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Enantioselective addition of diethylzinc to aldehydes catalyzed by (*R*)-1-phenylethylamine-derived 1,4-amino alcohols

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ABSTRACT

A series of *o*-xylylene-type 1,4-amino alcohols, synthesized from (*R*)-1-phenylethylamine, were used as chiral ligands for the enantioselective addition of diethylzinc to benzaldehyde. (*S*)-1-Phenyl-1-propanol was obtained with high enantioselectivity in all cases since the stereochemical outcome of the reaction was controlled by the chiral benzylic carbon bearing amino group. Highest catalytic activity was obtained by using (*R*)-1-{2-[1-(pyrrolidin-1-yl)ethyl]phenyl}cyclohexan-1-ol (**1n**) derived from (*R*)-1-(1-phenylethyl)pyrrolidine and cyclohexanone. Various chiral secondary alcohols were obtained by the reaction of diethylzinc and aldehydes in the presence of **1n** within 2 h with good to high enantioselectivities.

1. Introduction

During the past few decades, a number of chiral 1,2- and 1,3-amino alcohols have been developed and utilized as chiral ligands and chiral auxiliaries in various asymmetric reactions.[1] The asymmetric alkylation of aldehydes is one of the important method for the preparation of chiral secondary alcohols, which are useful as intermediate of natural products and pharmaceuticals.[2] Since the initial report by Oguni and Omi in 1984,[3] the enantioselective addition of organozinc compounds to aldehydes has been well-investigated using chiral 1,2- and 1,3-amino alcohol ligands.[2,4–6] Meanwhile, little attention has been paid to the reaction using chiral 1,4-amino alcohols, since the high levels of enantioinduction are generally difficult by chiral zinc catalysts containing relatively flexible seven-membered ring structures generated from organozinc compounds and 1,4-amino alcohol ligands.[7]

Recently, we reported the synthesis of novel diastereomeric 1,4-amino alcohols **2** with *o*-xylylene structure from an enantiopure chiral 1,4-diol, (*S,S*)-1,2-bis(1-hydroxypropyl)benzene, and their use in the enantioselective addition of diethylzinc to aldehydes (Fig. 1a and b).[8] Both enantiomers of the corresponding chiral secondary alcohols were obtained with high enantioselectivities by using the diastereomeric 1,4-amino alcohols (*R,S*)-**2** and (*S,S*)-**2** with different absolute configurations at the chiral carbon bearing amino group. The results are in contrast with those using 1,2-amino alcohols where the stereochemical outcome of the reaction is generally determined by the chiral carbon bearing hydroxy group.[2,4,9] Although the high selectivities were achieved in the reactions using our novel 1,4-amino alcohols, the preparation of them required multistep synthesis from commercially available compounds. This prompted us to develop novel chiral 1,4-amino alcohols with similar structure to **2** starting from chiral 1-phenylethylamine (**3**) as both enantiomers of **3** are commercially available. Herein, we report a short step synthesis of various 1,4-amino alcohols **1** with *o*-xylylene structure starting from **3** and their use in the enantioselective addition of diethylzinc to aldehydes (Fig. 1c).

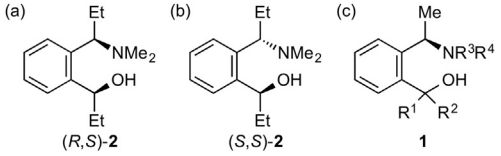

Fig. 1. 1,4-Amino alcohols with *o*-xylylene structure.

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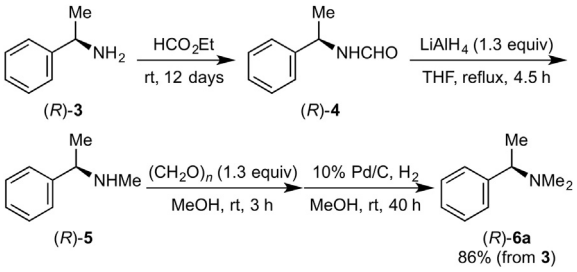
2. Results and discussion

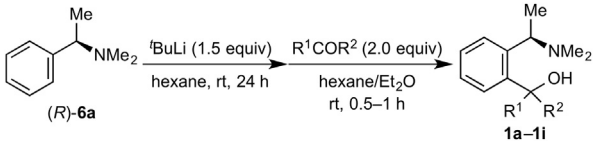
First, a stepwise methylation of (*R*)-1-phenylethylamine (**3**) was carried out as shown in Scheme 1. Primary amine (*R*)-**3** was stirred in ethyl formate at room temperature for 12 days, and the reduction of the resulting formamide (*R*)-**4** with lithium aluminum hydride in refluxing tetrahydrofuran gave (*R*)-*N*-methyl-1-phenylethylamine (**5**). The secondary amine **5** was mixed with paraformaldehyde in methanol at room temperature, followed by the hydrogenation in the presence of palladium on carbon afforded (*R*)-*N*,*N*-dimethyl-1-phenylethylamine (**6a**) in 86% yield from (*R*)-**3**.



Scheme 1. Synthesis of (*R*)-*N*,*N*-dimethyl-1-phenylethylamine (**6a**).

