Optical Resolution and Asymmetric Transformation of (*RS*)-*N*-Alkyl- and (*RS*)-*N*,*N*-Dialkyl-2-phenylglycines

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Optical resolution of (*RS*)-*N*-methyl-2-phenylglycine [(*RS*)-Mpg] and (*RS*)-*N*-ethyl-2-phenylglycine [(*RS*)-Epg] was carried out by using (1*S*)-10-camphorsulfonic acid [(*S*)-CS] as resolving agents, and that of (*RS*)-*N*-ethyl-*N*-methyl-2-phenylglycine [(*RS*)-Emp] by (*R*)- and (*S*)-1-phenylethylamine. Racemization rates of optically active Mpg, Epg, Emp, *N*,*N*-dimethyl-2-phenylglycine [Dmp], and six α-amino acids were measured by heating in carboxylic acids. The electron-donating amino acid side chain and *N*-substituted alkyl group decreased the rate to inhibit the formation of intermediary carbanions, whereas the electron-withdrawing side chain increased it. Asymmetric transformation of (*RS*)-Mpg, (*RS*)-Epg, and (*RS*)-Dmp was carried out on the basis of the results of optical resolution and racemization to give the corresponding enantiomers of approximately 100% optical purities in over 70% yield based on the starting racemates.

Some optically active *N*-alkyl amino acids have been found in nature as constituents of antibiotics.[1,2] For example, (*S*)-*N*-methyl-2-phenylglycine [(*S*)-α-phenylsarcosine] has been isolated from the hydrolysate of etamycin.[2] Such optically active *N*-alkyl amino acids, however, are not obtainable from natural products in large quantity. (*RS*)-*N*-Methyl-2-phenylglycine [abbreviated as (*RS*)-Mpg], therefore, has been obtained by the Strecker reaction of benzaldehyde with methylamine,[3] and resolved as the brucine[3] and ephedrine[4] salts of its *N*-acetyl and *N*-*t*-butoxycarbonyl derivatives respectively. We synthesized (*RS*)-*N*-ethyl-2-phenylglycine [(*RS*)-Epg], (*RS*)-*N*,*N*-dimethyl-2-phenylglycine [(*RS*)-Dmp], and (*RS*)-*N*-ethyl-*N*-methyl-2-phenylglycine [(*RS*)-Emp] from (*RS*)-2-bromo-2-phenylacetic acid [(*R*)-BPA] as well as (*RS*)-Mpg, and attempted to obtain their enantiomers without transformation into their derivatives, such as *N*-acyl amino acids.

Optical resolution of diastereomeric mixtures gives both enantiomers by a good choice of resolving agent. On the other hand, asymmetric transformation, which can efficiently convert a racemate into a desired enantiomer, has been realized in a heterogenious system by combination of selective crystallization of a less soluble diastereomeric salt with epimerization in a solution. One of the major problems in both procedures, however, is a choice of resolving agent, which is readily obtainable and gives good crystalline diastereomeric salts with a racemate. We assayed salt formations of Mpg, Epg, Dmp, and Emp with (1*S*)-10-camphorsulfonic acid [(*S*)-CS], (2*R*,3*R*)-tartaric acid [(*R*)-TA], and (*R*)- and (*S*)-1-phenylethylamine [(*R*)- and (*S*)-PEA] to accomplish the effective optical resolutions.

Another problem in the asymmetric transformation is racemization rate of optically active substances. The racemization of optically active *N*-alkyl- and *N*,*N*-dialkyl-2-phenylglycines in carboxylic acids is supposed to proceed via carbanion formation similarly to that of (*R*)-2-phenylglycine and (*R*)-2-(4-hydroxyphenyl)-glycine.[5] The racemization rates of optically active Mpg, Epg, Dmp, Emp, and other six α-amino acids were measured in carboxylic acids to examine influences of their side chains and *N*-substituted alkyl groups. The asymmetric transformation of (*RS*)-Mpg, (*RS*)-Epg, and (*RS*)-Dmp was attempted on the basis of the results of the optical resolution and racemization.

Results and Discussion

Configuration of Optically Active *N*-Alkyl- and *N*,*N*-Dialkyl-2-phenylglycines. (−)-Mpg has been known to have *R*-configuration and (+)-Mpg to be *S*-isomer,[4] but configurations of optically active Epg, Dmp, and Emp have not been determined. An optical resolution of (*RS*)-BPA was carried out by using (*R*)-PEA, as a resolving agent, to give (*R*)-BPA[6] (Table 1). Nucleophilic substitution reactions of the (*R*)-BPA·(*R*)-PEA salt with methylamine and ethylamine gave (*S*)-Mpg and (+)-Epg, respectively. Since (*S*)-Mpg and (+)-Epg of low optical purities were also obtained from the filtrate after recrystallization of the crude products, the nucleophilic substitution reactions were estimated to proceed with inversion plus partial racemization. In addition, *N*-methylation of (*R*)-Mpg and (+)-Epg gave (−)-Dmp and (+)-Emp, respectively. Consequently, (+)-Epg, (+)-Dmp, and (+)-Emp were determined to have *S*-configurations.

Optical Resolution of (*RS*)-*N*-Alkyl- and *N*,*N*-Dialkyl-2-phenylglycines. Salt formations of Mpg, Epg, Dmp, and Emp with several resolving agents were examined in ethanol. (*S*)-CS gave the good crystalline Mpg·(*S*)-CS and Epg·(*S*)-CS salts, but the Dmp·(*S*)-CS and Emp·(*S*)-CS salts were not obtained as crystals even by evaporation of ethanol from reaction solutions. Dmp formed a good crystalline salt with an equimolar amount of (*R*)-TA, but Mpg and Epg did not and the salt of Emp was a viscous mass. Emp formed a good crystalline salt with optically active PEA.

Table 1. Optical Resolutions [a]

Racemate	Resolving agent	Salt [b] Yield [c] %	Salt [b] Optical purity [d] %	Amino acid obtained Configuration	Amino acid obtained Yield [c] %	Amino acid obtained Optical purity %
(*RS*)-Mpg	(*S*)-CS	50.8[e]	100	(*R*)	45.6	100
		65.2[f,g]	79.3	(*S*)	59.3	76.2
(*RS*)-Epg	(*S*)-CS	20.8[e]	96.9	(*S*)	19.6	97.6
		16.6[f]	99.4	(*R*)	15.9	98.8
(*RS*)-Emp	(*S*)-PEA	52.2[e]	96.0	(*S*)	51.2	95.7
		75.2[f]	65.4	(*R*)	74.6	68.3
	(*R*)-PEA	50.6[e]	97.6	(*R*)	50.0	96.6
		76.8[f]	64.2	(*S*)	76.2	67.5
(*RS*)-BPA	(*R*)-PEA	16.2[e]	—	(*R*)[h]	15.3	100

a) Conditions of the optical resolutions were described in the experimental section. b) The salt purified. c) The yield was calculated on the basis of a half amount of the starting racemic amino acid. d) The optical purities were calculated on the basis of the specific rotations of the standard salts. e) The salt was first crystallized from a solution of the racemate. f) The salt was obtained from the filtrate. g) The salt was not purified. h) (*R*)-2-Bromo-2-phenylacetic acid.

