Synthesis of Chiral Aminophenols Based on Proline and Their Application in Enantioselective Addition of Diethylzinc to Aldehydes†

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Three 2-{(3*R*, 7*aS*)-1, 1-disubstituted-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-yl} phenols have been synthesized from salicylaldehyde and amino alcohols derived from *L*-proline, and used as ligands in enantioselective addition of diethylzinc to aldehydes, the *ee* values of obtained secondary alcohols were found in the range of 0—90%.

Keywords aminophenol, 2-{(3*R*, 7*aS*)-1,1-disubstituted-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-yl}-phenols, enantioselective addition, diethylzinc

Introduction

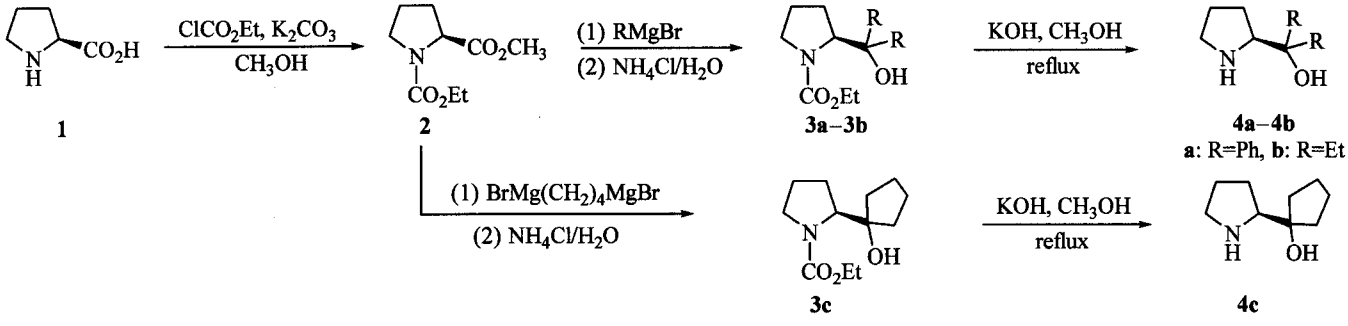
Catalytic asymmetric carbon-carbon bond formation is one of the most active research areas in organic synthesis. In this field, the application of chiral ligands in enantioselective addition of diethylzinc to aldehydes has attracted much attention, lots of ligands such as chiral amino alcohols,[1] amino thiols,[2] piperazines,[3] quaternary ammonium salts,[4] 1,2-diols,[5] oxazaborolidines[6] and transition metal complex with chiral ligands[7] have been reported. Among them, chiral amino alcohols have been widely used as chiral ligands in enantioselective addition of diethylzinc to aldehydes.[8] However, only a few amino phenols have been used as chiral ligands in enantioselective addition of diethylzinc to aldehydes.[9] In this paper we wish to report the synthesis of 2-{(3*R*, 7*aS*)-1,1-disubstituted-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-yl} phenols (**5a—5c**) and their applications in enantioselective addition of diethylzinc to aldehydes.

Results and discussion

Synthesis of aminophenols

As shown in Scheme 1, the chiral amino alcohols (**4a—4c**) were prepared from the naturally occurring *L*-proline using the reported method with modifications.[10] (*S*)-Proline-*N*-ethylcarbamate methyl ester (**2**) was prepared by treating (*S*)-proline with ethyl chloroformate and anhydrous potassium carbonate in absolute methanol. Then it was converted to ethyl (*S*)-2-[hydroxy(disubstituted)-methyl] pyrrolidine-1-carboxylate (**3a—3c**) by Grignard reaction and deprotected to give disubstituted (*S*)-(pyrrolidin-2-yl) methanols (**4a—4c**).

