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Asymmetric addition of trimethylsilyl cyanide to ketones catalyzed by Al(salen)/triphenylphosphine oxide

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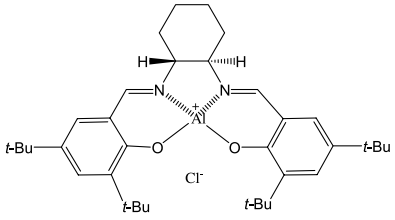
Abstract—Trimethylsilyl cyanide asymmetrically adds to various ketones by catalysis of **1**/triphenylphosphine oxide. This is a double activation where **1** acts as Lewis acid and Ph_3PO Lewis base. Various ketones were subjected to the enantioselective addition so as to give up to 92% ee and >90% yield.

1. Introduction

Asymmetric addition of trimethylsilyl cyanide (TMSCN) to carbonyl compounds and subsequent hydrolysis produces chiral cyanohydrins[1–3]. Such chiral compounds are useful intermediates for synthesis of pharmaceutics. The two functional groups (–OH and –CN) can be easily transformed into various homochiral ones including α-hydroxy acids[4,5], α-hydroxy aldehydes[6], α-hydroxy ketones[6], β-hydroxy amines[5,6] and α-amino acid derivatives[7].

A number of catalysts for the asymmetric addition of TMSCN to ketones are known. Belokon and North used a bimetallic titanium salen complex as a catalyst for the asymmetric addition of TMSCN to ketones[8]. Shibasaki has reported enantioselective catalytic additions of TMSCN to various ketones utilizing bifunctional ligand and $Ti(OiPr)_4$ or the lanthanide complexes[9]. The concept of dual activation has been pioneered by Shibasaki's group. Deng has first described method of cyanosilylation of ketones employing chiral Lewis bases which are free of metal ions[10]. Snapper and Hoveyda has described the addition of TMSCN to ketones catalyzed by peptide chiral ligand and $Al(OiPr)_3$[11]. Feng and Jiang has employed chiral *N*-oxide/titanium(IV) complex for the cyanosilylation of ketones[12]. Feng has utilized a catalytic double-activation method using chiral salen-Ti(IV) complex and various achiral *N*-oxides for the cyanosilylation of ketones[13]. Recently, Corey has shown that chiral oxazaborolidium salt is an excellent catalyst for the cyanosilylation of methyl ketones[14]. This method used TMSCN and diphenylmethyl phosphine oxide as co-reactants to generate $Ph_2MePOTMS(N{=}C{:})$ as a reactive intermediate. The cyanosilylations of aldehydes employing Al(salen)(**1**)/Ph_3PO and Mn(salen)/Ph_3PO, respectively were developed by us.[15] The former catalyst gives better % ee than the latter. We would like to herein report the cyanosilylation of ketones employing the same **1**/Ph_3PO as the catalysts.



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2. Results and discussion

p-Chlorophenyl methyl ketone was chosen as a test substrate to find out the best conditions for the cyanosilylations. Amount of triphenylphosphine oxide was varied to find out the optimal conditions (entries 1–4). No reaction took place without triphenylphosphine oxide (entry 1). Entry 4 of 10 mol% Ph_3PO is shown to be the proper quantity for the cyanosilylation reaction. Various solvents were used for the cyanosilylations and CH_2Cl_2 proved to be the proper medium for the reactions (entries 4–7). The substrate concentration of 1 M appears adequate (entries 4, 8 and 9). The reactions were run at four different temperatures and rt offers the best outcome (entries 4, 10,

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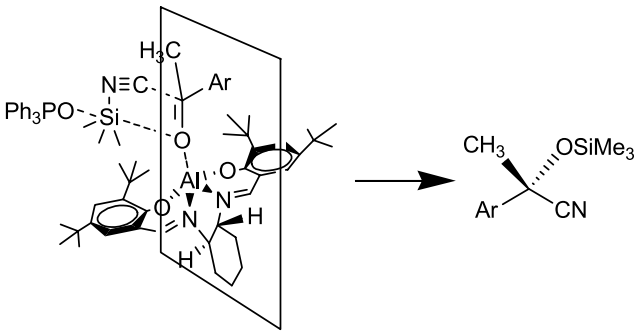


Figure 1. Transition state involved in the enantioselective cyanosilylation of ketones by double-activation catalysis.