The optical resolution of (*RS*)-Dmp was attempted by using (*R*)-TA under various conditions, but in vain. The results of optical resolutions of (*RS*)-Mpg, (*RS*)-Epg, and (*RS*)-Emp are summarized in Table 1; the yields were calculated on the basis of a half amount of the starting racemates.

The (*R*)-Mpg·(*S*)-CS and (*S*)-Epg·(*S*)-CS salts were obtained as the less soluble diastereomeric salts. The purified salts gave (*R*)-Mpg of 100% optical purity in 46% yield and (*S*)-Epg of 98% optical purity in 20% yield. Although the (*S*)-Mpg·(*S*)-CS salt obtained from the mother liquor was difficult to be recrystallized, the purified (*R*)-Epg·(*S*)-CS salt gave (*R*)-Epg of 99% optical purity in 16% yield.

The optical resolution of (*RS*)-Emp by use of (*S*)- and (*R*)-PEA gave the (*S*)-Emp·(*S*)-PEA and (*R*)-Emp·(*R*)-PEA salts of 80% optical purity as the less soluble diasteromeric salts, respectively. (*S*)- and (*R*)-Emp of over 95% optical purities were obtained in 50% yields from the purified salts. Although the (*R*)-Emp·(*S*)-PEA and (*S*)-Emp·(*R*)-PEA salts (40% optical purity) from the mother liquors were recrystallized from 1-propanol, (*R*)- and (*S*)-Emp of high optical purities were not obtained. However, the above result suggests that (*S*)- and (*R*)-Emp of high optical purity are obtainable by using (*S*)- and (*R*)-PEA, respectively.

Racemization of Optically Active *N*-Alkyl- and *N,N*-Dialkyl-2-phenylglycines. Influence of Carboxylic Acid Used as Solvent: The racemization rates of optically active Mpg, Epg, Dmp, and Emp were measured in acetic acid, propanoic acid, and butanoic acid at 100 °C in the presence of (1*RS*,4*SR*)-10-camphorsulfonic acid [(*RS*)-CS], aiming at asymmetric transformations for obtaining more efficiently the enantiomers. The racemization obeyed the first-order kinetics of

$$\ln \alpha_0/\alpha_t = k_R \cdot t, \quad (1)$$

where k_R is the racemization rate constant, α_t the optical rotation at time t, and α_0 the rotation extrapolated to zero time. The k_R values and half-life periods are summarized in Table 2 and shown in Fig. 1.

The racemization is estimated to proceed via protonation to the carbonyl oxygen atom by the carboxylic acid, followed by α-proton abstraction by the resulting carboxylate anion, namely, carbanion formation.[5,7] The acidity constants, at 100 °C, of the carboxylic acids were calculated from the data[8] at 0—60 °C and sug-

Table 2. Kinetic Data for Racemization [a]

Optically active amino acid	Carboxylic acid	Rate constant 10^{-4} s^{-1}	Half-life period 10^3 s
(*R*)-Mpg	AcA [b]	4.00	1.73
	PrA [c]	9.83	0.705
	BuA [d]	10.8	0.642
(*R*)-Epg	AcA	3.34	2.08
	PrA	9.52	0.728
	BuA	9.57	0.724
(*S*)-Dmp	AcA	1.91	3.63
	PrA	4.93	1.41
	BuA	5.36	1.29
(*S*)-Emp	AcA	1.75	3.96
	PrA	4.30	1.61
	BuA	4.65	1.49
(*R*)-Phg	AcA	6.56	1.06
(*R*)-Hpg	AcA	1.39	4.99
(*S*)-Phe	AcA	0.0841	82.4
(*S*)-Tyr	AcA	0.0530	131
(*S*)-Ser	AcA	4.62	1.50
(*S*)-Met·SO_2	AcA	1.09	6.36

a) Conditions: Amino acid 1.00 mmol; (*RS*)-CS 1.00 mmol; carboxylic acid 50 cm^3; temperature 100 °C. b) Acetic acid. c) Propanoic acid. d) Butanoic acid.

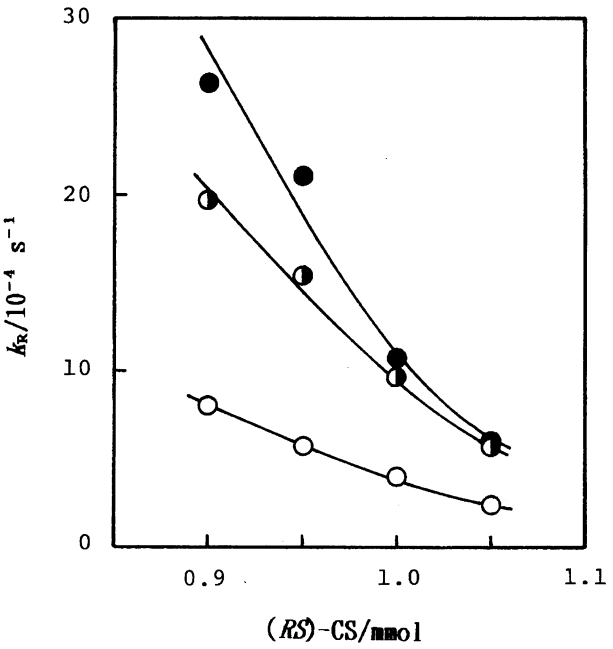

Fig. 1. Influence of amount of (1*RS*, 4*SR*)-10-camphorsulfonic acid on racemization rate of (*R*)-*N*-methyl-2-phenylglycine. Conditions: (*R*)-Mpg 1.00 mmol; (*RS*)-CS 0.900—1.05 mmol; carboxylic acid 50 cm^3; temperature 100 °C. Acetic acid: ○. Propanoic acid: ◑. Butanoic acid: ●. k_R/s^{-1}: Rate constant of racemization.

gested that the proton abstraction was estimated to be done in the order by acetate anion < propanoate anion < butanoate anion. The racemization was accelerated in the order by acetic acid < propanoic acid < butanoic acid, as found in Table 2 and shown in Fig. 1. This result suggests that the rate-determining step in the racemization is the carbanion formation.

Figure 1 shows that the racemization rate increases with a decrease in the amount of (*RS*)-CS; although only the result of (*R*)-Mpg was shown in Fig. 1, the similar tendencies were observed for (*R*)-Epg, (*S*)-Dmp, and (*S*)-Emp. Since 10-camphorsulfonate anion is an extremely weak base, the 10-camphorsulfonate anion has a poor ability for the α-proton abstraction. Therefore, the increase in (*RS*)-CS, namely, (1*RS*, 4*SR*)-10-camphorsulfonate anion is estimated to reduce the racemization rate.

