Enantioselective Autoinduction in the Asymmetric Hydrocyanation of 3-Phenoxybenzaldehyde Catalyzed by Cyclo[(*R*)-phenylalanyl-(*R*)-histidyl]

Hidenori Danda,* Hiroyuki Nishikawa, and Ken Otaka

Takarazuka Research Center, Sumitomo Chemical Co., Ltd., 2-1, 4-Chome, Takatsukasa, Takarazuka, Hyogo 665, Japan

Received May 6, 1991

Summary: A new example of enantioselective autoinduction, i.e., an asymmetric reaction that is promoted by a chiral catalyst into which the chiral product has been incorporated, has been found in the asymmetric hydrocyanation of 3-phenoxybenzaldehyde catalyzed by cyclo-[(*R*)-phenylalanyl-(*R*)-histidyl].

(*S*)-2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile ((*S*)-**2**) is an important alcoholic precursor of optically active pyrethroid insecticides.[1] Thus, obtaining it in high optical purity is of some importance. There are many reports of the enantioselective hydrocyanation or silylcyanation of aldehydes and ketones in the presence of a chiral catalyst[2] and of the enantioselective hydrocyanation of such compounds in the presence of enzymes.[3] Inoue et al.[4] have reported that chiral cyclic dipeptides which incorporate an (*S*)-histidine residue catalyze the enantioselective hydrocyanation of aldehydes. We have already described the essential factors for the enantioselective hydrocyanation of 3-phenoxybenzaldehyde (**1**) catalyzed by cyclo[(*R*)-phenylalanyl-(*R*)-histidyl] ((*R*,*R*)-**3**).[5] Recently, Alberts and Wynberg have described an example of enantioselective autoinduction in the asymmetric addition of ethyllithium to benzaldehyde.[6] We now describe another example of enantioselective autoinduction in the asymmetric hydrocyanation of **1** catalyzed by (*R*,*R*)-**3** (Scheme I).

We investigated the enantioselective addition of hydrogen cyanide to **1** catalyzed by (*R*,*R*)-**3** in detail.[7] The results are shown in Table I. However, an unusual phenomenon was observed: The enantiomeric excess (ee) of the product, (*S*)-**2**, increased as the fraction of **1** that was converted increased (method A). Furthermore, when a small amount of (*S*)-**2** was present in the reaction mixture prior to the introduction of HCN, the optical purity of the product remained at ca. 96% ee throughout the course of

Table I. Effect of the Initial Presence of (*S*)-2 or (*R*)-2 on the Enantioselective Addition of Hydrogen Cyanide to 3-Phenoxybenzaldehyde (1) Catalyzed by (*R*,*R*)-3[a]

method[a]	time (h)	conversion of 1[b,c] (%)	optical purity of (*S*)-2[c,d] (% ee)
A	0.5	21	34.4
	1	39	66.2
	2	92	91.6
	4	94	92.0
B	0.5	59 (55)	95.4 (95.8)
	1	81 (79)	96.0 (96.4)
	2	93 (92)	96.4 (96.8)
	4	95 (95)	96.2 (96.6)
C	0.5	24 (17)	25.1 (34.8)
	1	43 (38)	54.0 (66.2)
	2	93 (92)	77.8 (92.2)
	4	95 (95)	78.0 (92.4)

[a] Method A: (*R*,*R*)-3:1:HCN = 1.1:50:99 mmol; toluene (40 mL), 5 °C. Method B: As method A, except that (*S*)-2 of 92.0 % ee (4.4 mmol) was present initially. Method C: As method A, except that (*R*)-2 of 84.9 % ee (4.4 mmol) was present initially. [b] Determined by HPLC (LiChrosorb SI-60). No byproducts were observed by HPLC. [c] The values in parentheses are corrected by subtracting the appropriate value for the added cyanohydrin ((*S*)-2 or (*R*)-2). [d] Determined by HPLC (Sumipax OA-4100).

Table II. Effect of the Optical Purity of the (*R*,*R*)-3 Catalyst on the Enantioselective Autoinduction[a]

entry	optical purity of (*R*,*R*)-3[b] (% ee)	conversion of 1[c] (%)	optical purity of 2 (% ee) (configuration)[d,e]	method[a]
1	100	94	92.0 (*S*)	A
2	84.6	89	80.0 (*S*)	A
3	79.4	89	76.2 (*S*)	A
4	66.8	81	64.6 (*S*)	A
5	40.0	62	37.2 (*S*)	A
6	12.2	27	11.0 (*S*)	A
7	100	95	96.2 (*S*)	B
8	84.6	96	94.8 (*S*)	B
9	79.4	96	96.8 (*S*)[f]	B
10	66.8	89	96.0 (*S*)	B
11	40.0	90	90.2 (*S*)	B
12	12.2	79	86.6 (*S*)	B
13	12.2	68	39.6 (*R*)	C
14	2.0	4	3.4 (*S*)	A
15	2.0	43	81.6 (*S*)	B
16	2.0	39	74.0 (*R*)	C
17	no catalyst	no reaction		B
18	no catalyst	no reaction		C