Scheme 1 Synthesis of chiral aminoalcohols **4a—4c**



1 2 3a–3b 4a–4b (a: R=Ph, b: R=Et) 3c 4c

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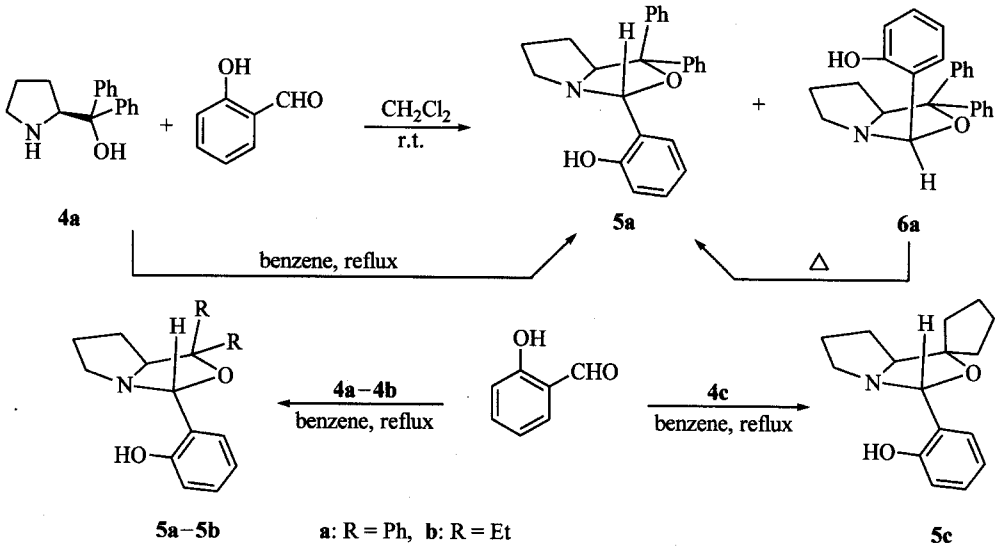
We supposed that the chiral aminophenols (**5a**—**5c**) could be obtained by the reactions of **4a**—**4c** with salicylaldehyde. In this step, a new chiral center would be generated and hence there would be two diastereomers formed. Indeed, it was the case when **4a** reacted with salicylaldehyde in methylene chloride at room temperature, two new spots on TLC, corresponding to **5a** and **6a**, respectively were observed. The pure form of **5a** could be obtained readily from the mixture by column chromatography, while the other diastereomer **6a** could be purified neither by column chromatography, nor by repeated recrystallization, because it generated **5a** constantly. These facts hint that the diastereomer **5a** is more thermodynamically stable than **6a**. In a practical preparation, **5a** was obtained by heating **4a** with excess of salicylaldehyde in benzene at reflux. These conversions are shown in Scheme 2. The structure of **5a** was confirmed by its X-ray single crystal analysis, which is shown in Fig. 1, the packing of molecules in a unit cell is shown in Fig. 2, and the selected bond lengths and bond angles are given in Table 1. Compounds **5b**—**5c** were similarly prepared by heating **4b**—**4c** with excess of salicylaldehyde in benzene at reflux.

One may argue that the compound **6a** might be an *O*- or *N*-semiacetal, which is ready to eliminate a water molecule to form **5a**. And this will explain the observed facts equally good. If this is true, the ^{1}H NMR spectum of **6a** should show the signals of OH of semiacetal and an alcohol OH or R_2NH. But these signals were not found in the ^{1}H NMR spectrum of impure **6a**.

Scheme 2 Syntheses of chiral aminophenols **5a**—**5c**



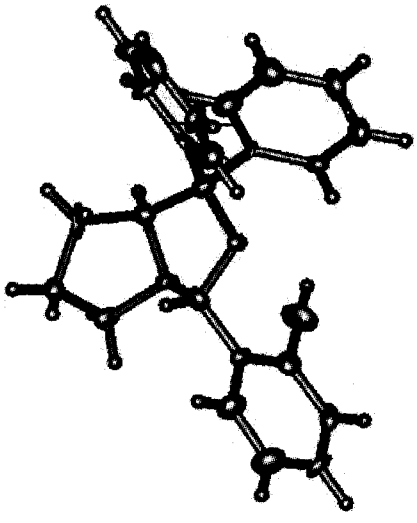


Fig. 1 Molecular structure of **5a**.

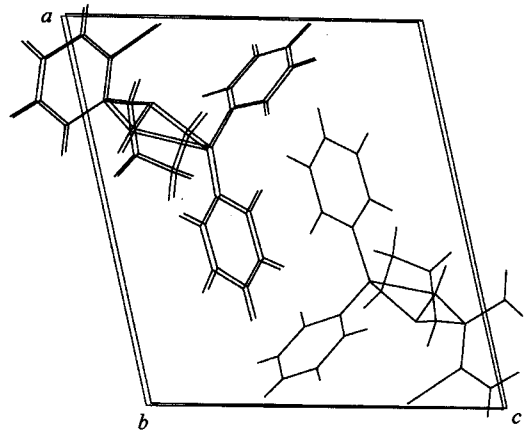


Fig. 2 Packing of molecules in a unit cell for **5a**.

