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Synthesis of *N*-α-pyridylmethyl amino alcohols and application in catalytic asymmetric addition of diethylzinc to aromatic aldehydes

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Abstract

A series of novel chiral ligands **2a**–**2f** were conveniently prepared from β-amino alcohols through a two-step reaction and applied to catalyze the enantioselective addition of diethylzinc to benzaldehyde. Among them, ligand **2c** was found to show the best asymmetric induction and catalyze the reaction of various aromatic aldehydes to provide (*R*)-secondary alcohols in up to 98.3% ee.

1. Introduction

Among asymmetric catalytic reactions for C–C bond formation, enantioselective addition of diorganozinc reagents to aldehydes in the presence of a catalytic amount of chiral β-amino alcohols is a convenient method for the preparation of optically active secondary alcohols.[1] Various catalysts derived from β-amino alcohols have been reported to catalyze this kind of reaction with excellent asymmetric induction.[2] Recently, pyridine-derived carbinols[3] including C_2-symmetric chiral ligands such as 2,2′-bispyridines, 2,6-disubstituted pyridines and plane-extended pyridyl alcohols[4] have been developed as chiral ligands in the enantioselective addition of dialkylzinc to aldehydes, but they only gave moderate enantiomeric excess. Herein, we demonstrate an efficient synthesis of novel chiral ligands, *N*-α-pyridylmethyl-β-amino alcohols **2a**–**e** and *N*-benzyl amino alcohol **2f**, through a two-step reaction approach and their application to the highly enantioselective addition of diethylzinc to various aromatic aldehydes.

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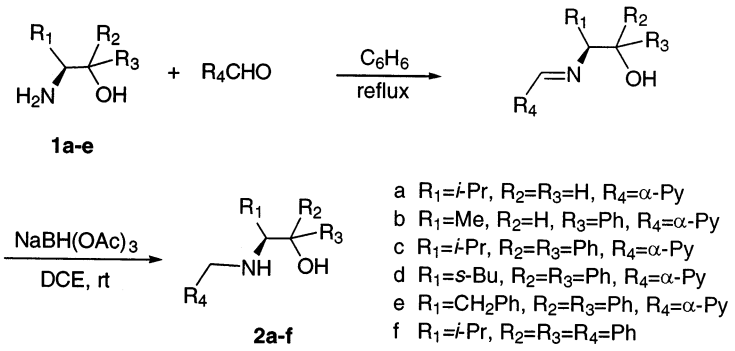
2. Results and discussion

2.1. Synthesis of N-α-pyridylmethyl amino alcohols 2a–2e and N-benzyl amino alcohol 2f

The synthesis of ligands **2a**–**2f** is shown in Scheme 1. Compounds **1a**, **1c**, **1d** and **1e** were prepared according to the literature method.[5] (1*R*,2*S*)-(−)-norephedrine **1b** is a commercially available reagent. The synthesis of **2** is described as follows. (*S*)-Amino alcohol **1** and the appropriate 2-pyridinecarboxaldehyde or benzaldehyde were mixed in dry benzene and refluxed for 2 hours with a Dean–Stark trap. The Schiff base was obtained in quantitative yield. The reduction of the Schiff base was carried out in dry 1,2-dichloroethane (DCE) with two equivalents of sodium triacetoborohydride.[6] The reaction mixture was stirred at room temperature for at least 24 hours. After work-up, **2a**–**2f** were obtained in high yields (72–98%). The characteristics of **2a**–**2f** are listed in Section 4. Recently, Christopher et al. have reported the synthesis of **2b** using a similar method.[7]



Scheme 1. Synthesis of **2a**–**2f**

2.2. Asymmetric addition of diethylzinc to benzaldehyde in the presence of 2

The novel chiral ligands **2a**–**2f** prepared were then set out to check their asymmetric induction efficiency for the addition of diethylzinc to benzaldehyde. The results were listed in Table 1.

