An Efficient and Practical Synthesis of L-α-Amino Acids Using (*R*)-Phenylglycinol as a Chiral Auxiliary[1)]

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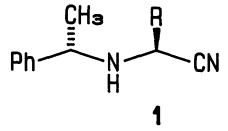
L-α-Amino acids including L-α-arylglycines were conveniently and stereoselectively synthesized via the α-amino carbonitriles given by the Strecker reaction of (*R*)-2-amino-2-phenylethanol with aldehydes and hydrogen cyanide. The stereoselectivity of these α-amino carbonitriles was thermodynamically controlled.

To date, artificial α-amino acids have been demanded in the fields of protein engineering and development of biologically active peptides. Among many methods for synthesizing optically active α-amino acids, the most important one is the asymmetric Strecker reaction, which can be performed under mild and convenient conditions. Although much effort was made in order to exploit sophisticated chiral auxiliaries,[2,3)] natural and unnatural L-α-amino acids have been synthesized by the Strecker reaction using a simple chiral auxiliary, (*S*)-α-methylbenzylamine via an intermediary α-amino carbonitrile (**1**).[4)] However, this method has some disadvantages: (i) the diastereomeric excess of **1** is relatively low (about 50%); (ii) hydrolysis of the cyano group of **1** requires severe reaction conditions to form intractable by-products;[4h)] and (iii) it is inapplicable to the synthesis of arylglycines because the chiral auxiliary must be removed by hydrogenolysis which also bring about the bond cleavage between the amino nitrogen and the aryl-substituted carbon.

Here we report that commercially available (*R*)-2-amino-2-phenylethanol (**2**) is an excellent chiral auxiliary for the thermodynamically controlled asymmetric Strecker reaction to be applicable to the preparation of L-α-arylglycines.[1)] At the final stage of our work, kinetically controlled one using **2** was reported by Chakraborty et al.[5)] The stereoselectivity reported therein is not higher than thermodynamically controlled one reported in the present paper.



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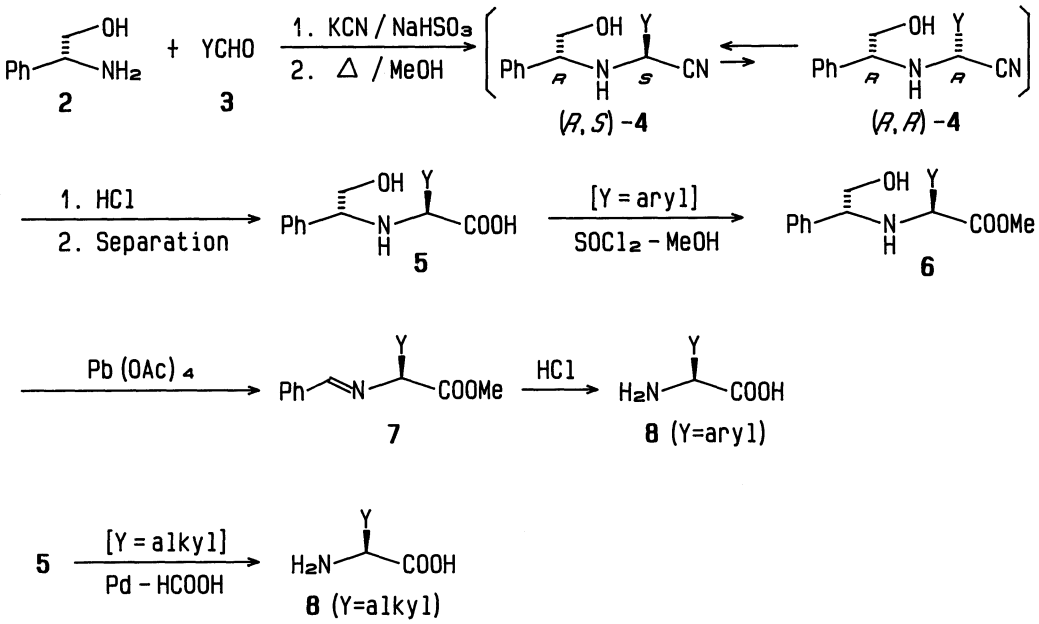
Results and Discussion

According to a modified conventional procedure,[6)] an α-amino carbonitrile (**4**) was prepared by simply stirring a mixture of **2**, an aldehyde (**3**), KCN, and $NaHSO_3$ in



2 **3** **5** **6** **7** **8** (Y=aryl) **8** (Y=alkyl)

Scheme 1.

Table 1. Chemical Yield and Equilibrium Ratio of α-Amino Nitriles (**4**)

	Y	Yield[a] %	(*R*,*S*):(*R*,*R*)[b]
a	4-$MeOC_6H_4$	93	(82:18)
b	4-FC_6H_4	83	(80:20)
c	1-Naphthyl	95	(81:19)
d	2-Thienyl	94	(82:18)
e	CH_3	100	(84:16)
f	$(CH_3)_2CH$	87	(83:17)
g	$(CH_3)_3C$	91	(87:13)
h	$PhCH_2$	91	(80:20)

a) Yield based on **2**. b) Equilibrium ratio in MeOH.

Table 2. Chemical Yield of **5**

	Y	Yield[a] %		Y	Yield[a] %
a	4-$MeOC_6H_4$	57	**e**	CH_3	42
b	4-FC_6H_4	40	**f**	$(CH_3)_2CH$	49
c	1-Naphthyl	100[b]	**g**	$(CH_3)C$	81
d	2-Thienyl	40	**h**	$PhCH_2$	40

a) The isolation yields of (*R*,*S*)-**5** after recrystallization. b) Diastereomerically pure (*R*,*S*)-**4c** was used.

water or water–MeOH (see Table 1). Aromatic aldehydes as well as aliphatic aldehydes gave **4** in excellent yields. The product (**4**) consisted of two diastereomers, and the equilibration between these isomers was attained at 80 °C in MeOH within 3 h. The equilibrium ratio of (*R*,*S*)-**4**: (*R*,*R*)-**4** was higher than that of the corresponding (*S*,*S*)-**1**: (*S*,*R*)-**1**.[7]

It is noteworthy that (*R*,*S*)-**4c** (Y=1-naphthyl) is effectively isolated from the equilibrium mixture by repeating recrystallization (hexane–ethyl acetate) and subsequent equilibration of the mother liquor for three times. The isolation yield of (*R*,*S*)-**4c** was 79%.

Hydrolysis of α-amino carbonitrile (**4**) occurred smoothly with concd HCl (12 M) (1 M=1 mol dm^{-3}) to give an *N*-(2-hydroxy-1-phenylethyl)amino acids (**5**). Smooth hydrolysis of (*R*,*S*)-**4** is probably due to the assistance of the neighboring hydroxyl group, because, in the case of hydrolysis of **4e** and **4h**, an insoluble lactone (**9**)[8] deposited as its HCl salt in the beginning of the reaction. Since **9** was converted to **5** by further treatment with dil HCl, the overall conversion of **4e** and **4h** to **5e** and **5h**, respectively, could be carried out in one pot. Isolation of (*R*,*S*)-**5** was easily and efficiently carried out by reacrystallization.[9] The isolation yields of (*R*,*S*)-**5** were shown in Table 2.

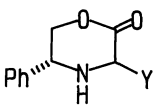


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Table 3. Chemical Yield and % ee of **8** (Y=Aryl)

	Y	(*R*,*S*)-**5**→(*R*,*S*)-**6** Yield %	(*R*,*S*)-**5**→**8** Yield/[ee][a] %
a	4-$MeOC_6H_4$	88	66 [>99]
b	4-FC_6H_4	96	72 [97]
c	1-Naphthyl	98	54 [92]
d	2-Thienyl	100	41 [79]

a) Determined by HPLC (Daicel Crownpak CR (+)).

