Registry No. **2a**, 80227-71-0; **2b**, 123075-35-4; **2c**, 123075-36-5; **2d**, 123075-37-6; **2e**, 107210-09-3; **2f**, 107-02-8; **3**, 77877-19-1; **4a**, 123075-32-1; **4b**, 123075-38-7; **4c**, 123075-39-8; **4d**, 123075-40-1; **4e**, 123075-41-2; **5a**, 123163-80-4; **5b**, 123163-81-5; **5c**, 123163-82-6; **5d**, 123163-83-7; **5e**, 123163-84-8; **5f**, 113489-83-1; **6**, 123237-15-0; **7**, 88636-00-4; **8**, 109215-41-0; **9**, 78655-79-5; **11**, 564-04-5; **12**, 72507-50-7; (±)-**13**, 123075-33-2; (±)-**14**, 123075-34-3; **15**, 123075-44-5; **16** (coordinate entry), 123163-86-0; **16** (covalent entry), 87758-64-3; thiophenol, 108-98-5; 2,4,6-trimethylthiophenol, 1541-10-2; 2,4,6-triisopropylthiophenol, 22693-41-0; 2-naphthalenethiol, 91-60-1; 2-methyl-2-propanethiol, 5954-68-7; propionaldehyde, 123-38-6; benzaldehyde, 100-52-7; (2′*R*,3′*S*,4*S*)-3-(3′-hydroxy-2′-methyl-1′-oxo-3′-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinone, 104758-28-3; (2′*S*,3′*S*,4*S*)-3-(3′-hydroxy-2′-methyl-1′-oxo-3′-phenylpropyl)-4-(1-methylethyl)-2-oxazolidinone, 77877-25-9; (2′*R*,3′*S*,4*S*)-3-(3′-hydroxy-2′-methyl-3′-(1″-naphthyl)-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone, 123075-42-3; (2′*S*,3′*S*,4*S*)-3-(3′-hydroxy-2′-methyl-3′-(1″-naphthyl)-1′-oxopropyl)-4-(1-methylethyl)-2-oxazolidinone, 123163-85-9; 1-naphthaldehyde, 66-77-3.

Supplementary Material Available: ^{1}H NMR spectra of oxazolidinone **3**, complex **15**, and enolate **16** (4 pages). Ordering information is given on any current masthead page.

The Cyclic Dipeptide *cyclo*[(*S*)-Phenylalanyl-(*S*)-histidyl] as a Catalyst for Asymmetric Addition of Hydrogen Cyanide to Aldehydes

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cyclo[(*S*)-Phenylalanyl-(*S*)-histidyl] (*cyclo*[(*S*)-Phe-(*S*)-His], **1**) catalyzes the addition of hydrogen cyanide to benzaldehyde in toluene at −20 °C to afford (*R*)-mandelonitrile with enantiomeric excess of 97% in high yield. *cyclo*[(*R*)-Phenylalanyl-(*R*)-histidyl]gives (*S*)-mandelonitrile. *cyclo*[(*S*)-Phe-(*S*)-His] (**1**) exhibits a broad substrate specificity, and a variety of aldehydes (**3a-r**) such as *m*-methoxybenzaldehyde (**3c**), 6-methoxy-2-naphthaldehyde (**3k**), and isobutyraldehyde (**3o**) similarly afforded the corresponding cyanohydrins with high enantiopurities (97% ee for **3c**, 93% ee for **3k**, 71% ee for **3o**). (*R*)-Mandelonitrile thus obtained was successfully converted to various chiral synthons such as mandelic acid (**7**), methyl mandelate (**8**), and 2-amino-1-phenylethanol (**9**) without any racemization.

The function of synthetic poly- and oligopeptides has received much attention as models for proteins in biological systems. Since enzymes exhibit stereochemical recognition and catalyze various biochemical reactions with a remarkably high degree of efficiency and specificity under mild conditions, the generation of an enzyme-like function by using synthetically designed compounds[1] has been challenging problem. In contrast with recent developments in the use of enzymes as catalysts for enantioselective chemical reactions,[2] few studies have been reported concerning the use of synthetic peptides as catalysts in organic reactions.[3] On the other hand, the preparation of efficient catalysts for the synthesis of optically active compounds has become a widely explored area in contemporary synthetic organic chemistry.[4] Particularly, asymmetric syntheses involving reactions forming carbon–carbon bonds have been the subject of numerous studies[5] because carbon–carbon bond formation plays an essential role in the construction of complex organic molecules. Among these, the addition of the cyano group to carbonyl compounds to give cyanohydrins has been considered a useful reaction, not only to introduce a C_1 unit into organic molecules, but to convert the resulting product to other useful chiral synthons such as α-hydroxy carboxylic acids, α-hydroxy esters, and β-amino alcohols by simple transformations. In spite of much effort to realize asymmetric induction in the addition of hydrogen cyanide to carbonyl groups using alkaloids,[6] poly(L-iminoisobutylethylene),[7] and cyclodextrin[8] as chiral catalysts, the enantioselectivities have been disappointing. On the other hand, an enzyme (oxynitrilase, a flavoprotein isolated from seeds and blossoms of various *Prunaceae*)[9] was reported to catalyze the addition of hydrogen cyanide to benzaldehyde to give (*R*)-mandelonitrile exclusively.[10]