Chiral ligand **2c** shows the best asymmetric induction. Under the experimental conditions, 91.8% ee of the 1-phenylpropanol was achieved with the catalysis of 5 mol% **2c** (entry 3). Obviously, the presence of two bulky phenyl groups at hydroxy-attached carbon is crucial for getting the best asymmetric induction. This conclusion was obtained from the results of entries 3–5 vs entries 1 and 2. The entries 1 and 2 in the catalysis of **2a** and **2b**, respectively, which have no or only one phenyl group at hydroxy-bearing carbon, resulted in poor ees. On the other hand, entries 3–5 in the catalysis of **2c**, **2d** and **2e**, respectively, in which there are two bulky phenyl groups, resulted in a dramatic enhancement in ees (63.1–91.8%). It is also interesting to note that the α-pyridylmethyl group in **2c** plays a very important role for the enantioselectivity of the reaction (entry 3 vs 6 and 7). Thus, it may be concluded that both the bulky groups on the α-carbon and the α-pyridylmethyl group at β-amino nitrogen are required for the high asymmetric induction of **2c**.

Table 1
Asymmetric addition of diethylzinc to benzaldehyde in the presence of **2**[a]

Entry	Ligand	Solvent	Time (h)	Yield[b] (%)	Ee[c] (%)	Confign[d]
1	**2a**	T–H[e]	5	69	2.5	*R*
2	**2b**	T–H	5	80	3.3	*S*
3	**2c**	T–H	5	98	91.8	*R*
4	**2d**	T–H	5	81	63.1	*R*
5	**2e**	T–H	5	92	77.2	*R*
6	**2f**	T–H	6	85	34.5	*R*
7	**1c**	T–H	12	71	4.7	*R*

[a] The reaction was carried out in toluene with 5 mol% of catalyst and 2.5 equiv. of diethylzinc (4.17 M solution in hexane) to benzaldehyde at rt.
[b] Isolated yields.
[c] Determined by HPLC using a chiral OD column.
[d] Configurations were determined by comparison of the optical rotations with the literature.[8]
[e] Toluene and hexane, 4/1 (v/v).

Furthermore, we examined the effects of the catalytic amount and temperature on the asymmetric induction in the presence of **2c**. The results are listed in Table 2.

From Table 2 it can be seen that reducing the ligand to benzaldehyde ratio from 10 to 3% did not affect the ees, but reducing the ratio to 2% remarkably reduced the ee. Further reducing the ratio to 1% significantly reduced both the yield and ee. On the other hand, increasing the ratio to 20% also reduced the ee. The temperature had little effect on ees.

Table 2
Asymmetric addition of diethylzinc to benzaldehyde in the presence of **2c**

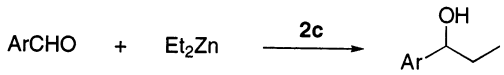
Entry	Mol%, **2c**	Temp., °C	Solvent[a]	Time, h	Yield,[b] %	% ee[c]	Confign[d]
1	1	rt	T–H	5	50	56.5	*R*
2	2	rt	T–H	5	98	86.8	*R*
3	3	rt	T–H	5	91	91.1	*R*
4	4	rt	T–H	5	88	90.3	*R*
5	5	rt	T–H	5	92	91.8	*R*
6	10	rt	T–H	2	87	91.3	*R*
7	20	rt	T–H	2	97	88.8	*R*
8	5	0	T–H	12	79	90.2	*R*
9	5	−25	T–H	12	79	90.4	*R*

[a] Toluene and hexane, 4/1 (v/v).
[b] Isolated yields.
[c] Determined by HPLC using a chiral OD column.
[d] Configuration was determined by comparison of the optical rotation with the literature.[8]

2.3. Asymmetric addition of diethylzinc to aromatic aldehydes in the presence of **2c**

Chiral ligand **2c** was then examined for the asymmetric ethylation of a series of aromatic aldehydes. The results are summarized in Table 3. It was found that **2c** was effective to various aromatic aldehydes, including *ortho*-, *para*- and *meta*-substituted benzaldehydes (entries 1–6), ferrocenecarboxaldehyde (entry 7) and thiophene-2-carboxaldehyde (entry 8). The best asymmetric induction as high as 98.3% ee was found by using ferrocenecarboxaldehyde as substrate. The results were listed in Table 3.