Table 4. Chemical Yield of **8** (Y=Alkyl)

	Y	Yield %	ee %
e	CH_3	86	97[a]
f	$(CH_3)_2CH$	54	92[b]
g	$(CH_3)_3C$	76	100[c]
h	$PhCH_2$	63	95[b]

a) Determined by HPLC (Daicel Chiralcel OD) after conversion to Z-Ala-OH. b) Determined by HPLC (Daicel Crownpak CR(+)). c) Determined by optical rotation.

We have established a novel transformation of (*R*,*S*)-**5** (Y=aryl) into α-arylglycines (**8**, Y=aryl) as shown in Scheme 1. At first, (*R*,*S*)-**5** was converted to the corresponding methyl ester (**6**) with $SOCl_2$ in MeOH in good to excellent yields.[10] Then oxidation of **6** with small excess of $Pb(OAc)_4$ in CH_2Cl_2–MeOH (2:1) at 0 °C for 3 min afforded an unstable Schiff base (**7**).[11] Hydrolysis of the resulting crude **7** with concd HCl and subsequent chromatography on active carbon yielded the expected L-α-arylglycine (**8a**—**d**). The yields and the enantiomeric excess of **8a**—**d** were summarized in Table 3.

It should be noted that the removal of the chiral auxiliary of **5** (Y=alkyl) was achieved by a Pd-catalyzed hydrogenolysis in the presence of formic acid[12] to give an L-α-amino acid (**8**) having an alkyl group as Y. The results were shown in Table 4.

In conclusion, (*R*)-2-amino-2-phenylethanol (**2**) is an excellent chiral auxiliary for the asymmetric Strecker reaction to provide an efficient method for preparing many kinds of L-α-amino acids under mild conditions. It should be noted that the present strategy can also be extended to preparation of various D-amino acids by employing the enantiomer of **2**, which is also commercially available, as a chiral auxiliary.

Experimental

General Procedures. Melting points were determined on a hotstage microscope apparatus (Yanagimoto) and are uncorrected. ^1H NMR spectra were obtained on JEOL JNM-FX 270 (270 MHz), JEOL JNM-GSX 400 (400 MHz), and JEOL JNM-GSX 500 (500 MHz) spectrometers. Chemical shifts are reported in ppm down field from TMS at the internal standard (δ scale) when solvent is $CDCl_3$. For other solvents,

a solution of tetramethylsilane in $CDCl_3$ sealed in a capillary was used as an external standard. Infrared spectra were determined with a JASCO A-200 spectrometer and data are presented in cm^{-1} for important diagnostic absorptions. Optical rotations were measured on a JASCO DIP-140 polarimeter. Microanalytical data were provided by the Analysis Center of Chiba University.

2-[(2-Hydroxy-1-phenylethyl)amino]-2-(4-methoxyphenyl)ethanenitrile (4a): To a stirred suspension of anisaldehyde (**3a**, 1.51 g, 11.1 mmol) in water (55.0 ml) was added $NaHSO_3$ (1.16 g, 11.1 mmol), KCN (750 mg, 11.5 mmol), and a solution of **2** (1.37 g, 10.0 mmol) in MeOH (20.0 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 2 h and refluxed for 1 h. The oily product was extracted with $CHCl_3$ (50 ml×3). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography of the residue on silica gel (hexane–ethyl acetate, 75:25) afforded a diastereomeric mixture (*R,S*/*R,R*=82/18) of **4a** as a pale yellow oil (2.62 g, 93%). The two diastereomers were separated by preparative HPLC[13] (hexane–ethyl acetate, 67:33).

(*R,S*)-**4a**: A pale yellow oil; ^1H NMR ($CDCl_3$, 270 MHz) δ=7.48—7.33 (m, 7H, Ar*H*), 6.91 (d, 2H, *J*=8.9 Hz, C*H*COCH$_3$), 4.44 (s, 1H, NC*H*CN), 4.24 (dd, 1H, *J*=4.0, 9.2 Hz, NC*H*Ph), 3.82 (dd, 1H, *J*=4.0, 10.3 Hz, CH_2OH), 3.81 (s, 3H, OCH_3), 3.63 (dd, 1H, *J*=9.3, 10.3 Hz, CH_2OH). Since this oil was shown by TLC to contain trace amount of the starting aldehyde, an analytical sample of (*R,S*)-**4a** was obtained as its hydrochloride: Colorless crystals; mp 82—85°C (AcOEt); $[\alpha]_D^{20}$ −58.4° (*c* 1.01, $CHCl_3$); IR (KBr) 3500, 3400, 3000, 2620, 1610, 1510, 1450, 1255, 1190, 1010, 840, 760, 710 cm^{-1}. Found: C, 63.16; H. 6.08; N, 8.59%. Calcd for $C_{17}H_{19}ClN_2O_2 \cdot 0.2\ H_2O$: C, 63.33; H, 6.07; N, 8.69%.

(*R,R*)-**4a**: A colorless oil; ^1H NMR ($CDCl_3$, 270 MHz) δ=7.48—7.26 (m, 7H, Ar*H*), 6.91 (d, 2H, *J*=8.9 Hz, C*H*COCH$_3$), 4.64 (s, 1H, NC*H*CN), 3.84 (dd, 1H, *J*=4.3, 7.9 Hz, NC*H*Ph), 3.82 (s, 3H, OCH_3), 3.74 (dd, 1H, *J*=4.3, 10.9 Hz, CH_2OH), 3.66 (dd, 1H, *J*=7.9, 10.9 Hz, CH_2OH). The hydrochloride of (*R,R*)-**4a**: Pale yellow crystals; mp 88°C (AcOEt); $[\alpha]_D^{20}$ −34.6° (*c* 1.00, $CHCl_3$); IR (KBr) 3400, 2940, 2720, 2630, 1610, 1585, 1515, 1455, 1430, 1335, 1310, 1255, 1180, 1070, 1050, 1030, 880, 830, 760, 700 cm^{-1}. Found: C, 63.73; H, 6.08; N, 8.78%. Calcd for $C_{17}H_{19}ClN_2O_2 \cdot 0.1\ H_2O$: C, 63.69; H, 6.04; N, 8.74%.

2-[(2-Hydroxy-1-phenylethyl)amino]-2-(4-fluorophenyl)ethanenitrile (4b): Similarly, a mixture (*R,S*/*R,R*=80/20) of **4b** was obtained in 83% yield.

(*R,S*)-**4b**: A colorless oil; ^1H NMR ($CDCl_3$, 270 MHz) δ=7.53—7.28 (m, 7H, Ar*H*), 7.12 (t, 2H, *J*=8.7 Hz, C*H*CF), 4.48 (br s, 1H, NC*H*CN), 4.25 (dd, 1H, *J*=4.3, 9.2 Hz, NC*H*Ph), 3.84 (dd, 1H, *J*=4.0, 10.9 Hz, CH_2OH), 3.64 (t like, 1H, *J*=8.9 Hz, CH_2OH). The hydrochloride of (*R,S*)-**4b**: Colorless crystals; mp 90—91°C (AcOEt); $[\alpha]_D^{20}$ −74.7° (*c* 0.5, THF); IR (KBr) 3350, 2750, 1610, 1510, 1440, 1410, 1240, 1190, 1090, 1000, 840, 830, 760, 700, 560, 490 cm^{-1}. Found: C, 61.99; H, 5.23; N, 8.82%. Calcd for $C_{16}H_{17}ClFN_2O \cdot 0.2\ H_2O$: C, 61.92; H, 5.33; N, 9.03%.

