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Efficient asymmetric addition of diethylzinc to aldehydes using C_2-novel chiral pyridine β-amino alcohols as chiral ligands

Weijie Zhang, Ruiren Tang*, Huirong Yu and Shu Gao

A series of novel C_2-symmetric chiral pyridine β-amino alcohol ligands have been synthesized from 2,6-pyridine dicarboxaldehyde, m-phthalaldehyde and chiral β-amino alcohols through a two-step reaction. All their structures were characterized by ^{1}H NMR, ^{13}C NMR and IR. Their enantioselective induction behaviors were examined under different conditions such as the structure of the ligands, reaction temperature, solvent, reaction time and catalytic amount. The results show that the corresponding chiral secondary alcohols can be obtained with high yields and moderate to good enantiomeric excess. The best result, up to 89% ee, was obtained when the ligand 3c (2*S*,2′*R*)-2,2′-((pyridine-2,6-diylbis(methylene)) bisazanediyl))bis(4-methyl-1,1-diphenylpentan-1-ol) was used in toluene at room temperature. The ligand 3g (2*S*,2′*R*)-2,2′-((1,3-phenylenebis(methylene))bis(azanediyl))bis(4-methyl-1,1-diphenylpentan-1-ol) was prepared in which the pyridine ring was replaced by the benzene ring compared to 3c in order to illustrate the unique role of the N atom in the pyridine ring in the inductive reaction. The results indicate that the coordination of the N atom of the pyridine ring is essential in the asymmetric induction reaction. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: amino alcohol; C_2-symmetric; diethylzinc; aldehydes; enantioselective addition; (*S*)-secondary alcohol

Introduction

Synthesis of a chiral secondary alcohol by asymmetric addition of dialkylzincs to an aldehyde is one of the most successful areas in asymmetric synthesis of optically and biologically active compounds. In order to develop more efficient ligands for the reaction, much effort has been devoted towards the design and preparation of various novel chiral ligands such as β-amino alcohols,[1] amino thiols,[2] pyridyl alcohols,[3] amines,[4] aminonaphthol,[5] *o*-hydroxylbenzylamines,[6] BINOL,[7] Ti complexes,[8] polymers tethered to chiral ligands[9] and their derivatives. Since the pioneering work of Oguni *et al.* in 1984,[10] the enantioselective addition of organozinc reagents to aldehydes using chiral amino alcohols has received wide attention as a model system for exploring asymmetric carbon–carbon bond formation. Recently, this method has been used to synthesize active natural product prostaglandin ω-side chain in high enantioselectivity.[11] β-Amino alcohols, as one kind of important ligand, may accelerate and direct the stereochemical outcome of the asymmetric alkylation of aldehydes by zinc dialkyls, sometimes achieving high stereoselectivity,[12] which can be easily prepared and modified from natural, cheap chiral amino acids, and are tolerant to moisture, oxygen and many types of reagents. On the other hand, chiral C_2-symmetric ligands are one of the most widely employed catalysts for asymmetric catalysis and have been shown to exhibit excellent enantioselectivity in the alkylzinc addition to aldehydes, because chiral C_2-symmetric ligands have the advantage of reducing the number of possible competing, diastereomeric transition states.[13] Taking into account the above advantage of C_2-symmetric ligands and β-amino alcohols, a series of ligands combining C_2-symmetric ligands and β-amino alcohols were designed and synthesized; also their chiral inductive effects in asymmetric addition of diethylzinc to aldehydes were investigated. The pyridyl moiety, whose N atom has strong coordination ability, was introduced into the ligands in order to investigate the influence of the pyridine unit of chiral β-amino alcohols on catalytic enantioselective additions of diethylzinc to aldehydes.

To the best of our knowledge, there has been only one report so far, disclosed by Williams and co-workers applying 2,6-disubstituted pyridiylmethyl amino alcohols as chiral ligands for the enantioselective diethylzinc addition to aldehydes.[14] Instead of setting (1*R*,2*S*)-ephedrine as the asymmetric center as Williams did, we initially use a serial of chiral amino acid analogues which comparatively make the study more systematic.

Williams carried out an extensive study on pyridine-based dimeric amino alcohol ligand **L_2** in diethylzinc addition and compared it with **L_1** containing no pyridine ring (Fig. 1). According to the catalytic results of C_2-symmetric ligands based upon incorporation of the two units (−)-(1*R*,2*S*)-ephedrine,[15] the two ligands were found to lead to products with opposite chirality under similar reaction conditions; in most cases, the enantioselectivity of **L_2** was higher than that of **L_1**. It was also found that **L_2** was the most enantioselective ligand, giving 90% ee for the addition reaction. Thus we hoped that C_2-symmetric novel chiral pyridine β-amino alcohol ligands could also catalyze the asymmetric addition of diethylzinc to aldehydes. Herein we report a new type

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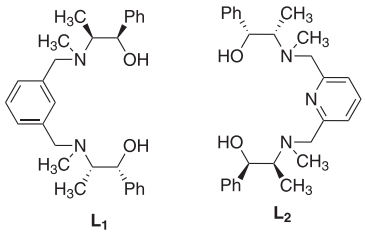


Figure 1. C_2-symmetric ligands based upon incorporation of the two units (−)-(1*R*,2*S*)-ephedrine.

of efficient C_2-symmetric β-amino alcohol ligand, obtained from naturally occurring L-α-amino acid based on active pyridine systems. Their enantioselective induction in enantioselective additions of diethylzinc to aldehydes are described and discussed in detail.

