Enantioselective Trimethylsilylcyanation of some Aldehydes Promoted by Modified Sharpless Catalyst

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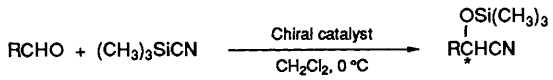
A highly enantioselective method for trimethylsilylcyanation of a variety of aldehydes was developed using a modified Sharpless reagent.

The asymmetric synthesis of optically active organic compounds has been the focus of a great deal of research. Optically active cyanohydrins, especially, are very important intermediates for obtaining α-hydroxy carboxylic acids, β-hydroxy amines, *etc.*, and have been prepared by biological methods[1] and chemical asymmetric synthesis. Several efficient methods have been reported for preparation of cyanohydrins in high optical purity. For example, the optically active cyanohydrins were obtained by the diastereoselective reaction of a cyanating reagent with chiral acetals,[2] and also by the hydrocyanation of aldehydes catalysed by cyclic dipeptides[3] and chiral alkoxytitanium reagents.[4,5]

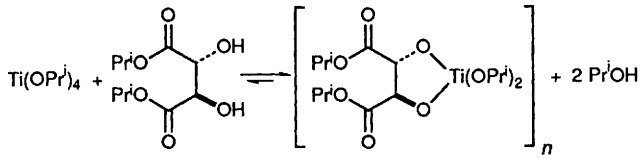
In this communication, we describe the highly enantioselective silylcyanation of some aldehydes by the modified Sharpless catalyst, which consists of titanium-tetraisopropoxide [$Ti(OPr^i)_4$] and chiral diisopropyltartrate (dipt), Scheme 1.



Scheme 1

First, we examined the enantioselective addition of trimethylsilyl cyanide to benzaldehyde using three types of catalysts. The first is the *in situ* mixture of $Ti(OPr^i)_4$ and L-(+)-dipt in a molar ratio of 1 : 1 (catalyst **A**).[6a] The second catalyst system has molecular sieves (MS) 4 Å added into the above catalyst (catalyst **B**).[6b] The third is the freeze-dried catalyst[7] (catalyst **C**) prepared by the equimolar reaction of $Ti(OPr^i)_4$ with L-(+)-dipt followed by removal of Pr^iOH. All of these catalytic reactions resulted in low enantioselectivity when used with an equimolar and catalytic amount of benzaldehyde (Table 1).

The reaction of $Ti(OPr^i)_4$ with L-(+)-dipt was reported to proceed to give the dimeric titanium compounds ($n = 2$) in Scheme 2.[8] The removal of isopropyl alcohol from the above



Scheme 2

Table 1 Enantioselective trimethylsilylcyanation of benzaldehyde[a]

Catalyst system	Equimolar reaction		Catalytic reaction (20 mol%)	
	% Yield[b]	% E.e.[c,d]	% Yield[b]	% E.e.[c,d]
A: $Ti(OPr^i)_4$-L-(+)-dipt *in situ*	95	78	19	48
B: $Ti(OPr^i)_4$-L-(+)-dipt + MS 4 Å *in situ*	100	50	15	6
C: $Ti(OPr^i)_2$(L-(+)-dipt)	100	32	14	58
D: [$Ti(OPr^i)_2$(L-(+)-dipt)]-Pr^iOH (1 : 1)	77	86	61	68
(1 : 1.5)	94	91	71	75
(1 : 2)	63	88	84	91

[a] All reactions were carried out in dichloromethane at 0 °C for 18 h using L-(+)-dipt. [b] Isolated yield. [c] Determined by HPLC analysis of MTPA ester. [d] Absolute configuration of the product was *R*.