Our research has thus been focused on the design of catalysts for asymmetric cyanohydrin synthesis by using synthetic peptides as an alternative to oxynitrilase. Among various kinds of synthetic peptides, cyclic dipeptides possessing a rigid conformation[11] are considered to be

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(9) Rosenthaler, L. *Biochem. Z.* **1908**, *14*, 238. Becker, W.; Benthin, U.; Eschenhof, E.; Pfeil, E. *Biochem. Z.* **1963**, *337*, 156.
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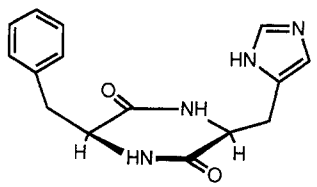
Table I. Asymmetric Addition of Hydrogen Cyanide to Benzaldehyde (3a) Catalyzed by *cyclo*[(*S*)-Phe-(*S*)-His] (1)

cat.	solvt	HCN, equiv	temp, °C	time, h	conv,[a] %	ee,[a] %
1	benzene	1.0	20	0.03	30	87 (*R*)
				20.0	91	68
				172.0	92	31
				435.0	92	7
1	benzene	1.0	10	2.5	98	82
1	toluene	2.0	0	0.5	41	90
				2.5	99	91
1	toluene	2.0	−20	8.0	97	97
1	toluene	5.0	−20	2.5	46	92
1	hexane	2.0	−20	8.0	56	16
1	ether	2.0	−20	8.0	79	90
1	EtOAc	2.0	−20	6.0	56	93
1	THF	2.0	−20	8.0	54	85
1	MeOH	2.0	−20	8.0	88	0
enantio 1[b]	toluene	2.0	−20	8.0	95	93 (*S*)

[a] The conversion and enantiomeric excess (ee) were determined by ^{1}H NMR measurement after the transformation of cyanohydrin **4a** to the corresponding menthyl carbonic ester **5**. [b] *cyclo*[(*R*)-Phenylalanyl-(*R*)-histidyl].

potential catalysts for asymmetric synthesis. Indeed, *cyclo*[(*S*)-phenylalanyl-(*S*)-histidyl] (*cyclo*[(*S*)-Phe-(*S*)-His], **1**), with the hisitidine imidazole moiety as the basic cat-



1 cyclo-[(S)-Phe-(S)-His]

alytic group, was found to be an excellent catalyst for the hydrocyanation reaction of various aldehydes in good yields with high enantiopurities.[12,13] This fact demonstrates that *the stereospecificity of an enzyme can be simulated by the employment of a simple compound formed from only two amino acids; by contrast, enzymes are composed of a large number of amino acid residues.* In this paper, we wish to disclose further improvements in the asymmetric synthesis of cyanohydrins catalyzed by the cyclic peptide **1**, through the addition of hydrogen cyanide to various aldehydes.

The synthesis of *cyclo*[(*S*)-Phe-(*S*)-His] (**1**) was carried out as illustrated in Scheme I. Coupling of (benzyloxycarbonyl)-(*S*)-phenylalanine [Z-(*S*)-Phe] with (*S*)-histidine methyl ester [(*S*)-His-OMe] afforded acyclic dipeptide **2**, which was treated with palladium on carbon under an atmosphere of hydrogen to remove the benzyloxycarbonyl group, followed by cyclization in refluxing methanol to give **1** in a good yield.

Addition of hydrogen cyanide to various aldehydes (**3**) was carried out by using 2 mol % (based on aldehyde **3**) of **1**. The conversion and selectivity (enantiomeric excess: ee) of the reaction were determined by ^{1}H NMR measurements or GC analyses after the transformation of cyanohydrins **4** to the corresponding diastereomeric menthyl carbonate **5**[14] or to the ester of (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) **6**.[15]