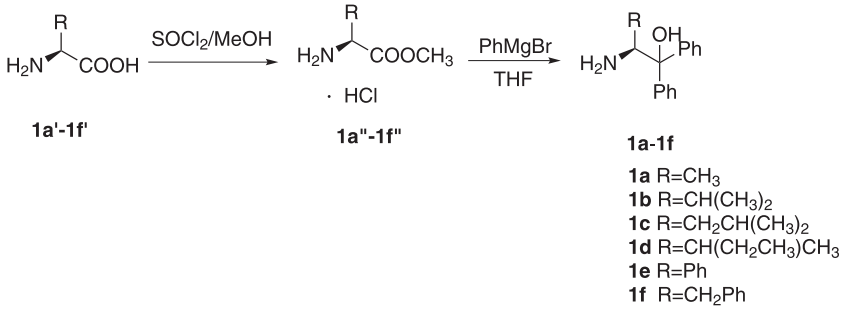
Results and Discussion

Synthesis of 1a–f, 2,6-Disubstituted Pyridylmethyl Amino Alcohols 3a–f and 1,3-Disubstituted Benzyl Amino Alcohol 3g.

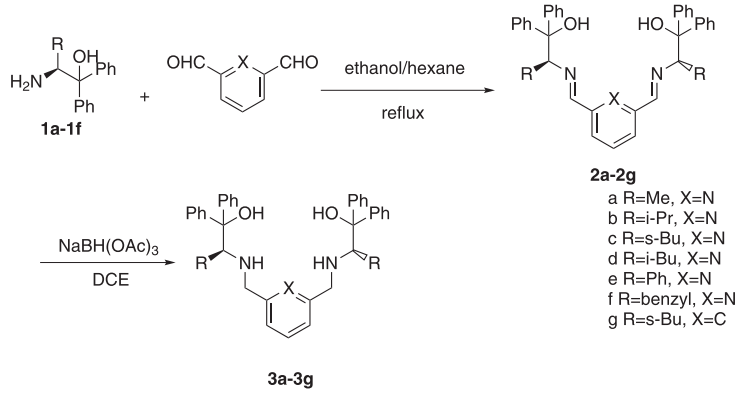
The synthesis of compounds **1a–f** is shown in Scheme 1. The corresponding β-amino alcohols **1a–f** could be prepared from the commercially available natural amino acids. We envisioned an alternative synthesis of **1a–f** in one-pot synthesis to give an economical preparative method in which the reaction product of the initial step was used directly without purification for the next step. The key steps are shown as follows. **1a′–f′** were converted into the methyl esters hydrochloride **1a″–f″** with excess $SOCl_2$ in MeOH, with 97% yield. Addition of excess phenylmagnesium bromide to the methyl ester hydrochloride in order to introduce a gem-diphenyl group to the methyl ester hydrochloride provided the corresponding amino alcohols **1a–f** with 46–63% yield.

The route to the novel chiral C_2-symmetric ligands **3a–g** is shown in Scheme 2. 2,6-Pyridinedicarboxaldehyde or *m*-phthalaldehyde was mixed with β-amino alcohols **1a–f** in dry ethanol and cyclohexane and refluxed for 2 h; a Dean–Stark trap for removing water was used for a further 2 h. Upon the removal of solvent, the Schiff bases **2** were obtained in viscous oil which could be directly used in the next step without purification. The reduction of the Schiff bases **2** is the key step for preparation of the ligands. Sodium borohydride was first employed in ethanol at room temperature for about 24 h; thin-layer chromatography (TLC) showed that the reductions proceeded rather sluggishly and too much solvent was needed in the reaction. Sodium triacetoxyborohydride was then used in dry l,2-dichloroethane (DCE) to reduce the Schiff bases following the procedure of Christopher[15] and **3a–g** were obtained in moderate yields (46-66%); the work-up step was simple.

Another route is designed to prepare the title compound as shown in Scheme 3. Pyridine-2,6-dicarbonyl dichloride and β-amino alcohol (take **1a** as an example) were mixed together in the presence of triethylamine in DCM and the **2a′** obtained with 74% yield, then lithium aluminum hydride was used to try to reduce amide **2a′** to afford the target product **3a**. Unfortunately, too many byproducts were found by TLC and the desired product **3a** could not be liberated through the reaction. This synthetic route is not suitable for the title compound.



Scheme 1. Synthesis of **1a–f**.



Scheme 2. Synthesis of **3a–g**.

Enantioselective Addition of Diethylzinc to Aldehydes

2,6-Disubstituted pyridylmethyl amino alcohols **3a–f** with different substituent groups R were used as optically active ligands to induct the asymmetric addition of diethylzinc to benzaldehyde. The results are summarized in Table 1.

The results showed that the enantioselectivity (% ee) of the product catalyzed by ligands **3b** (5% ee), **3d** (6% ee) and **3e** (9% ee) was low. However, when the ligand possessing a CH_2 group at the α-carbon was used to catalyze the addition reaction, the enantioselectivity improved greatly. Comparing **3c** with **3b**, the former has a CH_2 group at the α-carbon, while the latter does not; enantioselectivity was significantly improved from 5% to 86% in the asymmetric induction. The same result can also be found in ligands **3e** and **3f**, in which enantioselectivity increased from 9% ee to 78% ee for the latter after inserting a CH_2 side chain into the α-carbon of the ligand. It was also found that ligand **3c**, with an *s*-butyl group at the α-carbon, provided higher enantioselectivity than that of ligand **3a** or **3f**, which possessed a relatively smaller methyl or benzyl group. Bulkiness of the R group in **3a**, **3c** and **3f** increased in the order $CH_3 < CH_2Ph < CH_2CH(CH_3)_2$, while enantioselectivity improved from 55% ee (**3a**), to 78% ee (**3g**) and 86% ee (**3c**). These results suggest that the substituent at α-carbon plays a critical role in the enantioselection of the addition reaction.