(*R,R*)-**4b**: Colorless crystals; mp 76°C (hexane–ethyl acetate); $[\alpha]_D^{20}$ −40.4° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ=7.45—7.28 (m, 7H, Ar*H*), 7.10 (t, 2H, *J*=8.7 Hz, C*H*CF), 4.72 (s, 1H, NC*H*CN), 3.85 (dd, 1H, *J*=4.0, 7.9 Hz, NC*H*Ph), 3.76 (dd, 1H, *J*=4.0, 10.9 Hz, CH_2OH), 3.68 (dd, 1H, *J*=7.9, 10.9 Hz, CH_2OH); IR (KBr) 3350, 3300, 2850, 2230, 1600, 1510, 1470, 1220, 1160, 1080, 940, 920, 830, 750, 700, 520 cm^{-1}. Found: C, 70.67; H, 5.58; N, 10.19%. Calcd for $C_{16}H_{15}FN_2O \cdot 0.1\ H_2O$: C, 70.62; H, 5.63; N, 10.29%.

2-[(2-Hydroxy-1-phenylethyl)amino]-2-(1-naphthyl)ethanenitrile (4c): Similarly, a mixture (*R,S*/*R,R*=81/19) of **4c** was obtained in 95% yield. (*R,S*)-**4c** was colorless crystals; mp 123—124°C (hexane–ethyl acetate); $[\alpha]_D^{20}$ −161° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ=7.89—7.82 (m, 3H, Ar*H*), 7.71 (d, 1H, Ar*H*), 7.57—7.40 (m, 8H, Ar*H*), 5.10 (d, 1H, *J*=11.2 Hz, NC*H*CN), 4.35 (dd, 1H, *J*=4.3, 9.2 Hz, NC*H*Ph), 3.84 (td, 1H, *J*=4.3, 10.9 Hz, CH_2OH), 3.68 (ddd, 1H, *J*=6.9, 9.2, 10.9 Hz, CH_2OH), 2.53 (d, 1H, *J*=10.9 Hz, N*H*), 1.81 (dd, 1H, *J*=4.3, 6.9 Hz, O*H*); IR (KBr) 3500, 3340, 2940, 2440, 1123, 1050, 1035, 800, 775, 760, 705 cm^{-1}. Found: C, 79.70; H, 6.02; N, 9.32%. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26%.

(*R,R*)-**4c**: A colorless oil; $[\alpha]_D^{20}$ +82.0° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ=8.17 (d, 1H, *J*=8.2 Hz, Ar*H*), 7.90 (d, 1H, *J*=7.9 Hz, Ar*H*), 7.86 (d, 1H, *J*=7.2 Hz, Ar*H*), 7.66—7.51 (m, 3H, Ar*H*), 7.44 (dd, 1H, *J*=7.3, 8.3 Hz, Ar*H*), 7.31 (s like, 5H, Ar*H*), 5.51 (s, 1H, NC*H*CN), 4.04 (dd, 1H, *J*=4.0, 7.6 Hz, NC*H*Ph), 3.81 (dd, 1H, *J*=4.0, 10.9 Hz, CH_2OH), 3.74 (dd, 1H, *J*=7.9, 10.9 Hz, CH_2OH), 2.40 (br s, 1H, N*H*), 1.96 (br s, 1H, O*H*); IR (neat) 3450, 3320, 3050, 2440, 1720, 1450, 1245, 1110, 1040, 775, 700 cm^{-1}. The oxalate of (*R,R*)-**4c**: Colorless crystals; mp 111—112°C (decomp, AcOEt). Found: C, 66.76; H, 5.18; N, 6.92%. Calcd for $C_{20}H_{18}N_2O$ $(CO_2H)_2 \cdot 0.2\ H_2O$: C, 66.73; H, 5.19; N, 7.07%.

2-[(2-Hydroxy-1-phenylethyl)amino)-2-(2-thienyl)ethanenitrile (4d): Similarly, a mixture (*R,S*/*R,R*=82/18) of **4d** was obtained in 94% yield.

(*R,S*)-**4d**: A colorless oil; ^1H NMR ($CDCl_3$, 270 MHz) δ=7.56—7.32 (m, 6H, Ar*H*), 7.25 (m, 1H, Ar*H*), 6.99 (dd, 1H, *J*=3.6, 5.3 Hz, SC*H*), 4.68 (br d, 1H, *J*=9.9 Hz, NC*H*CN), 4.23 (dd, 1H, *J*=4.0, 9.2 Hz, NC*H*Ph), 3.83 (dd, 1H, *J*=4.0, 11.2 Hz, CH_2OH), 3.65 (br t, 1H, *J*=9.6 Hz, CH_2OH), 2.82 (br d, 1H, *J*=7.3 Hz, N*H*), 1.86 (br s, 1H, O*H*). The oxalate of (*R,S*)-**4d**: Colorless crystals; mp 149°C (decomp, AcOEt); $[\alpha]_D^{20}$ −89.6° (*c* 1.00, $CHCl_3$); IR (KBr) 3370, 2950, 1750, 1620, 1500, 1400, 1290, 1270, 1080, 1040, 1020, 850, 760, 735, 710 cm^{-1}. Found: C, 55.01; H, 4.77; N, 7.92%. Calcd for $C_{14}H_{14}N_2OS$ $(CO_2H)_2$: C, 55.16; H, 4.63; N, 8.04%.

(*R,R*)-**4d**: A colorless oil; ^1H NMR ($CDCl_3$, 270 MHz) δ=7.55—7.33 (m, 6H, Ar*H*), 7.11 (m, 1H, Ar*H*), 6.98 (dd, 1H, *J*=3.6, 5.3 Hz, SC*H*), 4.98 (s, 1H, NC*H*CN), 3.96 (dd, 1H, *J*=4.3, 8.2 Hz, NC*H*Ph), 3.78 (dd, 1H, *J*=4.3, 10.9 Hz, CH_2OH), 3.70 (dd, 1H, *J*=8.2, 10.9 Hz, CH_2OH), 2.50 (br d, 1H, *J*=7.3 Hz, N*H*), 1.95 (br s, 1H, O*H*). The oxalate of (*R,R*)-**4d**: Colorless crystals; mp 147°C (decomp, AcOEt); $[\alpha]_D^{20}$ −13.5° (*c* 1.00, $CHCl_3$); IR (KBr) 3180, 2960, 1710, 1620, 1460, 1225, 1025, 850, 755, 710 cm^{-1}. Found: C, 54.96; H, 4.79; N, 7.83%. Calcd for $C_{14}H_{14}N_2OS$ $(CO_2H)_2$: C, 55.16; H, 4.63; N, 8.04%.

2-[(2-Hydroxy-1-phenylethyl)amino]-3,3-dimethylbutanenitrile (4g): Similarly, a mixture (*R,S*/*R,R*=87/13) of **4g** was obtained as a colorless oil in 91% yield.

(*R,S*)-**4g**: Colorless crystals; mp 60—61°C (hexane); $[\alpha]_D^{20}$ −246° (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$–D_2O, 270 MHz) δ=7.37—7.28 (m, 5H, Ar*H*), 4.08 (dd, 1H, *J*=4.0, 9.2 Hz, PhC*H*N), 3.79 (dd, 1H, *J*=4.0, 10.9 Hz, CH_2OH), 3.55 (dd, 1H, *J*=9.2, 10.9 Hz, CH_2OH), 2.95 (s, 1H, NC*H*CN), 1.06 (s, 9H, C(CH_3)$_3$); IR (KBr) 3210, 2950, 2200, 1440, 1360, 1060, 1020, 760, 700 cm^{-1}. Found: C, 72.22; H, 8.63; N, 12.00%. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06%.

(*R,R*)-**4g**: A colorless oil; $[\alpha]_D^{20}$ −2.66° (*c* 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ=7.39—7.26 (m, 5H, Ar*H*), 3.95 (dd, 1H, *J*=4.6, 6.6 Hz, PhC*H*N), 3.79 (dd, 1H, *J*=4.6, 11.2 Hz, C*H*$_2$OH), 3.69 (dd, 1H, *J*=6.6, 11.2 Hz, C*H*$_2$OH), 3.33 (s, 1H, NC*H*CN), 1.99—1.59 (br s, 2H, O*H*+N*H*), 1.10 (s, 9H, C(C*H*$_3$)$_3$), IR (neat) 3450, 2950, 2880, 2240, 1470, 1400, 1360, 1120, 1060, 1020, 760, 700 cm^{-1}. Anal. (as a diastereomeric mixture, *R,R*/*R,S*=73/27). Found: C, 72.10; H, 8.52; N, 11.72%. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06%.