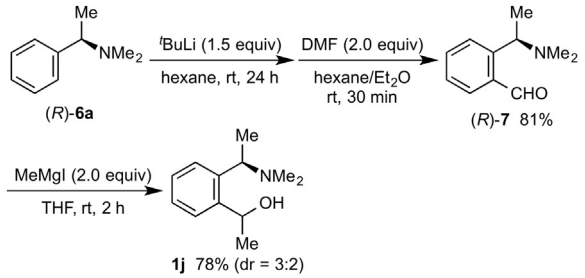
Next, a series of chiral 1,4-amino alcohols **1a**–**1i** were synthesized from (*R*)-**6a** and various carbonyl compounds (Table 1). The tertiary amine (*R*)-**6a** was treated with *tert*-butyllithium in hexane at room temperature for 24 h, and the reaction of the resulting *ortho*-lithiated species with propanal in hexane/diethyl ether at room temperature gave 1,4-amino alcohol **1a** in 83% yield as a diastereomeric mixture (dr=3:2, entry 1). Similarly, the reaction with isobutyraldehyde and benzaldehyde afforded the corresponding 1,4-amino alcohols **1b** and **1c** in 83% and 79% yields as diastereomeric mixtures, respectively (entries 2 and 3). When paraformaldehyde and symmetric ketones were used as electrophile, the corresponding 1,4-amino alcohols **1d**–**1i**, in which benzylic carbon bearing hydroxy group is achiral, were obtained in 23–62% yield (entries 4–9). 1,4-Amino alcohol **1j** was synthesized in two steps from (*R*)-**6a** (Scheme 2). The addition of the *ortho*-lithiated (*R*)-**6a** to *N*,*N*-dimethylformamide afforded aldehyde (*R*)-**7** in 81% yield. The reaction of (*R*)-**7** with methylmagnesium iodide in tetrahydrofuran at room temperature gave **1j** in 78% yield as a diastereomeric mixture (dr=3:2).

Table 1
Synthesis of amino alcohols **1a**–**1i**



Entry	1,4-Amino alcohol	R^1	R^2	Yield (%)
1	**1a**	Et	H	83[a]
2	**1b**	*i*-Pr	H	83[a]
3	**1c**	Ph	H	79[a]
4	**1d**	H	H	45
5	**1e**	Me	Me	37
6	**1f**	Et	Et	62
7[b]	**1g**	$-(CH_2)_4-$		23
8[b]	**1h**	$-(CH_2)_5-$		55
9[c]	**1i**	$-(CH_2)_6-$		54

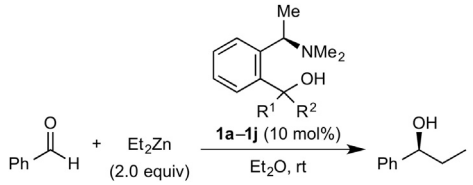
[a] Diastereomeric ratio was 3:2 by ^{1}H NMR analysis.
[b] The reaction with ketone was carried out at −78 °C.
[c] *t*-BuLi (1.0 equiv) and cycloheptanone (1.0 equiv) were used. The lithiation time was 3.5 h.



Scheme 2. Synthesis of 1,4-amino alcohol **1j**.

Enantioselective addition of diethylzinc to benzaldehyde was examined by using various 1,4-amino alcohols **1a**–**1j** (Table 2). When the reaction of benzaldehyde with 2.0 equiv of diethylzinc was carried out in the presence of **1a** in diethyl ether at room temperature, the reaction was completed in 8 h to afford (*S*)-1-phenyl-1-propanol in 84% yield with 95% ee (entry 1). The chiral secondary alcohol was obtained with high enantiomeric excess, although a diastereomeric mixture of **1a** (dr=3:2) was used in the reaction. This result confirms that the enantioselectivity of the reaction is controlled solely by the chiral carbon bearing amino group, as was observed in our previous publication.[8a] Diastereomeric mixtures of 1,4-amino alcohols **1b**, **1c**, and **1j** were then used in the same reaction, and the products were obtained with high enantiomeric excesses (>90% ee) in all cases (entries 2, 3, and 10). Moreover, the reaction using **1d** with single chiral carbon center also produced (*S*)-1-phenyl-1-propanol in 87% yield with 92% ee, clearly indicating that the chirality at the benzylic carbon bearing hydroxy group is unnecessary for the high levels of enantioinduction in this reaction (entry 4).[10] The introduction of two alkyl groups at benzylic carbon bearing hydroxy group was effective to enhance the reaction rate (entries 5–9), even though the reaction required 15 h when **1d** was used. Among them, good results were obtained by using **1g** (1.5 h, 82%, 95% ee) and **1h** (2.5 h, 87%, 95% ee) containing cyclopentane or cyclohexane rings, respectively (entries 7 and 8).

Table 2
Enantioselective addition of diethylzinc to benzaldehyde catalyzed by 1,4-amino alcohols **1a**–**1j**

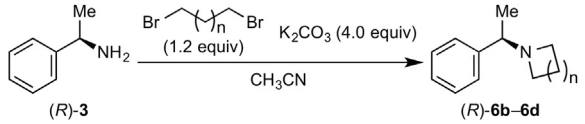


Entry	1,4-Amino alcohol	R^1	R^2	Time (h)	Yield (%)	ee[a] (%)
1	**1a**[b]	Et	H	8	84	95
2	**1b**[b]	*i*-Pr	H	6	88	94
3	**1c**[b]	Ph	H	9	85	90
4	**1d**	H	H	15	87	92
5	**1e**	Me	Me	6	88	91
6	**1f**	Et	Et	6	89	93
7	**1g**	$-(CH_2)_4-$		1.5	82	95
8	**1h**	$-(CH_2)_5-$		2.5	87	95
9	**1i**	$-(CH_2)_6-$		4	87	93
10	**1j**[b]	Me	H	14	88	94

[a] Determined by HPLC analysis.
[b] Diastereomeric ratio was 3:2 by ^{1}H NMR analysis.

To examine the effect of substituents on the amino group of the 1,4-amino alcohols, cyclic tertiary amines (*R*)-**6b**–**6d** were synthesized from (*R*)-**3** (Table 3). In the presence of 4.0 equiv of potassium carbonate, the reaction of (*R*)-**3** with 1,3-dibromopropane in acetonitrile at 50 °C gave (*R*)-1-(1-phenylethyl)azetidine (**6b**) in

Table 3
Synthesis of cyclic tertiary amines (*R*)-**6b**–**6d**



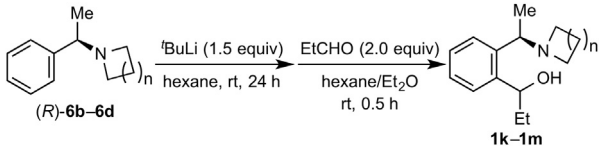
(*R*)-**3** (*R*)-**6b**–**6d**

Entry	Compound	Temp	Time (h)	Yield (%)
1	**6b** (*n*=1)	50 °C	120	61
2	**6c** (*n*=2)	Reflux	8	86
3	**6d** (*n*=3)	Reflux	8	94

61% yield (entry 1). When the reaction was carried out using 1,4-dibromobutane or 1,5-dibromopentane in refluxing acetonitrile, the corresponding cyclic tertiary amines (*R*)-**6c** and (*R*)-**6d** were obtained in 86% and 94% yields, respectively (entries 2 and 3).