Table 3
Asymmetric addition of diethylzinc to aromatic aldehydes in the presence of **2c**

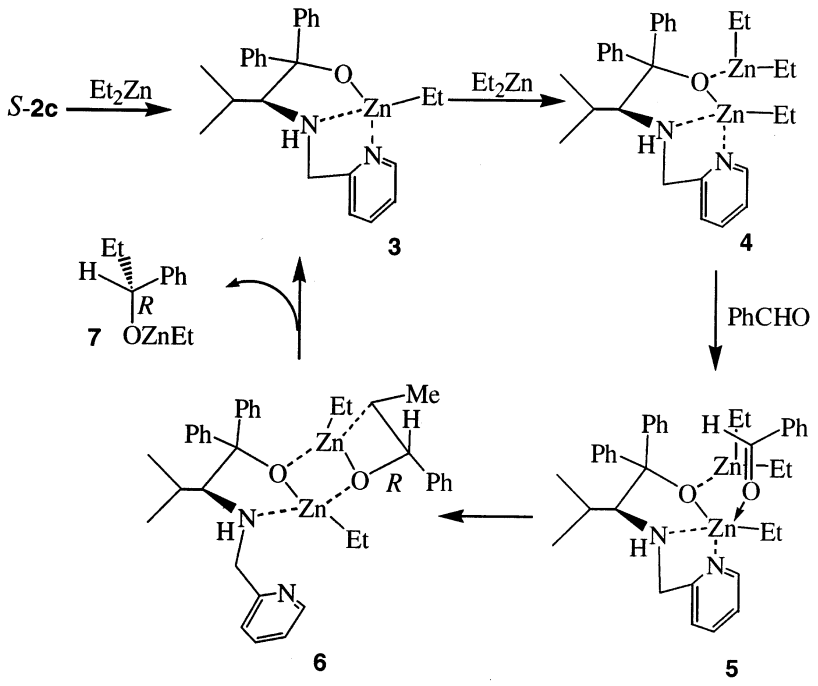


Entry[a]	Aldehyde	Solvent[b]	Time (h)	Yield[c] (%)	Ee[d] (%)	Config[e]
1	*p*-ClC_6H_4CHO	T–H	5	97	91.5	*R*
2	*p*-$MeOC_6H_4CHO$	T–H	6	96	92.3	*R*
3	*p*-MeC_6H_4CHO	T–H	5	98	96.2[g]	*R*
4	*m*-ClC_6H_4CHO	T–H	5	70	90.2	*R*
5	α-Naphthaldehyde	T–H	6	94	80.9	*R*
6	*o*-$MeOC_6H_4CHO$	T–H	5	95	88.1	*R*
7	FcCHO[f]	T–H	5	88	98.3	nd[h]
8	Thiophene-2-carboxaldehyde	T–H	5	95	94.4	*R*[i]
9	(*E*)-Cinnamaldehyde	T–H	6	99	78.4	*R*

[a] The reactions were carried out by using 5 mol% **2c** at rt.
[b] Toluene and hexane, 4/1 (v/v).
[c] Isolated yields.
[d] Determined by HPLC using a chiral OD column.
[e] Determined by comparison of the specific rotation with the literature.
[f] Ferrocenecarboxaldehyde.
[g] Determined by comparison of the optical rotation value with the literature value.[9]
[h] Not determined.
[i] Determined by comparison of the known elution order from a chiral OD column.[10]

Based on our experimental findings and related mechanism suggested by Corey,[11] a possible mechanism was proposed as shown in Scheme 2.

