

Asymmetric Cyanosilylation of Aldehydes by Chiral Ti-TADDOL Complex

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A variety of chiral cyanohydrins were readily prepared from aldehydes with TMSCN under the influence of chiral titanium complex formed *in situ* from Ti(OⁱPr)₄/TADDOL(I) in the presence of Ph₃PO as additive. The double activation method produces trimethylsilylethers in excellent yield (95%) with moderate enantiomeric excess.

Key Words : Cyanosilylation, Aldehyde, Ti-TADDOL, Double activation

Introduction

Enantiomerically pure cyanohydrins are important building blocks for the synthesis of several 1,2-bifunctional products such as α -hydroxy acids, α -hydroxy amines, α -hydroxy alcohols and α -amino acid derivatives.^{2,3}

A wide range of titanium complexes have been elaborated for organic transformations.⁴ The chiral ligand for titanium based catalyst include BINOLs,⁵ tartrate esters,⁶ sulfoximes,⁷ peptides,⁸ Schiff bases⁹ and others.¹⁰ In each case complexation of the ligand to a suitable titanium salt generated a chiral complex that induced the asymmetric addition of hydrogen and/or trimethylsilylcyanation to aldehydes.

Shibasaki¹¹ disclosed enantioselective catalytic addition of TMSCN to carbonyl compounds by using carbohydrate based ligands and Ti(OⁱPr)₄. Belokon and North¹² have reported the asymmetric silylcyanation of carbonyl compounds. Bu,¹³ Zhou,¹⁴ Feng,¹⁵ and Gennari¹⁶ have reported trimethylsilylcyanation of carbonyl compounds by using modified and bulky salen ligand and / Ti(OⁱPr)₄. Recently we reported¹⁷ asymmetric addition of TMSCN to carbonyl compounds by using Al(salen) and Mn(salen) complexes.

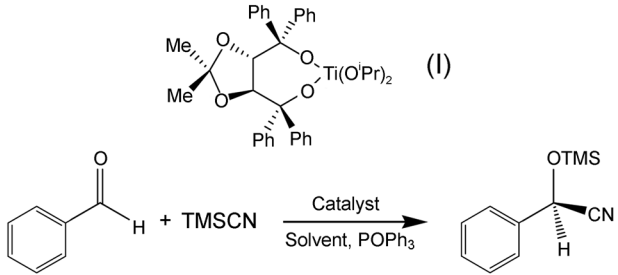
To the best of our knowledge, TADDOLs originated by Seebach¹⁸ represented a versatile class of chiral auxiliaries or ligands in asymmetric synthesis. However no example of cyanosilylation of carbonyl compounds has been reported using TADDOL / Ti(OⁱPr)₄ system. Thus we are interested in the exposing the usability of this ligand in cyanosilylation reactions.

Results and Discussion

Cyanosilylation reaction was started with benzaldehyde as a test substrate. The results of these reactions are summarized in Table 1. Various solvents including CH₂Cl₂, THF, CH₃CN and CHCl₃ were examined among which CHCl₃ was found to be the best solvent for this reaction at RT (Table 1, entries 1-4).

The enantioselectivity was greatly influenced by the reaction temperature. The best performance was at -10 °C, while at higher temperatures the enantioselectivity was poorly controlled (entries 5 and 6). The reaction was performed

Table 1. Cyanosilylation Benzaldehyde under various conditions

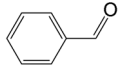
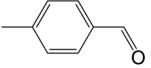
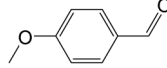
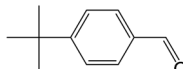
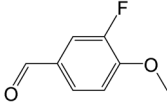
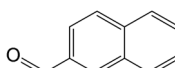
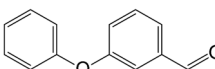
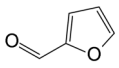
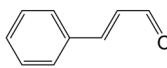
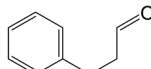


