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Cyclo-((S)-leucyl-(S)-histidyl). A Catalyst for Asymmetric Addition of Hydrogen Cyanide to Aldehydes

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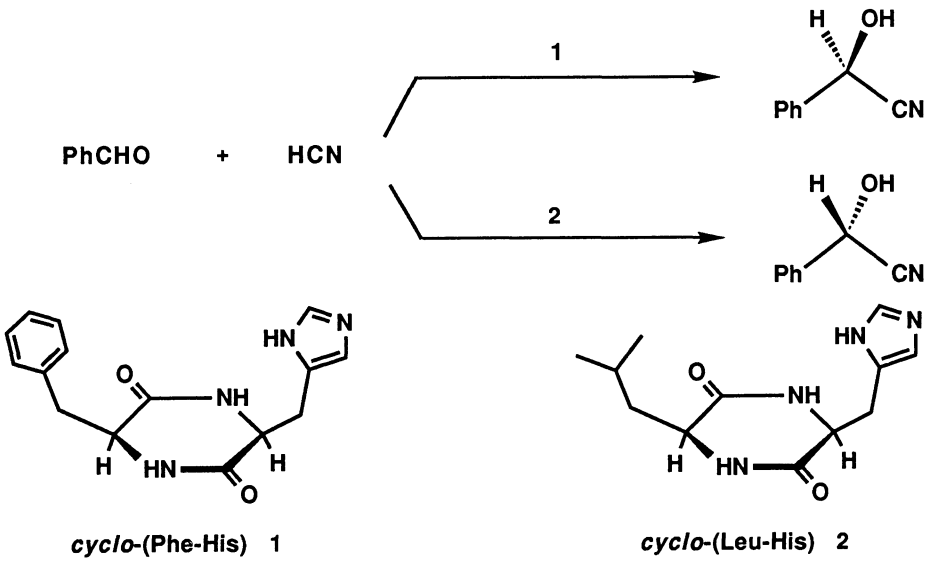
Asymmetric addition of hydrogen cyanide to various aldehydes in the presence of a catalytic amount of cyclo-((S)-leucyl-(S)-histidyl) affords the corresponding cyanohydrins in moderate to good optical yields. The reaction of benzaldehyde with hydrogen cyanide gives (S)-2-hydroxy-2-phenylacetonitrile (85%, 55% ee) whose stereochemistry is found to be opposite to our previous result using cyclo-((S)-phenylalanyl-(S)-histidyl).

We recently reported the asymmetric addition of hydrogen cyanide to aldehydes catalyzed by cyclo-((S)-phenylalanyl-(S)-histidyl): cyclo-(Phe-His) (**1**) to give optically active cyanohydrins with high degree of enantiopurities, in which (R)-2-hydroxy-2-phenylacetonitrile ((R)-mandelonitrile) was obtained in 97% yield with 97% ee.[1,2] In conjunction with this excellent catalyst activity, our interest has been focused on the relationship between the structure of the catalyst and its stereoselectivity. Among various cyclic peptides containing (S)-histidine residue, a cyclic peptide composed of (S)-leucine and (S)-histidine, cyclo-((S)-leucyl-(S)-histidyl): cyclo-(Leu-His) (**2**) surprisingly exhibited a stereochemical inversion: (S)-mandelonitrile was obtained in the reaction of benzaldehyde with hydrogen cyanide catalyzed by cyclo-(Leu-His) (**2**) in contrast to the formation of (R)-isomer by cyclo-(Phe-His) (**1**). Herein, we wish to describe this unexpected stereochemical outcome in the asymmetric addition of hydrogen cyanide to aldehydes catalyzed by a cyclic dipeptide cyclo-(Leu-His) (**2**).

The preparation of the catalyst cyclo-(Leu-His) (**2**) was carried out in a similar manner as cyclo-(Phe-His) (**1**): the coupling of benzyloxycarbonyl-(S)-leucine and (S)-histidine methyl ester followed by the cyclization of the corresponding acyclic dipeptide after hydrogenolysis of benzyloxycarbonyl group by palladium/carbon under hydrogen.[1,3] The catalyst (**2**) (0.02 mmol, 4.8 mg) and



cyclo-(Phe-His) 1 *cyclo*-(Leu-His) 2

benzaldehyde (0.5 mmol, 54 mg) was added to 1 cm^3 of ether. The resulting suspension was cooled to 0 °C followed by the addition of hydrogen cyanide via a cooled syringe (1.0 mmol, 0.040 cm^3). Stirring was continued until most of the starting aldehyde was consumed (by TLC; 0 °C, 5 h) and to the mixture was added dilute hydrochloric acid-methanol (0.25 cm^3) to quench the reaction. The excess hydrogen cyanide was removed under reduced pressure with alkali trap, and the crude product, which was obtained after usual work-up, was purified by silica-gel column chromatography to give a colorless oil (85%). The optical purity (55% ee) of the resulting cyanohydrin was determined by ^1H NMR analysis of the corresponding menthyl carbonic ester by the treatment of the cyanohydrin with (-)-menthyl chloroformate in the presence of pyridine.[4]

Asymmetric reactions catalyzed by cyclo-(Leu-His) (**2**) for various aldehydes were carried out similarly. The results were summarized in Table 1. Enantiopurities of the cyanohydrins were determined by ^1H NMR or GC analyses after treatment with (-)-menthyl chloroformate or (+)-2-methoxy-2-trifluoromethyl-phenylacetyl chloride (MTPA chloride)[5] to give corresponding diastereomers. ^1H NMR or GC analyses exhibited that the major peaks of diastereomers were identical with the minor ones when cyclo-(Phe-His) was employed as a catalyst,[1] apparently indicating that the opposite optical isomers were preferentially obtained. Remarkable solvent effect was observed in the reaction of benzaldehyde as a substrate. Among various solvents examined, ether exhibited the highest optical yield and the employment of isopropyl ether also showed a similar high selectivity. Toluene and ethyl acetate were found

to be less effective for asymmetric inductions. Lowering the reaction temperature decreased the reactivity (entry 7), but did not affect asymmetric inductions very much.[6] Moderate to good enantioselectivities were realized for several aromatic aldehydes, although a substrate which contains electron withdrawing group (CN, entry 8) in the aromatic ring exhibited inferior enantioselectivity. It should be pointed out that the reaction of aliphatic aldehydes catalyzed by **2** resulted in considerably higher selectivity than that of aromatic ones. Especially, superb selectivity was observed in the reaction of undecanal as a substrate (81% ee, entry 14).