Firstly, diethylzinc reacts rapidly with the ligand **2c** to give the corresponding zinc monoalkoxide **3** and then converts to the zinc monoalkoxide–diethylzinc complex **4**. The coordination geometry of the zinc atom is essentially tetrahedral. The nucleophilicity of the ethyl group of diethylzinc would be increased by coordination of the zinc atom with the oxygen atom of the ligand. Secondly, the benzaldehyde coordinates with the zinc monoalkoxide. In order to maintain the tetracoordinate status of zinc, the coordination of the 2-methylpyridyl group with zinc would be replaced by benzaldehyde with zinc. This transformation resulted in the formation of complex **5**. Thirdly, transfer of an ethyl group from zinc to the nearby benzaldehyde carbonyl group can occur via a six-membered cyclic structure to form the carbonyl adduct **6**. Elimination of zinc alkoxide from **6** produced the product **7** with regeneration of **3**. This preferred three-dimensional arrangement, shown more clearly in stereoformula **5**, exposes the *re* face of



Scheme 2.

the formyl carbon to the attacking ethyl group and led to the *R*-configuration of adduct **7**, in accord with the experimental result.

3. Conclusion

In conclusion, a series of novel chiral ligands **2a**–**2f** has been conveniently prepared from β-amino alcohols through a two-step reaction and **2c** was found to be highly efficient for enantioselective addition of diethylzinc to aromatic aldehydes. The excellent asymmetric induction of **2c** can be attributed to the presence of both steric hindrance of diphenyl groups at hydroxy attached carbon and α-pyridylmethyl group at β-amino nitrogen as a side chain, which provides the new understanding to design the novel chiral tridentate ligands for this type of reaction. Further work is undergoing to extend the variety of this type of chiral ligands and the applications of their metallic complexes to other types of asymmetric reactions.

4. Experimental

4.1. Instrumentation

Melting points were measured on a WC-1 apparatus and are uncorrected. Elemental analyses were determined with a Carlo Erba 1160 analyzer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer by using $CDCl_3$ as the solvent and TMS as an internal standard. IR spectra were recorded on a Shimadzu IR-408 spectrophotometer. Optical

rotations were measured with a Perkin–Elmer 341 polarimeter. HPLC analyses were carried out on a Waters 600E type instrument equipped with a chiralcolumn (chiralcel OD, Daicel Chemical Industries) and UV detector for determining the optical purity of the products. Preparative TLC was performed on dry silica gel (60 F_{254}) plates.

4.2. General methods

All reactions were carried out under an inert atmosphere of argon. Tetrahydrofuran and toluene were freshly distilled from sodium benzophenone ketyl prior to use. 1,2-Dichloroethane was freshly distilled from phosphoruspentoxide. Diethylzinc was prepared according to the literature method and diluted to a 4.17 M solution with dry hexane.

4.2.1. (S)-2-Amino-3-methylbutan-1-ol **1a**

L-Valine was reduced by 2.5 molar equivalents of sodium borohydride and one molar equivalent of iodine in THF under an argon atmosphere according to the literature procedures.[5a] Work-up: purification by distillation (bp 75°C/6 mmHg); colorless solid; yield 88%; mp 32–34°C; $[\alpha]_D^{18}=+22.9$ (*c* 0.6, EtOH) (lit.[5a] $[\alpha]_D^{20}=+17$ (*c* 5, EtOH)); IR (liq. film) $\nu_{max}=3200$, 2900, 1582, 1457, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (m, 6H, $2CH_3$), 1.65 (m, 1H, $CH(CH_3)_2$), 2.67 (m, 1H, $CHNH_2$), 3.35 (m, 1H, CH_AOH), 3.70 (m, 1H, CH_BOH). Anal. calcd for $C_5H_{13}NO$: C, 58.21; H, 12.70; N, 1.36. Found: C, 58.14; H, 12.67; N, 1.38.

4.2.2. (S)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol **1c**

L-Valine methyl ester hydrochloride reacted with an 8-fold excess of phenylmagnesium bromide in THF at 0–10°C for 5 h. Work-up: purification by recrystallization from EtOH; colorless needle; yield 67%; mp 97–98°C; $[\alpha]_D^{26}=-127.0$ (*c* 0.85, $CHCl_3$) (lit.[5b] $[\alpha]_D^{25}=-127.7$ (*c* 0.6, $CHCl_3$)); IR (KBr) $\nu_{max}=3300$, 3206, 2887, 1583, 1484, 1440, 1168, 1040, 743, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, $J=7.2$ Hz, 3H, CH_3), 0.94 (d, $J=7.2$ Hz, 3H, CH_3), 1.77 (m, 1H, $CH(CH_3)_2$), 3.88 (d, $J=1.6$ Hz, 1H, $CHNH_2$), 7.15–7.21 (m, 2H, Ph*H*), 7.26–7.34 (m, 4H, Ph*H*), 7.48 (d, $J=7.6$ Hz, 2H, Ph*H*), 7.60 (d, $J=8.0$ Hz, 2H, Ph*H*). Anal. calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.00; H, 8.28; N, 5.50.