Entries	Catalyst	POPh ₃	Solvent	Temp	Time (h)	Yield (%)	Ee (%)
1	10	10	CHCl ₃	r.t	20	90	20
2	10	10	CH ₂ Cl ₂	r.t	20	87	18
3	10	10	THF	r.t	20	6	5
4	10	10	CH ₃ CN	r.t	20	88	18
5	10	10	CHCl ₃	-10	20	95	50
6	10	10	CHCl ₃	40	10	98	5
7	10	10	CHCl ₃	-20	20	92	30
8	10	10	CHCl ₃	-30	20	90	22
9	10	10	CHCl ₃	-40	20	87	25
10	5	10	CHCl ₃	-10	20	90	5
11	10	5	CHCl ₃	-10	20	71	13
12	10	20	CHCl ₃	-10	20	79	18
13	10	30	CHCl ₃	-10	20	95	20
14	10	50	CHCl ₃	-10	20	40	38
15	10	0	CHCl ₃	-10	20	0	0

at very low temperatures (-20 °C to -40 °C), but decreased enantiomeric excesses were observed (entries 7, 8 and 9). Decreasing the catalytic loading affects the yield and e.e. negatively (entry 10). Additive quantity was varied (entries 5 and 11-14) and 10 mol% (entry 5) of triphenylphosphonium oxide proved to be optimal, without which no reaction took place (entry 15).

The reaction conditions in Entry 5 of the Table 1 were applied to the cyanosilylation reaction of various aldehydes with TMSCN (Table 2). Benzaldehydes with various substituents at *para* position were transformed into the corresponding chiral cyanohydrins (entries 1-7) with moderate enantioselectivity in over 95% yield.

Table 2. Trimethylsilylcyanation of Aldehydes^{a,b,c}

Entry	Substrate	Yield (%)	ee (%)
1		95	50
2		97	57
3		94	40
4		96	60
5		91	42
6		87	52
7		92	40
8		65	40
9		92	44
10		95	59

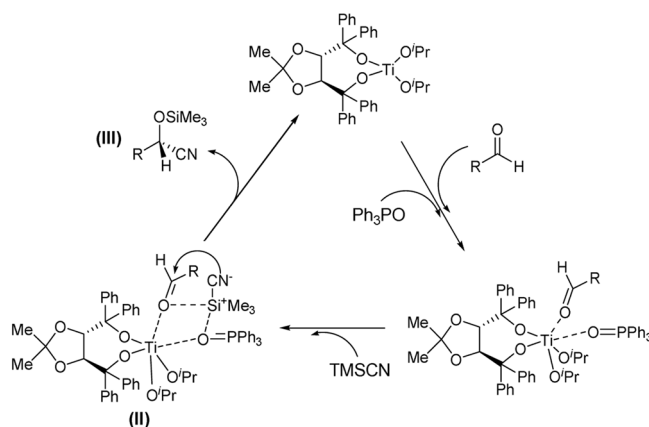
^a10 mol % of **1** and 10 mol % of Ph₃PO. ^bAll reactions were conducted at -10 °C for 20 h. ^cAll products are R configuration.

The e.e. obtained was good to moderate (40-60%). Replacement of benzene ring by furan moiety gave little difference on the isolated yield (entry 8). Introduction of conjugate double bond with respect to carbonyl group hardly produced significant effect on enantioselectivity (entry 9). 3-Phenylpropanal (entry 10) reacted smoothly with TMS-CN to give the corresponding cyanohydrin. Based on our previous experience¹⁷ in cyanosilylation reactions and related titanium based work^{18,19} the possible mechanism and transition state involved in the enantioselective reaction catalyzed by **I** is given in Figure 1.

In conclusion highly efficient double activation catalysis by TADDOL/ Ti(Oⁱ-Pr)₄ and Ph₃PO has been developed for the enantioselective cyanosilylation of various aldehydes. The cyanosilylation reaction takes place under comparatively mild conditions in terms of temperature and reaction time.