Table II. Asymmetric Addition of Hydrogen Cyanide to Aldehyde 3 Catalyzed by *cyclo*[(*S*)-Phe(*S*)-His] (1)[a]

aldehyde	time, h	conv,[b] %	ee,[b] %
3a (X = H)	8.0	97	97
3b (X = *p*-OMe)	10.0	57	78
3c (X = *m*-OMe)	8.0	83	97
3d (X = *o*-OMe)	10.0	45	84
3e (X = *m*-OPh)	8.0	97	92
3f (X = *p*-Me)	10.0	78	96
3g (X = *p*-NO_2)	2.5	99	53
3h (X = *m*-NO_2)	8.0	100	4
3i (X = *p*-CN)	8.0	100	32
3j (2-naphthaldehyde)	1.5	61	91
3k (6-methoxy-2-naphthaldehyde)	6.0	88	73
3k[c]	8.0	76	93
3l (furfural)	8.0	60	42
3m (nicotin-3-aldehyde)	0.5	73	54
3n (cyclohexanecarbaldehyde)	2.5	96	58
3o (isobutyraldehyde)	5.0	79	71
3p (isovaleraldehyde)	5.0	44	18
3q (hexanal)	8.0	90	56
3r (pivalaldehyde)	5.0	60	58

[a] The reaction was carried out by using 2 equiv of hydrogen cyanide based on aldehyde **3** in toluene at −20 °C. [b] The conversion and enantiomeric excess (ee) were determined by ^{1}H NMR measurement or GC analysis after the transformation of cyanohydrin **4** to the corresponding carbonic ester **5** (**3a–m**) or (+)-MTPA ester **6** (**3n–r**). [c] The reaction was carried out in the mixture of toluene and CH_2Cl_2 (1:2 by volume).

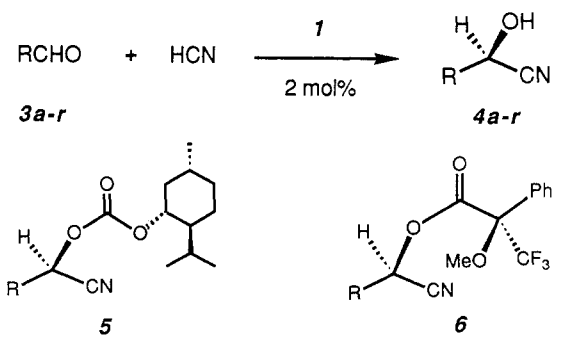


Table I summarizes the results of asymmetric addition of hydrogen cyanide to benzaldehyde (**3a**) under various

(11) Masuda, Y.; Tanihara, M.; Imanishi, Y.; Higashimura, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 497. Imanishi, Y. *Adv. Polym. Sci.* **1976**, *20*, 1.

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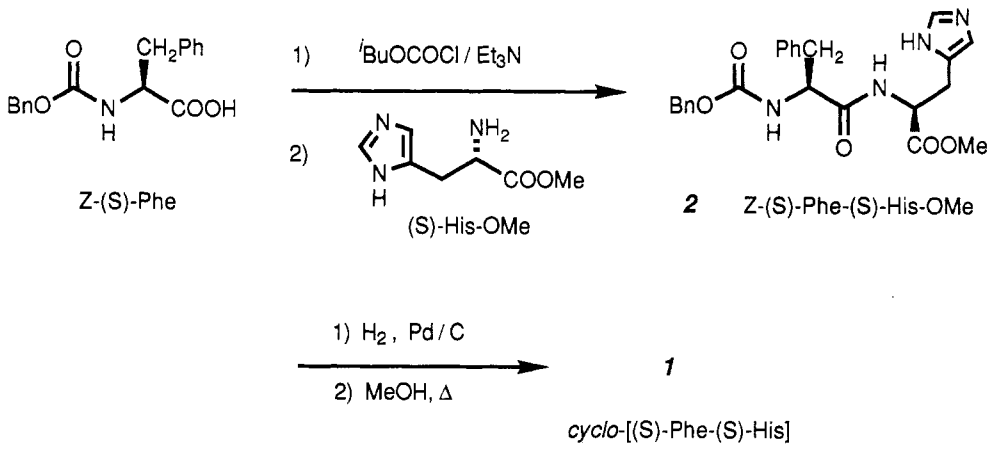
(13) (a) For asymmetric addition of cyanotrimethylsilane to aldehydes in the presence of Lewis acid: Narasaka, K.; Yamada, T.; Minamikawa, H. *Chem. Lett.* **1987**, 2073. Minamikawa, H.; Hayakawa, S.; Yamada, T.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379. Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *39*, 4721. Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294. (b) For asymmetric transhydrocyanation mediated by acetone cyanohydrin: Kobayashi, Y.; Hayashi, H.; Miyaji, K.; Inoue, S. *Chem. Lett.* **1986**, 931. Hayashi, H.; Kobayashi, Y.; Miyaji, K.; Inoue, S. *Nippon Kagaku Kaishi* **1987**, 345.

(14) Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978.

