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 $Ti(O^iPr)_4$/TADDOL(I) in the presence of Ph_3PO 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 bases[9] 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.

Shibasaki[11] disclosed enantioselective catalytic addition of TMSCN to carbonyl compounds by using carbohydrate based ligands and $Ti(O^iPr)_4$. Belokon and North[12] have reported the asymmetric silylcyanation of carbonyl compounds. Bu,[13] Zhou,[14] Feng,[15] and Gennari[16] have reported trimethylsilylcyanation of carbonyl compounds by using modified and bulky salen ligand and / $Ti(O^iPr)_4$. Recently we reported[17] asymmetric addition of TMSCN to carbonyl compounds by using Al(salen) and Mn(salen) complexes.

To the best of our knowledge, TADDOLs originated by Seebach[18] 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 / $Ti(O^iPr)_4$ system. Thus we are interested in the exposing the usability of this ligand in cyanosilylation reactions.

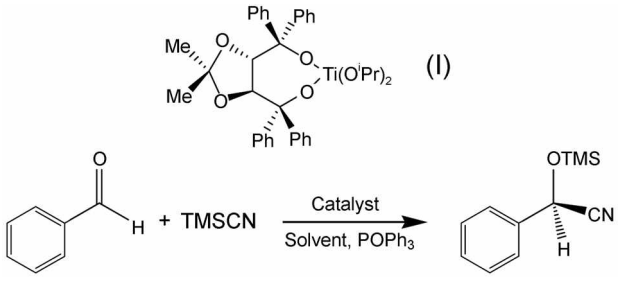
Results and Discussion

Cyanosilylation reaction was started with benzaldehyde as a test substrate. The results of these reactions are summarized in Table 1. Various solvents including CH_2Cl_2, THF, CH_3CN and $CHCl_3$ were examined among which $CHCl_3$ 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 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).

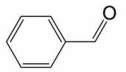
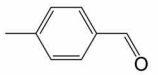
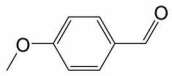
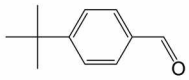
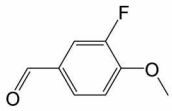
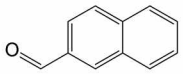
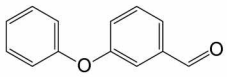
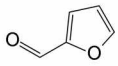
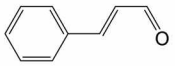
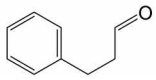
The reaction conditions in Entry 5 of the Table 1 were applied to the cyanosilylation reaction of various aldehydes with TMSCN (Table 2). Benzaldehydes with various substituents at *para* position were transformed into the corresponding chiral cyanohydrins (entries 1-7) with moderate enantioselectivity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

Table 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_2Cl_2	r.t	20	87	18
3	10	10	THF	r.t	20	6	5
4	10	10	CH_3CN	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

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

[a]10 mol % of 1 and 10 mol % of Ph_3PO. [b]All reactions were conducted at −10 °C for 20 h. [c]All 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 TMSCN to give the corresponding cyanohydrin. Based on our previous experience[17] 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(O-Pr)$_4$ and Ph_3PO 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

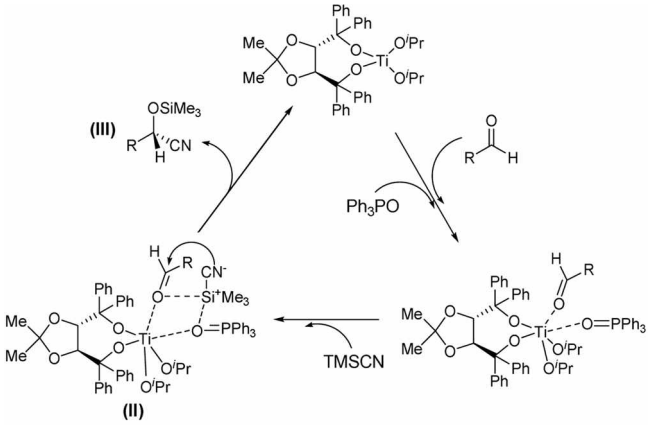


Figure 1

(TADDOL) (10 mol%) in choloroform (2 mL) was added titanium tetraisopropoxide (10 mol%) under N_2 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 benzalaldehyde (1 mmol) was added to the reaction mixture. The disappearance of the aldehyde was monitored by thin layer chromatography. After completion of the reaction $CHCl_3$ was evaporated. The crude product was purified by flash chromatography (hexane: ethyl acetate = 9 : 1).

2-Hydroxy-2-phenylacetonitrile. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.44 (m, 5H), 6.15 (s, 1H), 4.22 (m, 2H), 1.27 (t, J = 7.0 Hz, 3H) ^{13}C NMR ($CDCl_3$, 50 MHz): δ 153.6, 131.3, 130.8, 129.4, 127.9, 115.6, 66.3, 65.6, 14.3 HRMS (M^+) cacld for $C_{11}H_{11}NO_3$ 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-methyphenyl)acetonitrile. ^{1}H NMR ($CDCl_3$, 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) ^{13}C NMR ($CDCl_3$, 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^+) cacld for $C_{12}H_{13}NO_3$ 219.0895 found 219.0889 R entiomer 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. ^{1}H NMR ($CDCl_3$, 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 = 8.5Hz, 2H) ^{13}C NMR ($CDCl_3$, 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. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25 (s, 9H), 2.88 (s, 1H), 5.43 (s, 1H), 7.37 (m, 4H) ^{13}C NMR ($CDCl_3$, 50 MHz): δ 31.64, 35.18, 63.77, 119.46, 126.56, 126.94, 132.79, 153.56 HRMS (M^+) cacld for $C_{12}H_{15}NO$ 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. ^{1}H NMR ($CDCl_3$, 200 MHz): δ2.2 (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. ^{1}H NMR ($CDCl_3$, 200 MHz): δ8.01 (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. ^{1}H NMR ($CDCl_3$, 200 MHz): δ3.5 (brs, 1H), 5.46 (s, 1H), 7.5 (m, 9H) ^{13}C NMR ($CDCl_3$, 50 MHz): δ63.17, 116.63, 118.59, 119.65, 120.94, 123.94, 129.93, 130.52, 137.05, 156.34, 158.12 R entiomer 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. ^{1}H 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 entiomer 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. ^{1}H 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^+) cacld for $C_{12}H_{11}NO_2$ 201.0790 found 201.0782 R entiomer 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. ^{1}H NMR ($CDCl_3$, 200 MHz): δ7.31 (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 entiomer in 59% ee. HPLC (DAICEL CHIRALCEL OD) 8.7 min and 10.9 min.

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