The cyclic tertiary amines (*R*)-**6b**–**6d** were then converted to 1,4-amino alcohols **1k**–**1m** according to the same procedure used for the synthesis of **1a** (Table 4). That is, (*R*)-**6b**–**6d** were treated with *tert*-butyllithium in hexane, and the resulting *ortho*-lithiated species were reacted with propanal in hexane/diethyl ether to give **1k**–**1m** in 59–82% yield as diastereomeric mixtures (entries 1–3).

Table 4
Synthesis of amino alcohols **1k**–**1m**



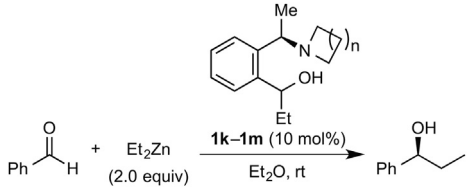
(*R*)-**6b**–**6d** **1k**–**1m**

Entry	1,4-Amino alcohol	Yield (%)
1	**1k** (*n*=1)	82[a]
2	**1l** (*n*=2)	72[b]
3	**1m** (*n*=3)	59[b]

[a] Diastereomeric ratio was 7:3 by ^{1}H NMR analysis.
[b] Diastereomeric ratio was 3:2 by ^{1}H NMR analysis.

The diastereomeric mixtures of 1,4-amino alcohols **1k**–**1m** were used in the reaction of benzaldehyde with diethylzinc under the same reaction conditions as those used in Table 2 (Table 5). In all cases, (*S*)-1-phenyl-1-propanol was obtained with high enantioselectivity (>93% ee), and a slightly better result than **1a** was obtained by using **1l** (96% ee, entry 2).

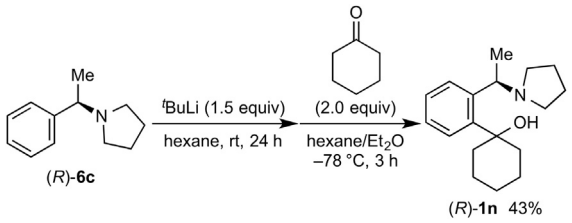
Table 5
Enantioselective addition of diethylzinc to benzaldehyde catalyzed by 1,4-amino alcohols **1k**–**1m**



Entry	1,4-Amino alcohol	Time (h)	Yield (%)	ee[a] (%)
1	**1k** (*n*=1)[b]	10	89	94
2	**1l** (*n*=2)[c]	8	85	96[d]
3	**1m** (*n*=3)[c]	20	83	93

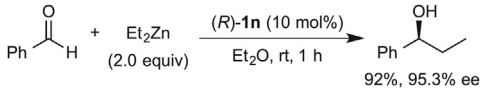
[a] Determined by HPLC analysis.
[b] Diastereomeric ratio was 7:3 by ^{1}H NMR analysis.
[c] Diastereomeric ratio was 3:2 by ^{1}H NMR analysis.
[d] The ee was 95.6% before rounding.

As good results were obtained by using **1h** (Table 2, entry 8) and **1l** (Table 5, entry 2), we examined the synthesis and the reaction of 1,4-amino alcohol (*R*)-**1n** containing both cyclohexane and pyrrolidine rings. According to the same procedure used for the synthesis of **1h**, (*R*)-**1n** was obtained from (*R*)-**6c** in 43% yield (Scheme 3). In the presence of 10 mol% of (*R*)-**1n**, the reaction of benzaldehyde with diethylzinc in diethyl ether was completed within 1 h to give (*S*)-1-phenyl-1-propanol in 92% yield with 95.3% ee (Scheme 4). The enantiomeric excess of the product was comparable to the one using **1l** (95.6% ee before rounding), and the product was obtained with highest yield in the shortest reaction time among the 1,4-amino alcohols examined in this study.



(*R*)-**6c** (*R*)-**1n** 43%

Scheme 3. Synthesis of 1,4-amino alcohol (*R*)-**1n**.

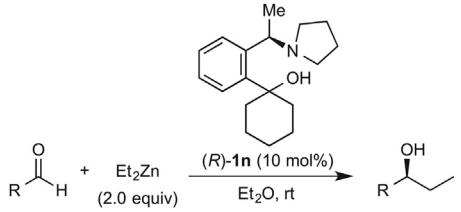


92%, 95.3% ee

Scheme 4. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by 1,4-amino alcohol (*R*)-**1n**.

The reaction of various aldehydes with diethylzinc was then examined by using 1,4-amino alcohol (*R*)-**1n** (Table 6). In the reactions of aromatic aldehydes bearing bromo or methoxy groups, 1-naphthaldehyde, and cyclohexanecarboxaldehyde, the corresponding chiral secondary alcohols were obtained in high yields with high enantioselectivities (85–96% ee, entries 1–5). The reactions of sterically less-hindered (*E*)-cinnamaldehyde and 3-phenylpropanal afforded the corresponding products with moderate enantioselectivities (entries 6 and 7).

Table 6
Enantioselective addition of diethylzinc to various aldehydes catalyzed by 1,4-amino alcohol (*R*)-**1n**



Entry	R	Time (h)	Yield (%)	ee[a] (%)
1	2-BrC_6H_4	1	85	95
2	1-Naphthyl	1.5	94	96
3	2-MeOC_6H_4	1	95	92
4	4-MeOC_6H_4	1.75	92	85
5	*c*-C_6H_{11}	2	75	94
6	(*E*)-PhCH=CH	2	82	54
7	$PhCH_2CH_2$	1.75	87	48

[a] Determined by HPLC analysis.

