

# Asymmetric Hydrocyanation of Benzaldehydes Catalyzed by (5*R*)-5-(4-Imidazolylmethyl)-2,4-imidazolidinedione

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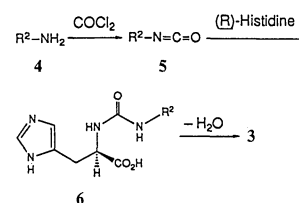
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**Synopsis.** The catalytic activity of (5*R*)-5-(4-imidazolylmethyl)-2,4-imidazolidinedione (**3**) was examined in the asymmetric hydrocyanation of 3-phenoxybenzaldehyde (**1a**) to (5*S*)-2-hydroxy-2-(3-phenoxyphenyl)acetonitrile ((*S*)-**2a**), an important alcohol moiety of optically active pyrethroid insecticides. Among the catalysts, 3-benzyl derivative (**3d**) exhibited moderate enantioselectivities for **1a** and other benzaldehydes.

(*S*)-2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile ((*S*)-**2a**) is an important alcohol moiety of optically active pyrethroid insecticides.<sup>1)</sup> With regard to the asymmetric synthesis of optically active cyanohydrins, there have been many reports concerning the enantioselective hydrocyanation or silylcyanation in the presence of a chiral catalyst.<sup>2)</sup> Recently, Inoue et al. have reported that the chiral cyclic dipeptides containing an (*S*)-histidine residue, such as *cyclo*[(*S*)-phenylalanyl-(*S*)-histidyl], exhibit high enantioselectivities in the asymmetric hydrocyanation of aldehydes.<sup>3)</sup> In conjunction with this finding, our interest has been focussed on the design and screening of catalysts containing the (*R*)-histidine residue to prepare (*S*)-**2a** in high optical yield. We thus prepared various kinds of (5*R*)-5-(4-imidazolylmethyl)-2,4-imidazolidinedione (**3**), which have a structural similar to that of *cyclo*[(*S*)-phenylalanyl-(*S*)-histidyl], and investigated their catalytic activities in the enantioselective addition of hydrogen cyanide to 3-phenoxybenzaldehyde (**1a**) as well as other benzaldehydes (**1b—d**) (Scheme 1). Herein, we report on the results concerning asymmetric hydrocyanation catalyzed by **3**.

## Results and Discussion

The preparation of the catalyst (**3**) was carried out as illustrated in Scheme 2. The urea (**6**) was prepared by coupling of (*R*)-histidine monohydrochloride hydrate



Scheme 2.

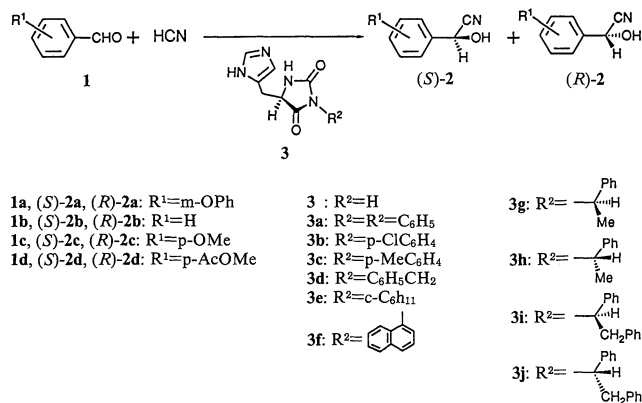
with the isocyanate (**5**) which was obtained by a reaction of the corresponding amine (**4**) with phosgene. The urea (**6**) was dehydrated under acidic conditions to give **3** in reasonable yields. The asymmetric hydrocyanation was carried out by using 2.2—5 mol% of the catalyst (**3**) (based on the aldehyde (**1**)). The optical yield (ee) of (*S*)-**2** was determined by HPLC analysis (Sumipax OA-4100).<sup>4)</sup>