The influence and contribution exerted by the pyridine of the ligands in the asymmetric diethylzinc addition to benzaldehyde were also investigated. Three β-amino alcohol derivatives – **3c**, **3g** and **1c** – were investigated.

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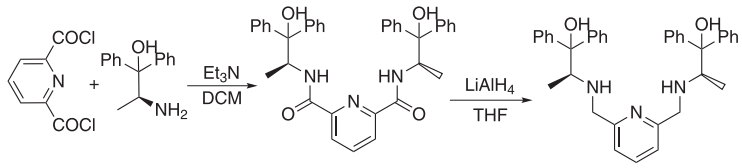


Scheme 3. Synthesis of **3a**.

From Table 1, ligand **3c**, possessing the pyridine ring, gave a product with enantioselectivity 86% ee, while **3g** and **1c**, which did not possess a pyridine ring, gave a lower enantioselectivity (75% ee and 68% ee). This result shows that the coordination of the pyridine ring in **3c** is required for high asymmetric induction.

Concerning the configuration (*R* or *S*) of product, only ligand **3e** induces the addition reaction to give (*R*)-configuration of alcohol, whereas a series of reverse (*S*)-configurations in the stereochemistry of the product are achieved by other ligands in the addition reaction.

Table 1. Screening of ligands **3a–g**, **1c** for the enantioselective addition of diethylzinc to benzaldehyde[a]

Ligand	R	Yield[b] (%)	ee[c] (%)	Config.[d]
3a	—CH_3	70	55	*S*
3b	—$CH(CH_3)_2$	79	5	*S*
3c	—$CH_2CH(CH_3)_2$	83	86	*S*
3d	—$CHCH_3(CH_2CH_3)$	72	6	*S*
3e	—Ph	82	9	*R*
3f	—CH_2Ph	78	78	*S*
3g	—$CH_2CH(CH_3)_2$	80	75	*S*
1c	—$CH_2CH(CH_3)_2$	79	68	*S*

[a]The reaction was carried out in toluene with 3 mol% ligand, 3.0–3.5 equiv. of diethylzinc (1.0 M solution in hexane) to benzaldehyde for 5 h at room temperature.
[b]Isolated yields by chromatographic purification.
[c]Determined by HPLC using a chiral OD-H column.
[d]Determined by comparison of optical rotations with the literature.

Table 2. Optimization of the asymmetric addition of diethylzinc to benzaldehyde catalyzed by **3c**[a]

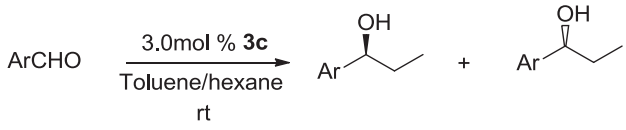
Entry	Mol%, **2c**	*T* (°C)	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)	Config.[d]
1	1.0	r.t.	T/H	5	75	69	S
2	3.0	r.t.	T/H	5	84	89	S
3	5	r.t.	T/H	5	86	84	S
4	20	r.t.	T/H	5	78	83	S
5	10	0	T/H	28	82	86	S
6	10	−20	T/H	28	74	88	S
7	5	0	T/H	28	74	84	S
8	10	r.t.	DCM/H	5	78	78	S
9	10	r.t.	THF/H	5	81	72	S

[a]T/H, Toluene/hexane, 4/1 (v/v); DCM/H, THF/H, 4/1 (v/v).
[b]Isolated yields by chromatographic purification.
[c]Determined by HPLC using a chiral OD-H column.
[d]Determined by comparison of optical rotations with the literature.

Subsequently, reaction factors such as type of solvent, catalytic amount and temperature for the asymmetric induction reaction were optimized, and the results are shown in Table 2. First, three types of solvent (THF, DCM, toluene) were examined and the results revealed that the less polar aromatic solvent toluene gave the product with the highest enantioselectivity and acceptable yield (Table 2**,** entries 2, 8 and 9). The effect of amount of ligand on enantioselectivity was also investigated. When the quantity of **3c** was decreased from 20 to 3 mol%, the enantioselectivity in the ethylation of benzaldehyde remained at 89% ee, but an even lower amount of ligand **3c** (1 mol%) led to a sharp decrease in the enantioselectivity (69% ee) in this reaction (Table 2, entry 1). Therefore, when the ratio of ligand **3c** to benzaldehyde was 3 mol%, high enantioselectivity can be achieved. Concerning reaction temperature, it is noteworthy that decreasing temperature affected neither the yield nor the enantioselectivity to a great extent (Table 2, entries 5 and 6; Table 1, entry 3).