We tentatively assume the stereochemical pathway of the reaction using 1,4-amino alcohols **1** as shown in Fig. 2.[7,8a,11] The

reaction of 1,4-amino alcohol **1** with diethylzinc produces zinc complex **A**, which acts as an actual catalyst in the enantioselective reaction. The coordination of another diethylzinc and aldehyde to **A** forms a transition structure **B**, which leads to the formation of the chiral secondary alcohol with *S*-configuration. A pseudo-boat conformation would be the most suitable structure of the seven-membered ring of **B**, in which the methyl group of the benzylic carbon bearing amino group occupy the pseudo-equatorial position to avoid the steric repulsion with the substituents of the amino group regardless of the configuration of another benzylic carbon bearing hydroxy group. Moreover, the R group of aldehyde and the ethyl group of another diethylzinc should avoid the steric repulsion with the ethyl group of the seven-membered zinc complex. These considerations explain the experimental results that the stereochemical outcome of the reaction was controlled solely by the absolute configuration of the benzylic carbon bearing amino group.

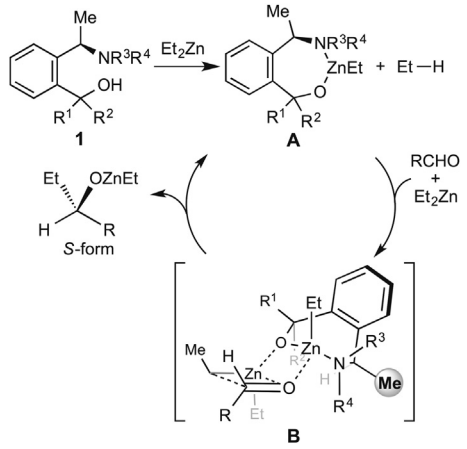


Fig. 2. Proposed reaction mechanism for enantioselective addition of diethylzinc to aldehydes using **1**.

3. Conclusion

In conclusion, various 1,4-amino alcohols **1** with *o*-xylylene skeleton were synthesized from easily available (*R*)-1-phenylethylamine (**3**) and used in the enantioselective addition of diethylzinc to benzaldehyde. In all cases, 1-phenyl-1-propanol with *S*-configuration was obtained with high enantioselectivity. The chirality of the benzylic carbon bearing hydroxy group was unnecessary for the high levels of enantioinduction in this reaction, and the best result was obtained by using (*R*)-**1n** containing both pyrrolidine and cyclohexane rings in the structure. The reactions of various aldehydes using (*R*)-**1n** were completed at room temperature within 2 h to give the corresponding chiral secondary alcohols with good to high enantioselectivities. New 1,4-amino alcohols developed in this study would find applications as chiral ligands and chiral auxiliaries in other asymmetric reactions.

4. Experimental section

4.1. General

All air-sensitive experiments were carried out under an atmosphere of argon unless otherwise noted. IR spectra were recorded on a HORIBA FT-730 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-EX-270 or Bruker DRX-300 spectrometer using tetramethylsilane as an internal standard. Optical rotations were measured on a JASCO P-1000 automatic polarimeter. HPLC analyses were carried out with JASCO instruments (pump, PU-2080 plus; detector, UV-2075). The enantiomeric excesses were determined by HPLC using Daicel Chiralcel OD-H, OB, or AS-H (25 cm×0.46 cm i.d.) column. Elemental analyses were carried out on a Vario EL III Elemental analyzer. TLC analyses were done on silica-gel 60 F_{254}-precoated aluminum backed sheets (E. Merck). Preparative TLC separations were performed on silica-gel-coated plates (Wakogel B-5F, 20 cm×20 cm). Wakogel C-200 and Silica gel 60 N (spherical, neutral, 63–210 μm) were used for column chromatography. Diethyl ether (dehydrated) and tetrahydrofuran (dehydrated, stabilizer free) were purchased from Kanto Chemical Co., Inc. Other solvents were purified and dried according to standard procedures. All new compounds were fully characterized by IR and ^{1}H, ^{13}C NMR spectroscopy and elemental analysis. Although some ^{13}C NMR signals of 1,4-amino alcohols **1** were not detected owing to the incidental overlapping or the broadening nature, other analytical data are sufficient for the characterization of these compounds.

4.2. Synthesis of (*R*)-*N*,*N*-dimethyl-1-phenylethylamine (6a)[12a]

An ethyl formate (106 mL) solution of (*R*)-1-phenylethylamine (**3**, 10.4 g, 85.5 mmol) was stirred at room temperature for 12 days. The mixture was concentrated to give crude (*R*)-*N*-(1-phenylethyl)formamide (**4**), which was used in the next step without further purification.

To a THF (50 mL) suspension of lithium aluminum hydride (4.24 g, 112 mmol), a THF (50 mL) solution of crude (*R*)-**4** was added dropwise at 0 °C. After the reaction mixture was refluxed for 4.5 h, water and Et_2O were added to the mixture and the resulting precipitate was removed by suction filtration. The filtrate was washed with water and brine, and dried over anhydrous Na_2SO_4 and anhydrous Na_2CO_3. After removal of the solvent under reduced pressure, crude (*R*)-*N*-methyl-1-phenylethylamine (**5**) was obtained and used in the next step without further purification.

To a methanol (40 mL) solution of (*R*)-**5** was added a methanol (50 mL) solution of paraformaldehyde (3.41 g, 113 mmol), and the reaction mixture was stirred at room temperature for 3 h. To the mixture was added 10% Pd/C (3.44 g) and the mixture was stirred under H_2 atmosphere (1 atm balloon) at room temperature for 40 h. The mixture was filtered through Celite to remove Pd/C. After the filtrate was concentrated under reduced pressure, crude product was distilled under reduced pressure (84–86 °C/32 mmHg) to give (*R*)-*N*,*N*-dimethyl-1-phenylethylamine (**6a**) in 86% yield (10.9 g).