Substituent Effect: We reported that racemization of optically active *N*-acetyl amino acids is subject to the inductive effect by side chain and that the rate-determining step is the carbanion formation.[9] The inductive effect is expressed by the Taft equation[7,9—11]

$$\log k_R/k_0 = \rho^* \cdot \sigma^*, \quad (2)$$

where k_0 is a racemization rate constant of standard substance, ρ^* the reaction constant, and σ^* the polar substituent constant.[9—11] The racemizations of *N*-alkyl- and *N*,*N*-dialkyl-2-phenylglycines are influenced by both electron-withdrawing phenyl group (a side chain) and electron-donating *N*-substituted alkyl group. If the inductive effects by the *N*-substituted alkyl group and by side chain influence independently the racemization rate, the polar substituent constants of *N*-substituted alkyl group (σ_N^*) and side chain (σ_C^*) must be expressed by the first-order combination. On this assumption, a relationship between log k_R, σ_C^*, and σ_N^* was examined for the optically active *N*-alkyl- and *N*,*N*-dialkyl-2-phenylglycines, 2-phenylglycine [Phg], tyrosine [Tyr], phenylalanine [Phe], 2-(4-hydroxyphenyl)glycine [Hpg], serine [Ser], and methionine sulfone [Met·SO_2] (Table 2).[12] The relationship is shown in Fig. 2 and given by

$$\log k_R = 4.95(\sigma_C^* + 0.0996\sigma_N^*) - 9.09, \quad (3)$$

where the correlation coefficient is 0.996. The racemization rate decreases as the electron-donating properties of the *N*-substituted alkyl group and side chain. The electron-withdrawing side chain increases the rate. This good linear relationship, therefore, suggests that the racemization is subject independently to the inductive effects by the *N*-substituted alkyl group and side chain. Equation 3 also suggests that the inductive effect by the *N*-substituted alkyl group is one tenth of that by the side chain. Since the optically active Mpg,

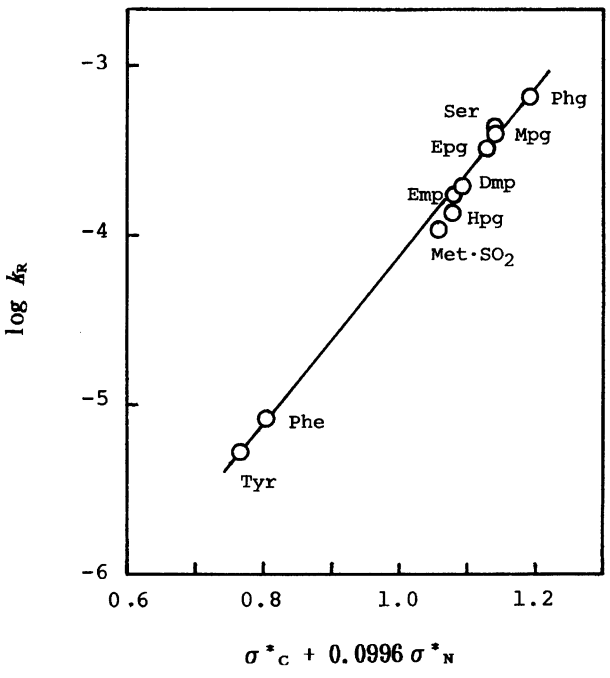

Fig. 2. Influences of amino acid side chain and *N*-substituted alkyl group on racemization rate of optically active amino acids. Conditions: Amino acid 1.00 mmol; (*RS*)-CS 1.00 mmol; acetic acid 50 cm^3; temperature 100 °C. k_R/s^{-1}: Rate constant of racemization. σ_N^*: Polar substituent constant of *N*-substituted alkyl group. σ_C^*: Polar substituent constant of amino acid side chain.

Epg, Dmp, and Emp have the strongly electron-withdrawing phenyl group as their side chains, the racemization is extremely faster than (*S*)-Tyr and (*S*)-Phe in spite of the presence of the electron-donating *N*-alkyl group. The above result suggests a possibility of asymmetric transformation for (*RS*)-Mpg, (*RS*)-Epg, (*RS*)-Dmp, and (*RS*)-Emp.

Asymmetric Transformation. (*RS*)-*N*-Methyl-2-phenylglycine: Although the asymmetric transformation of (*RS*)-Emp was attempted in the presence of excess optically active PEA similarly to *N*-acetyl-(*RS*)-amino acids[9] under various conditions, the formed salt did not crystallize from reaction solutions. However, the asymmetric transformation of (*RS*)-Mpg, (*RS*)-Epg, and (*RS*)-Dmp was successfully achieved on the basis of the results of optical resolution and racemization. The asymmetric transformation of (*RS*)-Mpg by use of (*S*)-CS in butanoic acid was summarized in Table 3.

The (*R*)-Mpg·(*S*)-CS salt of 86% optical purity was obtained in 93—96% yield by reacting for 5—8 h. Purification of the (*R*)-Mpg·(*S*)-CS salts, followed by isolation gave (*R*)-Mpg of approximately 100% optical purity in 71—77% yield based on the starting (*RS*)-Mpg.

The asymmetric transformation was also carried out by using (1*R*)-10-camphorsulfonic acid monohydrate [(*R*)-CS·H_2O] (Table 4). From a comparison of the results described in Tables 3 and 4, water of crystallization in (*R*)-CS·H_2O is considered to slow down the epimerization rate. However, the asymmetric transformation gave the (*S*)-Mpg·(*R*)-CS salt of 84% optical purity in 94% yield at 8 h. (*S*)-Mpg of 99% optical purity was obtained in 72% yield from the purified salt.

Table 3. Asymmetric Transformation of (*RS*)-*N*-Methyl-2-phenylglycine via Salt Formation with (1*S*)-10-Camphorsulfonic Acid [a]

Reaction time	(*R*)-Mpg·(*S*)-CS salt			(*R*)-Mpg	
	Yield	Specific	Optical	Yield[d]	Optical
h	g [%[b]]	rotation[c] °	purity %	%	purity %
1	3.85 [97.0]	+0.571	16.2	85.5	6.54
2	3.83 [96.5]	−14.3	36.7	87.1	26.2
3	3.82 [96.2]	−20.7	45.6	86.8	36.8
4	3.81 [96.0]	−30.5	59.1	89.4	55.9
5	3.71 [93.5]	−49.7	85.6	86.5	85.1
5[e]	3.34 [84.1]	−59.3	98.9	75.9	98.4
6	3.76 [94.7]	−50.5	86.7	91.9	82.0
6[e]	3.35 [84.4]	−58.5	97.8	71.1	98.4
7	3.76 [94.7]	−51.9	88.7	84.2	87.9
7[e]	3.40 [85.6]	−58.9	98.3	73.6	99.0
8	3.80 [95.7]	−50.9	87.3	89.2	84.4
8[e]	3.39 [85.4]	−59.5	99.2	77.0	98.4

a) Conditions: (*RS*)-Mpg 10.0 mmol; (*S*)-CS 9.50 mmol; butanoic acid 10 cm^3; temperature 100 °C. b) The yield was calculated on the basis of 10.0 mmol (3.97 g) of the Mpg·(*S*)-CS salt. c) $[\alpha]_D^{20}$ (*c* 1.00, 1 mol dm^{-3} HCl). d) The yield was calculated on the basis of 10.0 mmol (1.65 g) of Mpg. e) The salt obtained was purified.