4.2.3. (S)-2-Amino-4-methyl-1,1-diphenylpentan-1-ol **1d**

This compound was prepared by similar procedures to those for **1c**. Work-up: purification by recrystallization from EtOH; colorless needle; yield 52%; mp 132–134°C; $[\alpha]_D^{26}=-96.0$ (*c* 1.0, $CHCl_3$) (lit.[5b] $[\alpha]_D^{25}=-95.12$ (*c* 1.0, $CHCl_3$)); IR (KBr) $\nu_{max}=3250$, 2900, 1585, 1441, 1174, 1050, 830, 737, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, $J=6.8$ Hz, 3H, CH_3), 0.89 (d, $J=6.8$ Hz, 3H, CH_3), 1.10 (m, 1H, $CH_ACH(CH_3)_2$), 1.27 (m, 1H, $CH_BCH(CH_3)_2$), 1.60 (m, 1H, $CH(CH_3)_2$), 4.00 (dd, $J=10.4$ Hz, $J=2.0$ Hz, 1H, $CHNH_2$), 7.16–7.21 (m, 2H, Ph*H*), 7.26–7.33 (m, 4H, Ph*H*), 7.46 (d, $J=0.8$ Hz, 2H, Ph*H*), 7.61 (d, $J=0.8$ Hz, 2H, Ph*H*). Anal. calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 80.21; H, 8.63; N, 5.19.

4.2.4. (S)-2-Amino-1,1,3-triphenylpropan-1-ol **1e**

This compound was prepared by similar procedures to those for **1c**. Work-up: purification by recrystallization from EtOH; colorless needle; yield 56%; mp 144–146°C; $[\alpha]_D^{18}=-72.8$ (*c* 0.5, $CHCl_3$) (lit.[5b] $[\alpha]_D^{25}=-88.5$ (*c* 0.6, $CHCl_3$)); IR (KBr) $\nu_{max}=3300$, 3025, 2998, 2925, 2850, 1596, 1488, 1447, 1050, 760, 745, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (m, 1H, CH_APh), 2.64

(m, 1H, CH_BPh), 4.18 (dd, $J=10.8$ Hz, $J=2.8$ Hz, 1H, CHNH$_2$), 7.17–7.35 (m, 11H, PhH), 7.58–7.66 (m, 4H, PhH). Anal. calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.10; H, 7.01; N, 4.60.

4.3. Ligands **2a–2f**; general procedure

Compound **1** (2 mmol) and 2-pyridinecarboxaldehyde (0.214 g, 2 mmol) or benzaldehyde (0.212 g, 2 mmol) were dissolved in 30 ml dry benzene. The mixture was gently refluxed under an inert atmosphere of argon. The released water from the reaction was separated by a Dean–Stark trap. Normally 2 hours later, there was no water separated. The mixture was cooled to rt and concentrated under reduced pressure. Then the Schiff base was obtained as a yellow viscous oil or white solid in quantitative yield. IR indicated that there was only strong absorption of C=N at 1640–1650 cm^{-1} and the absorption of C=O at 1700 cm^{-1} completely disappeared. The Schiff base was dissolved in 7 ml dry DCE and then treated with sodium triacetoxyborohydride (0.86 g, 4 mmol). The mixture was stirred under an argon atmosphere for 24 to 96 h at rt. Then the mixture was quenched by addition of saturated Na_2CO_3 aqueous solution and extracted with dichloromethane. The dichloromethane extract was dried (Na_2SO_4) and the solvent was evaporated to give the crude **2**. After purification with preparative TLC (see below for individual work-up) pure **2** was obtained as a colorless oil or white solid. (The oil will turn dark during storage in air.)