Next, a series of aldehydes with different substituents were examined under the optimal reaction conditions and the results are summarized in Table 3. In all cases the reactions were carried out smoothly in toluene at room temperature and as with the addition to benzaldehyde, the corresponding alcohol of (*S*)-configuration was obtained as the major enantiomer. Obviously, the catalytic diethylzinc addition to aldehyde possessing an electron-withdrawing group in the *para* position of the aromatic ring proceeded with higher enantioselectivity than the addition to an aldehyde with an electron-donating group (Table 3, entries 1–4) probably due to an electronic effect,[13] and the same result (Table 3, entries 5 and 7) could be obtained from the *ortho*-substituent aromatic aldehydes. The best

Table 3. Enantioselective addition of diethylzinc to various aldehydes in the presence of ligand **3c**[a]



Entry	Aldehyde	Yield[b] (%)	ee[c] (%)	Config.[d]
1	4-MeC_6H_4CHO	79	82	*S*
2	4-$MeOC_6H_4CHO$	78	79	*S*
3	4-ClC_6H_4CHO	75	83	*S*
4	4-BrC_6H_4CHO	80	86	*S*
5	2-MeC_6H_4CHO	76	77	*S*
6	3-MeC_6H_4CHO	74	89	*S*
7	2-ClC_6H_4CHO	83	84	*S*
8	(*E*)-Cinnamaldehyde	78	76	*S*
9	2-Naphthaldehyde	80	85	*S*
10	2-Furaldehyde	78	32	*S*

[a]The reaction was carried out in toluene with 3 mol% ligand, 3.0–3.5 equiv. of diethylzinc (1.0 M solution in hexane) to benzaldehyde for 5 h at room temperature.
[b]Isolated yields by chromatographic purification.
[c]Determined by HPLC using a chiral OD-H or AD-H column.
[d]Determined by comparison of optical rotations with the literature.

asymmetric induction was found using *m*-methyl benzaldehyde as the substrate, which gave up to 89% ee compared with other substituted benzaldehydes (Table 3, entries 1–7). However, 2-furaldehyde was the poorest substrate of the addition reaction, giving 32% ee. This result can be explained by the heteroatoms on the ring participating in the competition coordination, which interfere with enantiomeric recognition (Table 3, entry 10). In testing some representative aromatic aldehydes, when the enantioselective addition of diethylzinc to α,β-unsaturated aldehyde (*E*)-cinnamaldehyde was performed under the same reaction conditions, unfortunately the enantioselectivity was at a lower level compared with that obtained from aromatic aldehydes (Table 3, entries 4, 6, 8 and 9). The reactions on aliphatic aldehydes cannot be carried out due to lack of baseline separation of products on chiral columns and the limited analysis conditions available in our laboratory.

Possible Reaction Mechanism

By comparing the experimental results catalyzed by ligand **3c** (up to 86% ee) with **3g** (up to 75% ee) (Table 1), we can conclude that the coordination of the *N* atom on the pyridine ring with diethylzinc plays an important role in the reaction. Perhaps it is because the modes of the initial coordination of the aldehyde in the ligand **3c** and **3g** system were different. Based on the above experimental results, theoretical analysis and the related mechanism suggested by Wu[16] and Corey[17] a possible reaction mechanism was proposed, as shown in Fig. 2. **3** reacts with diethylzinc to generate the corresponding zinc complex **4** and then converts to a tricyclic transition state **5**. The alkoxy oxygen atom in complex **5** coordinates with 1 equiv. of diethylzinc to give the transition state **6**. In the second step the benzaldehyde coordinates the zinc atom to afford **7**, then the ethyl group attacks the carbonyl group to form a six-membered cyclic structure **8**. Removal of zinc alkoxide from **8** afforded the product **9** with the elimination of **5**. Aqueous workup led to (*S*)-1-phenylpropan-1-ol, in accord with the experimental results.

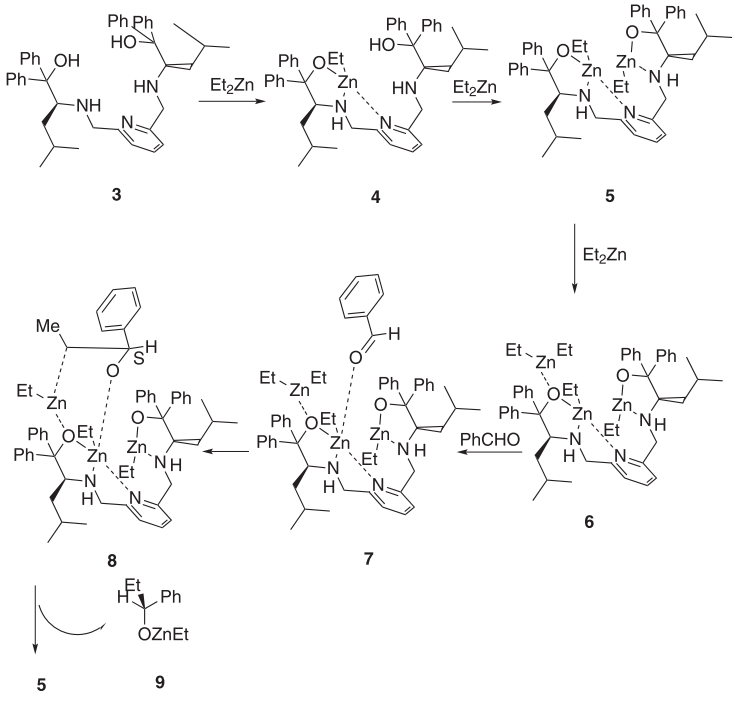


Figure 2. The proposed catalytic mechanism.

Conclusion

In summary, a novel range of C_2-symmetric chiral amino alcohols **3a–g** has been conveniently synthesized from 2,6-pyridinedicarboxaldehyde, m-phthalaldehyde and chiral β-amino alcohols. They were applied to the asymmetric addition to various aldehydes with diethylzinc. Among them, **3c** was found to give highly efficient asymmetric induction (up to 89% ee), which can be attributed to the presence of the pyridine ring and a CH_2 group at the α-carbon as a side chain. It is also noted that with 3 mol% ligand **3c**, at room temperature, the less polar aromatic solvent toluene was the most effective for asymmetric induction. Further applications of this type of chiral ligand for asymmetric reduction of prochiral ketone with borane are under investigation and will be reported in due course.