11 and 12). The amount of **1** for the reactions should be 1 mol% that gives highest % yield and % ee(entries 4, 13, 14 and 15) (Table 1). The reactions appears to be catalyzed by double activation process occurring through the catalysis of both chiral Lewis acid and achiral Lewis base. Al(salen) complex functions as a Lewis acid to activate the ketonic oxygen and Ph_3PO acts as a Lewis base for activation of TMSCN (Fig. 1).

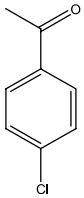
o-Chlorophenyl methyl ketone appears susceptible to steric effect compared to *p*-chloro- and *m*-chlorophenyl methyl ketone so as to give the much longer reaction time (23, 11 and 6 h) and lower % ee (62, 77 and 91%) although the % yield are nearly unaffected (entries 1, 2, 3 and 4). *p*-Chloro- and *m*-chloro group shorten the reaction time from 19 to 11 and 6 h (entries 1, 2 and 3). Electron-withdrawing substituents (entries 2, 4, 5, 6 and 7) exert favorable influence for the cyanosilylation in terms of reaction time (11, 6, 7, 5 and 2 h) to give excellent % yield and good % ee. On the other hand, electron-donating substituents indicate much longer reaction time (~20 h) and give a little sluggish effect on reactions (entries 8 and 9). The negative influence of longer reaction time is also shown in entry 10(25 h) and entry 11(40 h). However cyanosilylation of isobutylphenone (entry 11) produces excellent ee (92%). *p*-Methoxy phenyl acetone (entry 12), benzyl acetone (entry13) and 4-phenyl-3-buten-2-one (entry 14) take relatively short reaction time (3–4 h) (Table 2).

The % ee is quite good and % yield appears excellent that could be compared with other works.[9–14] The reaction temperature is milder (rt) than the previous cyanosilylations (below −20 °C).[9–11] Cyanosilylations by others[9–14] usually report quite longer reaction time. On the other hand *p*-nitrophenyl methyl ketone underwent cyanosilylation for only 2 h in our hand. The oxazaborolidium-catalyzed cyanosilylation of ketones[14] takes place at temperature of 25–40 °C that is higher than 0 °C at which similar reactions of the aldehydes[16] occur. Similar increase of reaction temperature from aldehydes (−40 to −50 °C)[15a] to ketones (rt)(present reactions) were also observed for our reactions. Compared to aldehydes, ketonic structure maintains steric hindrance so that TMSCN could add to the carbonyl at elevated temperature. However the steric effects render reaction time much longer for ketones[14] than aldehydes.[16] Such difference of reaction time between aldehydes[15a] and ketones (present work) appears not significant in our reactions.

3. Conclusion

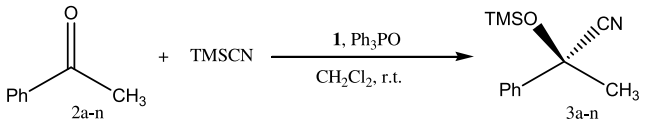
A highly efficient double activation catalysis by **1**/Ph_3PO has been developed for the enantioselective cyanosilylations of various ketones. The cyanosilylations take place under comparatively mild conditions in terms of temperature and reaction time. Several ketones with electron-withdrawing groups in phenyl ring (entries 2, 3 and 5–7) exhibit quite short reaction time that may indicate nucleophilic addition of CN^- group to carboxyl carbon as rate-determining process. Some other ketones without methyl group (entries 12, 13 and 14) undergo cyanosilylation also for quite short reaction time.

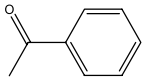
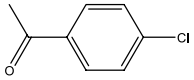
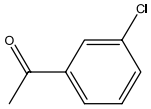
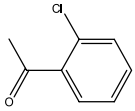
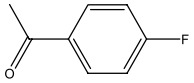
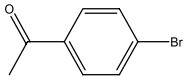
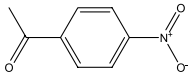
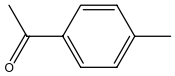
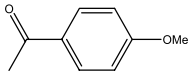
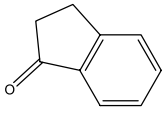
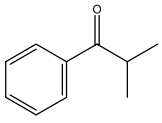
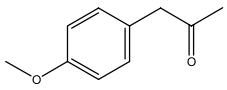
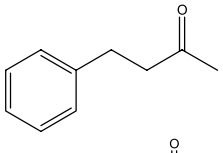
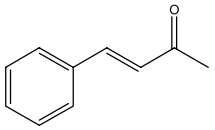
Table 1. Catalytic asymmetric cyanosilylation of methyl *p*-chlorophenyl ketone under various condition[a]