Table 4. Asymmetric Transformation of (*RS*)-*N*-Methyl-2-phenylglycine via Salt Formation with (1*R*)-10-Camphorsulfonic Acid Monohydrate[a]

Reaction time	(*S*)-Mpg·(*R*)-CS salt			(*S*)-Mpg	
	Yield	Specific	Optical	Yield[d]	Optical
h	g [%[b]]	rotation[c] °	purity %	%	purity %
2	3.82 [96.2]	+1.40	18.9	80.5	6.81
4	3.85 [97.0]	+18.9	43.1	84.9	39.4
6	3.86 [97.2]	+33.5	63.3	89.4	62.1
8	3.73 [94.0]	+48.4	83.8	86.8	82.0
8[e]	3.21 [80.9]	+59.5	99.2	72.1	99.0

a) Conditions: (*RS*)-Mpg 10.0 mmol; (*R*)-CS·H_2O 9.50 mmol; butanoic acid 10 cm^3; temperature 100 °C. b) The yield was calculated on the basis of 10.0 mmol (3.97 g) of the Mpg·(*R*)-CS salt. c) $[\alpha]_D^{20}$ (*c* 1.00, 1 mol dm^{-3} HCl). d) The yield was calculated on the basis of 10.0 mmol (1.65 g) of Mpg. e) The obtained salt was purified.

(*RS*)-*N*-Ethyl-2-phenylglycine: Although the asymmetric transformation of (*RS*)-Epg was attempted by using a resolving agent (*S*)-CS in propanoic acid and butanoic acid, the salt was dissolved in these carboxylic acids. The asymmetric transformation, therefore, was carried out in a mixture of propanoic acid and xylene. The result is summarized in Table 5.

In the optical resolution, the (*S*)-Epg·(*S*)-CS salt crystallized as the less soluble diastereomeric salt from the ethanol solution (Table 1). The asymmetric transformation gave the (*R*)-Epg·(*S*)-CS salt of 82—87% op-

Table 5. Asymmetric Transformation of (*RS*)-*N*-Ethyl-2-phenylglycine via Salt Formation with (1*S*)-10-Camphorsulfonic Acid[a]

Reaction time	(*R*)-Egp·(*S*)-CS salt			(*R*)-Epg	
	Yield	Specific	Optical	Yield[d]	Optical
h	g [%[b]]	rotation[c] °	purity %	%	purity %
10	4.01 [97.3]	+0.760	16.3	94.3	12.0
20	3.99 [96.8]	−15.1	38.7	92.2	33.2
30	3.70 [89.8]	−46.5	83.1	84.6	81.1
30[e]	3.08 [74.8]	−58.5	100	70.7	100
40	3.56 [86.4]	−46.0	82.3	82.1	80.7
40[e]	2.86 [69.4]	−58.5	100	66.5	100
50	3.62 [87.9]	−47.3	84.1	91.9	86.0
50[e]	3.10 [75.2]	−57.5	98.6	71.5	98.2
60	3.61 [87.6]	−46.9	83.6	81.4	84.1
60[e]	3.02 [73.3]	−58.4	99.9	69.2	100

a) Conditions: (*RS*)-Epg 10.0 mmol; (*S*)-CS 9.50 mmol; the employed solvent was a mixture of 3 cm^3 of propanoic acid and 7 cm^3 of xylene; temperature 90 °C. b) The yield was calculated on the basis of 10.0 mmol (4.12 g) of the Epg·(*S*)-CS salt. c) $[\alpha]_D^{20}$ (*c* 1.00, 1 mol dm^{-3} HCl). d) The yield was calculated on the basis of 10.0 mmol (1.79 g) of Epg. e) The obtained salt was purified.

tical purity in 86—90% yield at 30—60 h. (*R*)-Epg of 98—100% optical purity was obtained in 66—72% yield from the purified salt.

(*RS*)-*N*,*N*-Dimethyl-2-phenylglycine: The optical resolution of (*RS*)-Dmp did not give a good result by using (*R*)-TA as the resolving agent. The asymmetric transformation, however, was achieved in butanoic acid and pentanoic acid. The results are shown in Fig. 3[13] and summarized in Table 6.

As shown in Fig. 3, no large difference in the results of the asymmetric transformations is observed in butanoic acid and pentanoic acid. For example, the (*S*)-Dmp·(*R*)-TA salt of 84—90% optical purity was obtained in 84—90% yield after 3—6 h in butanoic acid and the salt of 81—89% optical purity in 94% yield after 3—7 h in pentanoic acid. The (*S*)-Dmp·(*R*)-TA salts obtained in pentanoic acid were purified to give optically pure (*S*)-Dmp in 66—73% yield.

Experimental

The optical rotations were measured at 589 nm with a Union Giken PM-101 digital polarimeter equipped with a quartz cell of 5.00 cm path length.

Materials. (*S*)-Tyr, (*S*)-Phe, (*R*)-Hpg, (*R*)-Phg, (*S*)-Ser, (*S*)-methionine, (*RS*)-CS, (*R*)-CS·H_2O, (*R*)-TA, and (*R*)- and (*S*)-PEA were purchased from Wako Pure Chemicals Ind. and (*S*)-CS and (*RS*)-BPA from Tokyo Kasei Kogyo Co., Ltd.