Colorless oil; bp 84–86 °C/32 mmHg (Kugelrohr) (lit.[12a] 62 °C/11 mmHg); $[\alpha]_D^{18}$ +64.3 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2976, 2815, 2766, 1452, 1370, 1348, 1257, 1153, 1078, 955, 756, 700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 7.20–7.35 (m, 5H), 3.23 (q, *J*=6.6 Hz, 1H), 2.19 (s, 6H), 1.37 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 143.7, 127.9, 127.2, 126.6, 65.8, 43.0, 20.1.

4.3. Typical experimental procedure for the synthesis of 1,4-amino alcohols 1a–1i

To a stirred solution of (*R*)-*N*,*N*-dimethyl-1-phenylethylamine (**6a**, 149 mg, 1.0 mmol) in hexane (2.1 mL), a pentane solution of *t*-BuLi (1.6 M, 0.94 mL) was added dropwise through a syringe at 0 °C. The reaction mixture was stirred at room temperature for 24 h, and Et_2O (2.6 mL) was added to the mixture. To the mixture was added an Et_2O (2.0 mL) solution of propanal (116 mg, 2.0 mmol) at 0 °C and the mixture was stirred at room temperature for 30 min. After the mixture was cooled to 0 °C, saturated aqueous ammonium chloride solution and 2 M aqueous HCl were added to the mixture. The aqueous layer was separated and the organic layer was extracted with 2 M aqueous HCl three times. To the combined aqueous layer was added 6 M aqueous NaOH until the solution

becomes alkaline (pH 14). The aqueous layer was then extracted with dichloromethane three times, and the combined organic layer was dried over anhydrous Na_2CO_3. After removal of solvent under reduced pressure, crude product was purified by sililca-gel column chromatography (hexane/triethylamine=10:1) to give 1-{2-[(*R*)-1-(dimethylamino)ethyl]phenyl}propan-1-ol (**1a**) in 83% yield (172 mg).

*4.3.1. 1-{2-[(R)-1-(Dimethylamino)ethyl]phenyl}propan-1-ol (**1a**).* Pale yellow oil; diastereomeric ratio=3:2; $[\alpha]_D^{23}$ −4.4 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3383, 2975, 2938, 2872, 2817, 1449, 1371, 1097, 1076, 1040, 972, 951, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.21–7.46 (m, 4H), 4.78 (dd, *J*=6.6, 6.9 Hz, 0.6H), 4.68 (dd, *J*=6.6, 7.8 Hz, 0.4H), 4.34 (q, *J*=6.8 Hz, 0.6H), 4.02 (q, *J*=7.0 Hz, 0.4H), 2.21 (s, 3.6H), 2.20 (s, 2.4H), 2.00–2.08 (m, 2H), 1.43 (d, *J*=6.8 Hz, 1.2H), 1.38 (d, *J*=7.0 Hz, 1.8H), 1.08 (t, *J*=7.5 Hz, 1.8H), 0.97 (t, *J*=7.3 Hz, 1.2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 143.1, 143.0, 140.9, 140.5, 128.7, 128.1, 127.4, 127.2, 126.7, 126.5, 125.3, 76.2, 70.4, 61.4, 57.8, 40.9, 39.2, 30.5, 27.0, 12.6, 11.3, 8.1 (two signals were not detected). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.32; H, 10.27; N, 6.78.

*4.3.2. 2-Methyl-1-{2-[(R)-1-(dimethylamino)ethyl]phenyl}propan-1-ol (**1b**).* Pale yellow oil; diastereomeric ratio=3:2; $[\alpha]_D^{21}$ +10.1 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3398, 2974, 2955, 2869, 2817, 2774, 1468, 1448, 1370, 1076, 1037, 1008, 950, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.19–7.48 (m, 4H), 4.44 (d, *J*=9.4 Hz, 0.6H), 4.29 (q, *J*=6.8 Hz, 0.6H), 4.20 (q, *J*=7.0 Hz, 0.4H), 4.19 (d, *J*=9.4 Hz, 0.4H), 2.19 (s, 3.6H), 2.18 (s, 2.4H), 1.96–2.41 (m, 1H), 1.37 (d, *J*=6.8 Hz, 3H), 1.22 (d, *J*=6.8 Hz, 1.8H), 1.17 (d, *J*=6.8 Hz, 1.2H), 0.88 (d, *J*=6.8 Hz, 1.8H), 0.67 (d, *J*=6.8 Hz, 1.2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 142.8, 142.6, 141.3, 140.2, 130.4, 127.5, 127.3, 127.0, 126.73, 126.67, 126.5, 126.1, 82.9, 74.8, 59.1, 58.0, 39.8, 39.6, 34.3, 30.7, 20.3, 20.1, 19.7, 10.2, 9.2 (one signal was not detected). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.89; H, 10.52; N, 6.35.

*4.3.3. {2-[(R)-1-(Dimethylamino)ethyl]phenyl}(phenyl)methanol (**1c**).*[12b] Pale yellow oil; diastereomeric ratio=3:2; $[\alpha]_D^{27}$ +49.4 (*c* 2.0, EtOH); IR (neat): ν_{max} 3331, 3060, 3026, 2978, 2945, 2863, 2829, 2784, 1491, 1449, 1177, 1074, 1038, 941, 761, 735, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.93 (br s, 1H), 6.69–7.47 (m, 9H), 6.19 (s, 0.4H), 5.76 (s, 0.6H), 4.50 (q, *J*=6.8 Hz, 0.4H), 3.61 (q, *J*=6.8 Hz, 0.6H), 2.27 (s, 2.4H), 2.11 (s, 3.6H), 1.42 (d, *J*=6.8 Hz, 1.2H), 1.12 (d, *J*=6.8 Hz, 1.8H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 145.3, 145.0, 143.9, 142.5, 140.8, 140.3, 131.5, 128.4, 128.2, 128.0, 127.9, 127.5, 127.3, 127.1, 126.90, 126.87, 126.7, 126.3, 125.4, 77.6, 72.2, 58.3, 57.9, 39.1, 38.9, 7.8, 7.7 (one signal was not detected). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.84; H, 8.34; N, 5.51.

