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Enantioselective Addition Reaction of Trimethylsilyl Cyanide with Aldehydes Using a Chiral Tin(II) Lewis Acid

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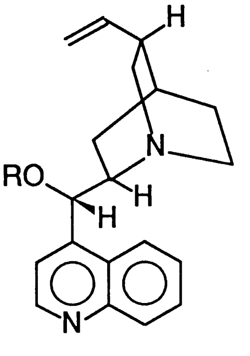
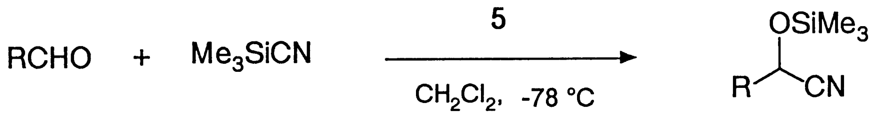
Trimethylsilyl cyanide (TMS-CN) enantioselectively reacts with aldehydes to afford the corresponding cyanohydrin trimethylsilyl ethers in good yields in the presence of a chiral tin(II) Lewis acid prepared from 1,1'-dimethylstannocene, triflic acid and (+)-cinchonine.

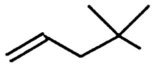
In the previous paper, we reported the Lewis base catalyzed addition reaction of trimethylsilyl cyanide (TMS-CN) with aldehydes,1) for examples, the reaction proceeds readily in the presence of only a catalytic amount of tertiary amine, and cyanohydrin trimethylsilyl ethers are obtained in excellent yields by a quite simple procedure under non-acidic conditions. Then, we next examined possibility of chiral induction using a chiral amine as a catalyst. Asymmetric hydrocyanation reaction is an important process in organic synthesis and recently some excellent works have been made in this area,2) however, there still remain some important problems to overcome, such as a stoichiometric use of chiral source or lower enantioselectivities in the reaction with aliphatic aldehydes.



1 R=H
2 $R = SiMe_3$
3 R=Ac
4 R=Bz
5 R = SnOTf

Firstly, the reaction of TMS-CN with cyclohexanecarboxyaldehyde was chosen as a model, and several chiral amines were screened under several reaction conditions. It was found there that (+)-cinchonine (**1**) was a good catalyst in this reaction; namely, in the presence of a catalytic amount of (+)-cinchonine (10 mol%), cyclohexanecarboxyaldehyde smoothly reacted with TMS-CN at -78 °C to give the corresponding cyanohydrin trimethylsilyl ether in 94% yield with 25% ee. Though the optical yield was still not satisfactory, this result seemed to be promising because the reaction proceeded via a catalytic process. We further checked the reaction mixture carefully and found that (+)-cinchonine was immediately silylated in the reaction mixture to give the corresponding trimethylsilyl ether. It was already reported that free alcohols reacted with TMS-CN in the presence of catalytic amounts of potassium cyanide and dicyclohexyl-18-crown-6 at 75 °C to yield the corresponding trimethylsilyl ethers.[3] As it was not clear whether the trimethylsilylation took place at -78 °C under the conditions, we prepared (+)-cinchonine trimethylsilyl ether **2** according to the conventional method and the model reaction was tried by using this ether as a catalyst. The reaction also proceeded with the same level of ee (25%) as that observed in the previous experiment. The importance of the silyl ether was revealed that almost no chiral induction was observed when (+)-cinchonine acetate **3** or benzoate **4** was employed as a catalyst. The proposed mechanism at this stage was that the tertiary amine part of (+)-cinchonine interacted with the silicon atom of TMS-CN to form the pentavalent silicate and, at the same time, the Lewis acidic silicon atom of the silyl ether activated an aldehyde. This "double activation" would provide a desirable transition state in the chiral



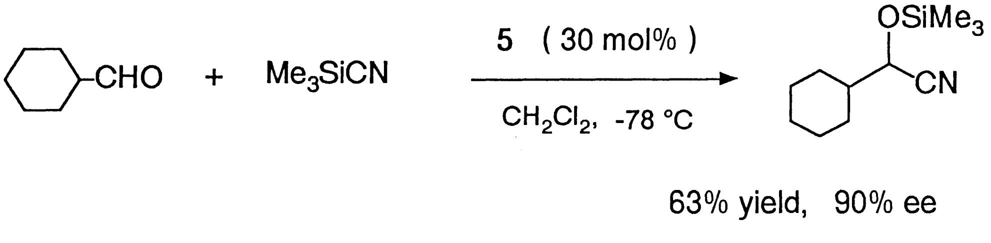
R	Yield / %	ee / %
$n\text{-}C_8H_{17}$	89	72
$c\text{-}C_6H_{11}$	79	96
i-Pr	67	95
t-Bu	49	83
	27	93

induction using chiral catalysts.[4] Based on this hypothesis we further examined several reaction conditions, however, the optical yield was not improved probably due to the weak interaction between the silicon atom and the aldehyde.

Recently we have developed the quite efficient asymmetric aldol reaction of silyl enol ethers with aldehydes by using chiral diamine-coordinated tin(II) triflate as a catalyst.[5] In this reaction, chiral tin(II) Lewis acid effectively activates an aldehyde forming an excellent asymmetric field to realize high level of chiral induction. This acquaintance promped us to introduce tin(II) ether instead of the silyl ether and a novel tin(II) Lewis acid, tin(II) monoalchoxymonotriflate 5 containing (+)-cinchonine part as a chiral source was designed. This chiral tin(II) Lewis acid was easily prepared from 1,1'-dimethylstannocene,[6] triflic acid and (+)-cinchonine. In the presence of this Lewis acid, the model reaction of TMS-CN with cyclohexanecarboxyaldehyde proceeded smoothly at -78 °C in dichloromethane to give the corresponding cyanohydrin trimethysilyl ether in 79% yield with 96% ee. Other examples are shown in Table and in every case cyanohydrin trimethylsilyl ethers are obtained in high ees.[7]

A typical experimental procedure is described for the reaction of TMS-CN with cyclohexanecarboxyaldehyde; to a dichloromethane solution (1 ml) of 1,1'-dimethylstannocene (0.44 mmol) and MS4A (120 mg) was added triflic acid (0.4 mmol) at 0 °C. The mixture was stirred for 5 min at this temperature and (+)-cinchonine (0.48 mmol) was added. After further stirring for 30 min at 0 °C, the reaction mixture was cooled to -78 °C. The mixture of TMS-CN (0.8 mmol) and cyclohexanecarboxyaldehyde (0.4 mmol) in dichloromethane (1.5 ml) was added and the reaction was kept standing for 14 h, and quenched with pyridine (0.2 ml) and then saturated aqueous sodium hydrogen carbonate was added. After usual work up, the cyanohydrin trimethylsilyl ether was isolated in 79% yield. The optical purity was determined by HPLC analysis after derivating to the corresponding (+)-MTPA ester.

In the present reaction, the products were isolated as a trimethylsilyl ether form and the reaction smoothly proceeded in the presence of 30 mol% of the tin(II) Lewis acid. The catalyst, tin(II) monoalkoxymonotriflate, was supposed to be regenerated from the initially produced tin(II) alkoxide and trimethylsilyl triflate.



It should be noted that highly enantioselective addition reaction of TMS-CN with an aldehyde is realized by using a novel tin(II) Lewis acid. Current works are focused on the development of other useful asymmetric reactions by using this novel tin(II) Lewis acid.

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7) Benzaldehyde did not react with TMS-CN at -78 °C under the conditions.

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