Table 1 Selected bond lengths (nm) and bond angles (°) for compound **5a**

Bond	Distance	Bond	Angle	Bond	Angle
O(1)—C(1)	0.1425(6)	C(1)-O(1)-C(2)	109.8(4)	C(1)-N(1)-C(3)	101.6(4)
O(1)—C(2)	0.1445(6)	C(1)-N(1)-C(6)	111.8(4)	C(3)-N(1)-C(6)	105.3(4)
O(2)—C(8)	0.1345(6)	O(1)-C(1)-N(1)	102.6(4)	O(1)-C(1)-C(7)	110.3(4)
N(1)—C(1)	0.1477(6)	N(1)-C(1)-C(7)	113.3(4)	O(1)-C(2)-C(3)	102.4(4)
N(1)—C(3)	0.1468(6)	O(1)-C(2)-C(13)	109.5(4)	C(3)-C(2)-C(13)	113.7(4)
N(1)—C(6)	0.1467(7)	O(1)-C(2)-C(19)	109.3(4)	C(3)-C(2)-C(19)	111.1(4)
C(1)—C(7)	0.1497(7)	C(13)-C(2)-C(19)	110.5(4)	N(1)-C(3)-C(2)	101.9(4)
C(2)—C(3)	0.1585(8)	N(1)-C(3)-C(4)	106.6(4)	C(2)-C(3)-C(4)	118.3(4)
C(2)—C(13)	0.1525(7)	C(3)-C(4)-C(5)	105.1(5)	C(4)-C(5)-C(6)	104.4(4)
C(2)—C(19)	0.1522(8)	N(1)-C(6)-C(5)	106.9(4)	C(1)-C(7)-C(8)	122.4(5)
C(3)—C(4)	0.1536(8)	C(1)-C(7)-C(12)	119.1(4)	C(8)-C(7)-C(12)	118.5(5)
C(4)—C(5)	0.1550(8)	O(2)-C(8)-C(7)	121.8(5)	O(2)-C(8)-C(9)	118.3(5)
C(5)—C(6)	0.1540(8)				

The relative stability of **5a—5c** compared to **6a—6c** also confirmed the evidences from the results of total energies calculated using the PM3 semi-empirical method. The total energies of **5a—5c** are lower than their diastereomers by 55—80 kJ/mol, as shown in Table 2.

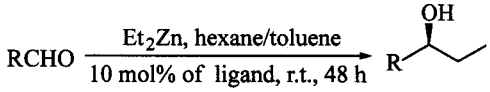
Table 2 Calculated total energies of **5a—5c** and **6a—6c**

Compound	Total energy ($kJ \cdot mol^{-1}$)
5a	-382229
6a	-382149
5b	-290619
6b	-290564
5c	-287633
6c	-287578

Enantioselective addition of diethylzinc to aldehydes

The results of enantioselective addition of diethylzinc to aldehydes using **5a—5c** as the ligands are summarized in Table 3. Surprisingly, although **5a—5c** have the same basic skeleton and all have the same kind of chiral centers, addition using **5a** as ligand gave (*S*)-form secondary alcohol as the major enatiomer in each case, while the addition using **5b—5c** as ligands resulted in the formation of (*R*)-form secondary alcohol as the major enatiomer. The relative stability of transition state should be responsible for this.[8,9a] Optimization of the reaction conformation of the addition of diethylzinc towards aldehydes using **5a/5b** as the ligand was performed using the PM3 semi-empirical method. When **5a** is employed as the ligand, the lowest-energy conformation is as shown in Fig. 3, wherein a *Si*-face attack by the ethyl group of the diethylzinc molecule is favored, resulting in the formation of (*S*)-form secondary alcohol as the major product. While using of **5b** as the ligand leads to a conformation shown in Fig. 4, favoring the *Re*-face attack, resulting in the formation of (*R*)-form secondary alcohol as the major product.