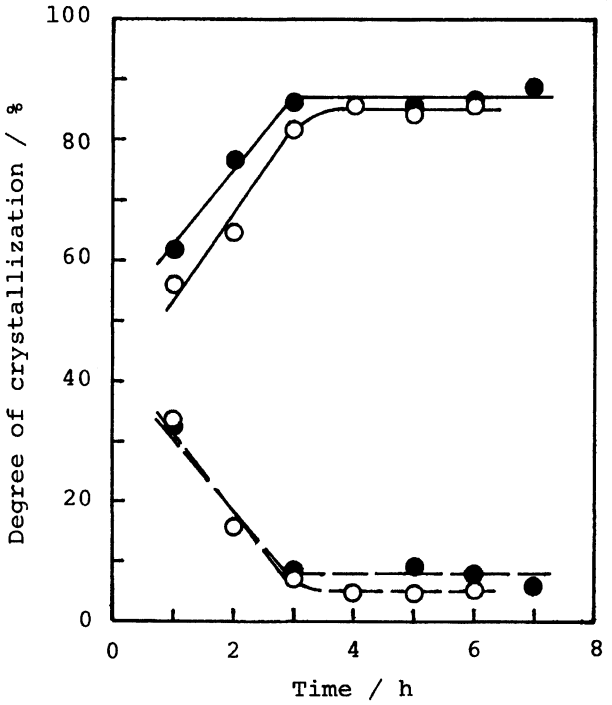

Fig. 3. Asymmetric transformation of (*RS*)-*N*,*N*-dimethyl-2-phenylglycine. Conditions: (*RS*)-Dmp 10.0 mmol; (*R*)-TA: 10.0 mmol; carboxylic acid 30 cm^3; temperature 100 °C. Butanoic acid: ○. Pentanoic acid: ●. Degree of crystallization:[13] — (*S*)-Dmp·(*R*)-TA salt; --- (*R*)-Dmp·(*R*)-TA salt.

Table 6. Asymmetric Transformation of (*RS*)-*N*,*N*-Dimethyl-2-phenylglycine via Salt Formation with (2*R*,3*R*)-Tartaric Acid[a]

Reaction time	(*S*)-Dmp·(*R*)-TA salt			(*S*)-Dmp	
	Yield	Specific rotation[c]	Optical purity	Yield[d]	Optical purity
h	g [%[b]]	°	%	%	%
1	3.12 [94.8]	+26.4	31.1	93.5	25.6
2	3.05 [92.7]	+51.2	66.4	90.8	63.2
3	3.10 [94.2]	+62.3	82.2	93.4	80.7
3[e]	2.25 [68.4]	+74.8	100	66.7	100
5	3.10 [94.2]	+61.5	81.1	92.6	80.0
5[e]	2.33 [70.8]	+74.3	99.3	70.1	100
6	3.08 [93.6]	+63.8	84.4	90.1	83.3
6[e]	2.38 [72.3]	+74.8	100	70.8	100
7	3.08 [93.6]	+66.8	88.6	93.1	88.4
7[e]	2.43 [73.9]	+74.8	100	73.0	100

a) Conditions: (*RS*)-Dmp 10.0 mmol; (*R*)-TA 10.0 mmol; pentanoic acid 30 cm^3; temperature 100 °C. b) The yield was calculated on the basis of 10.0 mmol (3.29 g) of the Dmp·(*R*)-TA salt. c) $[\alpha]_D^{20}$ (*c* 1.00, water). d) The yield was calculated on the basis of 10.0 mmol (1.79 g) of Dmp. e) The obtained salt was purified.

(*S*)-Methionine sulfone was obtained by oxidation of (*S*)-methionine with 30 wt% aqueous hydrogen peroxide in acetic acid; mp 254—256 °C (decomp) (Ref,[14] 257—258 °C (decomp)); $[\alpha]_D^{20}$ +11.6° (*c* 1.00, water) (Ref,[14] $[\alpha]_D$ +12.3° (water)). Found: C, 33.15; H, 6.18; N, 7.82%. Calcd for $C_5H_{11}NO_4S$: C, 33.14; H, 6.12; N, 7.73%.

(*R*)-Mpg, (*R*)-Epg, and (*S*)-Dmp were obtained by the asymmetric transformation and (*S*)-Epg and (*S*)-Emp by the optical resolution; the salts were subjected to repetition of purification, until the specific rotations revealed the constant values, and optically pure Mpg, Epg, Dmp, and Emp were isolated from the purified salts. The optical purities of the obtained Mpg, Epg, Dmp, and Emp were calculated on the basis of the specific rotations described to the bellow. (*R*)-Mpg: $[\alpha]_D^{20}$ −171° (*c* 0.50, 1 mol dm^{-3} HCl); Ref,[4] $[\alpha]_D^{20}$ −170.7° (*c* 0.57, 1 mol dm^{-3} HCl); the optical purities were calculated on the basis of the specific rotation reported.[4] (*R*)-Epg: $[\alpha]_D^{20}$ −127° (*c* 1.00, water); $[\alpha]_D^{20}$ −165° (*c* 1.00, 1 mol dm^{-3} HCl). (*S*)-Dmp: $[\alpha]_D^{20}$ +122° (*c* 1.00, water); $[\alpha]_D^{20}$ +162° (*c* 1.00, 1 mol dm^{-3} HCl). (*S*)-Emp: $[\alpha]_D^{20}$ +117° (*c* 1.00, water).

Syntheses. (*RS*)-*N*-Methyl-2-phenylglycine and (*RS*)-*N*-Ethyl-2-phenylglycine: A mixture of 0.100 mol (21.5 g) of (*RS*)-BPA and ten times molar amount of methylamine or ethylamine was stirred for 3 h at 20 °C; 104 cm^3 of 40 wt% methanol solution of methylamine and 90 cm^3 of 70 wt% aqueous solution of ethylamine correspond to 1 mol of the amines, respectively. After evaporating the mixture to dryness under reduced pressure at 40 °C, the (*RS*)-Mpg and (*RS*)-Epg obtained as the residue were recrystallized from 85% methanol and 75% ethanol, respectively.

(*RS*)-Mpg: Yield 11.9 g (72.1%); mp 248—250°C (sublimation) (lit,[3] 245—246 °C (sublimation)). Found: C, 65.66; H, 6.76; N, 8.46%. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48%.

(*RS*)-Epg: Yield 14.4 g (80.4%); mp 264—265 °C

(sublimation). Found: C, 67.02; H, 7.33; N, 7.79%. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82%.

(*S*)-*N*-Methyl-2-phenylglycine and (*S*)-*N*-Ethyl-2-phenylglycine: After adding 40 wt% methanol solution of methylamine (20.8 cm^3) or 70 wt% aqueous solution of ethylamine (18.0 cm^3) to a solution of the (*R*)-BPA·(*R*)-PEA salt (20.0 mmol, 6.72 g) in 20 cm^3 of 0.5 mol dm^{-3} sulfuric acid, the solution was stirred for 3 h at 20 °C; the employed (*R*)-BPA·(*R*)-PEA salt of 100% optical purity was obtained by the optical resolution of (*RS*)-BPA using (*R*)-PEA, as the resolving agent. To the oily residue obtained by evaporation was added 100 cm^3 of diethyl ether to precipitate crude (*S*)-Mpg or (*S*)-Epg. Recrystallization of the crude (*S*)-Mpg or (*S*)-Epg from respective 85% methanol or 75% ethanol gave optically pure (*S*)-Mpg (1.00 g (30.3%), $[\alpha]_D^{20}$ +171° (*c* 0.50, 1 mol dm^{-3} HCl)) or (*S*)-Epg (1.94 g (54.2%), $[\alpha]_D^{20}$ +165° (*c* 1.00, 1 mol dm^{-3} HCl)). Concentration of the filtrate, after recrystallization, gave partially racemized (*S*)-Mpg (1.91 g, $[\alpha]_D^{20}$ +75.1° (*c* 0.50, 1 mol dm^{-3} HCl)) or (*S*)-Epg (0.49 g, $[\alpha]_D^{20}$ +106° (*c* 1.00, 1 mol dm^{-3} HCl)).