Experimental Section

General method for the asymmetric addition of trimethylsilylcyanide to benzaldehyde: To a stirred solution of (+) 4,5-bis[dihydroxy (diphenyl)-methyl] 2,2-dimethyl-1,3-dioxane

**Figure 1**

(TADDOL) (10 mol%) in chloroform (2 mL) was added titanium tetraisopropoxide (10 mol%) under N₂ at room temperature and the mixture was stirred for 1 hour. Trimethylsilyl cyanide (2 mmol) was added to the reaction mixture and stirred for an additional 0.5 hour. Then, the reaction mixture was cooled to -10 °C and benzaldehyde (1 mmol) was added to the reaction mixture. The disappearance of the aldehyde was monitored by thin layer chromatography. After completion of the reaction CHCl₃ was evaporated. The crude product was purified by flash chromatography (hexane: ethyl acetate = 9 : 1).

2-Hydroxy-2-phenylacetonitrile. ¹H NMR (CDCl₃, 200 MHz): δ 7.44 (m, 5H), 6.15 (s, 1H), 4.22 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H) ¹³C NMR (CDCl₃, 50 MHz): δ 153.6, 131.3, 130.8, 129.4, 127.9, 115.6, 66.3, 65.6, 14.3 HRMS (M⁺) calcd for C₁₁H₁₁NO₃ 205.0739 found 205.0753 R enantiomer in 50% ee. HPLC (DAICEL CHIRALCEL OD) 11.5 min and 14.0 min (The enantiomeric excess was determined by HPLC after conversion to ethyl carbonate).

2-Hydroxy-2-(4-methylphenyl)acetonitrile. ¹H NMR (CDCl₃, 200 MHz): δ 7.44 (d, *J* = 8.25 Hz, 2H), 7.25 (d, *J* = 8.25 Hz, 2H), 6.22 (s, 1H), 4.28 (m, 2H), 2.39 (s, 3H), 1.35 (t, *J* = 7.3 Hz, 3H) ¹³C NMR (CDCl₃, 50 MHz): δ 153.5, 140.7, 129.9, 128.6, 127.9, 115.9, 66.2, 65.3, 21.4, 14.1 HRMS (M⁺) calcd for C₁₂H₁₃NO₃ 219.0895 found 219.0889 R enantiomer in 57% ee. HPLC (DAICEL CHIRALCEL OD) 17.4 min and 19.5 min (The enantiomeric excess was determined by HPLC after conversion to ethyl carbonate).

2-Hydroxy-2-(4-methoxy phenyl) acetonitrile. ¹H NMR (CDCl₃, 200 MHz): δ 2.8 (brs, 1H), 3.86 (s, 3H), 5.48 (s, 1H), 6.95 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H) ¹³C NMR (CDCl₃, 50 MHz): δ 55.40, 63.27, 114.52, 118.93, 127.50, 128.29, 160.70 R enantiomer in 40% ee. HPLC (DAICEL CHIRALCEL OD) 14.8 min and 12.7 min (The enantiomeric excess was determined by HPLC after conversion to the corresponding acetyl ester).

2-Hydroxy-2-(4-tert-butylphenyl) acetonitrile. ¹H NMR (CDCl₃, 200 MHz): δ 1.25 (s, 9H), 2.88 (s, 1H), 5.43 (s, 1H), 7.37 (m, 4H) ¹³C NMR (CDCl₃, 50 MHz): δ 31.64, 35.18, 63.77, 119.46, 126.56, 126.94, 132.79, 153.56 HRMS (M⁺) calcd for C₁₂H₁₅NO 189.1154 found 189.1143 R enantiomer

in 60% ee. HPLC (DAICEL CHIRALCEL OD) 21.5 min and 24.0 min.