Table 3 Diethylzinc addition to aldehydes promoted by **5a—5c**



Entry	Ligand	R	Yield[a] (%)	*ee* (%)	Config.
1	**5a**	C_6H_5	98	45[b]	*S*[d]
2	**5b**	C_6H_5	90	9[b]	*R*[d]
3	**5c**	C_6H_5	73	13[b]	*R*[d]
4	**5a**	*m*-ClC_6H_4	96	67[c]	*S*[e]
5	**5b**	*m*-ClC_6H_4	97	22[c]	*R*[e]
6	**5c**	*m*-ClC_6H_4	97	2[c]	*R*[e]
7	**5a**	$C_6H_5CH=CH$	84	90[d]	*S*[d]
8	**5b**	$C_6H_5CH=CH$	75	20[d]	*R*[d]
9	**5c**	$C_6H_5CH=CH$	66	22[d]	*R*[d]
10	**5a**	*p*-$CH_3OC_6H_4$	45	55[d]	*S*[d]
11	**5b**	*p*-$CH_3OC_6H_4$	49	0[d]	—
12	**5c**	*p*-$CH_3OC_6H_4$	59	0[d]	—

[a] Isolated yields; [b] determined by capillary chiral GC analysis using a chiral column SUPELCO BETA DEX 120™; [c] determined by HPLC analysis using a chiral column CHIREX S-LEU & NEA (phenomenex); [d] based on the reported specific rotations in Ref. 11; [e] based on the reported specific rotations in Ref. 12.

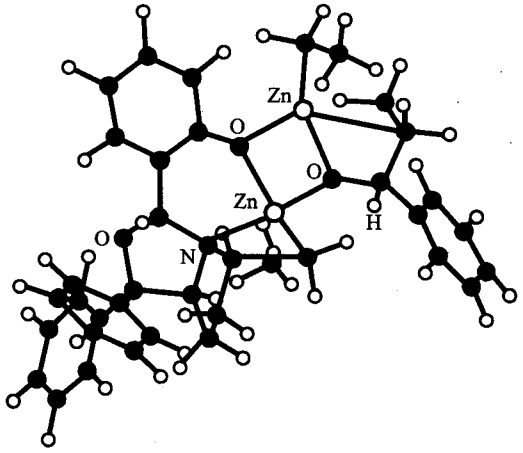


Fig. 3 Transition state of diethylzinc addition to benzaldehyde mediated by **5a**.

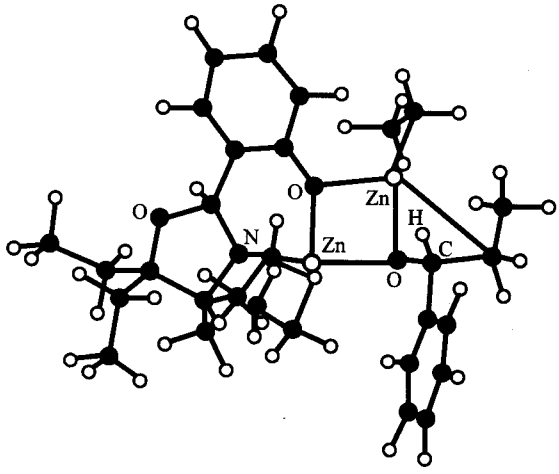


Fig. 4 Transition state of diethylzinc addition to benzaldehyde mediated by **5b**.

Experimental

General

Melting points were measured in capillaries and uncorrected. Optical rotationctra were recorded at 400 MHz, chemical shifts (δ) were reported in parts per million relative to tetramethylsilane (TMS). ^{13}C NMR were performed at 400 MHz. A Varian Inova-400 was used. Infrared spectra were recorded on an Nicolet Avatar 360 FT-IR. For preparative column chromatography, silica gel (H60) was used, with the solvent system given in the text. Organic solvents were dried and distilled prior to use.

Preparation of (S)-proline-N-ethylcarbamate methyl ester (**2**)

To a vigorously stirred suspension of *L*-proline (11.5 g, 100 mmol) and anhydrous potassium carbonate (27.6 g, 200 mmol) in 200 mL of absolute methanol with ice-water bath cooling, ethyl chloroformate (25.0 g, 220 mmol) was added dropwise within 1 h. Then the mixture was stirred for 9 h in an ice-water bath. After being stirred for one day at room temperature, the mixture was concentrated on a rotavapor. To the residue was added ethyl acetate (200 mL), the inorganic salts were removed by filtration and the filtrate was dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain **2** as colorless oil, yield 89%. It can be used for the next step without further purification.[10a]

