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(S)-3,3-Dimethyl-1,2,4-butanetriol as Ligand for Titanium Catalysed Asymmetric Silylcyanation

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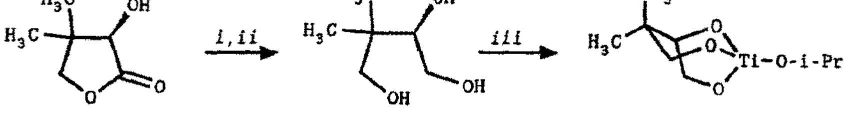
Abstract: Trimethylsilylcyanation of benzaldehyde was effected in up to 76% e.e. using a catalyst prepared from the triol obtained by reduction of D-Pantolactone and titanium isopropoxide.

Enantiopure cyanohydrins are valuable intermediates for the production of several pharmaceutical and agrochemical products[1,2]. A number of asymmetric syntheses have been developed for their preparation, some of which with remarkably high enantioselectivities.[3-11] Aside from enzymatic methods[3,4] two kinds of chemical catalysts are particularly useful. The use of cyclo-His-Phe (either R,R or S,S) as a catalyst allows the direct addition of HCN to aromatic aldehydes in high enantiomeric excess[5]. Use of tartrate derived diols as ligands in the titanium catalysed addition of trimethylsilylcyanide (TMSCN) to aldehydes also gives good e.e.'s with a number of aliphatic aldehydes[6-8]. More recently dipeptide based ligands have been succesfully used in the titanium catalysed asymmetric hydrocyanation[9] and trimethylsilylcyanation[10].

We were attracted by the versatility of the titanium-chiral alcohol catalyst system, but for economic application in tonne-scale production use of HCN is mandatory. The reason for the incompatibility of the known titanium diol catalysts with HCN is not known but displacement of alkoxide by cyanide might be the cause. We therefore searched for a more stable titanium alkoxide catalyst. In this paper we describe the synthesis of a titanium catalyst based on a chiral triol and its use as a catalyst[12].

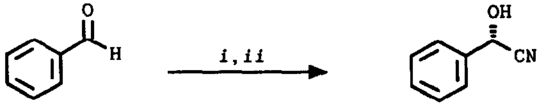


1 2 3

Scheme 1. *i*, $LiAlH_4$, THF; *ii*, $Na_2SO_4.10H_2O$; *iii*, $Ti(O^iPr)_4$, CH_2Cl_2

$LiAlH_4$ reduction of D-pantolactone (**1**) followed by hydrolysis with $Na_2SO_4.10H_2O$ gave the triol **2**[13], which after distillation and careful drying over molecular sieves was reacted with titanium tetra-isopropoxide in CH_2Cl_2 during 4 hours to give the catalyst **3** as a solid. ^1H-NMR of **3** confirmed the 1:1 ratio of triol-isopropoxide but showed mainly broad absorptions, characteristic of oligomeric titanium complexes. Curiously, the remaining isopropoxide peak appeared as a sharp singlet.

Unfortunately, no reaction occurred when **3** was added in stoichiometrical amount to a mixture of HCN and benzaldehyde in toluene. On the other hand, **3** proved to be an excellent catalyst in the asymmetric trimethylsilylation of aromatic aldehydes (Scheme 2.).



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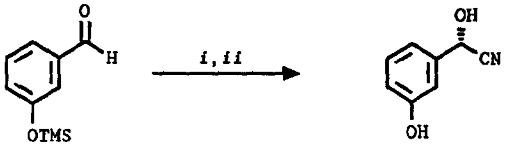
Scheme 2. *i*, TMSCN, **3**, solvent; *ii*, 1N H_2SO_4

Reaction of trimethylsilyl cyanide(TMSCN) with benzaldehyde at 0°C catalysed by an equivalent amount of **3** proceeded smoothly in a number of solvents (Table, entries 1-7) giving S-benzaldehyde cyanohydrin (**4**) after acidic hydrolysis in excellent yields with e.e's[14] up to 66%. Addition of activated 4Å molecular sieves gave a slight improvement in e.e. which could be augmented by lowering the temperature to -20°C, leading to a maximum e.e. of 76%. No reaction occurred when the temperature was lowered further to -65°C. Using **3** in catalytical amounts (10 mol%) led to a much slower reaction and had a detrimental effect upon the e.e. which decreased with conversion (entry 12). Curiously, addition of two equivalents of catalyst also gave a much lower e.e. The effect of the TMSCN concentration on the e.e. was probed by adding the reagent during one hour using the conditions of entry 9. This resulted in a lowered yield of 85% and an e.e. of 70%.

By adding hexane or pentane to the reaction mixture after the reaction is complete the catalyst could be precipitated and recovered by filtration. The recovered catalyst could be reused and under the conditions of entry 9 gave product with 71% e.e.. Since no apparent decomposition of the catalyst occurs under the reaction conditions it is not clear why the catalytical reaction gives a much lower e.e.. It is possible that the catalyst is converted into another oligomeric form after one turnover, which is reversed after precipitation with hexane. We are currently investigating this and other questions relating to the mechanism.

The scope of the use of this catalyst in asymmetric silylcyanation of other aldehydes remains to be determined. However, when 3-hydroxybenzaldehyde was subjected to the conditions of entry 9 no reaction took place. On the other hand, silylcyanation of the trimethylsilyl protected derivative **5** took place in good yield (Scheme 3.). The cyanohydrin was obtained as a solid material of unknown configuration and had an e.e of 30%.

There is no mention in the literature of asymmetric trimethyl silylation of ketones. Attempted silylcyanation of p-isobutyl-acetophenone under a number of different conditions using **3** as catalyst were unsuccesful.



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Scheme 3. *i*, **3**, TMSCN, CH_2Cl_2; *ii*, 1N H_2SO_4

Table. Trimethylsilylation of benzaldehyde

Entry	Conditions[a]	Reaction time (h)	Yield[b](%)	e.e (%)
1.	Toluene	1	92	60
2.	CH_2Cl_2	1	95	65
3.	Diethyl ether	1.25	93	54
4.	THF	1	92	66
5.	Hexane[c]	1.5	90	52
6.	Diphenyl ether	1	95	56
7.	Diisopropyl ether	1.5	90	40
8.	CH_2Cl_2, 4Å MS[d]	1	98	72
9.	CH_2Cl_2, 4Å MS, -20°C	2	92	76
10.	THF, -65°C		0	
11.	THF, 4Å MS, 0.1 eq. **3**	12	70	10
12.	CH_2Cl_2, 4Å MS, 0,1 eq. **3**	1		48
		3		44
		5	60	38
13.	CH_2Cl_2, 4Å MS, 2 eq. **3**	1	90	40
14.	CH_2Cl_2, 4Å MS, 2 eq. TMSCN	1	95	66

a. Reaction performed at 0°C with equimolar amounts of benzaldehyde, TMSCN and **3**, unless otherwise indicated
b. Determined by ^1H NMR
c. Catalyst remains largely undissolved
d. 100mg of 4Å MS/mmol of **3**

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14. Enantiomeric excess was determined using HPLC on a Daicel chiral OD column (n-hexane/2-propanol 9:1 as mobile phase)