The asymmetric hydrocyanation of the aldehyde (**1a**) catalyzed by **3** was examined; the results are summarized in Table 1. In all of the catalysts, except for **3f**, (*S*)-cyanohydrin ((*S*)-**2a**) was preferentially obtained, while **3f** gave the opposite enantiomer ((*R*)-**2a**) as a major product (Entry 8). Among the catalysts (**3**), **3d** and **3e** gave (*S*)-**2a** in moderate optical yields (37% ee and 18% ee, Entries 4 and 6). Extending the reaction time decreased the optical yield, which may be due to a racemization of the products (Entry 5). The use of DMF as a solvent decreased the optical yield, even

Table 1. Asymmetric Hydrocyanation of **1a** Catalyzed by **3**<sup>a)</sup>

Entry	Catalyst	Solvent	Time/h	Conv. of <b>1a</b> / <sup>b)</sup> %	Optical yield of <b>2a</b> / <sup>c)</sup> % ee (config.) <sup>c)</sup>
1	<b>3a</b>	Neat	6	90	2 ( <i>S</i> )
2	<b>3b</b>	Neat	4	88	1 ( <i>S</i> )
3	<b>3c</b>	Neat	4	89	10 ( <i>S</i> )
4	<b>3d</b>	Neat	1	90	37 ( <i>S</i> )
5	<b>3d</b>	Neat	4	99	13 ( <i>S</i> )
6	<b>3e</b>	Neat	4	22	18 ( <i>S</i> )
7	<b>3e</b>	DMF	1	69	12 ( <i>S</i> )
8	<b>3f</b>	DMF	4	91	6 ( <i>S</i> )
9	<b>3g</b>	Neat	4	94	6 ( <i>S</i> )
10	<b>3h</b>	Neat	4	97	2 ( <i>S</i> )
11	<b>3i</b>	Neat	4	82	7 ( <i>S</i> )
12	<b>3j</b>	Neat	4	73	1 ( <i>S</i> )

a) The reactions were carried out at 10 °C by using 1.1 mmol of the catalyst (**3**), 99 mmol of hydrogen cyanide and 50 mmol of the aldehyde (**1a**). In Entries 7 and 8, 40 mL of DMF was used as a solvent because of a poor solubility of **3e** and **3f**. b) Determined by HPLC (LiChrosorb SI-60). Any by-product was not observed on HPLC. c) Determined by HPLC (Sumipax OA-4100).



Scheme 1.

Table 2. Asymmetric Hydrocyanation of **1a** Catalyzed by **3d**<sup>a)</sup>

Entry	Solvent	Amount of <b>3d</b> /mol vs. <b>1a</b>	Temp/°C	Time/h	Conv. of <b>1a</b> / % <sup>b)</sup>	Optical yield of ( <i>S</i> )- <b>2a</b> / %ee <sup>c)</sup>
1	Toluene	2.2	10	4	No reaction <sup>d)</sup>	—
2	Cyclohexane	2.2	10	4	No reaction <sup>d)</sup>	—
3	CH <sub>3</sub> CN	2.2	10	1	89	17
4	CH <sub>2</sub> Cl <sub>2</sub>	2.2	10	4	No reaction <sup>d)</sup>	—
5	DMF	2.2	10	1	92	11
6	Neat	2.2	0	3	91	40
7	Neat	5	0	1	90	41

a) The reactions were carried out by using 99 mmol of hydrogen cyanide and 50 mmol of **1a**. 40 mL of solvent was used in Entries 1—5. b) Determined by HPLC (LiChrosorb SI-60). Any by-product was not observed on HPLC. c) Determined by (Sumipax OA-4100). d) **3d** is insoluble.