*4.3.4. (R)-{2-[1-(Dimethylamino)ethyl]phenyl}methanol (**1d**).*[12b] Pale yellow oil; $[\alpha]_D^{17}$ +15.0 (*c* 1.0, EtOH); IR (neat): ν_{max} 3363, 2976, 2945, 2863, 2829, 2784, 1451, 1075, 1022, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.50 (br s, 1H), 7.23–7.34 (m, 4H), 4.80 (d, *J*=12.1 Hz, 1H), 4.50 (d, *J*=12.1 Hz, 1H), 4.03 (q, *J*=6.8 Hz, 1H), 2.22 (s, 6H), 1.42 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 141.6, 141.0, 130.3, 127.6, 127.5, 127.4, 65.1, 60.9, 40.0, 9.6. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.73; H, 9.67; N, 7.96.

*4.3.5. (R)-2-{2-[1-(Dimethylamino)ethyl]phenyl}propan-2-ol (**1e**).*[12b] Pale yellow oil; $[\alpha]_D^{27}$ +0.2 (*c* 2.0, EtOH); IR (neat): ν_{max} 3374, 2976, 2864, 2817, 2783, 1443, 1372, 1170, 957, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.33 (br s, 1H), 7.13–7.36 (m, 4H), 4.11 (br s, 1H), 2.23 (s, 6H), 1.64 (s, 3H), 1.57 (s, 3H), 1.47 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 148.1, 139.7, 129.2, 128.1, 127.3, 126.1, 73.3, 40.7, 33.7, 33.4 (one signal was not detected). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.42; H, 10.27; N, 6.81.

*4.3.6. (R)-3-{2-[1-(Dimethylamino)ethyl]phenyl}pentan-3-ol (**1f**).* Pale yellow oil; $[\alpha]_D^{21}$ −18.0 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3398, 2966, 2937, 2874, 2823, 2783, 1456, 1371, 1167, 1039, 980, 957, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.17 (br s, 1H), 7.09–7.27 (m, 4H), 4.03 (br s, 1H), 2.23 (s, 6H), 1.69–2.00 (m, 4H), 1.47 (d, *J*=7.0 Hz, 3H), 0.79 (t, *J*=7.5 Hz, 3H), 0.75 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 144.7, 140.7, 128.4, 128.0, 126.0, 124.6, 78.7, 40.2, 37.5, 36.0, 7.4 (one signal was not detected). Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.66; H, 10.81; N, 6.14.

*4.3.7. (R)-1-{2-[1-(Dimethylamino)ethyl]phenyl}cyclopentan-1-ol (**1g**).* Pale yellow oil; $[\alpha]_D^{20}$ −51.1 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3367, 2971, 2950, 2867, 2827, 2783, 1446, 1371, 1039, 1006, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.94 (br s, 1H), 7.18–7.47 (m, 4H), 4.48 (br s, 1H), 2.20 (s, 6H), 1.66–2.35 (m, 8H), 1.39 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 146.7, 140.2, 128.2, 127.3, 126.8, 126.2, 82.8, 41.6, 41.4, 39.5, 24.2, 23.4 (two signals were not detected). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.30; H, 10.04; N, 6.13.

*4.3.8. (R)-1-{2-[1-(Dimethylamino)ethyl]phenyl}cyclohexan-1-ol (**1h**).*[12b] Pale yellow oil; $[\alpha]_D^{17}$ −12.5 (*c* 1.0, EtOH); IR (neat): ν_{max} 3422, 2929, 2856, 2824, 2783, 1446, 1371, 1270, 1038, 957, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.74 (br s, 1H), 7.12–7.42 (m, 4H), 4.06 (br s, 1H), 2.21 (s, 6H), 1.48 (d, *J*=7.2 Hz, 3H), 1.22–2.00 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 148.6, 140.2, 129.3, 128.0, 127.2, 125.9, 74.2, 41.0, 40.8, 40.3, 25.9, 22.3, 22.2 (one signal was not detected). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.53; H, 10.19; N, 5.90.

*4.3.9. (R)-1-{2-[1-(Dimethylamino)ethyl]phenyl}cycloheptan-1-ol (**1i**).* Pale yellow oil; $[\alpha]_D^{21}$ −34.8 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3401, 3099, 2923, 2857, 2823, 2782, 1456, 1443, 1370, 1039, 948, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.83 (br s, 1H), 7.09–7.40 (m, 4H), 4.07 (br s, 1H), 2.21 (s, 6H), 1.52–2.28 (m, 12H), 1.47 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 150.3, 139.5, 129.3, 128.0, 127.1, 125.8, 77.7, 45.0, 44.7, 41.0, 29.3, 29.1, 23.2, 22.7 (three signals were not detected). Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.93; H, 10.58; N, 5.39.

4.4. Synthesis of 1-{2-[(*R*)-1-(dimethylamino)ethyl]phenyl}ethan-1-ol (1j)

(*R*)-2-[1-(Dimethylamino)ethyl]benzaldehyde (**7**) was synthesized by the similar method to that of **1a**–**1i** using DMF as the electrophile. To a stirred solution of (*R*)-**7** (200 mg, 1.1 mmol) in THF (5.7 mL), an Et_2O solution of methylmagnesium iodide (1.0 M, 2.0 mL) was added dropwise through a syringe at room temperature. The reaction mixture was stirred at the same temperature for 1 h, and saturated aqueous ammonium chloride solution was added to the mixture at 0 °C. After the resulting precipitate was filtered off, the organic layer of the filtrate was separated and the aqueous layer was extracted with dichloromethane three times. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2CO_3. After removal of the solvent under reduced pressure, crude product was purified by preparative thin-layer chromatography (hexane/triethylamine=10:1) to give 1-{2-[(*R*)-1-(dimethylamino)ethyl]phenyl}ethan-1-ol (**1j**) in 78% yield (171 mg). Pale yellow oil; diastereomeric ratio=3:2; $[\alpha]_D^{20}$ −10.6 (*c* 0.99, $CHCl_3$); IR (neat): ν_{max} 3371, 2976, 2863, 2816, 1456, 1371, 1095, 1071, 1053, 1009, 952, 898, 762 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$): δ (ppm) 7.89 (br s, 1H), 7.20–7.51 (m, 4H), 5.08–5.17 (m, 1H), 4.36 (q, *J*=6.8 Hz, 0.6H), 3.82 (q, *J*=6.8 Hz, 0.4H), 2.22 (s, 3.6H), 2.21 (s, 2.4H), 1.61 (d, *J*=6.4 Hz, 1.8H), 1.58 (d, *J*=6.4 Hz, 1.2H), 1.49 (d, *J*=6.8 Hz, 1.2H), 1.39 (d, *J*=6.8 Hz, 1.8H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 144.1, 143.9, 141.1, 140.6, 128.8, 127.6, 127.5, 126.9, 126.78, 126.76, 125.1, 68.5, 64.7, 63.7, 57.7, 41.7, 39.0, 23.1, 20.1, 14.4, 7.6 (one signal was not detected). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.35; H, 10.11; N, 7.23.