2-[(2-Hydroxy-1-phenylethyl)amino]propanenitrile (4e): To a solution of acetaldehyde (147 mg, 3.00 mmol) in water (5.0 ml) were sequentially added $NaHSO_3$ (312 mg, 3.00 mmol), KCN (195 mg, 3.00 mmol), and (*R*)-2-phenylglycinol (**2**, 274 mg, 2.00 mmol) under ice-cooling. After stirring the mixture at room temperature for 3 h, a deposited oily product was extracted with CH_2Cl_2 (8 ml×3). The combined organic layers were dried over $MgSO_4$ and then the solvent was removed in vacuo. Flash chromatography of the residue on silica gel (hexane–ethyl acetate, 3 : 1) afforded a diastereomeric mixture (*R,S*/*R,R*=73/27) of **4e** (379 mg, 100%) as a colorless oil.

The two diastereomers were separated by preparative HPLC[13] (hexane–ethyl acetate, 40 : 60).

(*R,S*)-**4e**: A colorless oil; ^1H NMR ($CDCl_3$, 500 MHz) δ=7.37—7.28 (m, 5H, Ar*H*), 4.11 (dd, 1H, *J*=3.9, 9.1 Hz, PhC*H*N), 3.79 (dd, 1H, *J*=4.0, 11.0 Hz, C*H*$_2$OH), 3.59 (dd, 1H, *J*=9.1, 11.0 Hz, C*H*$_2$OH), 3.37 (q, 1H, *J*=7.1 Hz, NC*H*CN), 1.95 (br s, 2H, O*H*+N*H*), 1.48 (d, 3H, *J*=7.1 Hz, C*H*$_3$). The oxalate of (*R,S*)-**4e**: Colorless crystals; mp 124°C (decomp, AcOEt); $[\alpha]_D^{20}$ −163.9° (*c* 1.00, THF); IR (KBr) 3290, 3140, 3000, 2680, 1720, 1630, 1560, 1460, 1110, 1060, 760, 705, 575, 485 cm^{-1}. Found: C, 55.74; H, 5.78; N, 9.84%. Calcd for $C_{11}H_{14}N_2O$ $(CO_2H)_2$: C, 55.71; H, 5.75; N, 9.99%.

(*R,R*)-**4e**: A colorless oil; ^1H NMR ($CDCl_3$, 500 MHz) δ=7.37—7.28 (m, 5H, Ar*H*), 4.00 (dd, 1H, *J*=4.4, 7.4 Hz, PhC*H*N), 3.81 (q, 1H, *J*=7.2 Hz, NC*H*CN), 3.78 (dd, 1H, *J*=4.4, 11.3 Hz, C*H*$_2$OH), 3.51 (dd, 1H, *J*=7.4, 11.3 Hz, C*H*$_2$OH), 1.95 (br s, 2H, O*H*+N*H*), 1.46 (d, 3H, *J*=6.9 Hz, C*H*$_3$). The oxalate of (*R,R*)-**4e**: Colorless crystals; mp 129°C (decomp, AcOEt); $[\alpha]_D^{20}$ −33.8° (*c* 1.00, THF); IR (KBr) 3250, 2610, 2450, 1570, 1295, 1145, 1055, 770, 700, 580 cm^{-1}. Found: C, 60.98; H, 6.45; N, 11.69%. Calcd for $C_{11}H_{14}N_2O{\cdot}0.5(CO_2H)_2$: C, 61.26; H, 6.43; N, 11.91%.

2-[(2-Hydroxy-1-phenylethyl)amino]-3-methylbutanenitrile (4f): Similarly, a mixture (*R,S*/*R,R*=66/34) of **4f** was obtained in 87% yield.

(*R,S*)-**4f**: A colorless oil; ^1H NMR ($CDCl_3$, 500 MHz) δ=7.36—7.29 (m, 5H, Ar*H*), 4.09 (dd, 1H, *J*=4.0, 9.2 Hz, PhC*H*N), 3.80 (dd, 1H, *J*=4.0, 10.7 Hz, C*H*$_2$OH), 3.58 (dd, 1H, *J*=9.4, 10.7 Hz, C*H*$_2$OH), 3.10 (d, 1H, *J*=6.1 Hz, NC*H*CN), 2.25 (br s, 1H, N*H*), 1.97 (m, 1H, C*H*(CH$_3$)$_2$), 1.80 (br s, 1H, O*H*), 1.08 (d, 3H, *J*=6.6 Hz, C*H*$_3$), 1.06 (d, 3H, *J*=6.6 Hz, C*H*$_3$). The oxalate of (*R,S*)-**4f**: Colorless crystals; mp 108—110°C (decomp, AcOEt); $[\alpha]_D^{20}$ −148.8° (*c* 1.00, THF); IR (KBr) 3300, 2950, 1710, 1630, 1460, 1400, 1260, 1060, 720, 700 cm^{-1}. Found: C, 58.11; H, 6.56; N, 8.61%. Calcd for $C_{13}H_{18}N_2O$ $(CO_2H)_2{\cdot}0.1H_2O$: C, 58.09; H, 6.56; N, 9.03%.

(*R,R*)-**4f**: A colorless oil; ^1H NMR ($CDCl_3$, 500 MHz) δ=7.38—7.30 (m, 5H, Ar*H*), 3.96 (dd, 1H, *J*=4.4, 7.2 Hz, PhC*H*N), 3.77 (dd, 1H, *J*=4.4, 11.0 Hz, C*H*$_2$OH), 3.67 (dd, 1H, *J*=7.1, 11.0 Hz, C*H*$_2$OH), 3.50 (d, 1H, *J*=5.8 Hz, NC*H*CN), 2.08 (br s, 1H, N*H*), 2.01 (m, 1H, C*H*(CH$_3$)$_2$), 1.85 (br s, 1H, O*H*), 1.10 (d, 3H, *J*=6.6 Hz, C*H*$_3$), 1.07 (d, 3H, *J*=6.6 Hz, C*H*$_3$). The oxalate of (*R,R*)-**4f**: Colorless crystals; mp 126—128°C (decomp, AcOEt); $[\alpha]_D^{20}$ −23.5° (*c* 1.00, THF); IR (KBr) 3250, 2970, 2400, 1560, 1300, 1055, 775, 695 cm^{-1}. Found: C, 63.84; H, 7.27; N, 10.58%. Calcd for $C_{13}H_{18}N_2O{\cdot}0.5(CO_2H)_2$: C, 63.86; H, 7.27; N, 10.64%.

2-[(2-Hydroxy-1-phenylethyl)amino]-3-phenylpropanenitrile (4h): Similarly, a mixture (*R,S*/*R,R*=69/31) of **4h** was obtained in 91% yield.

(*R,S*)-**4h**: A colorless oil; $[\alpha]_D^{20}$ −150.2° (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ=7.36—7.20 (m, 10H, Ar*H*), 4.07 (dd, 1H, *J*=4.0, 8.9 Hz, PhC*H*N), 3.75 (dd, 1H, *J*=4.0, 11.2 Hz, C*H*$_2$OH), 3.53 (dd, 1H, *J*=8.9, 11.2 Hz, C*H*$_2$OH), 3.52 (t, 1H, *J*=6.6 Hz, NC*H*CN), 3.04 (d, 2H, *J*=6.6 Hz, PhC*H*$_2$), 2.20 (br s, 1H), 1.78 (br s, 1H); IR (neat) 3430, 3330, 3030, 2930, 2220, 1600, 1490, 1450, 1125, 1065, 1025, 755, 700 cm^{-1}. The oxalate of (*R,S*)-**4h**: Colorless crystals; mp 113—115°C (decomp, AcOEt). Found: C, 64.09; H, 5.79; N, 8.04%. Calcd for $C_{17}H_{18}N_2O$ $(CO_2H)_2$: C, 64.04; H, 5.66; N, 7.86%.