Preparation of ethyl (S)-2-[hydroxy (disubstituted) methyl]-pyrrolidine-1-carboxylate (**3**)

The reactions were carried out under dry nitrogen atmosphere. To a stirred solution of Grignard reagent (50.0 mmol) in 35 mL of THF with an ice-water bath cooling, a solution of **2** (2.82 g, 14.0 mmol) in 10 mL of dry THF was slowly dropped in within 10 min. After being stirred for 45 min, the reaction was quenched by addition of 100 mL of saturated solution of ammonium chloride. The mixture was extracted with chloroform (3 × 30 mL), the organic phases were combined and washed with 30 mL of brine, dried over anhydrous sodium sulfate and evaporated to obtain the crude product.

Ethyl (S)-2-[hydroxy (diphenyl) methyl] pyrrolidine-1-carboxylate (**3a**) Purified by recrystallization from ethyl acetate, colorless needles, yield 64%, m.p. 110—111 ℃ (lit.[13] 115—116.5 ℃), $[\alpha]_D^{25}$ − 61.4 (*c* 5.0, EtOAc).

Ethyl (S)-2-(1-ethyl-1-hydroxypropyl) pyrrolidine-1-carboxylate (**3b**) Purified by column chromatography (ethyl ether/petroleum ether = 1 : 3), colorless oil, yield 72%, $[\alpha]_D^{22}$ − 84.3 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.92 (t, J = 7.6 Hz, 3H, CH_3), 0.97 (t, J = 7.2 Hz, 3H, CH_3), 1.28 (t, J = 8.0 Hz, 3H, CH_3), 1.44—2.04 (m, 8H, 4 × CH_2), 3.17—3.73 (m, 3H, CH_2, CH), 4.06—4.18 (m, 2H, CH_2); IR (film) ν: 3474 (OH), 1670 (C = O) cm^{-1}. Anal. calcd for $C_{12}H_{23}NO_3$: C 62.85, H 10.11, N 6.11; found C 62.53, H 10.09, N 6.03.

Ethyl (S)-2-(1-hydroxycyclopentyl) pyrrolidine-1-carboxylate (**3c**) Prepared according to the reported method,[10b] colorless oil, yield 54%, $[\alpha]_D^{22}$ − 59 (*c* 0.8, toluene).

Preparation of aminoalcohol (**4**)

The mixture of **3** (22.2 mmol), absolute methanol and potassium hydroxide (12.4 g, 222 mmol) was refluxed for 24 h. Then the methanol was removed by evaporation under reduced pressure. Water (30 mL) was added to the residue, the mixture was extracted with chloroform (3 × 30 mL), the organic phase was washed with 30 mL of brine, dried over anhydrous sodium sulfate and evaporated. The crude product is pure enough for the next step.

(S)-Diphenyl (pyrrolidin-2-yl) methanol (**4a**) Colorless crystal, yield 95 %, m.p. 76—77.5 ℃, $[\alpha]_D^{25}$ − 65.8 (*c* 3.0, CH_3OH). [lit.[10a] 74—74.8 ℃, $[\alpha]_D^{20}$

-68 (c 3.0, CH_3OH)].

(*S*)-3-*Pyrrolidin*-2-*ylpentan*-3-*ol* (**4b**) Colorless solid, yield 93%, m.p. 44—45 ℃, $[\alpha]_D^{22}$ − 29 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.84 (t, J = 7.6 Hz, 6H, 2 × CH_3), 1.32—1.85 (m, 8H, 4 × CH_2), 2.88—2.96 (m, 2H, CH_2N), 3.10 (t, J = 6.0 Hz, 1H, CH); IR ν: 3275, 3107 (OH, NH) cm^{-1}. Anal. calcd for $C_9H_{19}NO$: C 68.74, H 12.18, N 8.91; found C 68.50, H 11.93, N 8.69.

(*S*)-1-*Pyrrolidin*-2-*ylcyclopentanol* (**4c**) Colorless solid, yield 65%, $[\alpha]_D^{22}$ − 33 (c 0.8, CH_2Cl_2) [lit.[10a] 74—74.8 ℃, $[\alpha]_D^{20}$ − 35 (c 0.3, CH_2Cl_2)].