Experimental

General Methods

Melting points were recorded on an X-4 apparatus and are uncorrected. ^{13}C NMR and ^{1}H NMR spectra were recorded on a Bruker DPX 500 or 400 spectrometer using $CDCl_3$ or deuterated DMSO-d_6 as the solvent and TMS as an internal standard. Optical rotations were recorded with a Jasco-P-2000 digital polarimeter. IR spectra were recorded on KBr pellets on a Nicolet Impact 400D spectrophotometer. Enantioselectivity values were measured by HPLC, which was carried out on a Waters 600E type instrument using a chiral column (Chiralcel OD-H, AD-H Daicel Chemical Industries) and UV detector at 254 nm for determining the optical purity of the products by elution of isopropanol and hexane. Preparative TLC was performed on dry silica gel (60 F_{254}) plates. Merck silica gel 60 (particle size 0.04–0.063 mm) was employed for flash chromatography.

General Procedure for the Synthesis of Amino Alcohols 1a–f

All reactions were carried out under nitrogen atmosphere. 1,2-Dichloroethane, THF and toluene were dried over 4 Å molecular sieves. L-α-Amino acids and diethylzinc as a 1.0 M solution in hexane were purchased from Aldrich Chemical Company.

*(S)-2-Amino-1,1-diphenyl-propan-1-ol (**1a**)*

1a was easily prepared by the portion-wise addition of L-alanine methyl ester hydrochloride (3.1 g, 22.4 mmol) to phenylmagnesium bromide (24.4 g, 134.4 mmol) in THF at 0°C; the above solution was heated to room temperature and stirred for 20 h. After quenching with crushed ice and NH_4Cl salt, the organic layer was separated and the aqueous layer was extracted with AcOEt (25 ml × 3). Combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate and petroleum

ether, 4:1, v/v) to give the title compound **1a**. White solid; yield 63%; m.p. 93–94°C; $[\alpha]_D^{25} = -55.0$ ($c = 0.5$, CH_2Cl_2); IR (KBr) ν_{max} = 3432, 3390, 3324, 3082, 3057, 2986, 2902, 1588, 1488, 1446, 1362, 1175, 968, 746, 702 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 0.80 (d, 3H, $J = 4.0$ Hz, CH_3), 3.99 (m, 1H, $CHNH_2$), 5.20 (s, 1H, OH), 7.11–7.62 (m, 10H, PhH).

*(S)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol (**1b**)*

This compound was synthesized by the same procedures as **1a** and purified by silica gel column chromatography (ethyl acetate and petroleum ether, ranging from 2:1 to 4:1, v/v) to give the title compound **1b**. White solid; yield 57%; m.p. 92–93°C; $[\alpha]_D^{25} = -128.0$ ($c = 0.5$, $CHCl_3$); IR (KBr) ν_{max} = 3344, 3277, 2960, 2873, 1592, 1491, 1446, 1380, 1173, 1048, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.86 (d, 3H, $J = 5.2$ Hz, CH_3), 0.88 (d, 3H, $J = 5.2$ Hz, CH_3), 1.70 (m, 1H, $CH(CH_3)_2$), 2.20 (s, 1H, OH), 3.85 (d, 1H, $J = 2.0$ Hz, $CHNH_2$), 5.38 (s, 2H, NH_2), 7.18–7.62 (m, 10H, PhH).

*(S)-2-Amino-4-methyl-1,1-diphenylpentan-1-ol (**1c**)*

This compound was synthesized by the same procedures as **1a** and purified by silica gel column chromatography (methylene chloride and petroleum ether, ranging from 1:2 to 1:0, v/v). White solid; yield 46%; m.p. 137–139°C; $[\alpha]_D^{25} = -106.0$ ($c = 0.5$, $CHCl_3$); IR (KBr) ν_{max} = 3337, 3267, 2954, 2886, 1595, 1492, 1448, 1056, 746, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.86 (d, 3H, $J = 6.8$ Hz, CH_3), 0.89 (d, 3H, $J = 6.4$ Hz, CH_3), 1.15 (m, 1H, $CH(CH_3)_2$), 2.20 (s, 1H, OH), 1.62 (m, 2H, $CH_2CH(CH_3)_2$), 3.97 (t, 1H, $CHNH_2$), 7.26–7.62 (m, 10H, PhH).

*(S)-2-Amino-3-methyl-1,1-diphenylpentan-1-ol (**1d**)*

This compound was synthesized by the same procedures as **1a** and purified by recrystallization from ethanol. White solid; yield 52%; m.p. 174–176°C; $[\alpha]_D^{25} = -95.0$ ($c = 0.9$, $CHCl_3$); IR (KBr) ν_{max} = 3320, 3200, 3100, 3016, 2920, 1483, 1446, 1170, 1000, 745, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 0.86 (d, 3H, $J = 5.2$ Hz, CH_3), 0.88 (d, 3H, $J = 5.2$ Hz, CH_3), 1.70 (m, 1H, $CH(CH_3)_2$), 2.20 (s, 1H, OH), 3.85 (d, 1H, $J = 12$ Hz, $CHNH_2$), 5.38 (s, 2H, NH_2), 7.18–7.62 (m, 10H, PhH).

