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

Hidenori DANDA
Takarazuka Research Center, Sumitomo Chemical Co., Ltd.,
2-1, 4-Chome, Takatsukasa, Takarazuka, Hyogo 665
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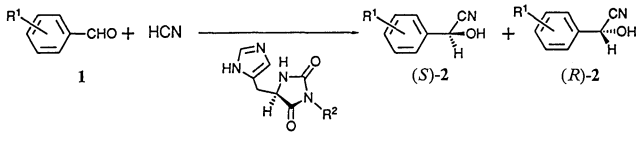
Synopsis. The catalytic activity of (5*R*)-5-(4-imidazolylmethyl)-2,4-imidazolidinedione (**3**) was examined in the asymmetric hydrocyanation of 3-phenoxybenzaldehyde (**1a**) to (*S*)-2-hydroxy-2-(3-phenoxyphenyl)acetonitrile ((*S*)-**2a**), an important alcohol moiety of optically active pyrethroid insecticides. Among the catalysts, 3-benzyl derivative (**3d**) exhibited moderate enantioselectivities for **1a** and other benzaldehydes.

(*S*)-2-Hydroxy-2-(3-phenoxyphenyl)acetonimle ((*S*)-**2a**) is an important alcohol moiety of optically active pyrethroid insecticides.[1] 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.[2] 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.[3] 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

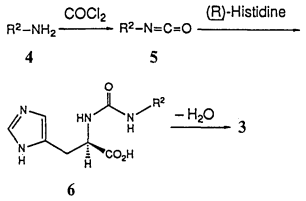


1a, (*S*)-**2a**, (*R*)-**2a**: R¹=m-OPh
1b, (*S*)-**2b**, (*R*)-**2b**: R¹=H
1c, (*S*)-**2c**, (*R*)-**2c**: R¹=p-OMe
1d, (*S*)-**2d**, (*R*)-**2d**: R¹=p-AcOMe

3 : R²=H
3a: R²=R²=C₆H₅
3b: R²=p-ClC₆H₄
3c: R²=p-MeC₆H₄
3d: R²=C₆H₅CH₂
3e: R²=c-C₆h₁₁
3f: R²=

3g: R²=
3h: R²=
3i: R²=
3j: R²=

Scheme 1.



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).[4]

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**[a]

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

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).

Table 2. Asymmetric Hydrocyanation of **1a** Catalyzed by **3d**[a]

Entry	Solvent	Amount of **3d** /mol vs. **1a**	Temp/°C	Time/h	Conv. of **1a**/%[b]	Optical yield of (*S*)-**2a**/%ee[c]
1	Toluene	2.2	10	4	No reaction[d]	—
2	Cyclohexane	2.2	10	4	No reaction[d]	—
3	CH_3CN	2.2	10	1	89	17
4	CH_2Cl_2	2.2	10	4	No reaction[d]	—
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 casrried 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**[a]

Entry	Aldehyde	Solvent	Time/h	Conv. of **1**/%[b]	Optical yield of (*S*)-**2**/%ee[c]
1	**1b**	Neat	1	90	33
2	**1c**	DMF	3	67	20
3	**1d**	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_2Cl_2 was used as a solvent, because of the poor solubility of **3d** in these solvents. The use of CH_3CN 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.[4] 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 atfording (*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].[3b] 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. ^1H 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; ^{13}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_3CN 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; $[\alpha]_D^{25}$ 10.6° (*c* 0.87, DMSO); IR (KBr) 3300, 1760, 1710, 1455, 1430 cm^{-1}; ^1H NMR (DMSO-d_6) δ=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%.

(5*R*)-5-(4-Imidazolylmethyl)-3-phenyl-2,4-imidazolidione (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) δ=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%.

(5*R*)-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 (*c* 0.86, DMSO); IR (KBr) 3300,1710, 1660, 1570, 1400, 1190 cm^{-1}; ^1H NMR (DMSO-d_6) δ=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%.

(5*R*)-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) δ=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%.

(5*R*)-3-Cyclohexyl-5-(4-imidazolylmethyl)-2,4-imidazolidinedione (3e). The procedure given **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) δ=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%.

(5*R*)-5-(4-Imidazolylmethyl)-3-(1-naphtyl)-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) δ=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%.

(5*R*)-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*)-α-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) δ=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%.

(5*R*)-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*)-α-methylhenzylamine 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) δ=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%.

(5*R*)-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) δ=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%.

(5*R*)-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) δ=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).

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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.[1b,3b]