4.3.1. (S)-3-Methyl-2-[(2-pyridylmethyl)amino]butan-1-ol **2a**

Starting material: 0.206 g (2 mmol) **1a**; reaction time: 24 h; work-up; purification by preparative TLC developed with EtOAc. After purification, **2a** was obtained as colorless oil in 98% yield. $[\alpha]_D^{20}=+28.2$ (c 1.0, CH_2Cl_2); IR (liq. film) $\nu_{max}=3250$, 2920, 2840, 1582, 1459, 1425, 1037, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, $J=6.8$ Hz, 3H, CH_3), 1.02 (d, $J=6.8$ Hz, 3H, CH_3), 1.90 (m, 1H, $CH(CH_3)_2$), 2.55 (m, 1H, CHNH), 3.55 (dd, $J=11.2$ Hz, $J=7.2$ Hz, 1H, CH_AOH), 3.73 (dd, $J=11.2$ Hz, $J=4.0$ Hz, 1H, CH_BOH), 4.07 (d, $J=4.0$ Hz, 2H, CH_2Py), 7.21 (m, 1H, PyH), 7.27 (m, 1H, PyH), 7.67 (m, 1H, PyH), 8.56 (m, 1H, PyH-α). ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.84 (CH_3), 19.59 (CH_3), 29.60 ($CH(CH_3)_2$), 52.51 ($CHNH$), 61.40 (CH_2OH), 64.87 (CH_2NH), 122.07, 123.10, 136.66, 149.1, 160.12 (all Py–C). Anal. calcd for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.42. Found: C, 68.21; H, 9.00; N, 14.36.

4.3.2. (1R,2S)-1-Phenyl-2-[(2-pyridylmethyl)amino]propan-1-ol **2b**

Starting material: 0.302 g (2 mmol) **1b**; reaction time: 48 h; work-up; purification by preparative TLC developed with EtOAc/MeOH (10:1). After purification, **2b** was obtained as colorless oil in 98% yield. $[\alpha]_D^{20}=+3.9$ (c 1.0, CH_2Cl_2); IR (KBr) $\nu_{max}=3300$, 3025, 2938, 2850, 1584, 1430, 744, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, $J=6.4$ Hz, 3H, CH_3), 3.09 (m, 1H, CHCH$_3$), 4.14 (s, 2H, CH_2Py), 4.97 (d, $J=2.4$ Hz, 1H, CHPh), 7.24–7.35 (m, 7H, PhH, PyH), 7.69 (m, 1H, PyH), 8.57 (d, $J=4.4$ Hz, 1H, PyH-α). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.17 (CH_3), 52.15 ($CHNH$), 58.81 ($CHPh$), 72.92 (CH_2Py), 122.29, 122.37, 126.07, 126.99, 128.07, 136.75, 141.29, 149.27, 158.96 (all Ph–C and Py–C). Anal. calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.29; H, 7.32; N, 11.58.

4.3.3. (S)-3-Methyl-2-[(2-pyridylmethyl)amino]-1,1-diphenylbutan-1-ol **2c**

Starting material: 0.513 g (2 mmol) **1c**; reaction time: 96 h; work-up; purification by preparative TLC developed with EtOAc/hexane (1/4). After purification, **2c** was obtained as a

colorless crystal in 81% yield; mp 119–121°C; $[\alpha]_D^{23}=-68.0$ (*c* 1.0, CH_2Cl_2); IR (KBr) $\nu_{max}=3304$, 3140, 3020, 2840, 1588, 1467, 1444, 1420, 1054, 759, 748, 710, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, 3H, CH_3), 0.95 (d, $J=6.8$ Hz, 3H, CH_3), 2.02 (m, 1H, $CH(CH_3)_2$), 3.38 (d, $J=14$ Hz, 1H, CH_APy), 3.52 (d, $J=14$ Hz, 1H, CH_BPy), 3.62 (d, $J=1.6$ Hz, 1H, *CH*NH), 6.89 (d, $J=8.0$ Hz, 1H, Ph*H*), 7.12–7.74 (m, 12H, Ph*H*, Py*H*), 8.52 (d, $J=4.8$ Hz, 1H, Py*H*-α). ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.00 (CH_3), 22.52 (CH_3), 28.91 ($CH(CH_3)_2$), 55.41 (*C*HNH), 68.78 (CH_2NH), 78.61 (*C*–OH), 122.03, 122.37, 125.74, 126.06, 126.39, 127.86, 128.02, 136.29, 145.41, 149.14, 159.09 (all Ph–*C* and Py–*C*). Anal. calcd for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found: C, 79.73; H, 7.63; N, 8.10.