(15) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Scheme I

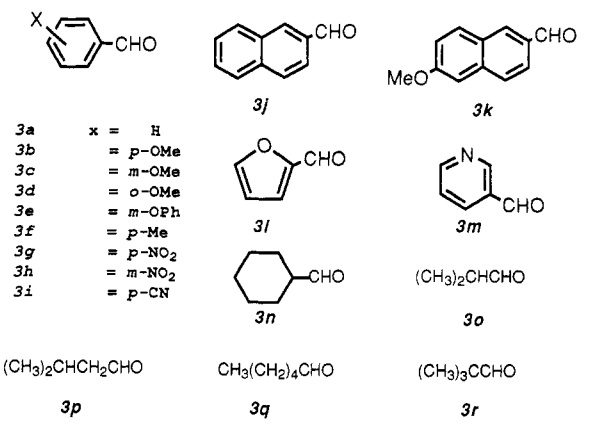


conditions. The reaction with **3a** in benzene at 20 °C gave (*R*)-(−)-mandelonitrile (2-hydroxy-2-phenylacetonitrile, **4a**) in good enantioselectivity (87% ee) in the early stages of the reaction (30% conversion). Racemization of the product was observed as conversion increased (68% ee, 91% conversion), when the reaction mixture changed from a gel to homogeneous. Prolonged reaction times lowered the enantiopurities of **4a** (31% ee at 172 h, 7% ee at 435 h). However, switching the solvent to toluene, which allowed the reaction to be carried out at lower temperature and as a gel throughout the reaction, resulted in high enantiopurity even at higher conversion. Lowering the reaction temperature increased the degree of asymmetric induction. The molar ratio of hydrogen cyanide and aldehyde was found to be optimum at 2:1. An excess amount of hydrogen cyanide seemed to accelerate the reaction as well as to suppress the racemization. At −20 °C, with 2 equiv of hydrogen cyanide in toluene, an extremely high enantioselectivity (97% ee, 97% conversion) was observed. Among various solvents examined (toluene, hexane, ether, ethyl acetate, and THF), the highest efficiency was attained with toluene. In methanol no enantioselectivity was observed. A reaction using *cyclo*[(*R*)-phenylalanyl-(*R*)-histidyl],[16] the enantiomer of *cyclo*[(*S*)-Phe-(*S*)-His] (**1**), as a catalyst afforded (*S*)-(+)-mandelonitrile in 95% yield with ee of 93%.

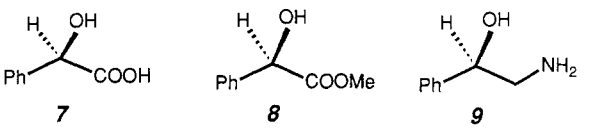
The reactions of other aldehydes were also examined in a similar manner. As shown in Table II, the majority of aromatic aldehydes (**3a–f,j,k**[17]) afforded the corresponding cyanohydrins (**4a–f,j,k**) with high optical yields, except **3g–i**, which contain electron-withdrawing groups on the aromatic ring (Chart I). Reaction with the heteroaromatic aldehydes furfural (**3l**) and nicotinic aldehyde (**3m**) gave moderate asymmetric inductions. For aliphatic aldehydes (**3n–r**), the reactions proceeded much more rapidly than with aromatic aldehydes and gave moderate to high asymmetric inductions. Thus, *cyclo*[(*S*)-Phe-(*S*)-His] (**1**) was shown to be applicable to a variety of aldehydes.

Mandelonitrile (**4a**) thus obtained can be readily converted to other functional groups without any serious racemizations. **4a** was treated with concentrated hydrochloric acid to give (*R*)-(−)-mandelic acid (**7**) and with methanolic hydrochloric acid to give (*R*)-(−)-methyl mandelate (**8**), respectively. Reduction of the cyano group

Chart I



by BH$_3$–THF afforded (*R*)-(−)-2-amino-1-phenylethanol (**9**).



In addition to the importance of the solvent effect in the asymmetric addition reaction, it is also essential to select an appropriate solvent for the purification of *cyclo*[(*S*)-Phe-(*S*)-His] (**1**). When purified by nonaqueous solvents, **1** exhibited high catalytic activities and asymmetric inductions. For example, the addition of hydrogen cyanide to benzaldehyde (**3a**) in toluene (−20 °C, 8 h) using catalyst **1** *purified from methanol–ether* afforded (*R*)-(−)-mandelonitrile (**4a**) in 97% yield with 97% ee, and **1** *recrystallized from methanol* gave **4a** in 94% yield with 98% ee. In contrast, quite low catalytic activities as well as enantioselectivities were observed when **1** was purified by solvent systems containing water, such as *aqueous methanol–ether* (18% conversion, 77% ee) or *water* (9% conversion, 37% ee). In addition, the X-ray diffraction pattern of *cyclo*[(*S*)-Phe-(*S*)-His] (**1**) purified by the aqueous systems was found to be sharp, suggesting high crystallinity, while **1** purified by the nonaqueous solvents showed a broad X-ray diffraction pattern. Consequently, **1** used as catalyst in this study was purified with the water-free system. On the other hand, nonaqueous conditions in the hydrocyanation reaction are not necessarily required; when **1** purified from the nonaqueous solvents was used, the addition of water–MeOH (1:1 in volume, 70 μL) to the reaction mixture of hydrogen cyanide with benzaldehyde

(16) We are indebted to Ajinomoto Co. for generous donation of *cyclo*[(*R*)-phenylalanyl-(*R*)-histidyl], which was recrystallized twice from ether–methanol prior to use.