4.5. Typical experimental procedure for the synthesis of cyclic tertiary amines (*R*)-6b–6d

To a mixture of 1,3-dibromopropane (1.50 g, 7.4 mmol) and potassium carbonate (3.43 g, 24.8 mmol) in acetonitrile (40 mL) was added an acetonitrile (22 mL) solution of (*R*)-1-phenylethylamine (**3**, 752 mg, 6.2 mmol), and the mixture was stirred at 50 °C for 120 h. After the mixture was filtered, the filtrate was concentrated under reduced pressure. Crude product was purified by silica-gel column chromatography (hexane to hexane/triethylamine=10:1) and distilled under reduced pressure (64 °C/10 mmHg) to give (*R*)-1-(1-phenylethyl)azetidine (**6b**) in 61% yield (612 mg).

*4.5.1. (R)-1-(1-Phenylethyl)azetidine (**6b**).*[12c] Colorless oil; bp 64 °C/10 mmHg; $[\alpha]_D^{18}$ +94.4 (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 2963, 2817, 1492, 1449, 1290, 1221, 1186, 1030, 761, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.20–7.31 (m, 5H), 3.25 (q, *J*=6.6 Hz, 1H), 3.03–3.22 (m, 4H), 1.97–2.01 (m, 2H), 1.20 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 143.4, 128.3, 127.1, 126.9, 68.8, 53.9, 20.9, 16.6.

*4.5.2. (R)-1-(1-Phenylethyl)pyrrolidine (**6c**).*[12d] Colorless oil; bp 67 °C/2 mmHg (lit.[12e] 111 °C/13 mmHg for racemic mixture); $[\alpha]_D^{18}$ +60.3 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2970, 2779, 1491, 1452, 1143, 762, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.19–7.35 (m, 5H), 3.17 (q, *J*=6.6 Hz, 1H), 2.51–2.58 (m, 2H), 2.32–2.40 (m, 2H), 1.69–1.82 (m, 4H), 1.40 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 145.7, 128.2, 127.2, 126.8, 66.0, 53.0, 23.4, 23.2.

*4.5.3. (R)-1-(1-Phenylethyl)piperidine (**6d**).*[12f] Colorless oil; bp 120–130 °C/2.3 mmHg (Kugelrohr) (lit.[12g] 110–116 °C/4 mmHg for *S* isomer); $[\alpha]_D^{18}$ +27.0 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2971, 2933, 2851, 2790, 2751, 1491, 1451, 1372, 1320, 1258, 1118, 939, 756, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.18–7.33 (m, 5H), 3.38 (q, *J*=6.8 Hz, 1H), 2.29–2.41 (m, 4H), 1.50–1.58 (m, 4H), 1.33–1.41 (m, 2H), 1.36 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 143.9, 128.0, 127.7, 126.6, 65.2, 51.5, 26.3, 24.6, 19.4.

4.6. Synthesis of 1,4-amino alcohols 1k–1n

1,4-Amino alcohols **1k**–**1n** were synthesized by the similar method to that of **1a**–**1i**.

*4.6.1. 1-{2-[(R)-1-(Azetidin-1-yl)ethyl]phenyl}propan-1-ol (**1k**).* White solid; diastereomeric ratio=7:3; mp 117.4–118.0 °C; $[\alpha]_D^{21}$ +43.6 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 3192, 2969, 2927, 2874, 2851, 1444, 1373, 1222, 1184, 1091, 976, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.18–7.44 (m, 4H), 4.94 (t, *J*=6.8 Hz, 1H), 3.86 (q, *J*=6.6 Hz, 0.3H), 3.56 (q, *J*=6.6 Hz, 0.7H), 3.06–3.23 (m, 4H), 1.78–2.06 (m, 4H), 1.38 (d, *J*=6.6 Hz, 2.1H), 1.32 (d, *J*=6.6 Hz, 0.9H), 1.10 (t, *J*=7.3 Hz, 2.1H), 1.05 (t, *J*=7.3 Hz, 0.9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 142.6, 142.4, 140.2, 140.0, 129.0, 127.3, 127.2, 127.1, 126.3, 126.0, 71.8, 71.0, 53.4, 51.6, 30.6, 29.4, 18.3, 16.9, 16.52, 16.49, 11.2, 10.9 (four signals were not detected). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.45; H, 9.68; N, 6.34.

*4.6.2. 1-{2-[(R)-1-(Pyrrolidin-1-yl)ethyl]phenyl}propan-1-ol (**1l**).* Pale yellow oil; diastereomeric ratio=3:2; $[\alpha]_D^{21}$ +7.3 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3378, 2969, 2933, 2874, 2803, 1449, 1370, 1142, 1091, 973, 762 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.16–7.42 (m, 4H), 6.94 (br s, 1H), 4.89 (t, *J*=7.0 Hz, 0.6H), 4.86 (t, *J*=7.0 Hz, 0.4H), 4.34 (q, *J*=6.8 Hz, 0.4H), 3.67 (q, *J*=6.8 Hz, 0.6H), 2.40–2.64 (m, 4H), 1.88–2.02 (m, 2H), 1.66–1.80 (m, 4H), 1.55 (d, *J*=6.8 Hz, 1.8H), 1.44 (d, *J*=6.8 Hz, 1.2H), 1.07 (t, *J*=7.5 Hz, 1.8H), 1.05 (t, *J*=7.5 Hz, 1.2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 142.6, 142.5, 142.3, 142.0, 128.9, 127.3, 127.2, 127.10, 127.08, 126.9, 126.7, 125.8, 72.4, 71.3, 64.0, 55.6, 51.6, 48.0, 29.1, 28.4, 23.4, 23.2, 18.3, 12.3, 11.3, 11.1. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.24; H, 10.19; N, 6.26.