(*R,R*)-**4h**: A colorless oil; $[\alpha]_D^{20}$ −39.4° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ=7.41—7.15 (m, 10H, Ar*H*), 3.97 (dd, 1H, *J*=4.3, 7.3 Hz, PhC*H*CH$_2$O), 3.92 (dd, 1H, *J*=6.3, 6.9 Hz, NC*H*CN), 3.74 (dd, 1H, *J*=4.3, 10.9 Hz, C*H*$_2$OH), 3.62 (dd, 1H, *J*=7.3, 10.9 Hz, C*H*$_2$OH), 3.03 (dd, 1H, *J*=5.9, 11.9 Hz, PhC*H*$_2$), 3.01 (dd, 1H, *J*=6.3, 11.9 Hz, PhC*H*$_2$), 1.92 (br s, 1H), 1.65 (br s, 1H); IR (neat) 3440, 3340, 3040, 2940, 2240, 1600, 1490, 1450, 1120, 1025, 755, 700 cm^{-1}. The oxalate of (*R,R*)-**4h**: Colorless crystals; mp 144—146°C (decomp, AcOEt). Found: C, 65.36; H, 5.77; N, 8.27%. Calcd for $C_{17}H_{18}N_2O{\cdot}0.85(CO_2H)_2$: C, 65.51; H, 5.79; N, 8.17%.

Determination of Equilibrium Ratio of 4. Individual samples (10.0 mg) of (*R**,*R**)-**4** and (*R**,*S**)-**4**, obtained by preparative HPLC separation were dissolved in MeOH (0.5 ml) and heated at 80°C in a sealed tube, until the diastereomeric ratio in each tube showed a stable value by HPLC analysis (generally 3 h). The final ratio was determined by ^1H NMR spectroscopy (in $CDCl_3$, 500 or 270 MHz). The α-amino carbonitriles **4e**, **4f**, and **4h** obtained by the Strecker reaction were converted to their equilibrium mixtures by reflux in MeOH for 3 h before hydrolysis to give **5**. Other amino nitriles **4** were given as equilibrium mixtures by the Strecker reaction performed at reflux temperature of MeOH.

(*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]-2-(4-methoxyphenyl)ethanoic Acid [(*R*,*S*)-5a]: An equilibrium mixture of **4a** (2.15 g, 7.54 mmol) was dissolved in concd HCl (35%, 7.0 ml), and the solution was heated at 50°C for 2 h. The mixture was neutralized with solid $NaHCO_3$. The formed precipitate was collected by filtration, washed with water and CH_2Cl_2, and dried under reduced pressure to give (*R,S*)-**5a** (1.30 g, 57%) as colorless crystals. Purification of the mother liquor by column chromatography on active carbon (MeOH–H_2O, 50 : 50) gave a mixture (43 : 57) of (*R,S*)-**5a** and (*R,R*)-**5a** (707 mg). The yield of this reaction was calculated to be 88%.

(*R,S*)-**5a**: Colorless crystals; mp 194—195°C (MeOH–H_2O); $[\alpha]_D^{20}$ +54.6° (*c* 1.00, MeOH); ^1H NMR (D_2O, 270 MHz) δ=7.54—7.43 (m, 5H, Ar*H*), 7.17 (d, 2H, *J*=8.9 Hz, C*H*CHCOCH$_3$), 6.96 (d, 2H, *J*=8.9 Hz, C*H*COCH$_3$), 4.51 (t, 1H, *J*=6.8 Hz, NC*H*Ph), 4.46 (s, 1H, NC*H*CO$_2$), 4.07 (d, 2H, *J*=6.9 Hz, NCHC*H*$_2$O), 3.83 (s, 3H, OC*H*$_3$); IR (KBr) 3500, 3050, 2950, 2850, 1600, 1510, 1460, 1390, 1325, 1270, 1210, 1100, 1060, 860, 830, 790, 760, 740, 620, 560, 520 cm^{-1}; Found: C, 65.47; H, 6.66; N, 4.35%. Calcd for $C_{17}H_{19}NO_4{\cdot}0.6\,H_2O$: C, 65.41; H, 6.52; N,

4.49%.

(*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]-3,3-dimethylbutanoic Acid [(*R,S*)-5g]: Similarly, (*R,S*)-**5g** was obtained from an equilibrium mixture of **4g** in 81% yield.

(*R,S*)-**5g**: Colorless crystals; mp 240—241 °C (sublimation, MeOH–H_2O); $[\alpha]_D^{20}$ −37.5° (*c* 1.00, 1 M HCl); ^{1}H NMR (DMSO-d_6, 270 MHz) δ=7.29—7.21 (m, 5H, Ar*H*), 5.05 (s, 1H, NC*H*CO_2H), 3.51 (dd, *J*=4.0, 9.2 Hz, NC*H*Ph), 3.37—3.29 (m, 2H, CH_2OH), 0.89 (s, 9H, C(CH_3)$_3$); IR (KBr) 3200, 2950, 1610, 1560, 1480, 1440, 1360, 1220, 1045, 740, 700, 620, 580 cm^{-1}. Found: C, 66.82; H, 8.44; N, 5.44%. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57%.

(*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]-2-(4-fluorophenyl)ethanoic Acid [(*R,S*)-5b]: An equilibrium mixture of **4b** (2.22 g, 8.20 mmol) was dissolved in concd HCl (35%, 15 ml), and the solution was stirred at room temperature for 16 h and at 80 °C for 30 min. The mixture was neutralized with solid $NaHCO_3$. Column chromatography on active carbon (MeOH–H_2O, 50:50) and subsequent recrystallization from EtOH gave (*R,S*)-**5b** (958 mg, 40%) as colorless crystals; mp 210—211 °C (decomp, EtOH); $[\alpha]_D^{20}$ +72.3° (*c* 1.00, 1 M HCl); ^{1}H NMR (D_2O, 270 MHz) δ=7.53—7.42 (m, 5H, Ar*H*), 7.25—7.08 (m, 4H, Ar*H*), 4.51 (t, 1H, *J*=6.9 Hz, NC*H*Ph), 4.47 (s, 1H, NC*H*CO_2O), 4.06 (d, 2H, *J*=7.3 Hz, NCHCH_2O); IR (KBr) 3400, 3050, 1620, 1510, 1365, 1230, 1190, 1160, 1080, 1040, 1010, 840, 810, 760, 700, 580, 500 cm^{-1}. Found: C, 64.54; H, 5.74; N, 4.54%. Calcd for $C_{16}H_{16}FNO_3$·0.5 H_2O: C, 64.42; H, 5.74; N, 4.70%.

(*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]-2-(2-thienyl)ethanoic Acid [(*R,S*)-5d]: Similarly, (*R,S*)-**5d** was obtained from an equilibrium mixture of **4d** in 40% yield as colorless crystals; mp 206—209 °C (decomp, EtOH); $[\alpha]_D^{20}$ +14.8° (*c* 1.00, MeOH); ^{1}H NMR (D_2O, 270 MHz) δ=7.51 (m, 3H, Ar*H*), 7.44 (m, 3H, Ar*H*), 7.04 (m, 2H, Ar*H*), 4.59 (s, 1H, NC*H*CO_2), 4.30 (br t, 1H, *J*=6.3 Hz, NC*H*Ph), 3.97 (d, 2H, *J*=5.8 Hz, NCHCH_2O); IR (KBr) 3200, 3060, 1640, 1570, 1450, 1375, 1050, 700 cm^{-1}. Found: C, 60.33; H, 5.16; N, 5.02%. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05%.