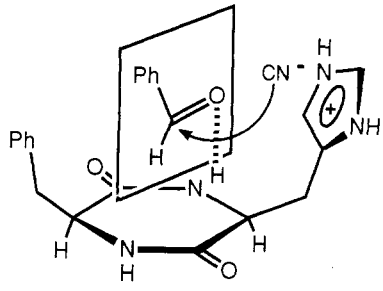
(17) For the preparation of **3k**, see: Eriguchi, A.; Takegoshi, T. *Chem. Pharm. Bull.* **1982**, *30*, 428.

(3a) in toluene (1 mL, −20 °C, 8 h) did not affect the reactivity or the selectivity very much (83% conversion, 85% ee).

Other cyclic dipeptides containing a histidine moiety, such as *cyclo*[(*S*)-Ala-(*S*)-His], *cyclo*-[(*S*)-His-(*S*)-His], *cyclo*-[(*S*)-Val-(*S*)-His], and *cyclo*[(*S*)-Pro-(S)-His], were also examined, but the enantiopurities obtained were quite low (0–10% ee).

Since the acyclic dipeptide *Z*-(*S*)-Phe-(*S*)-His-OMe (2) showed no asymmetric induction, it is essential for the asymmetric catalysis to possess a cyclic structure.

The carbonyl oxygen of benzaldehyde is considered to coordinate to *cyclo*[(*S*)-Phe-(*S*)-His] (1) by a hydrogen bond with the peptide hydrogen of the histidine residue, and hydrogen cyanide interacts with the imidazolyl moiety of the histidine residue to form cyanide ion which attacks the *si* face of the activated carbonyl group, while the *re* face is blocked by the aromatic ring of phenylalanine residue (see I).



In conclusion, a successful simulation of the stereospecificity of an enzyme (oxynitrilase) can be realized by the employment of a cyclic peptide [*cyclo*[(*S*)-Phe-(*S*)-His] (1)] composed of only two readily available amino acids. Owing to the broad substrate specificity of 1 as catalyst, the enantioselective addition of hydrogen cyanide to various aldehydes catalyzed by 1 enables the synthesis of a variety of optically active cyanohydrins (4).

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were taken on a JASCO DIP-360 digital polarimeter. ^{1}H NMR spectra were obtained at 270 MHz. Gas chromatographic analyses were recorded with a flame ionization detector and capillary column OV-101. The X-ray diffraction patterns were recorded on a Rigaku RU-200 spectrometer (λ = 1.541 84 Å). For thin-layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. High-resolution mass spectra (HRMS) were measured at Toray Research Center, Kamakura, Kanagawa, Japan.[18] In experiments requiring dry solvent, ether, tetrahydrofuran, toluene, and benzene were distilled from sodium benzophenone ketyl. Methylene chloride and chloroform were distilled over calcium hydride. Pyridine and triethylamine were distilled over potassium hydroxide. Hydrogen cyanide was prepared by adding an aqueous solution of sodium cyanide dropwise into dilute sulfuric acid according to the reported procedure[19] and stored in a freezer. The preparation and the reaction of hydrogen cyanide should be carried out in the hood with gloves. Other solvents and chemicals were used as such without further purification.

Preparation of *cyclo*[(*S*)-Phe-(*S*)-His] (1). *N*-(Benzyloxycarbonyl)-(*S*)-phenylalanyl-(*S*)-histidine Methyl Ester (2). To a suspension of (*S*)-histidine methyl ester dihydrochloride (20.6 g, 85 mmol) in THF (90 mL) was added triethylamine (23.7 mL, 170 mmol), and the mixture was stirred at room temperature for 3 h to afford free amino acid ester as a suspension. Triethylamine (11.2 mL, 80 mmol) and isobutyl chloroformate (10.4 mL, 80 mmol) were added to a stirred solution of (benzyloxycarbonyl)-(*S*)-phenylalanine (23.9 g, 80 mmol) in THF (200 mL) at −20 °C. To this mixture was added the suspension of (*S*)-histidine methyl ester, and the resulting mixture was vigorously stirred mechanically at 0 °C for 1.5 h and at room temperature for 12 h. Removal of the solvent in vacuo left a white solid which was dissolved in a mixture of ethyl acetate (300 mL) and water (100 mL). The organic layer was separated, washed successively with 10% pottassium carbonate (50 mL), saturated aqueous sodium chloride (50 mL), and 0.5 M boric acid (50 mL), and evaporated in vacuo to leave a crude solid of 2 (32.5 g, 90%) which was directly used for the following reaction without further purification.