Racemic and Optically Active *N,N*-Dimethyl-2-phenylglycine and *N*-Ethyl-*N*-methyl-2-phenylglycine: Nitrogen atoms on racemic and optically active Mpg and Epg were methylated according to the procedure of *N*-methylation for *N*-benzyl amino acids;[1] (*R*)-Mpg and (*S*)-Epg were employed as the optically active starting materials. After refluxing a mixture of 20.0 mmol of Mpg (3.30 g) or Epg (3.58 g), 5.23 cm^3 of 37% aqueous formaldehyde, 3.77 cm^3 of formic acid, and 5 cm^3 of water for 4 h, the mixture was evaporated to dryness under reduced pressure at 50 °C. To a solution of the oily residue in 10 cm^3 of methanol was added 200 cm^3 of diethyl ether and then the mixture was stirred for 0.5 h in an ice bath. The crude Dmp and Emp precipitated were collected by filtration and dried.

After stirring a solution of the crude (*RS*)-Dmp (4.25 g) or (*R*)-Dmp (3.35 g, $[\alpha]_D^{20}$ +72.9° (*c* 1.00, water)) in 93% ethanol (6 $cm^3\,g^{-1}$) for 0.5 h in an ice bath, the precipitated (*RS*)- and (*R*)-Dmp were collected by filtration. The filtrate of (*R*)-Dmp was evaporated to dryness and then the residue was recrystallized from ethanol to give the optically pure (*R*)-Dmp.

(*RS*)-Dmp: Yield 3.23 g (90.2%); mp 252—253 °C (sublimation). Found: C, 66.97; H, 7.28; N, 7.77%. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82%.

(*R*)-Dmp: Yield 1.68 g (46.9%); mp 247—248 °C (sublimation); $[\alpha]_D^{20}$ −122° (*c* 1.00, water). Found: C, 67.02; H, 7.31; N, 7.80%.

The crude (*RS*)-Emp (3.63 g) was recrystallized from 93% ethanol. The crude (*S*)-Emp (3.72 g) was dissolved in a mixture of ethanol (40 cm^3) and 1-propanol (20 cm^3) by reflux; $[\alpha]_D^{20}$ +53.3° (*c* 1.00, water). After being allowed to stand overnight at 5 °C, and then removing 1.58 g of partially racemized (*S*)-Emp ($[\alpha]_D^{20}$ +3.80° (*c* 1.00, water)) by filtration, the filtrate was evaporated to dryness under reduced pressure to give optically pure (*S*)-Emp.

(*RS*)-Emp: Yield 3.05 g (79.0%); mp 214—215 °C. Found: C, 68.10; H, 7.86; N, 7.19%. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%.

(*S*)-Emp: Yield 1.53 g (39.6%); mp 207—209 °C; $[\alpha]_D^{20}$ +117° (*c* 1.00, water). Found: C, 68.17; H, 7.82; N, 7.25%.

Preparation of Standard Salt. (*RS*)-Mpg or (*RS*)-Epg (20.0 mmol) and equimolar amount of (*S*)-CS were dissolved in 100 cm^3 of methanol. After evaporating the solution to dryness under reduced pressure, the residue was washed thoroughly with diethyl ether. The (*RS*)-Dmp·(*R*)-TA and (*RS*)-Emp·(*S*)-PEA salts were prepared similarly. The (*R*)-Mpg·(*S*)-CS, (*R*)-Epg·(*S*)-CS, and (*S*)-Dmp·(*R*)-TA salts were obtained by asymmetric transformation and the (*S*)-Emp·(*S*)-PEA salt by the optical resolution. These salts were subjected to repetition of recrystallization to give their respective standard salts.

(*RS*)-Mpg·(*S*)-CS Salt: Mp 198—204 °C; $[\alpha]_D^{20}$ +12.3° (*c* 1.00, 1 mol dm^{-3} HCl). Found: C, 57.37; H, 6.88; N, 3.55%. Calcd for $C_{19}H_{27}NO_6S$: C, 57.41; H, 6.85; N, 3.52%.

(*R*)-Mpg·(*S*)-CS Salt: Mp 204—205 °C; $[\alpha]_D^{20}$ −60.1° (*c* 1.00, 1 mol dm^{-3} HCl). Found: C, 57.32; H, 6.79; N, 3.54%.

(*RS*)-Epg·(*S*)-CS Salt: Mp 210—230 °C; $[\alpha]_D^{20}$ +12.3° (*c* 1.00, 1 mol dm^{-3} HCl). Found: C, 58.30; H, 7.16; N, 3.50%. Calcd for $C_{20}H_{29}NO_6S$: C, 58.37; H, 7.10; N, 3.40%.

(*R*)-Epg·(*S*)-CS Salt: Mp 240—242 °C; $[\alpha]_D^{20}$ −58.5° (*c* 1.00, 1 mol dm^{-3} HCl). Found: C, 58.37; H, 7.24; N, 3.40%.

(*RS*)-Dmp·(*R*)-TA Salt: Mp 168—170 °C; $[\alpha]_D^{20}$ +4.51° (*c* 1.00, water). Found: C, 51.21; H, 5.91; N, 4.36%. Calcd for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25%.

(*S*)-Dmp·(*R*)-TA Salt: Mp 175—176 °C; $[\alpha]_D^{20}$ +74.8° (*c* 1.00, water). Found: C, 51.00; H, 5.75; N, 4.25%.

(*RS*)-Emp·(*S*)-PEA Salt: Mp 135—195 °C; $[\alpha]_D^{20}$ −8.90° (*c* 1.00, water). Found: C, 72.63; H, 8.36; N, 8.88%. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91%.

(*S*)-Emp·(*S*)-PEA Salt: Mp 215—216 °C; $[\alpha]_D^{20}$ +49.2° (*c* 1.00, water). Found: C, 72.50; H, 8.39; N, 8.85%.