*(S)-2-Amino-1,1,2-triphenylethanol (**1e**)*

This compound was synthesized by the same procedures as **1a** and purified by recrystallization from ethanol. White solid; yield 50%; m.p. 146–148°C; $[\alpha]_D^{25} = -76.0$ ($c = 0.5$, $CHCl_3$); IR (KBr) ν_{max} = 3385, 3312, 3060, 3027, 1578, 1491, 1448, 749, 730, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.65 (s, 2H, NH_2), 5.04 (s, 1H, PhCHN), 4.71 (s, 1H, OH), 7.46–7.79 (m, 2H, PhH), 7.15–7.33 (m, 4H, PhH), 7.03–7.09 (6H, m, PhH).

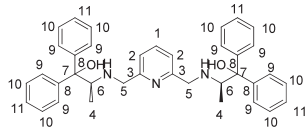
*(S)-2-Amino-1,1,3-triphenylpropan-1-ol (**1f**)*

This compound was synthesized by the same procedures as **1a** and purified by recrystallization from ethanol. White solid; yield 55%; m.p. 152–153°C; $[\alpha]_D^{25} = -67.0$ ($c = 0.5$, $CHCl_3$); IR (KBr) ν_{max} = 3366, 3058, 3023, 2962, 2861, 1597, 1491, 1449, 1055, 748, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.20 (s, 2H, NH_2), 2.34 (t,1H, $J = 12$ Hz, H_2Ph), 2.56 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 2.20 (s, 1H, OH), 3.85 (d, 1H, $J = 12.0$ Hz, $CHNH_2$), 7.10–7.58 (m, 15H, PhH).

General Procedure for the Synthesis of Ligands 3a–3g

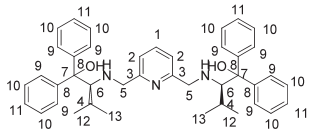
A solution of compound **1a–f** (7.4 mmol), 2,6-disubstituted pyridinecarboxaldehyde (0.25 g, 3.7 mmol) or *m*-phthalaldehyde (0.25 g, 3.72 mmol) in ethanol/cyclohexane was heated to reflux for 2 h, followed by use of a Dean–Stark trap for removing water for a further 2 h. The solvent was evaporated under reduced pressure, and followed by the addition of 1,2-dichloroethane (20 ml) and sodium triacetoxyborohydride (6.3 g, 114.8 mmol). The mixture was stirred at room temperature for 4 h. After removal of the solvent, saturated aqueous Na_2CO_3 (35 ml) solution was added to the residue and stirred for 0.5 h. The aqueous solution was extracted with ethyl acetate (25 ml × 3). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was loaded on a silica gel column chromatograph and purified by methanol and water or ethanol to afford the pure product.

*(2S,2′R)-2,2′-((Pyridine-2,6-diylbis(methylene))bis(azanediyl))bis(1,1-diphenylpropan-1-ol) (**3a**)*



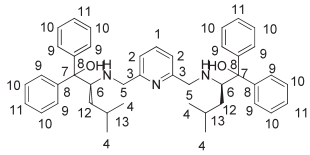
The crude product was purified by silica gel column chromatography (methylene chloride and ethyl acetate, 1:2, v/v), then recrystallized by methanol and water. **3a** was obtained as a white solid in 66% yield; m.p. 88–89°C; $[\alpha]_D^{25} = -28.0$ ($c = 0.5$, CH_2Cl_2); IR (KBr) ν_{max} = 3326, 3261, 3086, 3057, 2968, 2926, 1574, 1491, 1449, 748, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.93 (d, 6H, $J = 8.0$ Hz, CH_3), 1.15–1.19 (s, 2H, OH), 3.75–3.79 (m, 2H, CHNH), 3.61–3.39 (m, 4H, $PyCH_2$), 5.44 (s, 2H, CHNH), 6.93–6.95 (d, 2H, $J = 8.0$ Hz, PhH), 7.08–7.49 (m, 21H, PyH, PhH). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 15.7 (C4), 54.8 (C5), 67.9 (C6), 78.8 (C7), 120.0 (C11), 125.8, 126.0, 126.3, 126.5 (C9), 127.3, 127.9 (C10), 136.9 (C8), 146.2 (C2), 149.7 (C1), 158.2 (C3).

*(2S,2′R)-2,2′-((Pyridine-2,6-diylbis(methylene))bis(azanediyl))bis(3-methyl-1,1-diphenylbutan-1-ol) (**3b**)*



The crude product was purified by silica gel column chromatography (methylene chloride and ethyl acetate ranging from 1:0 to 0:1, v/v), then recrystallized by ethanol. **3b** was obtained as a white solid in 46% yield; m.p. 174–175°C; $[\alpha]_D^{25} = -76.0$ ($c = 0.5$, CH_2Cl_2); IR (KBr) ν_{max} = 3325, 3062, 3022, 2952, 2871, 1580, 1489, 1446, 1059, 754, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.71 (d, 6H, $J = 4.2$ Hz, $CH(CH_3)_2$), 0.87 (d, 6H, $J = 4.0$ Hz, $CH(CH_3)_2$) 1.95–1.98 (m, 2H, $CH(CH_3)_2$), 3.24 (s, 2H, $PyCH_2$), 3.38 (s, 2H, $PyCH_2$), 3.52 (s, 2H, CHNH), 5.23 (s, 2H, CHNH), 6.65–7.65 (m, 23H, PhH, PyH). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 16.0(C12), 22.7 (C13), 29.0 (C4), 55.3 (C5), 68.7 (C6),78.6 (C7), 120.7(C11), 125.8, 126.1, 126.4 (C9), 127.9, 136.6 (C10), 145.4(C2), 149.2(C1), 158.5(C3).