(3*S*,6*S*)-3-Benzyl-6-(4-imidazolylmethyl)piperazine-2,5-dione (1). 2 (10.1 g, 22.4 mmol) was stirred in methanol (1.0 L) at room temperature under hydrogen atmosphere in the presence of 10% palladium–carbon (1.0 g) for 12 h. The palladium–carbon catalyst was removed by filtration to give a clear solution which was heated at reflux for 24 h. The solution was concentrated until a gellike product began to form, and to this was added a 5-fold excess of ether (1.0 L). The precipitate formed was filtered, washed with ether, and dried in vacuo: 5.0 g (80%); mp 248–251 °C, $[\alpha]^{25}_D$ −65.2° (*c* 1.97, acetic acid); ^{1}H NMR (DMSO-d_6) δ 8.10 (s, 1 H), 7.78 (s, 1 H), 7.51 (s, 1 H), 7.18–7.33 (m, 5 H), 6.60 (s, 1 H), 4.14 (br s, 1 H), 3.85 (d, J = 13.5 Hz, 1 H), 2.84 (d, J = 10.8 Hz, 2 H), 1.53–1.63 (m, 1 H); IR (KBr) 3050–3700 (br), 1660, 1440, 1330, 1080, 810, 740, 690, 610 cm^{-1}; the X-ray diffraction pattern showed broad peaks [lit. (recrystallized from water) mp 267–268 °C; $[\alpha]^{23}_D$ −72° (*c* 2.0, acetic acid)].[20]

In the other purification procedures for 1, the methanol solution was evaporated to dryness to leave a solid residue. The crude solid (0.61 g) was recrystallized from 100 mL of water to afford 0.40 g of 1 (66%) whose X-ray diffraction pattern exhibited sharp peaks; mp 261–264 °C, $[\alpha]^{25}_D$ −67.7° (*c* 1.97, acetic acid). The crude solid (0.63 g) was dissolved in a mixture of methanol (50 mL) and water (50 mL), and the solution was added dropwise to 500 mL of ether to give 0.24 g of 1 (38%) after removal of the solvent by filtration. The X-ray diffraction pattern analysis indicated sharp peaks; mp 241–243 °C; $[\alpha]^{25}_D$ −73.4 (*c* 1.97 acetic acid). Recrystallization of the crude solid (0.61 g) from 100 mL of methanol gave 0.28 g of 1 (46%). The X-ray diffraction pattern was found to be broad; mp 251–253 °C, $[\alpha]^{25}_D$ −63.2° (*c* 1.96, acetic acid).

General Procedure for Asymmetric Addition of Hydrogen Cyanide to Aldehyde (Analytical Scale). To *cyclo*[(*S*)-Phe-(*S*)-His] (1, 2.8 mg, 0.01 mmol) in toluene (1 mL) was added an aldehyde (3, 0.5 mmol) under nitrogen. After cooling the mixture to −20 °C, hydrogen cyanide (0.040 mL, 1.0 mmol) was added dropwise via a precooled syringe, and stirring was continued at that temperature for the period shown in Tables I and II. The reaction mixture was quenched by 0.1 N methanolic hydrochloric acid (0.5 mL) and the remaining hydrogen cyanide was removed under reduced pressure. The reaction mixture was washed with 2 N hydrochloric acid and the aqueous layer was extracted twice with ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to leave a crude oil which was subjected to column chromatography on silica gel to give the corresponding cyanohydrin. The ^{1}H NMR and IR spectra of thus obtained product were found to be identical with those of the authentic samples.

Preparative-scale hydrocyanation of benzaldehyde (3a) was carried out with 0.53 g (5.0 mmol) of 3a in the same manner as described above. Purification by column chromatography on silica gel (hexane–ethyl acetate, 5:1) gave 0.62 g (94%) of 4a: $[\alpha]^{25}_D$ −39.9° (*c* 4.66, benzene) [lit. (for *S* isomer) $[\alpha]^{25}_D$ 43.75° (*c* 5.006, benzene)].[21]

(2*R* and *S*)-2-Phenyl-2-[(1*R*,2*S*,5*R*)-((menthyloxy)carbonyl)oxy]acetonitrile. To a mixture of (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate (0.55 g, 2.5 mmol) and pyridine (0.20 g, 2.5 mmol) in benzene (2.5 mL) was added (±)-mandelonitrile (0.13 g, 1.0 mmol), and stirring was continued for 12 h at room tem-

(18) We acknowledge Dr. T. Tajima, Toray Research Center for Measurement of HRMS (FAB).