4.3.4. (S)-4-Methyl-2-[(2-pyridylmethyl)amino]-1,1-diphenylpentan-1-ol **2d**

Starting material: 0.539 g (2 mmol) **1d**; reaction time: 48 h; work-up; purification by preparative TLC developed with EtOAc/hexane (1/3). After purification, **2d** was obtained as a white solid in 91% yield; mp 97–98°C; $[\alpha]_D^{26}=-51.8$ (*c* 0.6, CH_2Cl_2); IR (KBr) $\nu_{max}=3300$, 3010, 2940, 1585, 1560, 1459, 1423, 1050, 750, 726, 705, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, $J=6.4$ Hz, 3H, CH_3), 0.83 (d, $J=6.8$ Hz, 3H, CH_3), 1.30 (m, 2H, $CH_2CH(CH_3)_2$), 1.64 (m, 1H, $CH(CH_3)_2$), 3.30 (d, $J=14$ Hz, 1H, CH_APy), 3.48 (d, $J=14$ Hz, 1H, CH_BPy), 3.71 (dd, $J=9.2$ Hz, $J=2.8$ Hz, 1H, *CH*NH), 6.89 (d, $J=7.6$ Hz, 1H, Ph*H*), 7.14–7.69 (m, 12H, Ph*H* and Py*H*), 8.51–8.52 (m, 1H, Py*H*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.58 (CH_3), 23.95 (CH_3), 25.23 ($CH(CH_3)_2$), 28.91 ($CH_2CH(CH_3)_2$), 55.41 (*C*HNH), 68.78 (CH_2Py), 78.61 (*C*–OH), 121.99, 122.37, 125.88, 126.13, 126.25, 126.48, 127.95, 128.07, 136.30, 145.15, 147.99, 149.16, 159.26 (all Ph–*C* and Py–*C*). Anal. calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77. Found: C, 79.98; H, 7.82; N, 7.76.

4.3.5. (S)-2-[(2-Pyridylmethyl)amino]-1,1,3-triphenylpropan-1-ol **2e**

Starting material: 0.607 g (2 mmol) **1e**; reaction time: 48 h; work-up; purification by preparative TLC developed with EtOAc/hexane (1/3). After purification, **2e** was obtained as a white solid in 89% yield; mp 80–82°C; $[\alpha]_D^{26}=-49.0$ (*c* 0.8, CH_2Cl_2); IR (KBr) $\nu_{max}=3300$, 3010, 1588, 1483, 1435, 1050, 734, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (m, 1H, CH_APh), 2.96 (m, 1H, CH_BPh), 3.27 (m, 2H, CH_2Py), 4.01 (dd, $J=10.4$ Hz, $J=2.8$ Hz, 1H, C*H*NH), 6.65 (d, $J=8$ Hz, 1H, Ph*H*), 7.02–7.75 (m, 17H, Ph*H* and Py*H*), 8.31 (d, $J=4.8$ Hz, 1H, Py*H*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 37.72 (CH_2Ph), 54.04 (*C*HNH), 65.98 (CH_2NH), 78.58 (*C*–OH), 121.68, 121.86, 125.78, 126.12, 126.25, 126.47, 128.18, 128.94, 136.09, 139.48, 145.06, 147.34, 148.97, 158.77 (all Ph–*C* and Py–*C*). Anal. calcd for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10. Found: C, 82.20; H, 6.63; N, 7.09.