Table 3. Asymmetric Hydrocyanation of Aldehydes Catalyzed by **3d**<sup>a)</sup>

Entry	Aldehyde	Solvent	Time/h	Conv. of <b>1</b> / % <sup>b)</sup>	Optical yield of ( <i>S</i> )- <b>2</b> / %ee <sup>c)</sup>
1	<b>1b</b>	Neat	1	90	33
2	<b>1c</b>	DMF	3	67	20
3	<b>1d</b>	DMF	1	93	16

a) The reactions were carried out at 0 °C by using 1.1 mmol of **3d**, 99 mmol of hydrogen cyanide and 50 mmol of aldehyde. 40 mL of DMF was used in Entries 2 and 3. b) Determined by HPLC (LiChrosorb SI-60). Any by-product was not observed on HPLC. c) Determined by HPLC (Sumipax OA-4100).

though the conversion of **1a** increased (compare Entry 7 with Entry 6). And even though the 3-substituent of **3d** was replaced by chiral benzyl groups, using **3g**—**j**, the optical yield was not improved (Entries 9—12).

Next, the optimal conditions were investigated in the asymmetric hydrocyanation of **1a** catalyzed by **3d**. The results are summarized in Table 2. No reaction was observed when toluene, cyclohexane or CH<sub>2</sub>Cl<sub>2</sub> was used as a solvent, because of the poor solubility of **3d** in these solvents. The use of CH<sub>3</sub>CN or DMF as a solvent decreased the optical yields. When the reaction temperature was lowered to 0 °C, the optical yield of (*S*)-**2a** was improved (40% ee, Entry 6), whereas it was not improved so much by increasing **3d** (41% ee, Entry 7).

The asymmetric hydrocyanation of benzaldehydes (**1b**—**d**) catalyzed by **3d** was examined. The results are exemplified in Table 3. In all cases, (*S*)-cyanohydrin ((*S*)-**2**) was obtained preferentially, ranging from 16% ee to 33% ee.<sup>4)</sup> However, racemic cyanohydrin was obtained when isobutyraldehyde was employed for the reaction under the same reaction condition as Entry 1 (90% conv. at 1 h).

Thus, **3d** exhibited moderate enantioselectivities in the asymmetric hydrocyanation of benzaldehydes (**1**), particularly affording (*S*)-**2a** with a maximum optical yield of 41% ee.

We can discuss the mechanism of the enantioselective hydrocyanation catalyzed by **3d**, based on the mechanism which Inoue et al. postulated for the enantioselective hydrocyanation catalyzed by *cyclo*[(*S*)-phenylalanyl-(*S*)-histidyl].<sup>3b)</sup> The carbonyl oxygen of

the aldehyde (**1**) is considered to coordinate to the catalyst (**3d**) by a hydrogen bond with the NH group of the histidine residue, and hydrogen cyanide interacts with the imidazolyl moiety of the histidine residue to form a cyanide ion which attacks the *re*-face of the activated carbonyl group, while the *si*-face is blocked by the aromatic ring of benzyl isocyanate residue. However, the blocking by the aromatic ring would be too loose to afford a satisfying enantioselectivity.

A further study dedicated to improving the enantioselectivity is in progress.

## Experimental

**General.** The melting points are uncorrected. Optical rotations were taken on a JASCO DIP-140 digital polarimeter. <sup>1</sup>H NMR spectra were obtained at 200 MHz on a Varian XL-200, except for those of **3**, which were obtained at 90 MHz on a Hitachi R-40; <sup>13</sup>C NMR spectra were obtained at 50.3 MHz on a Varian XL-200. IR spectra were obtained on a Hitachi 260-10. HPLC were recorded on a Shimadzu LC-6A, LiChrosorb SI-60 and Sumipax OA-4100 being used as columns for determination of the conversion of **1** and the optical yield of the resulting cyanohydrins ((*S*)-**2**: (*R*)-**2**), respectively. Toluene and xylene were distilled from sodium benzophenone ketyl. DMF and CH<sub>3</sub>CN were distilled immediately prior to use. Hydrogen cyanide was provided by Ehime Factory. All other solvents and chemicals were used without further purification.