(*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]-2-(1-naphthyl)ethanoic Acid [(*R,S*)-5c]: Similarly, (*R,S*)-**5c** was quantitatively obtained from (*R,S*)-**4c**.

(*R,S*)-**5c**: Colorless crystals; mp 140—143 °C (ethyl acetate); $[\alpha]_D^{20}$ +50.4° (*c* 1.00, 1 M HCl); ^{1}H NMR (CD_3OD, 270 MHz) δ=7.83 (d, 1H, *J*=7.9 Hz, Ar*H*), 7.80 (d, 1H, *J*=8.2 Hz, Ar*H*), 7.46—7.27 (m, 10 H, Ar*H*), 4.96 (s, 1H, NC*H*CO_2), 4.32 (br t, 1H, *J*=6.6 Hz, NC*H*Ph), 3.81 (d, 2H, *J*=6.6 Hz, NCHCH_2O); IR (KBr) 3320, 3050, 1630, 1510, 1450, 1365, 1040, 775, 700 cm^{-1}. Found: C, 72.31; H, 5.83; N, 4.02%. Calcd for $C_{20}H_{19}NO_3$·0.6 H_2O: C, 72.32; H, 6.13; N, 4.24%.

(*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]-3-methylbutanoic Acid [(*R,S*)-5f]: Similarly, (*R,S*)-**5f** was obtained from an equilibrium mixture of **4f** in 49% yield as colorless crystals; mp 240—241 °C (decomp, EtOH–H_2O); $[\alpha]_D^{20}$ −35.5° (*c* 1.00, 1 M HCl); ^{1}H NMR (D_2O, 270 MHz) δ=7.55—7.47 (m, 5H, Ar*H*), 4.30 (ABX, 1H, *J*=7.7, 10.8 Hz, NC*H*CH_2O), 4.10 (ABX, 1H, *J*=10.8, 14.3 Hz, NCHCH_2O), 4.04 (ABX, *J*=7.7, 14.3 Hz, NCHCH_2O), 3.24 (d, 1H, *J*=4.3 Hz, NC*H*CO_2), 2.11 (m, 1H, C*H*(CH_3)$_2$), 0.92 (d, 3H, *J*=6.9 Hz, CH_3), 0.85 (d, 3H, *J*=6.9 Hz, CH_3); IR (KBr) 3270, 3010, 1625, 1570, 1500, 1460, 1405, 1375, 1335, 1235, 1070, 1050, 765, 710, 630, 600, 590, 500 cm^{-1}. Found: C, 65.39; H, 8.07; N, 5.74%. Calcd for $C_{13}H_{19}NO_3$·0.1 H_2O: C, 65.30; H, 8.09; N, 5.89%.

(*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]propanoic Acid [(*R,S*)-5e]: An equilibrium mixture of **4e** (1.90 g, 10.0 mmol) was dissolved in concd HCl (35%, 3.8 ml), and the solution was heated at 50 °C for 15 min. After the solution was solidified, water (10 ml) was added and then the suspension was refluxed for 1 h. The reaction was quenched by neutralization with saturated aqueous $NaHCO_3$. Column chromatography on active carbon (MeOH–H_2O, 50:50) and subsequent recrystallization from water gave (*R,S*)-**5e** (884 mg, 42%) as colorless crystals; mp 252—255 °C (decomp, water); $[\alpha]_D^{20}$ −61.3° (*c* 1.00, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ=7.54—7.53 (m, 3H, Ar*H*), 7.47—7.44 (m, 2H, Ar*H*), 4.47 (ABX, 1H, *J*=5.3, 8.2 Hz, NC*H*CH_2O), 4.06 (ABX, 1H, *J*=8.2, 12.2 Hz, NCHCH_2O), 4.03 (ABX, 1H, *J*=5.3, 12.2 Hz, NCHCH_2O), 3.43 (q, 1H, *J*=7.1 Hz, NC*H*CO_2), 1.41 (d, 3H, *J*=7.2 Hz, CH_3); IR (KBr) 3350, 3050, 1610, 1580, 1460, 1385, 1360, 1085, 1040, 700, 555, 500 cm^{-1}. Found: C, 63.22; H, 7.25; N, 6.59%. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69%.

(*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]-3-phenylpropanoic Acid [(*R,S*)-5h]: Similarly, (*R,S*)-**5h** was obtained from an equilibrium mixture of **4h** in 40% yield as colorless crystals; mp 228—229 °C (decomp, DMF–H_2O); $[\alpha]_D^{20}$ −76.0° (*c* 0.50, DMF); ^{1}H NMR (DMSO-d_6, 270 MHz) δ=7.29—7.06 (m, 10H, Ar*H*), 3.66 (dd, 1H, *J*=4.0, 8.9 Hz, PhC*H*CH_2OH), 3.36 (dd, 1H, *J*=4.0, 10.5 Hz, PhCHCH_2OH), 3.21 (dd, 1H, *J*=9.2, 10.2 Hz, PhCHCH_2OH), 3.04 (dd, 1H, *J*=5.9, 7.7 Hz, NC*H*CO_2), 2.83 (dd, 1H, *J*=5.9, 13.2 Hz, NCHCH_2Ph), 2.75 (dd, 1H, *J*=7.9, 13.2 Hz, NCHCH_2Ph); IR (KBr) 3370, 2950, 2850, 2400, 1575, 1445, 1385, 1235, 1090, 750, 700, 550 cm^{-1}. Found: C, 71.73; H, 6.75; N, 4.72%. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91%.

(3*S*,5*R*)-3,4,5,6-Tetrahydro-3-methyl-5-phenyl-2*H*-1,4-oxazin-2-one (9e): An equilibrium mixture of (*R,S*)-**4e** and (*R,R*)-**4e** (1.90 g, 10.0 mmol) was dissolved in concd HCl (35%, 5.5 ml), and the solution was heated at 50 °C for 4 h. At the beginning of the reaction, the solution solidified. To the reaction mixture was added CH_2Cl_2 (50 ml). Then the mixture was neutralized with saturated aqueous $NaHCO_3$ and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (30 ml×2). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography of the residue on silica gel (hexane–ethyl acetate, 2:1) afforded a mixture (3*S*,5*R*/3*R*,5*R*=95/5) of **9e** (1.36 g, 71%) as a colorless solid. The two diastereomers were separated by preparative HPLC[13] (hexane–ethyl acetate, 60:40).

(*R,S*)-**9e**: Colorless crystals; mp 79 °C (hexane–ethyl acetate); $[\alpha]_D^{20}$ −95.4° (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ=7.41 (dd, 2H, *J*=1.4, 8.0 Hz, Ar*H*), 7.39—7.33 (m, 3H, Ar*H*), 4.37 (ABX, 1H, *J*=3.3, 11.3 Hz, NCHCH_2O), 4.29 (ABX, 1H, *J*=10.4, 11.3 Hz, NCHCH_2O), 4.27 (ABX, 1H, *J*=3.3, 10.4 Hz, NC*H*CH_2O), 3.87 (q, 1H, *J*=6.9 Hz, NC*H*CO), 1.90 (br s, 1H, N*H*), 1.53 (d, 3H, *J*=6.6 Hz, CH_3); IR (KBr) 3310, 2920, 1740, 1450, 1300, 1210, 1145, 1055, 1020, 820, 760, 700 cm^{-1}. Found: C, 69.12; H, 6.86; N, 7.29%. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%.

(*R,R*)-**9e**: Colorless crystals; mp 78—79 °C (hexane–ethyl acetate); $[\alpha]_D^{20}$ +36.2° (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ=7.45—7.29 (m, 5H, Ar*H*), 4.46—4.25 (m, 3H, NC*H*CH_2O), 3.95 (q, 1H, *J*=6.9 Hz, NC*H*CO), 1.73 (br s, 1H, N*H*), 1.50 (d, 3H, *J*=6.9 Hz, CH_3); IR (KBr) 3350, 2910, 1725, 1480, 1440, 1370, 1250, 1180, 1140, 1055, 1025, 820, 750,

700 cm^{-1}. Found: C, 69.08; H, 6.95; N, 7.25%. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%.

