

The Asymmetric Hydrocyanation of Aldehydes with
Cyanotrimethylsilane Promoted by a Chiral Titanium Reagent

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The asymmetric hydrocyanation of aldehydes with cyanotrimethylsilane proceeds by the use of a chiral alkoxy titanium(IV) to give the corresponding cyanohydrins with good enantioselectivity.

Asymmetric synthesis of cyanohydrins is an important process in organic synthesis because cyanohydrins can be easily converted into a variety of valuable synthetic intermediates such as α -hydroxy acids, α -hydroxy ketones, and β -amino alcohols. Optically active cyanohydrins are obtained with good selectivity by the nucleophilic attack of cyanating reagents to chiral acetals. However, the chiral auxiliaries are destroyed and not recovered.¹⁾ In catalytic processes with chiral boron compounds,²⁾ D-oxynitrilase,³⁾ and synthetic peptides,⁴⁾ the optical purities of the resulting cyanohydrins are not sufficient except in the case of the preparation of mandelonitrile derivatives.

In the previous paper, we reported an enantioselective Diels-Alder reaction by the use of the chiral alkoxy titanium(IV)-Molecular Sieve (MS) 4A system.⁵⁾ In this communication, we describe the enantioselective hydrocyanation of aliphatic and aromatic aldehydes with cyanotrimethylsilane utilizing the chiral titanium(IV) compound.

Firstly, we examined the reaction of 3-phenylpropanal (2c) and cyanotrimethylsilane using the chiral alkoxy titanium(IV) prepared from dichlorodisopropoxytitanium(IV) and the chiral 1,4-diol 1. When 3-phenylpropanal was treated with cyanotrimethylsilane in the presence of the chiral titanium reagent in toluene, almost no reaction occurred even at room temperature, and only a trace amount of the corresponding cyanohydrin 3c was generated even after 2 days.

However, by the addition of MS 4A to this solution, the reaction proceeded smoothly. Thus, to a toluene (1 ml) solution of dichlorodiisopropoxytitanium(IV) (118.5 mg, 0.5 mmol) was added a toluene (2 ml) solution of the chiral diol 1 (290.7 mg, 0.55 mmol) at room temperature. After 1 h, powdered MS 4A (65 mg, heated in vacuo prior to use) and a toluene (1 ml) solution of 3-phenylpropanal (62 mg, 0.5 mmol) were added to this solution, and then a toluene (1 ml) solution of cyanotrimethylsilane (250 mg, 2.5 mmol) was added at -65°C . After stirring for 12 h at this temperature, the reaction was quenched with pH 7 phosphate buffer, and the resulting mixture was filtered. Organic materials were extracted with ethyl acetate, and the combined extracts were washed with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by preparative TLC (silica gel) to afford 2-hydroxy-4-phenylbutanenitrile (70 mg, 89%, 74% e.e.).

Same level of enantioselectivity was observed when dichloromethane, 1,3,5-trimethylbenzene, and cumene were used as solvents, but the enantioselectivity decreased when diethyl ether, tetrahydrofuran, and acetonitrile were employed.⁶⁾

Therefore, the asymmetric hydrocyanation of various aldehydes was examined in toluene at -65°C , and the results are listed in Table 1.

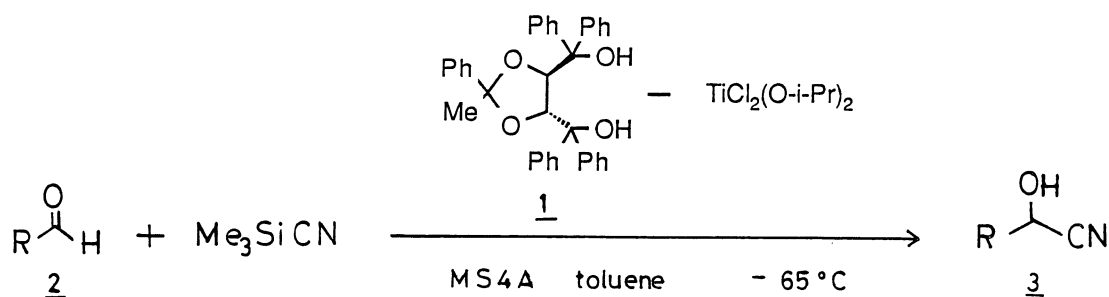


Table 1. Asymmetric hydrocyanation of aldehydes with cyanotrimethylsilane^{a)}

Aldehydes R	React. time h	Yield %	Opt. pur. of <u>3</u> ^{b)} % e.e.
Ph <u>2a</u>	12	79	96 ^{c)}
PhCH ₂ <u>2b</u>	12	66	77
PhCH ₂ CH ₂ <u>2c</u>	12	89	74
c-C ₆ H ₁₁ <u>2d</u>	48	77	68
C ₈ H ₁₇ <u>2e</u>	24	66	76

- a) All products gave satisfactory $^1\text{H-NMR}$ and IR spectra.
- b) The optical purities were determined by HPLC analysis of the corresponding MTPA esters.
- c) The preferred configuration of mandelonitrile was R.
 $[\alpha]_D^{21} +45.5^\circ$ (c 3.53, CHCl_3), Lit. $[\alpha]_D^{25} +43.5^\circ$ (c 5, CHCl_3),
Ref. 1.

As shown in Table 1, these aldehydes generally react with cyanotrimethylsilane to give the optically active cyanohydrins in good optical yields (68-96% e.e.). In particular, benzaldehyde is converted into (R)-mandelonitrile (3a) in high optical purity (96% e.e.).

The following experiment was carried out in order to examine whether the optically active cyanohydrins were obtained thermodynamically or kinetically. When benzaldehyde was treated with cyanotrimethylsilane in the presence of the chiral titanium reagent and MS 4A at room temperature and then the reaction mixture was stirred at -65°C for 1 day, the optical purity of the cyanohydrin was low (about 10% e.e.). This result may indicate that the cyanohydrin was generated as a kinetically controlled product in the above reaction.

Furthermore, the $^1\text{H-NMR}$ spectrum of the mixture of dichlorodiisopropoxytitanium(IV) and cyanotrimethylsilane in toluene shows a strong absorption at $\delta=0.20$, which corresponds to chlorotrimethylsilane, and a very weak absorption at $\delta=-0.09$, which corresponds to cyanotrimethylsilane (tetramethylsilane was used as the internal standard). Accordingly, it is considered that the chiral cyanotitanium(IV) species may be formed from the chiral alkoxy titanium(IV) and cyanotrimethylsilane and react with aldehydes in an enantioselective manner.

It is noted that, by the present method, the optically active cyanohydrins can be obtained from aliphatic and aromatic aldehydes in good optical yields, and this chiral auxiliary can be easily recovered without losing its optical purity.

The present work was partially supported by a Grant-in-Aid for Scientific Research No. 62101008 and 62116003 from the Ministry of Education, Science and Culture.

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- 6) The cyanation with other cyanating reagents gave no asymmetric induction (in the case of cyanotributyltin(IV)), or didn't react with aldehydes (KCN-18-crown-6; t-butylisocyanide).

(Received July 28, 1987)