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A Facile Synthesis of Optically Active γ-Cyanoallylic Alcohols Using Asymmetric Hydrocyanation of α, β-Alkenyl Aldehydes Followed by Stereospecific [3.3]Sigmatropic Chirality Transfer of the Cyanohydrin Acetates

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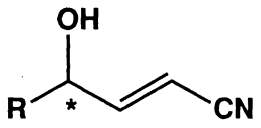
Optically active γ-cyanoallylic alcohols were synthesized by using asymmetric hydrocyanation of α, β-alkenyl aldehydes catalyzed by peptide-titanium complex to give α-cyanoallylic alcohols (cyanohydrins) with high optical yields followed by palladium complex catalyzed [3.3]sigmatropic chirality transfer of the corresponding acetates.

Optically active γ-cyanoallylic alcohols[1] (**1**) can be an important synthetic intermediate of several natural products and biologically active compounds. A general and facile synthetic route to **1**, therefore, has been a center of interest in synthetic organic chemistry. Our recent success in an asymmetric hydrocyanation of aldehyde by the addition of hydrogen cyanide catalyzed by peptide-titanium complex[2, 3] encouraged us to develop a facile route to optically active **1** utilizing the asymmetric reaction of α, β-alkenyl aldehyde followed by [3.3]sigmatropic chirality transfer of the corresponding cyanohydrin acetate catalyzed by palladium complex as shown in Scheme 1.



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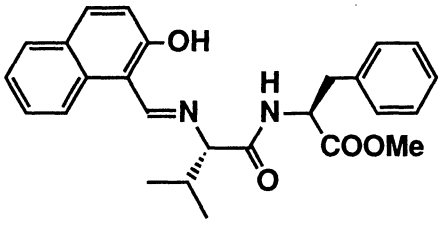
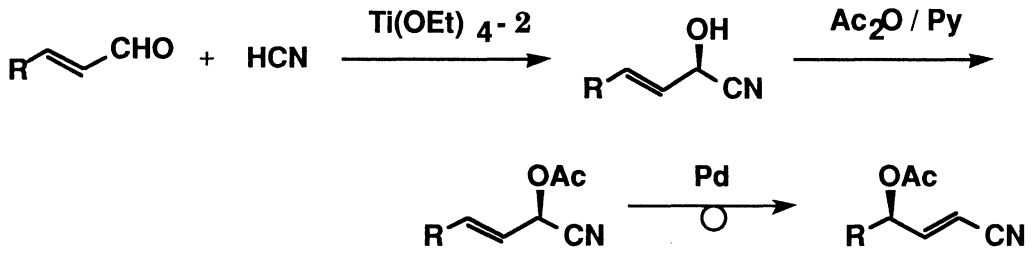
For example, the hydrocyanation of *trans*-2-octenal (0.5 mmol) by hydrogen cyanide (0.75 mmol as a toluene solution) was carried out in toluene (3 mL) for 119 h at -60 ℃ under N_2 in the presence of 10 mol% of a complex formed by mixing equimolar amounts of titanium (IV)



Nap-S-Val-S-Phe-OMe (2)

ethoxide and Nap-*S*-Val-*S*-Phe-OMe (**2**) at room temperature for 30 min, to give the corresponding cyanohydrin in 83% yield[4] with enantiomeric purity of 89% *(R)*.[5] The results of the hydrocyanation of several α, β-alkenyl aldehydes are summarized in Table 1. The reactions of *trans*-2-octenal, *trans*-2-hexenal, and *trans*-cinnamaldehyde proceeded in good yields as well as with high enantioselectivities.

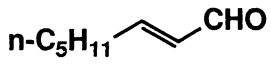
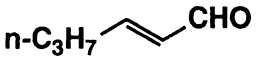
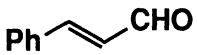
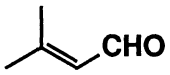
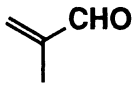
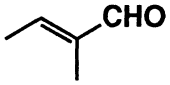
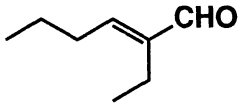
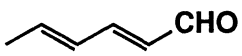


Scheme 1.