3-Benzyl-3,4,5,6-tetrahydro-5-phenyl-2*H*-1,4-oxazin-2-one (9h): Similarly, a mixture (3*S*,5*R*/3*R*,5*R*=82/18) of **9h** was obtained in 86% yield as a colorless solid from an equilibrium mixture of **4h**.

(*R*,*S*)-**9h**: Colorless crystals; mp 76—77°C (hexane–ethyl acetate); $[\alpha]_D^{20}$ −176.9° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ=7.36—7.22 (m, 10H, Ar*H*), 4.29 (ABX, 1H, *J*=3.8, 13.7 Hz, PhCHCH_2O), 4.17 (ABX, 1H, *J*=11.5, 13.7 Hz, PhCHCH_2O), 4.15 (ABX, 1H, *J*=3.8, 11.5 Hz, PhC*H*CH_2O), 3.98 (br d, 1H, *J*=9.9 Hz, NC*H*CO), 3.56 (dd, 1H, *J*=3.0, 13.8 Hz, NCHCH_2Ph), 3.00 (dd, 1H, *J*=9.9, 13.8 Hz, NCHCH_2Ph), 1.84 (br s, 1H, N*H*); IR (KBr) 3330, 1730, 1450, 1315, 1200, 1018, 745, 700 cm^{-1}. Found: C, 76.40; H, 6.43; N, 5.22%. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24%.

(*R*,*R*)-**9h**: Colorless crystals; mp 109—110°C (hexane–ethyl acetate); $[\alpha]_D^{20}$ +75.6° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ=7.35—7.23 (m, 10H, Ar*H*), 4.37 (ABX, 1H, *J*=3.4, 12.5 Hz, NCHCH_2O), 4.31 (ABX, 1H, *J*=10.2, 12.5 Hz, NCHCH_2O), 4.29 (ABX, 1H, *J*=3.4, 10.2 Hz, NC*H*CH_2O), 4.08 (dd, 1H, *J*=4.1, 9.6 Hz, NC*H*CO), 3.29 (dd, 1H, *J*=4.1, 13.7 Hz, PhCH_2), 3.18 (dd, 1H, *J*=9.6, 14.0 Hz, PhCH_2), 1.82 (br s, 1H, N*H*); IR (KBr) 3350, 2910, 1724, 1600, 1490, 1445, 1380, 1178, 1129, 1035, 750, 700 cm^{-1}. Found: C, 76.30; H, 6.44; N, 5.23%. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24%.

Methyl (*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]-2-(4-methoxyphenyl)ethanoate [(*R*,*S*)-6a]: Thionyl chloride (0.39 ml, 5.35 mmol) was added dropwise to MeOH (5.0 ml, 124 mmol) at −78°C, and then (*R*,*S*)-**5a** (443 mg, 1.47 mmol) was added at this temperature. The resulting solution was allowed to warm to room temperature and refluxed for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the separated oil was extracted with CH_2Cl_2 (20 ml×3). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography of the residue on silica gel (hexane–ethyl acetate, 50 : 50) afforded (*R*,*S*)-**6a** (411 mg, 88%) as colorless crystals; mp 80°C (hexane–ethyl acetate); $[\alpha]_D^{20}$ +34.55° (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ=7.35—7.28 (m, 5H, Ar*H*), 7.24 (d, 2H, *J*=8.9 Hz, C*H*CHCOCH$_3$), 6.84 (d, 2H, *J*=8.9 Hz, CHC*H*COCH$_3$), 4.26 (s, 1H, NC*H*CO_2), 3.81 (dd, 1H, *J*=4.3, 8.6 Hz, NC*H*Ph), 3.78 (s, 3H, OCH_3), 3.74 (dd, 1H, *J*=4.3, 10.6 Hz, CH_2OH), 3.70 (s, 3H, OCH_3), 3.59 (dd, 1H, *J*=8.6, 10.6 Hz, CH_2OH), 2.50 (br s, 2H, N*H*+O*H*); IR (KBr) 3300, 2950, 1735, 1602, 1503, 1450, 1300, 1240, 1205, 1170, 1128, 1055, 1025, 980, 828, 760, 700 cm^{-1}. Found: C, 68.62; H, 6.73; N, 4.64%. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44%.

Methyl (*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]-2-(4-fluorophenyl)ethanoate [(*R*,*S*)-6b]: Similarly, (*R*,*S*)-**6b** was obtained in 96% yield from (*R*,*S*)-**5b** as colorless crystals; mp 90°C (hexane–ethyl acetate); $[\alpha]_D^{20}$ +7.2° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ=7.36—7.26 (m, 7H, Ar*H*), 6.99 (t, 2H, *J*=8.9 Hz, FCC*H*), 4.28 (s, 1H, NC*H*CO_2), 3.82 (dd, 1H, *J*=4.1, 8.4 Hz, NC*H*Ph), 3.74 (dd, 1H, *J*=4.1, 10.7 Hz, CH_2OH), 3.71 (s, 3H, OCH_3), 3.60 (dd, 1H, *J*=8.4, 10.7 Hz, CH_2OH); IR (KBr) 3240, 1740, 1600, 1510, 1440, 1305, 1200, 1160, 1135, 1100, 1060, 980, 830, 760, 705, 510 cm^{-1}. Found: C, 67.41; H, 6.01; N, 4.54%. Calcd for $C_{17}H_{18}FNO_3$: C, 67.31; H, 5.98; N, 4.62%.

Methyl (*S*)-2-[(*R*)-2-Hydroxy-1-phenylethylamino]-2-(1-naphthyl)ethanoate [(*R*,*S*)-6c]: Similarly, (*R*,*S*)-**6c** was obtained in 98% yield from (*R*,*S*)-**5c** as a pale yellow oil; $[\alpha]_D^{20}$ +18.5° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ=7.86—7.76 (m, 3H, Ar*H*), 7.50—7.29 (m, 9H, Ar*H*), 5.01 (s, 1H, NC*H*CO_2), 3.98 (dd, 1H, *J*=4.3, 8.6 Hz, NC*H*Ph), 3.77 (dd, 1H, *J*=4.3, 10.6 Hz, CH_2OH), 3.70 (s, 3H, OCH_3), 3.61 (dd, 1H, *J*=8.6, 10.6 Hz, CH_2OH), 2.53 (br s, 2H, N*H*+O*H*); IR (neat) 3450, 3350, 2970, 1740, 1450, 1220, 1025, 780, 760, 710 cm^{-1}. The hydrochloride of (*R*,*S*)-**6c**: Colorless crystals; mp 154—157°C (ethyl acetate). Found: C, 65.88; H, 6.06; N, 3.61%. Calcd for $C_{21}H_{22}ClNO_3 \cdot 0.67\ H_2O$: C, 65.71; H, 6.13; N, 3.65%.

Methyl (*S*)-2[(*R*)-2-Hydroxy-1-phenylethylamino]-2-(2-thienyl)ethanoate [(*R*,*S*)-6d]: Similarly, (*R*,*S*)-**6d** was obtained quantitatively from (*R*,*S*)-**5d** as colorless crystals; mp 76—77°C (hexane–ethyl acetate); $[\alpha]_D^{20}$ −22.4° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ=7.38—7.28 (m, 5H, Ar*H*), 7.23 (dd, 1H, *J*=1.7, 4.6 Hz, Ar*H*), 6.96—6.92 (m, 2H, Ar*H*), 4.53 (s, 1H, NC*H*CO_2), 3.85 (dd, 1H, *J*=4.3, 8.2 Hz, NC*H*Ph), 3.78 (s, 3H, OCH_3), 3.75 (dd, 1H, *J*=4.3, 10.9 Hz, CH_2OH), 3.63 (dd, 1H, *J*=8.2, 10.9 Hz, CH_2OH), 2.26 (br s, 2H, O*H*+N*H*); IR (KBr) 3250, 2920, 1740, 1440, 1310, 1200, 1140, 1060, 980, 855, 760, 705 cm^{-1}. Found: C, 61.77; H, 5.97; N, 4.69%. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81%.