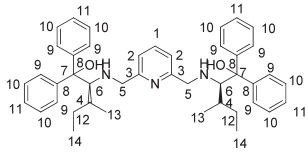
*(2S,2′R)-2,2′-((Pyridine-2,6-diylbis(methylene))bis(azanediyl))bis(4-methyl-1,1-diphenylpentan-1-ol) (**3c**)*



The crude product was purified by silica gel column chromatography (methylene chloride and ethyl acetate ranging from

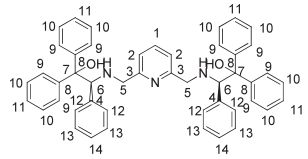
1:0 to 0:1, v/v), then recrystallized by ethanol. **3c** was obtained as white solid in 51% yield; m.p. 137–138°C; $[\alpha]_D^{25} = -60.0$ ($c = 0.5$, CH_2Cl_2); IR (KBr) $\nu_{max} = 3349$, 3060, 3027, 2951, 1591, 1491, 1449, 1031, 749, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.66 (d, 6H, $J = 6.4$ Hz, CH(CH_3)$_2$), 0.76 (d, 6H, $J = 6.4$ Hz, CH(CH_3)$_2$), 1.34–1.65 (m, 6H, $CHCH_2$(CH_3)$_2$), 3.10–3.39 (s, 2H, PyCH_2), 3.40–3.60 (s, 2H, PyCH_2), 3.60–3.70 (s, 2H, *CH*NH), 4.70–5.40 (s, 2H, CHN*H*), 6.70–6.80 (d, 2H, $J = 8.2$ Hz, Ph*H*), 7.10–7.58 (m, 21H, Py*H*, Ph*H*). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 21.6 (C4), 24.0 (C13), 40.6(C12), 54.3(C6), 62.8(C5), 78.6(C7), 120.7(C11), 125.9, 126.1, 126.3, 126.5(C9), 128.0 (C10), 136.6(C8), 145.2(C2), 148.1(C1), 158.9(C3).

*(2S,2′R)-2,2′-((Pyridine-2,6-diylbis(methylene))bis(azanediyl))bis(3-methyl-1, 1-diphenylpentan-1-ol) (**3d**)*



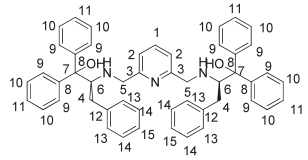
The crude product was purified by silica gel column chromatography (methylene chloride and ethyl acetate ranging from 1:0 to 0:1, v/v), then recrystallized by ethanol. **3d** was obtained as a white solid in 49% yield; m.p. 177–179°C; $[\alpha]_D^{25} = -84.0$ (c = 0.5, CH_2Cl_2); IR (KBr) $\nu_{max} = 3349$, 3060, 3027, 2951, 1591, 1575, 1491, 1449, 1050, 749, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.52 (s, 8H, CH_2CH_3), 0.78 (m, 10H, CH_2CH_3, CH_2CH), 3.33 (s, 2H, PyCH_2), 3.46–3.49 (s, 2H, $J = 12.0$ Hz, PyCH_2), 5.75 (s, 2H, CHN*H*), 6.66–6.68 (d, 2H, $J = 8.0$ Hz, Ph*H*), 7.06–7.64 (m, 21H, Ph*H*, Py*H*). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 12.3 (C14), 18.7 (C13) 22.4 (C12), 36.2 (C16), 55.3 (C5), 69.7 (C6), 78.5 (C7), 120.7(C11), 125.9, 126.1, 126.2, 126.5 (C9), 127.8(C10), 136.8 (C8), 145.4 (C2), 149.2 (C1), 158.5 (C3).

*(2S,2′R)-2,2′-((Pyridine-2,6-diylbis(methylene))bis(azanediyl))bis(1,1,2-triphenylethanol) (**3e**)*



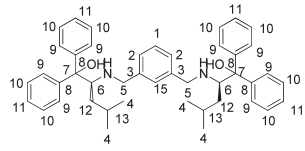
The crude product was purified by silica gel column chromatography (ethyl acetate and petroleum ether, 1:8, v/v), then recrystallized by methanol and water. **3e** was obtained as a white solid in 56% yield; m.p. 185–187°C; $[\alpha]_D^{25} = -42.0$ ($c = 0.5$, CH_2Cl_2); IR (KBr) $\nu_{max} = 3419$, 3059, 3026, 1592, 1492, 1449, 1032, 748, 697 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.51–3.52 (d, 4H, PyCH_2), 4.69 (s, 2H, Py*CH*), 5.65 (s, 2H, N*H*), 6.94–7.24 (m, 31H, Ph*H*, Py*H*), 7.57–7.62 (m, 2H, Py*H*). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 52.8 (C5), 70.2 (C6), 78.4 (C7) 112.0 (C11), 124.9 (C9, C12), 125.7 (C14), 127.7 (C10, C13), 128.4 (C4), 135.6 (C8), 139.2 (C2), 144.7 (C1), 148.2 (C3).