Table 2 Enantioselective addition of trimethylsilyl cyanide to some aldehydes promoted by modified Sharpless catalyst[a]

Aldehyde	Equimolar reaction		Catalytic reaction (20 mol%)	
	% Yield[b]	% E.e.[c,d]	% Yield[b]	% E.e.[c,d]
p-Tolualdehyde	89	77[e]	79	65
p-Anisaldehyde	90	81[f]	88	77
2-Naphthaldehyde	89	73[g]	80	60
2-Thiophenecarboxaldehyde	92	81[h]	84	83

[a] Reactions were carried out in dichloromethane at 0 °C for 18 h using L-(+)-dipt. [b] Isolated yield. [c] Determined by HPLC analysis of MTPA ester. [d] All absolute configurations were determined as *R* by comparison of the rotation values with those in the literature.[12] [e] $[\alpha]_D^{24}$ +37.0° (*c* 2.0, $CHCl_3$). [f] $[\alpha]_D^{24}$ +35.4° (*c* 1.5, $CHCl_3$). [g] $[\alpha]_D^{24}$ +11.8° (*c* 1.0, C_2H_5OH). [h] $[\alpha]_D^{24}$ +46.5° (*c* 1.0, C_2H_5OH).

Table 3 Asymmetric amplification in enantioselective trimethylsilylcyanation of benzaldehyde[a]

Entry	% E.e. of L-(+)-dipt	Product	
		% Yield	% E.e.
1	15	65	27
2	25	78	50
3	50	83	70

[a] Reactions were run at 0 °C for 21 h by using 1:2:3:1:1.1 molar ratio of benzaldehyde : trimethylsilyl cyanide : $Ti(OPr^i)_4$: L-(+)-dipt.

mixture gave the slurry compounds† which showed the complex NMR spectrum to be different from that of the dimeric titanium compounds. This implies that the freeze-dried product is a mixture of the various associated complexes.

However, it was found that highly enantioselective reaction was initiated by the addition of one to two molar equiv. of isopropyl alcohol per titanium into the above catalyst **C** system (catalyst **D**), initiation occurred even in the catalytic reaction (*i.e.* use of a 20% molar amount of the catalyst to benzaldehyde). The catalyst **D** reaction was reproducible with regard to enantiomeric excess (e.e.) of the products. The above results would indicate that catalyst **D** is not the same as catalyst **A**. That is, the equilibrium between the components in Scheme 2 exists in catalyst **A**, but not in catalyst **D**. The results of the enantioselective addition of trimethylsilyl cyanide to other aldehydes are summarized in Table 2. The typical experimental procedure is as follows: To a solution of L-(+)-dipt (130 mg, 0.55 mmol) in CH_2Cl_2 (5 ml) was added $Ti(OPr^i)_4$ (0.15 ml, 0.50 mmol) dropwise at 0 °C. After stirring for 30 min at room temperature, isopropyl alcohol was removed *in vacuo* (30 °C, 20 min); benzene (2 ml) was then added to the above residue and freeze-dried. To the resulting slurry a mixture of isopropyl alcohol (77 μl, 1.0 mmol) and CH_2Cl_2 (50 ml) was added, then trimethylsilyl cyanide (0.75 ml, 5.62 mmol) and benzaldehyde (261 mg, 2.46 mmol) were added at 0 °C. After stirring the reaction mixture for 18 h at this temperature it was then quenched with 1 M HCl (30 ml) and stirred vigorously for 1 h at room temperature. The usual extractive work-up and silica-gel column chromatography of the residue gave (*R*)-cyanobenzyl alcohol (275 mg, 84%). $[\alpha]_D^{22}$ +41.6° (*c* 1.1, $CHCl_3$). The e.e. of the product was determined as 91% by HPLC analysis of its MTPA ester.[9] t_R of (*R*)-(+)-isomer: 13 min; t_R of (*S*)-(−)-isomer: 15 min (hexane–ethyl acetate 100:5, 1.0 ml min^{-1}).

We also observed the asymmetric amplification[10] in the enantioselective trimethylsilylcyanation of benzaldehyde using the catalyst **D** consisting of $Ti(OPr^i)_4$ and partially resolved L-(+)-dipt (Table 3). Interestingly, we observed similar results to those found in enantioselective epoxidation of geraniol with a titanium catalyst by Kagan.[11]

At present, the mechanism of the asymmetric silylcyanation of aldehydes with the titanium catalyst is obscure, but it will be clarified in the near future.

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† The elemental analysis showed $(C_{16}H_{30}O_8Ti)_n$ for this compound, which was in accord with the calculated value of the product in Scheme 2.

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