Optical Resolution. (*RS*)-*N*-Methyl-2-phenylglycine: A mixture of 30.0 mmol of (*RS*)-Mpg (4.96 g) and (*S*)-CS (6.97 g) in 210 cm^3 of ethanol was stirred for 0.5 h at 40 °C and then for 0.5 h at 25 °C. The precipitated (*R*)-Mpg·(*S*)-CS salt (3.51 g) was collected by filtration; $[\alpha]_D^{20}$ −51.6° (*c* 1.00, 1 mol dm^{-3} HCl). After the filtrate was allowed to stand overnight at 5 °C, the precipitated (*S*)-Mpg·(*S*)-CS salt was filtered off; yield 3.89 g; $[\alpha]_D^{20}$ +69.7° (*c* 1.00, 1 mol dm^{-3} HCl). The (*R*)-Mpg·(*S*)-CS salt was purified similarly to the procedure described in the asymmetric transformation of (*RS*)-Mpg; yield 3.03 g; $[\alpha]_D^{20}$ −60.1° (*c* 1.00, 1 mol dm^{-3} HCl). The (*R*)- and (*S*)-Mpg were obtained from the (*R*)-Mpg·(*S*)-CS salt purified and the (*S*)-Mpg·(*S*)-CS salt, respectively; the (*S*)-Mpg·(*S*)-CS salt was treated without purification.

(*R*)-Mpg: Yield 1.13 g; $[\alpha]_D^{20}$ −171° (*c* 0.50, 1 mol dm^{-3} HCl).

(*S*)-Mpg: Yield 1.47 g; $[\alpha]_D^{20}$ +130° (*c* 0.50, 1 mol dm^{-3} HCl).

(*RS*)-*N*-Ethyl-2-phenylglycine: (*RS*)-Epg (50.0 mmol, 8.96 g) and 50.0 mmol (11.6 g) of (*S*)-CS were dissolved in 50 cm^3 of ethanol by heating. The solution was cooled gradually with stirring to 38 °C and then the precipitated (*S*)-Epg·(*S*)-CS salt was rapidly filtered off; yield 6.07 g; $[\alpha]_D^{20}$ +32.2° (*c* 1.00, 1 mol dm^{-3} HCl). The filtrate was allowed to stand for 24 h at room temperature to give the (*R*)-Epg·(*S*)-CS salt; yield 6.14 g; $[\alpha]_D^{20}$ −1.11° (*c* 1.00, 1 mol dm^{-3} HCl). After refluxing a suspension of the (*S*)-Epg·(*S*)-CS salt in 18 cm^3 of ethanol for 10 min, followed by cooling to 60 °C, the purified (*S*)-Epg·(*S*)-CS salt was filtered off; yield 2.14 g; $[\alpha]_D^{20}$ +80.9° (*c* 1.00, 1 mol dm^{-3} HCl). The (*R*)-Epg·(*S*)-CS salt was obtained by the similar treatment; yield 1.71 g; $[\alpha]_D^{20}$ −58.1° (*c* 1.00, 1 mol dm^{-3}

HCl). (*S*)- and (*R*)-Epg were isolated from their respective salts by the procedure described in the asymmetric transformation of (*RS*)-Epg.

(*S*)-Epg: Yield 0.88 g; $[\alpha]_D^{20}$ +161° (*c* 1.00, 1 mol dm^{-3} HCl).

(*R*)-Epg: Yield 0.71 g; $[\alpha]_D^{20}$ −163° (*c* 1.00, 1 mol dm^{-3} HCl).

(*RS*)-*N*-Ethyl-*N*-methyl-2-phenylglycine: (*RS*)-Emp (20.0 mmol, 3.86 g) was dissolved by heating in 40 cm^3 of ethanol and then 20.0 mmol (2.42 g) of (*S*)-PEA was added to the solution. After stirring the solution for 1 h at 20 °C, the precipitated (*S*)-Emp·(*S*)-PEA salt was collected by filtration; yield 1.46 g; $[\alpha]_D^{20}$ +38.4° (*c* 1.00, water). The filtrate was allowed to stand for 24 h at 5 °C to collect the further precipitated (*S*)-Emp·(*S*)-PEA salt by filtration; yield 0.83 g; $[\alpha]_D^{20}$ +36.6° (*c* 1.00, water). Evaporation of ethanol from the filtrate gave the (*R*)-Emp·(*S*)-PEA salt; yield 3.50 g; $[\alpha]_D^{20}$ −33.7° (*c* 1.00, water). After stirring a suspension of the (*S*)-Emp·(*S*)-PEA salt in 9 cm^3 of ethanol for 0.5 h at 40 °C and then for 0.5 h at 10 °C, the (*S*)-Emp·(*S*)-PEA salt purified was filtered off; yield 1.64 g; $[\alpha]_D^{20}$ +46.9° (*c* 1.00, water). The (*R*)-Emp·(*S*)-PEA salt was dissolved in 13 cm^3 of 1-propanol by heating. After stirring the solution for 0.5 h at 5 °C, the precipitated (*S*)-Emp·(*S*)-PEA salt (0.70 g) was removed by filtration; $[\alpha]_D^{20}$ +25.6° (*c* 1.00, water). The filtrate was evaporated to dryness under reduced pressure to give the (*R*)-Emp·(*S*)-PEA salt as the residue; yield 2.36 g; $[\alpha]_D^{20}$ −46.9° (*c* 1.00, water). The obtained (*S*)-Emp·(*S*)-PEA and (*R*)-Emp·(*S*)-PEA salts were stirred in water (30 cm^3 g^{-1}) for 1 h with Amberlite IR-120 B (H^+ form; 0.76 g per 1.00 g of the salt) at room temperature. The resins were filtered and washed thoroughly with water. The filtrate and washings were combined and evaporated under reduced pressure to give (*S*)- or (*R*)-Emp.

(*S*)-Emp: Yield 0.99 g; $[\alpha]_D^{20}$ +112° (*c* 1.00, water).

(*R*)-Emp: Yield 1.44 g; $[\alpha]_D^{20}$ −79.9° (*c* 1.00, water).

The optical resolution was carried out similarly by use of (*R*)-PEA; the (*R*)-Emp·(*R*)-PEA salt ($[\alpha]_D^{20}$ −47.8° (*c* 1.00, water)) was obtained in 1.59 g yield and the (*S*)-Emp·(*R*)-PEA salt ($[\alpha]_D^{20}$ +28.4° (*c* 1.00 water)) in 2.41 g yield.

(*R*)-Emp: Yield 0.97 g; $[\alpha]_D^{20}$ −113° (*c* 1.00, water).

(*S*)-Emp: Yield 1.47 g; $[\alpha]_D^{20}$ +79.0° (*c* 1.00, water).