(*S*)-α-(4-Methoxyphenyl)glycine (8a): To a solution of (*R*,*S*)-**6a** (5.27 g, 16.7 mmol) in CH_2Cl_2 (80 ml) and MeOH (40 ml) was added $Pb(OAc)_4$ (7.43 g, 16.7 mmol) under ice-cooling. After being stirred at this temperature for 3.0 min, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (160 ml). The resulting insoluble material was removed by filtration and washed with CH_2Cl_2 (150 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (150 ml×2). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a colorless solid. The residue was dissolved in 6 M HCl aqueous solution (160 ml) and stirred at room temperature for 18 h, at 50°C for 1 h, and 110°C for 45 min. The reaction mixture was neutralized with solid $NaHCO_3$. Chromatography on active carbon (H_2O–MeOH, 50 : 50) gave **8a** (1.86 g, 66%) as colorless crystals; mp 248°C (sublimation, MeOH–H_2O); $[\alpha]_D^{20}$ +141.2° (*c* 1.00, 1 M HCl); HPLC analysis[14] (perhydrochloric acid (pH=2.0), 0.9 ml min^{-1}) t_R=17.3 min (99.7%ee); ^1H NMR (CF_3CO_2D, 400 MHz) δ=7.86 (d, 2H, *J*=7.9 Hz, MeOCCHC*H*), 7.52 (d, 2H, *J*=7.9 Hz, MeOC*H*CH), 5.78 (s, 1H, NC*H*CO_2), 4.37 (s, 3H, OCH_3); IR (KBr) 2950, 1600, 1510, 1390, 1250, 1180, 1030, 900, 830, 740, 580 cm^{-1}. Found: C, 59.56; H, 5.94; N, 8.02%. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73%.

(*S*)-α-(4-Fluorophenyl)glycine (8b): Similarly, **8b** was obtained from (*R*,*S*)-**6b** in 72% yield as colorless crystals; mp 260°C (MeOH–H_2O); $[\alpha]_D^{20}$ +105.5° (*c* 1.00, 1 M HCl); HPLC analysis[14] (perhydrochloric acid (pH=2.0), 1.0 ml min^{-1}) t_R= 9.6 min (97%ee); ^1H NMR (CF_3COOD, 500 MHz) δ=7.97 (br s, 2H, Ar*H*), 7.65 (br s, 2H, Ar*H*), 5.89 (br s, 1H, NC*H*CO_2); IR (KBr) 2950, 1610, 1510, 1400, 1240, 810, 740, 570 cm^{-1}. Found: C, 56.55; H, 4.59; N, 8.10%. Calcd for $C_8H_8FNO_2$: C, 56.80; H, 4.77; N, 8.28%.

(*S*)-α-(1-Naphthyl)glycine (8c): Similarly, **8c** was obtained from (*R*,*S*)-**6c** in 54% yield as colorless crystals; mp 176°C (decomp, MeOH–H_2O); $[\alpha]_D^{20}$ +166.1° (*c* 1.00, 1 M HCl); HPLC analysis[14] (perhydrochloric acid (pH=2.0), 1.1 ml min^{-1}) t_R=32.5 min (92%ee); ^1H NMR (CF_3COOD, 400 MHz)

δ=8.49—8.40 (m, 3H, Ar*H*), 8.13—8.03 (m, 3H, Ar*H*), 7.97 (t, 1H, *J*=7.7 Hz, Ar*H*), 6.67 (s, 1H, NC*H*CO_2); IR (KBr) 3000, 1620, 1510, 1360, 1330, 795, 770 cm^{-1}. Found: C, 69.45; H, 5.66; N, 6.64%. Calcd for $C_{12}H_{11}NO_2 \cdot 0.33\ H_2O$: C, 69.55; H, 5.67; N, 6.76%.

(*S*)-α-(2-Thienyl)glycine (8d): Similarly, **8d** was obtained from (*R,S*)-**6d** in 41% yield as colorless crystals; mp 228—232 °C (decomp, MeOH–H_2O); $[\alpha]_D^{20}$ +90.1° (*c* 1.00, 1 M HCl); HPLC analysis[14] (perhydrochloric acid (pH=1.5), 0.3 ml min^{-1}) t_R=19.3 min (79%ee); ^1H NMR (CF_3COOD, 500 MHz) δ=7.96 (d, 1H, *J*=5.0 Hz, SC*H*), 7.78 (d, 1H, *J*=3.3 Hz, SCHCHC*H*), 7.56 (t, 1H, *J*=4.1 Hz, SCHC*H*), 6.14 (s, 1H, NC*H*CO_2); IR (KBr) 2970, 1580, 1510, 1400, 1360, 1350, 720, 690 cm^{-1}. Found: C, 46.04; H, 4.48; N, 8.81%. Calcd for $C_6H_7NO_2S$: C, 45.85; H, 4.49; N, 8.91%.

L-Alanine (8e): To a suspension of Pd black, freshly prepared from 600 mg of $PdCl_2$, in a mixture of MeOH (10 ml), water (10 ml), and formic acid (7.5 ml), was added (*R,S*)-**5e** (600 mg, 2.11 mmol). The resulting suspension was stirred under N_2 atmosphere at room temperature for a week. After removal of Pd black by filtration, the filtrate was evaporated in vacuo to give a colorless solid. Column chromatography of the solid on active carbon (H_2O) gave L-alanine (161 mg, 86%) as colorless crystals; mp 270 °C (decomp, H_2O–EtOH); $[\alpha]_D^{20}$ +14.03° (*c* 3.00, 5 M HCl). These physical data were consistent with those of commercial L-alanine. The enantiomeric excess of thus obtained L-alanine was determined to be 97% by HPLC analysis of its *N*-benzoxycarbonyl derivative. HPLC analysis:[15] Dicel Chiralcel OD (hexane–isopropyl alcohol–trifluoroacetic acid, 80 : 20 : 1, 0.9 ml min^{-1}) t_R= 7.2 min.

L-Valine (8f): Similarly, L-valine was obtained from (*R,S*)-**5f** in 54% yield as colorless crystals; mp>280 °C (sublimation H_2O–EtOH); $[\alpha]_D^{20}$ +26.02° (*c* 4.00, 6 M HCl); HPLC analysis[14] (perhydrochloric acid (pH=1.0), 0.2 ml min^{-1}) t_R=10.8 min (92%ee).

L-3-Methylvaline (8g): Similarly, L-3-methylvaline was obtained from (*R,S*)-**5g** in 76% yield as colorless crystals; mp>240 °C (sublimation, H_2O–acetone); $[\alpha]_D^{20}$ +31.48° (*c* 1.00, AcOH) [Lit,[16] $[\alpha]_D^{20}$ +30.0° (*c* 1.00, AcOH)]. The enantiomeric excess was determined from its optical rotation to be 100%.

L-Phenylalanine (8h): Similarly, L-phenylalanine was obtained from (*R,S*)-**5h** in 63% yield as colorless crystals; mp 207—208 °C (decomp, H_2O–EtOH); $[\alpha]_D^{20}$ −34.6° (*c* 1.00, H_2O); HPLC analysis[14] (perhydrochloric acid (pH=1.5), 1.0 ml min^{-1}) t_R=7.5 min (95%ee).

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9) In the case of Y=*t*-butyl or 4-methoxyphenyl, (*R,S*)-**5** was obtained in a pure crystalline form when the reaction mixture was neutralized with $NaHCO_3$. Other (*R,S*)-α-aminocarboxylic acids (**5**) were isolated by evaporation of the neutralized mixture, removal of NaCl by chromatography on active carbon, and recrystallization (see Table 2). See experimental section.

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