**Preparation of (5*R*)-5-(4-imidazolylmethyl)-2,4-imidazolidinedione (**3**).** (5*R*)-3-Benzyl-5-(4-imidazolylmethyl)-2,4-imidazolidinedione (**3d**). To a solution of 7.49 g (70 mmol) of benzylamine in 50 mL of xylene was added at 120 °C over 100 min 27.7 g (280 mmol) of phosgene. After removing the solvent and excess phosgene in vacuo, the crude isocyanate was subjected to the following procedure.

To a solution of 15.7 g (75 mmol) of (*R*)-histidine monohydrochloride hydrate in 180 mL of water was added 2 equiv NaOH until the solution showed pH 9. After the addition of the crude isocyanate obtained above, the reaction mixture was kept at 40 °C for 1 h, adjusted to pH 1 with 35% aqueous HCl, and kept under reflux for 1 h. After being cooled to 5 °C and neutralized to pH 5 with 2 equiv NaOH, the reaction mixture was allowed to stand at 5 °C overnight. The precipitate was filtered, washed with cold water and recrystallized from aqueous ethanol to give 15.2 g (85%) of **3d** as white crystals: Mp 219 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> 10.6° (c 0.87, DMSO); IR (KBr) 3300, 1760, 1710, 1455, 1430 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ =2.95 (d, *J*=5.2 Hz, 2H), 4.36 (t, *J*=5.2 Hz, 1H), 4.47 (s, 2H), 6.80 (s, 1H), 6.9—7.4 (m, 5H), 7.52 (s, 1H), 8.17 (br.s, 1H). Found: C, 65.41; H,

5.49; N, 16.23%. Calcd for  $C_{14}H_{14}N_3O_2$ : C, 65.61; H, 5.51; N, 16.40%.

**(5R)-5-(4-Imidazolylmethyl)-3-phenyl-2,4-imidazolidinedione (3a).** The procedure given for **3d** was carried out on the same scale using aniline to give 14.0 g (83%) of **3a** as white crystals: Mp 192–194 °C;  $[\alpha]_D^{25}$  151.1° (c 1.02, methanol); IR (KBr) 3200, 1760, 1700, 1430, 1190  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$ =3.08 (d,  $J$ =6.0 Hz, 2H), 4.44 (t,  $J$ =6.0 Hz, 1H), 6.90 (s, 1H), 7.2–7.5 (m, 5H), 7.60 (s, 1H), 8.20 (br.s, 1H). Found: C, 64.39; H, 4.87; N, 17.22%. Calcd for  $C_{13}H_{12}N_3O_2$ : C, 64.45; H, 4.99; N, 17.35%.

**(5R)-3-(4-Chlorophenyl)-5-(4-imidazolylmethyl)-2,4-imidazolidinedione (3b).** The procedure given for **3d** was carried out on the same scale using 4-chloroaniline to give 14.3 g (74%) of **3b** as white crystals: Mp 220–221 °C;  $[\alpha]_D^{25}$  14.5° (c 0.86, DMSO); IR (KBr) 3300, 1710, 1660, 1570, 1400, 1190  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$ =3.01 (d,  $J$ =5.8 Hz, 2H), 4.45 (t,  $J$ =5.8 Hz, 1H), 6.89 (s, 1H), 7.1–7.7 (m, 4H), 7.73 (s, 1H), 9.00 (br.s, 1H). Found: C, 56.27; H, 3.89; N, 14.93%. Calcd for  $C_{13}H_{11}N_3O_2Cl$ : C, 56.43; H, 4.01; N, 15.19%.

**(5R)-5-(4-Imidazolylmethyl)-3-(4-methylphenyl)-2,4-imidazolidinedione (3c).** The procedure given for **3d** was carried out on the same scale using *p*-toluidine to give 13.8 g (77%) of **3c** as white crystals: Mp 243 °C;  $[\alpha]_D^{25}$  113.7° (c 0.872, DMSO); IR (KBr) 3200, 3000, 1760, 1705, 1600, 1520, 1430, 1190  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$ =2.30 (s, 3H), 3.02 (d,  $J$ =5.8 Hz, 2H), 4.42 (t,  $J$ =5.8 Hz, 1H), 6.86 (s, 1H), 7.0–7.4 (m, 4H), 7.56 (s, 1H), 8.27 (br.s, 1H). Found: C, 65.59; H, 5.35; N, 16.17%. Calcd for  $C_{14}H_{14}N_3O_2$ : C, 65.61; H, 5.51; N, 16.40%.