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perature. The mixture was subjected to silica gel column chromatography (hexane–ether, 5:1) to give 0.25 g of the corresponding carbonic ester as a mixture of diastereomers (80%); ^{1}H NMR ($CDCl_3$) δ 7.45–7.55 (m, 5 H), 6.27 (s, 1/2 H, *S* isomer), 6.24 (s, 1/2 H, *R* isomer), 4.60 (m, 1 H), 0.72–2.16 (m, 18 H); IR (film) 2960, 2930, 2880, 1740, 1240, 935, 900, 680 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.28; H, 7.91; N, 4.67. HRMS found m/z, 316.1890, calcd for $C_{19}H_{25}NO_3$ (M + 1) 316.1913.

Determination of the Optical Yield of Cyanohydrins 4: Method A (for Aromatic Aldehydes 3a–m). To a solution of (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate (0.22 g, 1.0 mmol)[14] in benzene (1 mL) was added pyridine (0.08 g, 1.0 mmol) followed by a small portion of the obtained crude cyanohydrin which contained unreacted aldehyde. After stirring for 12 h at room temperature, the mixture was passed through a silica gel short-path column. The eluate was concentrated to give a crude mixture of the corresponding diastereomeric carbonic esters **5**. The conversion and diastereomeric excess were determined by ^{1}H NMR analyses, showing a singlet signal of the formyl proton of unreacted aldehyde around δ 10 and a couple of singlets around δ 6, corresponding to the methine proton α to the cyano group of each diastereomer of **5**. ^{1}H NMR ($CDCl_3$): **5a** δ 6.27 (minor), 6.24 (major); **5b** δ 6.20 (minor), 6.18 (major); **5c** δ 6.23 (minor), 6.21 (major); **5d** δ 6.12 (minor), 6.10 (major); **5e** δ 6.21 (minor), 6.19 (major); **5f** δ 6.20 (minor), 6.18 (major); **5g** δ 6.34 (minor), 6.32 (major); **5h** δ 6.29 (minor), 6.27 (major); **5i** δ 6.34 (minor), 6.32 (major); **5j** δ 6.43 (minor), 6.40 (major); **5k** δ 6.38 (minor), 6.36 (major); **5l** 6.27 (minor), 6.25 (major); **5m** δ 6.30 (minor), 6.27 (major).

Method B (for Aliphatic Aldehydes 3n–r). To a small portion of cyanohydrin were added carbon tetrachloride (0.2 mL) and pyridine (0.2 mL), followed by (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MTPA-Cl, (0.015 mL, 0.08 mmol)][15] and a small amount of 4-(dimethylamino)pyridine. The mixture was stirred for 12 h and passed through a short-path column of silica gel to give the corresponding MTPA ester as an oil whose diastereomeric excess was determined by ^{1}H NMR or GC analyses. ^{1}H NMR ($CDCl_3$): **6n** δ 5.34 (major, d, J = 7.3 Hz), 5.30 (minor, d, J = 7.3 Hz); **6r** δ 5.19 (major, s), 5.14 (minor, s). GC (220 °C): **6o** t_R = 10.2 (major), 10.5 (minor) min; **6p** t_R = 11.2 (major), 11.5 (minor) min; **6q** t_R = 15.3 (major), 15.9 (minor) min.

(−)-(*R*)-2-Hydroxy-2-phenylacetic Acid (7). To mandelonitrile (**4a**, 0.15 g, 1.2 mmol, 94% ee) was added 12 N hydrochloric acid (2 mL), and the mixture was heated under reflux for 6 h. The mixture was extracted with ether repeatedly. The ethereal extract was dried over anhydrous sodium sulfate and evaporated to afford a white solid which was washed with benzene and dried in vacuo (0.15 g, 88%): mp 125–130 °C; $[\alpha]^{25}_D$ −135° (*c* 2.5, water) [lit. mp 131–133 °C; $[\alpha]^{23}_D$ −153° (*c* 2.5, water)].[22] The ^{1}H NMR and IR spectra of **7** are identical with those of the authentic sample.

(−)-(*R*)-Methyl 2-Hydroxy-2-phenylacetate (8). A solution of mandelonitrile (0.39 g, 2.9 mmol, 97% ee) in ether (5 mL) was added to a 3:1 mixture of ether and methanol saturated with hydrogen chloride (20 mL) at 0 °C, and the mixture was allowed to stand at 4 °C for 12 h to yield a white precipitate. After the solvent was removed, the residue was washed with ether, dried in vacuo, and then dissolved in water (10 mL). The aqueous solution was extracted with ether repeatedly. The ethereal extract was dried over anhydrous sodium sulfate and concentrated to give a viscous oil which crystallized upon standing (0.25 g, 50%): mp 51.0–53.0 °C; $[\alpha]^{25}_D$ −178° (*c* 0.83, benzene) [lit. mp 54–55 °C; $[\alpha]^{20}_D$ −176° (*c* 0.83, benzene)].[23] The ^{1}H NMR and IR spectra of **8** are identical with those of the authentic sample.