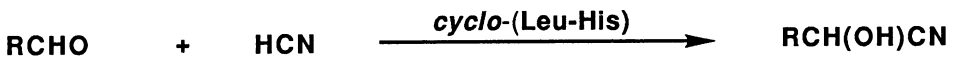


Table 1. Asymmetric Addition of Hydrogen Cyanide to Aldehydes Catalyzed by **2**[a)]

Entry	Aldehyde/R	Solvent	Time/h	Yield/%[b)]	% ee (method)[c)]
1	C_6H_5	ether	5	85	55 (A)
2		*i*-Pr_2O	6	84	46 (A)
3		toluene	6	77	27 (A)
4		AcOEt	6	45	19 (A)
5	*p*-MeC_6H_4	ether	5	97	60 (A)
6	*m*-$MeOC_6H_4$	ether	20	89	56 (A)
7	*m*-$PhOC_6H_4$	ether	24	75[d)]	38 (A)
8	*p*-CNC_6H_4	ether	5	96	15 (A)
9		ether	20	66	41 (A)
10	*t*-Bu	ether	5	99	61 (B)
11	*i*-Pr	ether	5	91	66 (C)
12	*c*-C_6H_{11}	ether	7	83[e)]	64 (C)
13	*n*-C_5H_{11}	ether	5	98[e)]	74 (C)
14	*n*-$C_{10}H_{21}$	ether	4	93[e)]	81 (C)

a) The reactions were carried out by using 2 equiv. of hydrogen cyanide and 4 mol% of the catalyst in 1 cm^3 of the solvent at 0 °C. b) Unless specified, the yield was based on ^1H NMR of the cyanohydrin and/or the corresponding menthyl carbonic esters. c) A: Determined by ^1H NMR analyses of the corresponding menthyl carbonic ester. B: Determined by ^1H NMR analyses of the corresponding (+)-2-methoxy-2-trifluoromethyl-2-phenylacetic acid (MTPA) esters. C: Determined by GC analyses of MTPA esters. d) At room tempereture, no reaction at 0 °C for 5 h. e) Isolated yield.

It is remarkable that only a slight structural difference of the substituent (phenyl vs isopropyl) between the catalysts **1** and **2**, although the mechanism of the asymmetric induction has not been clear, dramatically changes the absolute configuration of the products. Thus, the method to afford both optical isomers of the cyanohydrins is in hand by the catalysis of cyclic dipeptide prepared from readily available natural (S)-amino acids.

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References

1) K. Tanaka, A. Mori, and S. Inoue, J. Org. Chem., in press. See also; J. Oku, and S. Inoue, J. Chem. Soc., Chem. Commun., 1981, 229, Y. Kobayashi, S. Asada, I. Watanabe, H. Hayashi, Y. Motoo, and S. Inoue, Bull. Chem. Soc. Jpn., 59, 893 (1986), and references cited therein.

2) For asymmetric hydrocyanations catalyzed by Lewis acid: H. Minamikawa, S. Hayakawa, S. Yamada, N. Iwasawa, and K. Narasaka, Bull. Chem. Soc. Jpn., 61, 4379 (1988); M. T. Reetz, G. Kunisch, and P. Heitmann, Tetrahedron Lett., 39, 4721 (1986); J. D. Elliott, V. M. F. Choi, and W. S. Johnson, J. Org. Chem., 48, 2294 (1983).

3) cyclo-(Leu-His) (**2**): mp 190-195 °C (lit. 204-206 °C); IR (KBr) 3250-3650 br, 3100-3250 br, 2960, 1675, 1460, 1340, 840 cm^{-1}; ^{1}H NMR (D_2O, 270 MHz) δ 7.71 (s, 1 H), 6.96 (s, 1 H), 4.35-4.42 (m, 1 H), 3.90 (d d, J = 3.9, 9.8 Hz, 1 H), 3.27 (d d, J = 3.9, 15.1 Hz, 1 H), 3.00 (d d, J = 4.6, 15.1 Hz), 1.36-1.51 (m, 1 H), 1.08-1.21 (m, 1 H), 0.75-0.81 (m, 6 H), 0.22-0.37 (m, 1 H); ^{13}C NMR (D_2O, 68 MHz) δ 172.2, 170.2, 137.2, 132.6, 119.9, 56.4, 54.2, 44.6, 32.0, 24.6, 23.8, 21.7; $[\alpha]^{25}_{D}$ -16.1° (c 1.16, H_2O), (lit. $[\alpha]_D$ -17.2° (c 1.16, H_2O)), see: F. Schneider, Hoppe-Seyler's Z. Phys. Chem. 338, 131 (1964).

4) J. W. Westley, and B. Halpern, J. Org. Chem., 33, 3978 (1968).

5) MTPA esters were employed for determination of the enantiopurities of aliphatic aldehyde cyanohydrins; J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969).

6) A reaction of hexanal at -20 °C for 9 h resulted in 91% yield with 66% ee.

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