**(5R)-3-Cyclohexyl-5-(4-imidazolylmethyl)-2,4-imidazolidinedione (3e).** The procedure given for **3d** was carried out on the same scale using cyclohexylamine to give 13.9 g (80%) of **3e** as white crystals: Mp 172–174 °C;  $[\alpha]_D^{25}$  15.6° (c 0.87,  $H_2O$ ); IR (KBr) 3300, 2950, 1620, 1580, 1400  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$ =0.8–0.9 (m, 11H), 2.90 (d,  $J$ =6.0 Hz, 2H), 4.33 (t,  $J$ =6.0 Hz, 1H), 6.93 (s, 1H), 7.90 (s, 1H). Found: C, 62.71; H, 7.19; N, 16.84%. Calcd for  $C_{13}H_{18}N_3O_2$ : C, 62.88; H, 7.31; N, 16.92%.

**(5R)-5-(4-Imidazolylmethyl)-3-(1-naphthyl)-2,4-imidazolidinedione (3f).** The procedure given for **3d** was carried out on the same scale using 1-aminonaphthalene to give 16.6 (81%) of **3f** as white crystals: Mp 205–206 °C;  $[\alpha]_D^{25}$  –39.4° (c 0.76, DMSO);  $^1H$  NMR (DMSO- $d_6$ )  $\delta$ =3.07 (d,  $J$ =6.2 Hz, 2H), 4.53 (t,  $J$ =6.2 Hz, 1H), 6.97 (s, 1H), 7.3–7.7 (m, 4H), 7.8–8.3 (m, 4H), 8.80 (br.s, 1H). Found: C, 69.76; H, 4.64; N, 14.25%. Calcd for  $C_{17}H_{14}N_3O_2$ : C, 69.85; H, 4.83; N, 14.38%.

**(5R)-5-(4-Imidazolylmethyl)-3-[(R)-1-phenylethyl]-2,4-imidazolidinedione (3g).** The procedure given for **3d** was carried out on the same scale using (*R*)- $\alpha$ -methylbenzylamine to give 12.3 g (65%) of **3g** as white crystals:  $[\alpha]_D^{25}$  –20.1° (c 1.00, DMSO); IR (KBr) 3300, 1755, 1630, 1550  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$ =1.33 (d,  $J$ =6.5 Hz, 3H), 2.88 (d,  $J$ =6.0 Hz, 2H), 4.36 (t,  $J$ =6.0 Hz, 1H), 4.73 (q,  $J$ =6.5 Hz, 1H), 6.82 (s, 1H), 7.15–7.4 (m, 5H), 7.65 (s, 1H). Found: C, 66.41; H, 5.80; N, 15.39%. Calcd for  $C_{15}H_{16}N_3O_2$ : C, 66.65; H, 5.97; N, 15.55%.

**(5R)-5-(4-Imidazolylmethyl)-3-[(S)-1-phenylethyl]-2,4-imidazolidinedione (3h).** The procedure given for **3d** was carried out on the same scale using (*S*)- $\alpha$ -methylbenzylamine to give 11.5 g (61%) of **3h** as white crystals:  $[\alpha]_D^{25}$  –36.8° (c 0.40, DMSO); IR (KBr) 3300, 1760, 1630, 1560  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$ =1.30 (d,  $J$ =6.5 Hz, 3H), 2.88 (d,  $J$ =6.0 Hz, 2H), 4.30 (t,  $J$ =6.0 Hz, 1H), 4.71 (q,  $J$ =6.5 Hz, 1H), 6.83 (s, 1H), 7.13–7.43 (m, 5H), 7.65 (s, 1H). Found: C, 66.60; H, 5.92; N, 15.47%. Calcd for  $C_{15}H_{16}N_3O_2$ : C, 66.65; H, 5.97; N, 15.55%.