*4.6.3. 1-{2-[(R)-1-(Piperidin-1-yl)ethyl]phenyl}propan-1-ol (**1m**).* Pale yellow oil; diastereomeric ratio=3:2; $[\alpha]_D^{22}$ −21.3 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3381, 2972, 2933, 2854, 1451, 1372, 1157, 1116, 1048, 970, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.19–7.46 (m, 4H), 4.77 (t, *J*=7.0 Hz, 0.6H), 4.64 (t, *J*=7.0 Hz, 0.4H), 4.35 (q, *J*=6.8 Hz, 0.6H), 4.12 (q, *J*=6.8 Hz, 0.4H), 2.40–2.65 (br m, 4H), 1.79–2.07 (m, 2H), 1.31–1.62 (m, 9H), 1.07 (t, *J*=7.3 Hz, 1.8H), 0.95 (t, *J*=7.3 Hz, 1.2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 143.4, 143.3, 140.9, 140.3, 129.3, 128.5, 127.5, 127.2, 126.5, 126.4, 125.4, 77.1, 70.4, 61.2, 58.4, 30.4, 26.6, 26.0, 25.8, 24.3, 24.2, 11.8, 11.4, 11.3, 8.9 (three signals were not detected). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.43; H, 10.22; N, 5.70.

*4.6.4. (R)-1-{2-[1-(Pyrrolidin-1-yl)ethyl]phenyl}cyclohexan-1-ol (**1n**).* Pale yellow oil; $[\alpha]_D^{20}$ +1.5 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max} 3417, 2968, 2929, 2846, 2803, 1460, 1371, 1266, 1140, 1034, 1000, 976, 750 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 8.91 (br s, 1H), 7.06–7.38 (m, 4H), 3.63 (br s, 1H), 2.48 (br s, 4H), 1.62 (d, *J*=6.9 Hz, 3H), 1.19–1.99 (m, 14H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 148.4, 141.2, 130.1, 128.9, 126.8, 125.8, 74.8, 51.6, 42.0, 40.9, 26.0, 23.5, 22.4, 22.3. Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 78.82; H, 10.09; N, 5.15.

4.7. Typical experimental procedure for the addition of diethylzinc to aldehydes

To an Et_2O (2.0 mL) solution of (*R*)-**1n** (41 mg, 0.15 mmol) under an atmosphere of argon was added a hexane solution of diethylzinc (1.05 M, 2.9 mL) through a syringe at 0 °C, and the mixture was stirred at room temperature for 30 min. After the mixture was cooled to 0 °C, an Et_2O (2.0 mL) solution of benzaldehyde (159 mg, 1.5 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. Saturated ammonium chloride solution and 2 M aqueous HCl were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane three times. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, crude product was purified by silica-gel column chromatography (hexane/ethyl acetate=6:1) to give (*S*)-1-phenyl-1-propanol (188 mg, 92%). The ee was determined to be 95% by HPLC analysis using a chiral column (Daicel Chiralcel OD-H (25 cm×0.46 cm i.d.); 254 nm UV detector; eluent, hexane/*i*-PrOH=97:3; flow rate, 0.5 mL/min; t_R, 18.4 min for minor peak, 22.1 min for major peak).

4.7.1. 1-(2-Bromophenyl)-1-propanol. Daicel Chiralcel OD-H (25 cm×0.46 cm i.d.); eluent, hexane/*i*-PrOH=99:1; flow rate, 0.5 mL/min; t_R, 33.4 min for *R* isomer, 36.4 min for *S* isomer.

4.7.2. 1-(1-Naphthyl)-1-propanol. Daicel Chiralcel OD-H (25 cm×0.46 cm i.d.); eluent, hexane/*i*-PrOH=90:10; flow rate, 0.5 mL/min; t_R, 14.4 min for *S* isomer, 24.9 min for *R* isomer.

4.7.3. 1-(2-Methoxyphenyl)-1-propanol. Daicel Chiralcel OB (25 cm×0.46 cm i.d.); eluent, hexane/*i*-PrOH=90:10; flow rate, 0.5 mL/min; t_R, 10.6 min for *S* isomer, 13.6 min for *R* isomer.

4.7.4. 1-(4-Methoxyphenyl)-1-propanol. Daicel Chiralcel OB (25 cm×0.46 cm i.d.); eluent, hexane/*i*-PrOH=90:10; flow rate, 0.5 mL/min; t_R, 17.1 min for *S* isomer, 20.5 min for *R* isomer.

4.7.5. 1-Cyclohexyl-1-propanol (as the corresponding 4-methoxybenzoate). Daicel Chiralcel AS-H (25 cm×0.46 cm i.d.); eluent, hexane/*i*-PrOH=99.9:0.1; flow rate, 0.5 mL/min; t_R, 11.9 min for *R* isomer, 13.4 min for *S* isomer.

4.7.6. (E)-1-Phenyl-1-penten-3-ol. Daicel Chiralcel OD-H (25 cm×0.46 cm i.d.); eluent, hexane/*i*-PrOH=95:5; flow rate, 0.5 mL/min; t_R, 22.2 min for *R* isomer, 37.3 min for *S* isomer.

4.7.7. 1-Phenyl-3-pentanol. Daicel Chiralcel OB (25 cm×0.46 cm i.d.); eluent, hexane/*i*-PrOH=99.5:0.5; flow rate, 0.3 mL/min; t_R, 64.3 min for *R* isomer, 73.9 min for *S* isomer.

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