2-(3-fluoro-4-methoxyphenyl)-2-(trimethylsilyloxy) acetonitrile. ^1H NMR (CDCl_3 , 200 MHz): δ 2.2 (brs, 1H), 3.83 (s, 3H), 5.48 (s, 1H), 6.95 (d, $J = 8.5$ Hz, 2H), 7.06 (s, 1H) ^{13}C NMR (CDCl_3 , 50 MHz): δ 55.80, 65.27, 115.52, 116.93, 118.50, 127.29, 147.70, 151.3 R enantiomer in 42% ee. HPLC (DAICEL CHIRALCEL OD) 12.8 min and 14.7 min.

2-(naphthalen-2-yl)-2-(trimethylsilyloxy) acetonitrile. ^1H NMR (CDCl_3 , 200 MHz): δ 8.01 (m, 3H), 7.55 (m, 3H), 7.17 (m, 1H), 5.02 (s, 1H), ^{13}C NMR (CDCl_3 , 50 MHz): δ 132.81, 128.9, 128.08, 127.63, 126.77, 126.58, 125.6, 123.5, 119.0, 63.795 R enantiomer in 52% ee. HPLC (DAICEL CHIRALCEL OD) 15.5 min and 18.0 min.

2-Hydroxy-2-(3-phenoxyphenyl) acetonitrile. ^1H NMR (CDCl_3 , 200 MHz): δ 3.5 (brs, 1H), 5.46 (s, 1H), 7.5 (m, 9H) ^{13}C NMR (CDCl_3 , 50 MHz): δ 63.17, 116.63, 118.59, 119.65, 120.94, 123.94, 129.93, 130.52, 137.05, 156.34, 158.12 R enantiomer in 40% ee. HPLC (DAICEL CHIRALCEL OD) 28.1 min and 40.9 min (The enantiomeric excess was determined by HPLC after conversion to the corresponding acetyl ester).

2-(2-Furyl)-2-hydroxyethanenitrile. ^1H NMR (CDCl_3 , 200 MHz): δ 7.50 (dt, $J = 1.8$ Hz, 1H), 6.65 (d, $J = 3.4$ Hz, 1H), 6.44 (s, 1H), 6.47 (dd, $J = 3.4, 1.8$ Hz, 1H), 2.15 (s, 3H) ^{13}C NMR (CDCl_3 , 50 MHz): δ -0.43, 57.41, 109.70, 110.78, 117.11, 143.84, 148.20 R enantiomer in 40% ee. HPLC (DAICEL CHIRALCEL AS) 8.7 min and 9.7 min (The enantiomeric excess was determined by HPLC after conversion to the corresponding acetyl ester).

2-Hydroxy-4-phenyl-3-butenenitrile. ^1H NMR (CDCl_3 , 200 MHz): δ 7.43 (m, 5H), 6.98 (d, $J = 15.9$ Hz, 1H), 6.19 (dd, $J = 15.9, 6.7$ Hz, 1H), 6.03 (dd, $J = 6.7, 0.9$ Hz), 2.15 (s, 3H) ^{13}C NMR (CDCl_3 , 50 MHz): δ 168.9, 137.9, 134.6, 129.6, 128.9, 127.1, 118.4, 115.7, 61.5, 20.5 HRMS (M^+) cacl'd for $\text{C}_{12}\text{H}_{11}\text{NO}_2$ 201.0790 found 201.0782 R enantiomer in 44% ee. HPLC (DAICEL CHIRALCEL OD) 18.1 min and 22.3 min (The enantiomeric excess was determined by HPLC after conversion to the corresponding acetyl ester).

2-Hydroxy-4-phenylbutanenitrile. ^1H NMR (CDCl_3 , 200 MHz): δ 7.31 (m, 2H), 7.22 (m, 3H), 4.44 (t, $J = 6.4$ Hz, 1H), 2.80 (m, 2H), 2.15 (m, 2H), 0.92 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H) ^{13}C NMR (CDCl_3 , 50 MHz): δ 140.0, 128.5, 128.4, 126.2, 119.9, 61.3, 37.9, 25.8, 18.1, 20.51, 25.3 R enantiomer in 59% ee. HPLC (DAICEL CHIRALCEL OD) 8.7 min and 10.9 min.

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