.4$ Hz); IR (KBr): 3307, 3061, 3026, 2964, 2936, 2877, 1600, 1494, 1457, 1396, 1371, 1168, 1122, 1030, 955, 731, 699 cm^{-1}; HR-MS calcd For (M+H)+: 262.2165, found: 262.2169.

4.6. Typical procedure of asymmetric addition of diethylzinc to aldehydes

To a solution of chiral β-amino alcohol **4c** (5.5 mg, 0.02 mmol) in hexane (1.0 ml) was added dropwise a solution of diethyl zinc (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 reduce pressure to give an oily residue. The residue was analyzed by HPLC to give the yield and ee value.

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