**(5R)-5-(4-Imidazolylmethyl)-3-[(R)-1,2-diphenylethyl]-2,4-imidazolidinedione (3i).** The procedure given for **3d** was carried out on the same scale using (*R*)-1,2-diphenylethylamine to give 13.2 g (55%) of **3i** as white crystals:  $[\alpha]_D^{25}$  –15.1° (c 1.01, DMSO); IR (KBr) 3340, 1630, 1550, 1510, 1260  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$ =2.85 (d,  $J$ =6.5 Hz, 2H), 2.88 (d,  $J$ =6.5 Hz, 2H), 4.27 (t,  $J$ =6.0 Hz, 1H), 4.80 (t,  $J$ =6.5 Hz, 1H), 6.80 (s, 1H), 6.9–7.5 (m, 10H), 7.68 (s, 1H). Found: C, 72.68; H, 5.70; N, 11.99%. Calcd for  $C_{21}H_{20}N_3O_2$ : C, 72.81; H, 5.82; N, 12.13%.

**(5R)-5-(4-Imidazolylmethyl)-3-[(S)-1,2-diphenylethyl]-2,4-imidazolidinedione (3j).** The procedure given for **3d** was carried out on the same scale using (*S*)-1,2-diphenylethylamine to give 12.9 g (53%) of **3j** as white crystals:  $[\alpha]_D^{25}$  –37.0° (c 1.01, DMSO); IR (KBr) 3350, 1630, 1560, 1520, 1260  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$ =2.83 (d,  $J$ =6.5 Hz, 2H), 2.90 (d,  $J$ =6.0 Hz, 2H), 4.25 (t,  $J$ =6.0 Hz, 1H), 4.82 (t,  $J$ =6.5 Hz, 1H), 6.80 (s, 1H), 7.0–7.6 (m, 10H), 7.68 (s, 1H). Found: C, 72.77; H, 5.71; N, 11.95%. Calcd for  $C_{21}H_{20}N_3O_2$ : C, 72.81; H, 5.82; N, 12.13%.

**General Procedure for Asymmetric Addition of Hydrogen Cyanide to Benzaldehyde (1) Catalyzed by 3.** To a mixture of 1.1 mmol of the catalyst (**3**) and 50 mmol of the aldehyde (**1**) (if necessary, 40 mL of an appropriate solvent was used) at 5 °C was added dropwise 3.8 mL (2.67 g, 99 mmol) of hydrogen cyanide under nitrogen; stirring was continued at 0 °C (or 10 °C) for an appropriate period. The reaction mixture was quenched with 0.5% aqueous HCl, and the crude cyanohydrin was extracted twice with toluene. The combined organic layers were dried over  $Na_2SO_4$  and concentrated in vacuo, producing a brown oil which was chromatographed on silica gel to give the pure cyanohydrin. The  $^1H$  NMR and IR spectra were found to be identical with those of an authentic sample. The optical yield of the resulting cyanohydrin ((*S*)-2: (*R*)-2) was determined by HPLC analysis (column, Sumipax OA-4100; eluent, hexane/1,2-dichloroethane/ethanol/ethyl acetate=800/200/10/1; flow rate, 1.0 mL  $min^{-1}$ ; detection, 254 nm light). The conversion of **1** was also determined by HPLC analysis (column, LiChrosorb SI-60; eluent, hexane/ethyl acetate/acetic acid=500/60/3; flow rate, 1.0 mL  $min^{-1}$ ; detection, 254 nm light).

## References

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- 4) The  $^1H$  NMR and IR spectra were found to be identical with those of the authentic sample. The absolute configuration of the resulting cyanohydrins ((*S*)-2 and (*R*)-2) has already been determined.<sup>1b,3b)</sup>