Entry	Substrate	Solvent	Temperature	1 (mol%)	Time (h)	Yield (%)	ee (%)	M (mol/l)
1[b]		CH_2Cl_2	rt	1	40	—	—	1
2[c]		CH_2Cl_2	rt	1	20	80	74	1
3[d]		CH_2Cl_2	rt	1	10	98	75	1
4		CH_2Cl_2	rt	1	11	98	77	1
5		$CHCl_3$	rt	1	12	92	68	1
6		THF	rt	1	16	97	72	1
7		Toluene	rt	1	20	67	69	1
8		CH_2Cl_2	rt	1	21	96	75	0.5
9		CH_2Cl_2	rt	1	7	96	73	2
10		CH_2Cl_2	0 °C	1	34	97	76	1
11		CH_2Cl_2	−10 °C	1	72	93	77	1
12		CH_2Cl_2	−40 °C	1	200	10	81	1
13		CH_2Cl_2	rt	3	9	97	68	1
14		CH_2Cl_2	rt	5	3	99	72	1
15		CH_2Cl_2	rt	10	3	98	57	1

[a] 10 mol% Ph_3PO has been used for all the cyanosilylation, except for otherwise stated.
[b] 0 mol% Ph_3PO has been used for the cyanosilylation.
[c] 5 mol% Ph_3PO has been used for the cyanosilylation.
[d] 20 mol% Ph_3PO has been used for the cyanosilylation.

Table 2. Catalytic Asymmetric Cyanosilylation of Ketones Catalyzed by **1**/$POPh_3$[a]



Entry	Substrate[b]	Time (h)	Yield (%)	ee (%)	Config.[c]
1		19	93	78	S[d]
2		11	97	77	S[d]
3		6	98	91	S[d]
4		23	98	62	—
5		7	95	73	—
6		5	96	73	—
7		2	95	72	—
8		21	90	66	S[d]
9		20	87	71	—
10		25	87	68	S[d]
11		40	80	92	—
12		3	85	65	—
13		3	90	75	S[d]
14		4	75	60	S[d]

[a] CH_2Cl_2 is the solvent for the reactions. The reactions were run at rt 1 mol% **1** was used for all the cyanosilylations. 30 mol% of Ph_3PO has been used except for entry 2. 10 mol% Ph_3PO was employed for the reaction of entry 2.
[b] Substrate concentration is 1 M.
[c] Determined by HPLC (see Refs. 9,11)
[d] The specific rotations carry minus values while the reported ones indicate positive values with R configuration.[9a,11,17]

4. Experimental

4.1. General methods

To a stirred CH_2Cl_2 solution of **1** (1 mol%), $POPh_3$ (30 mol%) was added an aldehyde (2 mmol) and stirred for 30 min at rt TMSCN (2.4 mmol) was added to the reaction mixture using syringe pump and the mixture was reacted at the same temperature for 2–25 h. The solvent was evaporated. The crude product was futher purified by flash chromatography (hexane: ethyl acetate=9:1) to give a cyanohydrin in more than 90% yield. The enantiomeric excesses of some products were determined after conversion to acetylester, ethylcarbonate, and *t*-butyl dimethylsilylether by the known methods. The sample was identified by ^1H, ^{13}C–MR, HRMS and ee % was determined by chiral HPLC column (DAICEL CHIRALCEL OJ-H, DAICEL CHIRALCEL OD-H and DAICEL CHIRALCEL OB-H). All ketones and Al(salen) were purchased from Sigma-Aldrich. ^1H and ^{13}C NMR were taken utilizing Varian Jemini 2000 (200 MHz) or Varian Unity Inova 400 (400 MHz) NMR spectrometer. Hewlett–Packard 5890A Gas Chromatograph/Jeol JMS-DX303 Mass Spectrometer was used for HRMS data. Analytical high performance liquid chromatography (HPLC) was performed on Gilson 305 series HPLC using the indicated chiral column. All data was in accordance with literature values. Absolute configurations were determined by optical rotation, see: (a) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412; (b) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett*. **2001**, *42*, 691; (c) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; kanai, M.; Du, W.; Curran, D.P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908;. and references cited therein.;(c) Deng, H. -B.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed*. **2002**, *41*, 1009.