4.3.6. (S)-3-Methyl-2-benzylamino-1,1-diphenylbutan-1-ol **2f**

This compound was prepared by the similar procedures for **2a** except that using 2 mmol benzaldehyde instead of 2-pyridinecarboxaldehyde. Starting material 0.513 g (2 mmol) **1c**; reaction time: 48 h; work-up; purification by preparative TLC developed with EtOAc/hexane (1/4). After purification, **2f** was obtained as colorless crystals in 72% yield; mp 133–134°C; $[\alpha]_D^{28}=-40.8$ (*c* 0.5, CH_2Cl_2); IR (KBr) $\nu_{max}=3290$, 3025, 2992, 2900, 1590, 1485, 1443, 1049, 750, 738, 720, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (m, 3H, CH_3), 0.976 (d, $J=7.2$ Hz, 3H, CH_3), 2.06 (m, 1H, $CH(CH_3)_2$), 3.28 (d, $J=12$ Hz, CH_APh), 3.46 (d, $J=12$ Hz, 1H, CH_BPh), 3.65 (s, 1H, *CH*NH), 7.10–7.19 (m, 4H, Ph*H*), 7.22–7.33 (m, 7H, Ph*H*), 7.57 (d, $J=7.6$ Hz, 2H, Ph*H*), 7.72 (d, $J=8.0$ Hz, 2H, Ph*H*). ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.99 (CH_3),

22.68 (CH_3), 28.72 ($CH(CH_3)_2$), 54.99 ($CHNH$), 68.51 (CH_2NH), 78.64 (C–OH), 125.80, 126.08, 126.20, 127.25, 127.91, 128.09, 128.43 (all Ph–C and Py–C). Anal. calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.06. Found: C, 83.43; H, 7.89; N, 4.06.

4.4. A typical procedure for the enantioselective addition of diethylzinc to aromatic aldehydes in the presence of chiral **2**

To a solution of chiral **2** (0.01 mmol) in toluene (0.5 ml) was added diethylzinc (4.17 M in *n*-hexane, 2.5 mmol) by syringe and the mixture was stirred for 1 h at rt. Then an aromatic aldehyde (0.2 mmol) was added and the mixture was stirred for 5–12 h at rt. Aqueous hydrochloric acid (1N) was added to quench the reaction. The resulting mixture was extracted with ether, and the extract was washed with brine, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on preparative TLC (hexane/AcOEt = 4/1). The product was identified with comparing the ^1H NMR and IR spectra with those of authentic samples. Experimental results were summarized in Tables 1–3. Optical purities (% ee) were determined by HPLC using a chiral OD column or by optical rotation. Conditions of HPLC analyses: chiral column, Chiralcel OD, 4.6×250 mm; detection, 216-nm light. For 1-phenylpropanol: eluent, 2% 2-propanol in hexane; flow rate, 1 ml/min; retention time (min), *S* isomer 16.79, *R* isomer 14.53. For 1-(*p*-chlorophenyl)propanol: 3% 2-propanol in hexane; 0.5 ml/min; *S* isomer 20.24, *R* isomer 21.79. For 1-(*p*-methoxyphenyl)propanol: 3% 2-propanol in hexane; 0.5 ml/min; *S* isomer 35.06, *R* isomer 29.93. For 1-(*o*-methoxyphenyl)propanol: 3% 2-propanol in hexane; 0.5 ml/min; *S* isomer 23.75, *R* isomer 25.83. For 1-(1-naphthyl)propanol: 3% 2-propanol in hexane; 0.5 ml/min; *S* isomer 19.04, *R* isomer 40.11. For 1-(*m*-chlorophenyl)propanol: 3% 2-propanol in hexane; 0.5 ml/min; *S* isomer 21.43, *R* isomer 23.20. For 1-ferrocylpropanol: 0.45% 2-propanol in hexane; 1.5 ml/min; minor isomer 25.99, major isomer 24.35. For 1-(2-thienyl)propanol: 0.5% 2-propanol in hexane; 1.5 ml/min; *S* isomer 27.36, *R* isomer 24.89. For (*E*)-1-phenylpent-1-en-3-ol: 3% 2-propanol in hexane; 1 ml/min; *S* isomer 33.20, *R* isomer 18.30.

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