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ASYMMETRIC TRANSCYANOHYDRINATION

Yoshiyuki KOBAYASHI, Hiroaki HAYASHI, Koji MIYAJI, and Shohei INOUE*

Department of Synthetic Chemistry, Faculty of Engineering,

The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Transcyanohydrination, the reaction between an aldehyde and acetone cyanohydrin to give the cyanohydrin of the aldehyde, catalyzed by cyclo((S)-phenylalanyl-(S)-histidyl) gives the product with optical yield up to 63% from some aromatic and aliphatic aldehydes. The reaction catalyzed by (S)-α-dimethylamino-ε-caprolactam gives the product with optical yield of 15-25% from aliphatic aldehydes.

Asymmetric reaction catalyzed by synthetic peptide is of much interest and importance in relation to the high stereospecificity of enzymatic reaction. We have studied the asymmetric addition of hydrogen cyanide to aldehyde to form cyanohydrin (Eq. 1) catalyzed by synthetic peptides containing (S)-histidine residue as an enzyme model.[1] Optically active cyanohydrin is an important

$$\text{R-CHO} + \text{HCN} \xrightarrow{\text{Cat.}^*} \text{R-}\overset{*}{\text{C}}\text{H(OH)CN} \qquad (1)$$

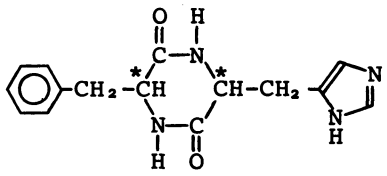
starting material for the synthesis of various optically active compounds, including physiologically active compounds such as a particularly effective insecticide.[2] Among the synthetic peptides we examined, cyclo((S)-phenylalanyl-(S)-histidyl) was the most excellent catalyst for the asymmetric cyanohydrin synthesis (Eq. 1) from benzaldehyde and its substituted derivatives to give the product with a high optical yield such as 90%. The reactions of some aliphatic aldehydes afforded the optical yield ranging from 30 to 40%, which was higher than that reported for enzymatic reactions by oxynitrilase.[3] In contrast, the corresponding linear dipeptide, benzyloxycarbonyl-(S)-phenylalanyl-(S)-histidine methyl ester, gave optically inactive product, demonstrating the importance of the

rigid structure of cyclic dipeptide. On the other hand, an alternative convenient method of the synthesis of cyanohydrin is the base catalyzed exchange of a cyanohydrin with another carbonyl compound. In fact, various cyanohydrins can be synthesized by the transcyanohydrination reaction between readily available acetone cyanohydrin and an aldehyde.[4] This procedure is of advantage since no

$$R\text{-}CHO + (CH_3)_2C(OH)CN \xrightarrow{Cat.} R\text{-}CH(OH)CN + (CH_3)_2CO \quad (2)$$

direct use of hydrogen cyanide is involved. The asymmetric transcyanohydrination, however, has not ever been reported.

In this paper, we report the first example of the asymmetric transcyanohydrination catalyzed by cyclo((S)-phenylalanyl-(S)-histidyl) (cyclo(-(S)-Phe-(S)-His-), 1). The reaction catalyzed by (S)-α-dimethylamino-ε-caprolactam (2), a cyclic amide carring a tertiary amino group with more flexible ring, was also examined.



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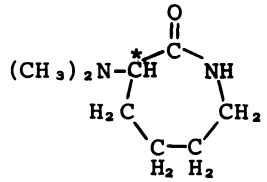

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Catalyst (1.0 mmol)[5,6] was placed in a 50 cm^3 round-bottomed flask equipped with a three-way cock, and the atmosphere of the flask was replaced with nitrogen. To this were added benzene (10 cm^3), acetone cyanohydrin (25 mmol), and aldehyde, for example, isobutyraldehyde (25 mmol), and the mixture was kept at 50 °C with magnetic stirring. The reaction mixture was heterogeneous in the case of cyclo(-(S)-Phe-(S)-His-), whereas for (S)-α-dimethylamino-ε-caprolactam the mixture was homogeneous. The conversion of aldehyde was determined on the basis of ^{1}H-NMR signals due to -C<u>H</u>$_3$ (δ=1.63 ppm) of unreacted acetone cyanohydrin and due to -C<u>H</u>(OH)CN (δ=4.1 — δ=4.5 ppm) of the product in the mixture. The reaction was stopped by adding 0.5 cm^3 of 2 mol·dm^{-3} HCl-CH_3OH. Benzene and unreacted aldehyde were removed from the mixture under reduced pressure. Ether was added to the residue, and the mixture was filtered to remove most of the catalyst, then ether was removed under reduced pressure to leave a viscous liquid. This liquid was chromatographed over silica gel with ethyl acetate to remove the

catalyst completely, then the eluted solution was concentrated in vacuo. The residue was found to be a mixture of the product and unreacted acetone cyanohydrin from ^{1}H-NMR and IR analyses. Finally, unreacted acetone cyanohydrin was removed under reduced pressure at 50 °C to give the pure product which was identified by ^{1}H-NMR, IR and mass spectra, and elemental analysis. The optical yield of the obtained cyanohydrin was calculated from the optical rotation of the product.[1d,e]

The results of the asymmetric transcyanohydrination catalyzed by cyclo((S)-Phe-(S)-His) and (S)-α-dimethylamino-ε-caprolactam are summarized in Tables 1 and 2, respectively.