(*RS*)-2-Bromo-2-phenylacetic Acid: After adding (20.0 mmol, 2.42 g) of (*R*)-PEA to a solution of (*RS*)-BPA (20.0 mmol, 4.30 g) in 20 cm^3 of 1-butanol at 40 °C, the solution was allowed to stand for 6 d at 5 °C to precipitate 1.30 g of the (*R*)-BPA·(*R*)-PEA salt; $[\alpha]_D^{20}$ −65.2° (*c* 1.00, methanol). A suspension of the salt in 3 cm^3 of ethanol was stirred for 1 d at room temperature. The purified (*R*)-BPA·(*R*)-PEA salt (0.55 g) was collected by filtration, washed with a small amount of diethyl ether, and dried. After stirring a solution of the salt in 20 cm^3 of 1 mol dm^{-3} hydrochloric acid for 1 h in an ice bath, the liberated oily (*R*)-BPA was extracted with four 15 cm^3 portions of diethyl ether. The organic layer was washed with two 5 cm^3 portions of water and then was allowed to stand overnight at 5 °C, after adding anhydrous sodium sulfate. After removing sodium sulfate by filtration, the filtrate was evaporated to dryness under reduced pressure to give (*R*)-BPA as the residue.

(*R*)-BPA·(*R*)-PEA Salt: Mp 115—116 °C; $[\alpha]_D^{20}$ −71.7° (*c* 1.00, methanol). Found: C, 57.39; H, 5.38; N, 4.13%. Calcd for $C_{16}H_{18}NO_2Br$: C, 57.15; H, 5.40; N, 4.17%.

(*R*)-BPA: Yield 0.33 g; mp 83—86 °C (lit,[6] mp 87—89 °C); $[\alpha]_D^{20}$ −105° (*c* 0.53, diethyl ether) (lit,[6] $[\alpha]_D^{20}$ −104.6° (diethyl ether)). Found: C, 44.90; H, 3.36%. Calcd for $C_8H_7O_2Br$: C, 44.68; H, 3.28%.

Asymmetric Transformation. (*RS*)-*N*-Methyl-2-phenylglycine: A mixture of 10.0 mmol (1.65 g) of (*RS*)-Mpg and 9.50 mmol (2.20 g) of (*S*)-CS in 10 cm^3 of butanoic acid was stirred for 1—8 h at 100 °C. After further adding 0.12 g (0.50 mmol) of (*S*)-CS to the mixture, the mixture was stirred for 5 min at 50 °C and then for 15 min in an ice bath. The (*R*)-Mpg·(*S*)-CS salt precipitated was collected by filtration, washed thoroughly with diethyl ether, and dried. The asymmetric transformation by use of (*R*)-CS·H_2O was similarly carried out in butanoic acid to obtain the (*S*)-Mpg·(*R*)-CS salt.

After refluxing a suspension of the salt of over 85% optical purity in 1-propanol (5 cm^3 g^{-1}) for 5 min and then stirring for 10 min at 60 °C, the purified salt was rapidly collected by filtration, washed with a small amount of cold 1-propanol, and dried. To a suspension of the salt in ethanol (6 cm^3 g^{-1}) was added an equimolar amount of triethylamine. After stirring the mixture for 0.5 h in an ice bath, (*R*)- and (*S*)-Mpg were collected by filtration, washed with a small amount of methanol, and dried.

(*RS*)-*N*-Ethyl-2-phenylglycine: After adding 10.0 mmol (1.79 g) of (*RS*)-Epg and 9.50 mmol (2.20 g) of (*S*)-CS to a mixture of propanoic acid (3 cm^3) and xylene (7 cm^3), the reaction mixture was stirred for 10—60 h at 90 °C. After adding further 0.12 g of (*S*)-CS to the mixture at 60 °C, the mixture was stirred for 10 min and then for 15 min in an ice bath. The precipitated (*R*)-Epg·(*S*)-CS salt was collected by filtration, washed with diethyl ether, and dried.

After refluxing the (*R*)-Epg·(*S*)-CS salt of over 80% optical purity in a mixture (6 cm^3 g^{-1}) of 1-propanol and xylene in volume ratio of 1 : 1 for 5 min, the mixture was cooled to 20 °C and filtered to give the purified salt. To a suspension of the salt in 1-propanol (6 cm^3 g^{-1}) was added an equimolar amount of triethylamine. After stirring for 2 h at room temperature and then for 2 h in an ice bath, the mixture was filtered to give (*R*)-Epg.

(*RS*)-*N*,*N*-Dimethyl-2-phenylglycine: A mixture of 10.0 mmol of (*RS*)-Dmp (1.79 g) and (*R*)-TA (1.50 g) was stirred for 1—7 h in 30 cm^3 of butanoic acid or pentanoic acid at 100 °C. After cooling to 30 °C, the mixture was stirred for 5 min at 30 °C and then for 15 min in an ice bath. The precipitated (*S*)-Dmp·(*R*)-TA salt was collected by filtration, washed with diethyl ether, and dried.

The (*S*)-Dmp·(*R*)-TA salt of over 80% optical purity was stirred for 0.5 h at 50 °C in a methanol solution (5 cm^3 g^{-1}) of (*R*)-TA, for 0.5 h at 30 °C, and then for 5 min in an ice bath; one cm^3 of the methanol solution contained 0.20 g of (*R*)-TA. The (*S*)-Dmp·(*R*)-TA salt collected by filtration was dissolved in methanol (50 cm^3 g^{-1}). After adding 0.87 cm^3 of concetrated aqueous ammonia for 1 g of the salt to the solution, followed by stirring for 1 h in an ice bath, the precipitated diammonium (2*R*,3*R*)-tartarate was removed by filtration. The filtrate was evaporated to dryness under reduced pressure to give (*S*)-Dmp as the residue.

Racemization Rate Constant. After dissolving

1.00 mmol of the optically active amino acid and 0.90—1.05 mmol of (*RS*)-CS in 50 cm^3 of acetic acid, propanoic acid, or butanoic acid, the solution was stirred at 100 °C. A portion of the solution was pippeted out at appropriate time intervals and the optical rotation was measured. The racemization rate constant (k_R/s^{-1}) and half-life period ($t_{1/2}/s$) were calculated by the least-squares method from Eq. 1.

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12) The σ_c^* values were taken as sum of the σ^* values of amino acid side chain and hydrogen atom and the σ_N^* values as sum of the σ^* values of alkyl group and hydrogen atom or those of alkyl groups;[9—11] the σ_N^* value for Phg, Tyr, Phe, Hpg, Ser, and Met·SO_2 was taken as twice the σ^* value of hydrogen atom.
13) In Fig. 3, the degrees of crystallization of the (*S*)-Dmp·(*R*)-TA and (*R*)-Dmp·(*R*)-TA salts ($DC_{(S)}$ and $DC_{(R)}/\%$) were calculated from

$$DC_{(S)}/\% = (1/2)[\text{Yield}/\% \times (100 - OP/\%)]/100,$$
$$DC_{(R)}/\% = \text{Yield}/\% - CD_{(S)}/\%,$$

where the yield is calculated on the basis of 10.0 mmol of the Dmp·TA salt and *OP* is optical purity.
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