[a] Method A: (*R*,*R*)-3:1:HCN = 1.1:50:99 mmol; toluene (40 mL), 5 °C. Method B: As method A, except that (*S*)-2 of 92.0 % ee (4.4 mmol) was present initially. Method C: As method A, except that (*R*)-2 of 84.9 % ee (4.4 mmol) was present initially. [b] Determined by HPLC (Ultron ES-OVM). [c] Determined by HPLC (LiChrosorb SI-60). No byproducts were observed by HPLC. [d] Determined by HPLC (Sumipax OA-4100). [e] For the absolute configurations of (*R*)-2 and (*S*)-2 see: Tanaka, K.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. [f] $[\alpha]^{25}_{D}$ −17.5° (*c* 0.80, benzene).

(1) (a) Matsuo, T.; Nishioka, T.; Hirano, M.; Suzuki, Y.; Tsushima, K.; Itaya, N.; Yoshioka, H. *Pestic. Sci.* **1980**, 11, 202. (b) Aketa, K.; Ohno, N.; Yoshioka, H. *Agric. Biol. Chem.* **1978**, *42*, 895.

(2) (a) Oku, J.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229. (b) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294. (c) Reetz, M. T.; Kunishi, G.; Heitmann, P. *Tetrahedron Lett.* **1986**, *27*, 4721. (d) Kobayashi, Y.; Asada, S.; Watanabe, I.; Hayashi, H.; Motoo, Y.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 983. (e) Minamikawa, H.; Hayakawa, S.; Yamada, S.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1988**, 61, 4379. (f) Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1990**, 1364. (g) Danda, H.; Chino, K.; Wake, S. *Chem. Lett.* **1991**, 731.

(3) (a) Rosenthaler, L. *Biochem. Z.* **1908**, 14, 238. (b) Becker, W.; Benthin, U.; Eschenhof, E.; Pfeil, E. *Biochem. Z.* **1963**, 337, 156. (c) Becker, W.; Freund, H.; Pfeil, E. *Angew. Chem.* **1965**, 77, 1139. (d) Becker, W.; Pfeil, E. *Biochem. Z.* **1966**, 346, 301. (e) Becker, W.; Pfeil, E. *J. Am. Chem. Soc.* **1966**, 88, 4299. (f) Effenberger, F.; Ziegler, T.; Förster, S. *Angew. Chem.* **1987**, 99, 491. (g) Effenberger, F.; Hörsch, B.; Weingart, F.; Ziegler, T.; Kühner, S. *Tetrahedron Lett.* **1991**, 32, 2605.

(4) (a) Mori, A.; Ikeda, Y.; Kinoshita, K.; Inoue, S. *Chem. Lett.* **1989**, 2119. (b) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, 55, 181.

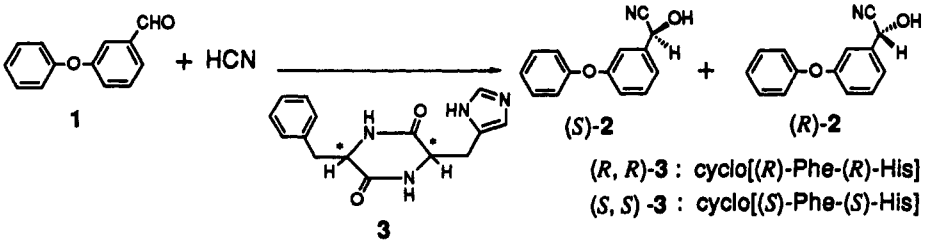
(5) We have correlated the ee of the product, (*S*)-**2**, with the degree of gelation and the degree of crystallinity of the catalyst (*R*,*R*)-**3**. See: Danda, H. *Synlett* **1991**, 263.

(6) Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, 111, 7265. For nonlinear effects in asymmetric synthesis, see: (a) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, 108, 2353. (b) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, 110, 7877. (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, 111, 4028. (d) Noyori, R. *Science* **1990**, 248, 1194.