Table 1. Transcyanohydrination between aldehyde and acetone cyanohydrin catalyzed by cyclo(-(S)-Phe-(S)-His-)[a)]

Run	Aldehyde R	Time h	Conv. %	$[\alpha]_D^{r.t.}$ [b)]	Optical yield of product %
1	C_6H_5	0.5	10	16.6	37.8 (R)
2	C_6H_5	1	10	18.4	42.1 (R)
3	C_6H_5	3	15	12.7	29.0 (R)
4	C_6H_5	9	20	5.94	13.6 (R)
5	2-Me-C_6H_4	1	25	11.6	28.9
6	3-Me-C_6H_4	1	20	19.0	46.4
7	4-Me-C_6H_4	1	10	23.0	21.3
8	3-PhO-C_6H_4	1	25	11.4	45.8 (R)
9	Me_2CH	0.5	10	7.47	56.9
10	Me_2CH	1	25	8.23	62.7
11	Me_2CH	3	45	6.21	47.2
12	Me_2CH	9	50	1.90	14.4
13	$Me(CH_2)_3$	1	15	8.24	38.9
14	cyclo-C_6H_{11}	1	25	16.1	52.8

a) Aldehyde, 25 mmol; acetone cyanohydrin, 25 mmol; catalyst, 1 mmol; benzene, 10 cm^3; 50 °C.
b) Runs 1-7, c 5, benzene; runs 8-14, c 5, chloroform.

Table 2. Transcyanohydrination between aldehyde and acetone cyanohydrin catalyzed by (S)-α-dimethylamino-ε-caprolactam[a)]

Run	Aldehyde R	Time m	Conv. %	$[\alpha]_D^{r.t.}$ [b)]	Optical yield of product %
1	Me_2CH	10	25	-2.12	16.1
2	Me_2CH	20	35	-3.07	23.4
3	Me_2CH	30	35	-2.40	18.3
4	Me_2CH	60	60	-1.69	12.9
5	$MeCH_2$	20	40	-3.87	—
6	$Me(CH_2)_2$	20	30	-4.77	14.5 (S)
7	$Me(CH_2)_3$	20	40	-5.40	25.5
8	cyclo-C_6H_{11}	20	65	-4.07	13.4
9	C_6H_5	20	40	-1.77	4.0 (S)

a) Aldehyde, 25 mmol; acetone cyanohydrin, 25 mmol; catalyst, 1 mmol; benzene, 10 cm^3; 50 °C.
b) Runs 1-8, c 5, chloroform; run 9, c 5, benzene.

The reaction of aromatic aldehyde and acetone cyanohydrin catalyzed by cyclo(-(S)-Phe-(S)-His-) proceeded slowly under the conditions examined. For benzaldehyde, optical yield of 42% was observed in the reaction for 1 hour. In a prolonged reaction, the optical yield was found to decrease, similarly to the case of the asymmetric addition of hydrogen cyanide to benzaldehyde by the same catalyst.[1b,c] 3-Methylbenzaldehyde and 3-phenoxybenzaldehyde gave optical yields of about 46%, repectively, under the same conditions. The reaction of aliphatic aldehyde proceeded more rapidly. Isobutyraldehyde afforded the highest optical yield of 63% in the reaction for 1 hour. Optical yield of 40-50% was observed for other aliphatic aldehydes. These findings are in contrast to the asymmetric addition of hydrogen cyanide to aldehyde by the same catalyst, where much lower optical yields are obtained for aliphatic aldehydes than for aromatic aldehydes.[1d,e] Preferred configuration of the products from benzaldehyde and 3-phenoxybenzaldehyde was R, similarly to the asymmetric addition of hydrogen cyanide to these aldehydes by the same catalyst.

The reaction catalyzed by (S)-α-dimethylamino-ε-caprolactam proceeded much more rapidly than by cyclo(-(S)-Phe-(S)-His-). Isobutyraldehyde gave the highest optical yield of 23% in the reaction for 20 minutes. Under the same conditions, various aliphatic aldehydes afforded optical yield of 15-25%. However, optical yield was low for benzaldehyde. Preferred configuration of the product from butyraldehyde and benzaldehyde was S, differently from that by cyclo(-(S)-Phe-(S)-His-), although the constituent amino acid residues in both catalysts are in S configuration.

Thus, the first example of asymmetric transcyanohydrination was achieved by using cyclo(-(S)-Phe-(S)-His-) or (S)-α-dimethylamino-ε-caprolactam as catalyst. Cyclo(-(S)-Phe-(S)-His-) with rigid ring was found to be a better catalyst for the reaction of both aromatic and aliphatic aldehydes.

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5) Cyclo((S)-phenylalanyl-(S)-histidyl) was prepared according to ref. 1d, e .
6) (S)-α-Dimethylamino-ε-caprolactam was kindly supplied by Toray Co.

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