Since optically active α-cyanoallylic alcohols with high enantiopurities were in hand, palladium complex catalyzed [3.3]sigmatropic chirality transfer of the corresponding acetates was examined. [3.3]Sigmatropic rearrangement of allylic acetates in the presence of a catalytic amount of palladium complex was systematically studied by Overman,[6] and the rearrangement of the racemic cyanohydrin derivatives was reported by Mandai.[7] However, the chirality transfer of optically active α-cyanoallylic alcohols in the rearrangement has not been studied. The rearrangement was carried out using the corresponding optically active cyanohydrin acetate which was readily prepared by treatment of the cyanohydrin with acetic anhydride and pyridine. When 10 mol% of $PdCl_2(CH_3CN)_2$ was used as catalyst, the rearrangement of *(R)-trans*-2-octenal cyanohydrin acetate (89% ee) in THF at room temperature proceeded in good yield with complete stereospecificity. *(R)*-4-Hydroxy-nona-2-enonitrile (**1**, R=*n*-C_5H_{11}) was obtained after hydrolysis of the acetate (89% ee).[8] Similarly, *(R)*-4-hydroxy-hepta-2-enonitrile (82% ee)(**1**, R=*n*-C_3H_7) was obtained from *(R)-trans*-2-hexenal cyanohydrin (85% ee). The rearrangement of cinnamaldehyde cyanohydrin acetate (73% ee) smoothly proceeded in the presence of $Pd(OAc)_2$ (5 mol%) and PPh_3 (12.5 mol%) to give the corresponding γ-cyanoallylic alcohol (60% ee)(**1**, R=Ph). These are the first examples of the

chirality transfer of optically active α-cyanoallylic alcohols in the [3.3]sigmatropic rearrangement.

Table 1. Asymmetric hydrocyanation of α,β-alkenyl aldehydes catalyzed by the complex from **2** and $Ti(OEt)_4$

Aldehyde	Temp / °C	Time / h	Conv / %	% ee(confign)
	-60	119	83	89 (R)
	-20	22	93	85 (R)
	-40	18	82	81 (R)
	-60	71	74	70
	-60	46	90	72
	-60	20	22	37
	-60	143	28	60
	-60	143	78	60
n-Bu-C≡C-CHO	-40	2	57	68

Thus, the asymmetric hydrocyanation of α, β-alkenyl aldehyde followed by [3.3]sigmatropic chirality transfer of the corresponding acetate catalyzed by palladium complex offers a facile synthetic route to optically active γ-cyanoallylic alcohols.

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References

1) a) Y. Kitano, T. Matsumoto, T. Wakasa, S. Okamoto, T. Shimazaki, Y. Kobayashi, and F. Sato, *Tetrahedron Lett.*, **28**, 6351 (1987); b) I. Yamakawa, H. Urabe, Y. Kobayashi, and F. Sato, *ibid.*, **32**, 2045 (1991) and references cited therein.

2) A. Mori, H. Nitta, M. Kudo, and S. Inoue, *Tetrahedron Lett.*, **32**, 4333 (1991); H. Nitta, D. Yu, M. Kudo, A. Mori, and S. Inoue, *J. Am. Chem. Soc.*, in press.

3) Other asymmetric cyanohydrin syntheses: K. Tanaka, A. Mori, and S. Inoue, *J. Org. Chem.*, **55**, 181 (1990); A. Mori, H. Ohno, H. Nitta, K. Tanaka, and S. Inoue, *Synlett*, **1991**, 563; H. Ohno, H. Nitta, K. Tanaka, A. Mori, and S. Inoue, *J. Org. Chem.*, in press; H. Minamikawa, S. Hayakawa, T. Yamada, N. Iwasawa, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, **61**, 4379 (1988); M. Hayashi, Y. Miyamoto, T. Inoue, and N. Oguni, *J. Chem. Soc., Chem. Commun.*, **1991**, 1752; S. Kobayashi, Y. Tsuchiya, and T. Mukaiyama, *Chem. Lett.*, **1991**, 541.

4) Based on the measurement of ^{1}H NMR of the reaction mixture.

5) The ee value was determined by ^{1}H NMR analysis of the corresponding (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester.

6) L. E. Overman, *Angew. Chem.*, **96**, 565 (1984).

7) T. Mandai, S. Hashio, J. Goto, and M. Kawada, *Tetrahedron Lett.*, **22**, 2187 (1981).

8) $[\alpha]_D^{26}$ -28.8° (c 0.62, $CHCl_3$). lit.[1a] $[\alpha]_D^{25}$ +36.8° (c 0.99, $CHCl_3$) as *(S)*-form ; The ee value was confirmed to be 89% by ^{1}H NMR analysis of the corresponding MTPA ester.

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