(7) The catalysts ((*R*,*R*)-**3** and (*S*,*S*)-**3**) were prepared by the method of Inoue et al.[4b] and were activated by precipitation from MeOH/Et_2O with vigorous stirring.[5] The enantioselective hydrocyanation of **1** was carried out in the gelatinous reaction mixture.[5] The ^1H NMR and IR spectra of the product cyanohydrins, (*S*)-**2** and (*R*)-**2**, were identical to those of authentic samples. The absolute configurations of (*S*)-**2** and (*R*)-**2** have already been determined.[4b]

0022-3263/91/1956-6740$02.50/0

Scheme I



the reaction (method B). In contrast, when a small amount of (*R*)-**2** was present initially, the optical purity of the product, (*S*)-**2**, gradually increased, from a relatively low value, as the fraction of **1** that was converted increased (method C). These results suggested that the (*S*)-**2** that is produced is incorporated into the active chiral catalyst.

Next, we examined what effect the presence of (*S*)-**2** or (*R*)-**2** had as the optical purity of the (*R*,*R*)-**3** catalyst was varied. The results are summarized in Table II. The initial presence of a small amount of (*S*)-**2** (method B) led to the formation of (*S*)-**2** of high optical purity (81.6–96.8% ee) regardless of the optical purity of (*R*,*R*)-**3**. It is noteworthy that the use of an essentially racemic catalyst ((*R*,*R*)-**3** in 2.0% ee) led to the formation of (*S*)-**2** in 81.6% ee when a small amount of (*S*)-**2** was present initially. In contrast, the use of the same catalyst led to the formation of the other enantiomer, (*R*)-**2**, when a small amount of (*R*)-**2** was present initially (entries 15 and 16). Apparently, (*R*,*R*)-**3** in 2.0% ee displays little catalytic activity (entry 14). That this is so is believed to be due to formation of an (*R*,*R*)-**3**·(*S*,*S*)-**3** complex.[8] It is clear that neither (*S*)-**2** nor (*R*)-**2** alone display any catalytic activity (entries 17 and 18). These results also suggest that the (*R*,*R*)-**3**·(*S*,*S*)-**3** complex dissociates when a small amount of (*S*)-**2** is present. Thus, it is an (*R*,*R*)-**3**·(*S*)-**2** complex that functions as the active chiral catalyst. That species is catalytically more active than (*S*,*S*)-**3** alone. Similarly the (*S*,*S*)-**3**·(*R*)-**2** complex is also catalytically active (entry 16). That the optical purity of the product (*S*)-**2** decreases when prepared by method B may be due to the formation of (*R*)-**2** catalyzed by the (*S*,*S*)-**3**·(*R*)-**2** complex.

Evidence that (*R*,*R*)-**3** and (*S*)-**2** do form a complex was that a gel that contained both compounds was isolated from a mixture of racemic **2** and optically pure (*R*,*R*)-**3** in toluene.[9] A 93.3:6.7 mixture of (*S*)-**2** and (*R*)-**2** was recovered from the gel. The mole ratio of (*S*)-**2** to (*R*,*R*)-**3** in the gel was approximately 0.8:1. The ratio of (*S*)-**2** to (*R*)-**2** in the solution that remained was 46.7:53.3. These facts seem to provide evidence that (*R*,*R*)-**3** preferentially associates with (*S*)-**2**. Furthermore, when the gelatinous (*R*,*R*)-**3**·(*S*)-**2** complex was employed as a catalyst in the enantioselective hydrocyanation of **1**, (*S*)-**2** in 97% ee was formed regardless of what fraction of **1** had been converted.[10]

Thus, a new example of enantioselective autoinduction, i.e., an asymmetric reaction that is promoted by a chiral catalyst into which the chiral product has been incorporated, has been found.

A study aimed at elucidating the mechanism of the enantioselective autoinduction is in progress. The results will be published in the near future.

Acknowledgment. We thank Mr. Kiyoshi Yamashina of Ehime Research Laboratory for his valuable aid in recording the spectra and performing the HPLC analyses.

Supplementary Material Available: Experimental details, optical rotations, and spectroscopic characteristics (^{1}H and ^{13}C NMR) for (*R*,*R*)-**3** and (*S*,*S*)-**3** (3 pages). Ordering information is given any current masthead page.

(8) The X-ray diffraction pattern of (*R*,*R*)-**3** of 2.0% ee was different from that of optically pure (*R*,*R*)-**3**.

(9) A mixture of racemic **2** (22.2 mmol) and optically pure (*R*,*R*)-**3** (2.1 mmol) in toluene (40 mL) was stirred vigorously at 0 °C for 1 h. The mixture, which became gelatinous, was then diluted with cold toluene (200 mL). A gel that contained (*R*,*R*)-**3** was then isolated from the mixture by centrifugation. The gel and the solution that remained were analyzed by HPLC.

(10) A gelatinous (*R*,*R*)-**3**·(*S*)-**2** complex was prepared from (*R*,*R*)-**3** (1.1 mmol) in the manner described above. All of the complex was employed in the enantioselective hydrocyanation of **1** (50 mmol) at 5 °C for 4 h.