(−)-(*R*)-2-Amino-1-phenylethanol (9). To a solution of **4a** (0.62 g, 4.6 mmol, 95% ee) in THF (4 mL) was added BH_3–THF complex (9.0 mmol, 9.0 mL of 1 M THF solution). The mixture was heated with reflux for 1 h and stirred for 12 h at room temperature. The excess BH_3 was destroyed by adding 0.5 mL of methanol. HCl was bubbled into the solution for 3 min to form a precipitate. Recrystallization of the collected solid afforded 0.70 g of **9** as HCl salt (88%): mp 215–216 °C; $[\alpha]^{25}_D$ −49.1° (*c* 5.10, water) [lit. (for (+)-**9**) mp 209–210 °C; $[\alpha]^{13}_D$ 48.8 ± 1.2° (*c* 5.08, water)].[24] The ^{1}H NMR and IR spectra of **9** are identical with those of authentic sample.

Registry No. **1**, 56586-95-9; *enantio*-**1**, 93301-56-5; **2**, 16689-13-7; **3a**, 100-52-7; **3b**, 123-11-5; **3c**, 591-31-1; **3d**, 135-02-4; **3e**, 39515-51-0; **3f**, 104-87-0; **3g**, 555-16-8; **3h**, 99-61-6; **3i**, 105-07-7; **3j**, 66-99-9; **3k**, 3453-33-6; **3l**, 98-01-1; **3m**, 500-22-1; **3n**, 2043-61-0; **3o**, 78-84-2; **3p**, 590-86-3; **3q**, 66-25-1; **3r**, 630-19-3; **4a**, 10020-96-9; DL-**4a**, 613-88-7; (*S*)-**4a**, 28549-12-4; **4b**, 97070-73-0; **4c**, 10049-65-7; **4d**, 121985-99-7; **4e**, 71962-66-8; **4f**, 10017-04-6; **4g**, 121986-07-0; **4h**, 97070-77-4; **4i**, 121986-03-6; **4j**, 97070-72-9; **4k**, 123311-35-3; **4l**, 10017-07-9; **4m**, 107986-64-1; **4n**, 100007-62-3; **4o**, 10021-64-4; **4p**, 110905-95-8; **4q**, 116297-10-0; **4r**, 106863-49-4; **5a** (major diastereomer), 123311-36-4; **5a** (minor diastereomer), 123311-51-3; **5b** (major diastereomer), 123311-37-5; **5b** (minor diastereomer), 123311-52-4; **5c** (major diastereomer), 123311-38-6; **5c** (minor diastereomer), 123311-53-5; **5d** (major diastereomer), 123311-39-7; **5d** (minor diastereomer), 123311-54-6; **5e** (major diastereomer), 123311-40-0; **5e** (minor diastereomer), 123311-55-7; **5f** (major diastereomer), 123311-41-1; **5f** (minor diastereomer), 123311-56-8; **5g** (major diastereomer), 123330-30-3; **5g** (minor diastereomer), 123330-32-5; **5h** (major diastereomer), 123330-31-4; **5h** (minor diastereomer), 123330-33-6; **5i** (major diastereomer), 123311-42-2; **5i** (minor diastereomer), 123311-57-9; **5j** (major diastereomer), 123311-43-3; **5j** (minor diastereomer), 123311-58-0; **5k** (major diastereomer), 123311-44-4; **5k** (minor diastereomer), 123311-59-1; **5l** (major diastereomer), 123311-45-5; **5l** (minor diastereomer), 123311-60-4; **5m** (major diastereomer), 123311-46-6; **5m** (minor diastereomer), 123311-61-5; **6n** (major diastereomer), 123311-47-7; **6n** (minor diastereomer), 123311-62-6; **6o** (major diastereomer), 123311-48-8; **6o** (minor diastereomer), 123311-63-7; **6p** (major diastereomer), 123330-18-7; **6p** (minor diastereomer), 123311-64-8; **6q** (major diastereomer), 123311-49-9; **6q** (minor diastereomer), 123311-65-9; **6r** (major diastereomer), 123311-50-2; **6r** (minor diastereomer), 123311-66-0; **7**, 611-71-2; **8**, 20698-91-3; **9**·HCl, 18867-43-1; (+)-MTPA-Cl, 20445-33-4; H-His-OMe·2HCl, 7389-87-9; Z-Phe-OH, 1161-13-3; HCN, 74-90-8; (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate, 14602-86-9.

(22) Data available from Aldrich Chemical Co.

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