Preparation of aminophenol (**5**)

A mixture of aminoalcohol **4** (5 mmol) and salicylaldehyde (7 mmol) in benzene (20 mL) was refluxed for 6 h. The solvent was removed under reduced pressure. Diethyl ether (15 mL) and petroleum ether (15 mL) were added to the residue. After most of the solvent was removed, the crude product was filtered and diluted with petroleum ether to obtain **5**.

2-{ (3*R*,7*aS*)-1,1-*Diphenyltetrahydro*-1*H*-*pyrrolo* [1,2-*c*][1,3] *oxazol*-3-*yl*} *phenol* (**5a**) Colorless needles, yield 64%, m.p. 127—128 ℃, $[\alpha]_D^{22}$ − 179 (c 0.9, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ: 1.57—1.90 (m, 4H, 2 × CH_2), 2.81—2.85, 3.14—3.20 (m, 2H, NCH_2), 4.58 (t, J = 7.2 Hz, 1H, NCH), 5.57 (s, 1H, CH), 6.70—7.48 (m, 14H, 2 × C_6H_5, C_6H_4), 12.01 (s, 1H, OH); IR ν: 3463 (OH), 1622, 1593 (C_6H_5) cm^{-1}. Anal. calcd for $C_{24}H_{23}NO_2$: C 80.64, H 6.49, N 3.92; found C 80.46, H 6.56, N 3.95. Crystal System: monoclinic; space group $P2_1$, a = 1.1185(7) nm, b = 0.7059(4) nm, c = 1.2241(7) nm, β = 105.765(13), V = 0.9302(9) nm^3, D_{calc} = 1.276 g/cm^3, Z = 2, F(000) = 380.00, μ (Mo Kα) = 0.81 cm^{-1}.

2-{(3*R*,7*aS*)-1,1-*diethyltetrahydro*-1*H*-*pyrrolo* [1,2-*c*][1,3] *oxazol*-3-*yl*} *phenol* (**5b**) Pale yellow solid, yield 53%, m.p. 84—85 ℃, $[\alpha]_D^{22}$ + 46 (c 0.3, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ: 0.84 (t, J = 7.6 Hz, 3H, CH_3), 0.96 (t, J = 7.6 Hz, 3H, CH_3), 1.50—2.12 (m, 8H, 4 × CH_2), 2.67—2.73, 2.99—3.05 (m, 2H, NCH_2), 3.67 (t, J = 7.6 Hz, 1H, NCH), 5.12 (s, 1H, CH), 6.76—7.26 (m, 4H, C_6H_4), 12.65 (s, 1H, OH); IR ν: 3416 (OH), 1615, 1595 (C_6H_5) cm^{-1}. Anal. calcd for $C_{16}H_{23}NO_2$: C 73.53, H 8.87, N 5.36; found C 73.43, H 8.87, N 5.22.

2-(3′*R*,7*aS*)-*Tetrahydrospiro*[*cyclopentane*-1,1′-*pyrrolo*[1,2-*c*][1,3]*oxazol*]-3′-*ylphenol* (**5c**) Pale yellow solid, yield 48%, m.p. 68—69 ℃, $[\alpha]_D^{22}$ + 31 (c 0.7, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ: 1.59—2.00 (m, 12H, 6 × CH_2), 2.75—2.80, 3.04—3.08 (m, 2H, NCH_2), 3.75 (t, J = 6.0 Hz, 1H, NCH), 5.15 (s, 1H, CH), 6.77—7.28 (m, 4H, C_6H_4), 12.88 (s, 1H, OH); IR ν: 3448 (OH), 1610, 1596 (C_6H_5) cm^{-1}. Anal. calcd for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40; found C 73.95, H 8.24, N 5.32.

Typical procedure for the addition of diethylzinc to aldehydes catalyzed by **5a—5c**

A solution of 0.2 mmol chiral ligand in 20 mL of dry toluene and hexane (V/V = 1:1) was cooled to 0 ℃ and diethylzinc (0.5 mL, 4.8 mmol) was added under a nitrogen atmosphere. After 20 min, 2 mmol of aldehyde was added while stirring. The reaction mixture was gradually warmed to room temperature and stirred for 48 h. The reaction was quenched by addition of 10 mL of 10% hydrochloric acid at 0 ℃, then the organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ and NaCl solutions successively before drying over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography (ethyl acetate:petroleum ether = 1:10) to afford the optically active secondary alcohol.

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