*(2S,2′R)-2,2′-((Pyridine-2,6-diylbis(methylene))bis(azanediyl))bis(1,1,3-triphenylpropan-1-ol) (**3f**)*



The crude product was purified by silica gel column chromatography (methylene chloride and ethyl acetate ranging from 1:0 to 0:1), then recrystallized by methanol and water. **3f** was obtained as a white solid in 56% yield; m.p. 72–73°C; $[\alpha]_D^{25} = -32.0$ ($c = 0.5$, CH_2Cl_2); IR (KBr) $\nu_{max} = 3326$, 3058, 3062, 1594, 1492, 1449, 1052, 746, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.96–3.00 (d, 2H, $J = 16.0$ Hz, PhCH_2), 3.13–3.24 (m, 6H, PhCH_2 , PyCH_2), 3.99–4.01 (d, 2H, $J = 8.0$ Hz, *CH*NH), 5.32 (s, 2H, CHN*H*), 6.47–6.49 (d, 2H, $J = 8.0$ Hz, Ph*H*), 7.05–7.70 (m, 31H, Ph*H*, Py*H*). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 37.8 (C4), 53.9 (C5), 68.5(C6), 78.6(C7) , 119.9 (C11, C15), 125.8(C9), 126.1, 126.2(C10), 126.5(C13), 126.7(C14), 128.2(C12), 136.29(C8), 139.6 (C2), 145.2 (C1), 147.6 (C3).

*(2S,2′R)-2,2′-((1,3-Phenylenebis(methylene))bis(azanediyl))bis(4-methyl-1, 1-diphenylpentan-1-ol (**3g**)*



The crude product was purified by silica gel column chromatography (ethyl acetate and petroleum ether, 1:9, v/v) and **3g** was obtained as white solid in 46% yield; m.p. 56–58°; $[\alpha]_D^{25} = -68.0$ ($c = 0.5$, CH_2Cl_2); IR (KBr) $\nu_{max} = 3432$, 3057, 3026, 2954, 1597, 1491, 1448, 1464, 1383,1364, 1031, 748, 703 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 0.76–0.80 (dd,12H, $J = 16.0$ Hz, CH(CH_3)$_2$), 1.07–1.13 (m, 2H, $CH(CH_3)_2$), 1.13–1.49 (m, 4H, CH_2CH), 1.59–1.63 (s, 2H, O*H*), 3.06–3.09 (d, 2H, $J = 12.0$ Hz, PyCH_2), 3.26–3.29 (d, 2H, $J = 12.0$ Hz, PyCH_2), 3.59–3.61 (m, 2H, $CHCH_2(CH_3)_2$), 6.89–7.29 (m, 16H, Ph*H*), 7.52–7.69 (m, 8H, Ph*H*). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 20.1 (C4), 24.9 (C13), 39.8 (C12), 53.2 (C6), 61.4 (C5), 78.5 (C7), 119.0 (C11), 123.2 (C2), 124.7, 125.1, 124.9 (C9), 125.6 (C1), 127.3 (C10), 130.2 (C15), 131.4 (C3), 136.8 (C8).

General Procedure for the Enantioselective Diethylzinc Addition to Aldehydes

To a stirring mixture of ligand **3c** (0.01 mmol) in toluene, diethylzinc (1.0 M in *n*-hexane, 3.0–3.5 mmol) was added by syringe at room temperature and the mixture was stirred for 2 h, followed by addition of the corresponding aldehyde (0.1 mmol). The mixture was stirred for 5–28 h at room temperature, and then quenched with 10–15 ml of a 10% solution of hydrochloric acid. The organic layer was separated and the aqueous phase was extracted with AcOEt (15 ml × 3). The organic layers were combined and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate and petroleum ether, 1:9, v/v) to afford the corresponding chiral alcohol as a colorless oil or light-yellow solid. Enantioselectivity was determined by HPLC analysis using a Chiralcel OD-H or AD-H column. Conditions of HPLC analysis: Chiralcel OD-H and Chiralcel AD-H 4.0 mm × 250 mml; detection, 254 nm light. OD-H: for (*R*)-1-phenyl-propan-1-ol: eluent: hexane/*i*-PrOH, 98:2; flow rate: 1.0 ml min^{-1}. For (*R*)-1-(2-naphthyl)-propan-1-ol: eluent: hexane/*i*-PrOH, 95:5; flow rate: 1.0 ml min^{-1}. For (*R*)-1-(4-Bromo-phenyl)-propan-1-ol: eluent: hexane/*i*-PrOH, 96:4; flow rate: 0.5 ml min^{-1}. For (*R*)-1-(4-methoxy-phenyl)-propan-1-ol: eluent: hexane/*i*-PrOH, 97:3; flow rate: 0.5 ml min^{-1}. For (*R*)-1-m-tolyl-propan-1-ol: eluent: hexane/*i*-PrOH 98:2; flow rate: 0.5 ml min^{-1}. For (*R*)-1-(4-chloro-phenyl)-propan-1-ol: eluent: hexane/*i*-PrOH, 97:3; flow rate: 0.5 ml min^{-1}. For 1-phenyl-pent-1-

en-3-ol: eluent: hexane/*i*-PrOH, 97:3; flow rate: 1.0 ml min^{-1}. For (*R*)-1-(2-furyl)-1-propanol: eluent: hexane/*i*-PrOH, 99:1; flow rate: 1.0 ml min^{-1}. AD-H: for (*R*)-1-*o*-tolyl-propan-1-ol, (*R*)-1-*p*-tolyl-propan-1-ol, (*R*)-1-(2-chloro-phenyl)-propan-1-ol: eluent: hexane/*i*-PrOH, 99:1; flow rate: 1.0 ml min^{-1}.

Acknowledgments

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