4.1.1. 2-Trimethylsilyloxy-2-phenylpropanenitrile (3a). ^1H NMR ($CDCl_3$) δ 0.19 (s, 9H), 1.87 (s, 3H), 7.38–7.58 (m,5H, aromatic H) ^{13}C NMR ($CDCl_3$) δ 1.03, 33.5, 71.6, 121.6, 128.6, 142.0 $[\alpha]_D^{24}$ −16.0° (*c* 1.18, $CHCl_3$, 78% ee) [lit. $[\alpha]_D^{20}$ +21.9° (*c* 1.18, $CHCl_3$, for *R* enantiomer with 93% ee)][9a] HRMS(M+) calcd for $C_{12}H_{17}NOSi$: 219.1079; found: 219.1082 HPLC (DAICEL CHIRALCEL OB-H, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 14.9 and 15.4 min.

4.1.2. 2-Trimethylsilyloxy-2-(4′-chlorophenyl)propanenitrile (3b). ^1H NMR ($CDCl_3$) δ 0.21 (s, 9H), 1.83 (s, 3H), 7.38 (m, 2H), 7.49 (m,2H) ^{13}C NMR ($CDCl_3$) δ 1.05, 33.53, 71.06, 121.25, 126.07, 128.83, 134.60, 140.71 $[\alpha]_D^{24}$ −17.3° (*c* 1.78, $CHCl_3$, 77% ee) [lit. $[\alpha]_D^{20}$ +29.5° (*c* 1.04, $CHCl_3$, for *R* enantiomer with 92% ee)][9a] HRMS (M+) calcd for $C_{12}H_{16}ClNOSi$: 253.0690; found: 253.0687 HPLC (DAICEL CHIRALCEL OJ-H, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 19.5 and 20.5 min.

4.1.3. 2-Trimethylsilyloxy-2-(3′-chlorophenyl)propanenitrile (3c). ^1H NMR ($CDCl_3$) δ 0.22 (s, 9H), 1.86 (s, 3H), 7.34–7.55 (m, 4H aromatic H) ^{13}C NMR ($CDCl_3$) δ 1.0, 33.4, 70.9, 121.0, 122.7, 124.8, 128.8, 129.9, 134.6, 144.0 $[\alpha]_D^{24}$ −19.3° (*c* 1.28, $CHCl_3$, 91% ee) [lit. $[\alpha]_D^{26}$ +7.1° (*c* 0.34, $CHCl_3$, for *R* enantiomer with 33% ee)][17] HRMS(M+) calcd for $C_{12}H_{16}ClNOSi$: 253.0690; found: 253.0692 HPLC (DAICEL CHIRALCEL OB-H, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 14.6 and 17.4 min.

4.1.4. 2-Trimethylsilyloxy-2-(2′-chlorophenyl)propanenitrile (3d). ^1H NMR ($CDCl_3$) δ 0.23 (s, 9H), 1.88 (s, 3H), 7.37–7.62 (m, 4H aromatic H) ^{13}C NMR ($CDCl_3$) δ 1.0, 33.4, 70.9, 121.0, 122.7, 124.8, 128.8, 129.9, 134.6, 144.0 $[\alpha]_D^{24}$ −12.3° (*c* 1.58, $CHCl_3$, 62% ee) HRMS(M+) calcd for $C_{12}H_{16}ClNOSi$: 253.0691; found: 253.0687 HPLC (DAICEL CHIRALCEL OD-H, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 24.2 and 25.0 min.

4.1.5. 2-Trimethylsilyloxy-2-(4′-fluorophenyl)propanenitrile (3e). ^1H NMR ($CDCl_3$) δ 0.18 (s, 9H), 1.84 (s, 3H), 7.08 (m, 2H), 7.52 (m, 2H) ^{13}C NMR ($CDCl_3$) δ 1.0, 33.5, 71.0, 115.6, 121.4, 126.5, 138.0, 162.2 $[\alpha]_D^{22}$ −17.3° (*c* 1.4, $CHCl_3$, 73% ee) HRMS(M+) calcd for $C_{12}H_{16}FNOSi$: 237.0985; found: 237.0981 HPLC (DAICEL CHIRALCEL OB-H, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 16.4 and 17.8 min.

4.1.6. 2-Trimethylsilyloxy-2-(4′-bromophenyl)propanenitrile (3f). ^1H NMR ($CDCl_3$) δ 0.19 (s, 9H), 1.83 (s, 3H), 7.40–7.4 (m, 2H), 7.51–7.55 (m, 2H) ^{13}C NMR ($CDCl_3$) δ 1.0, 33.4, 71.0, 121.1, 122.7, 126.3, 131.7, 141.2 $[\alpha]_D^{22}$ −14.6° (*c* 1.69, $CHCl_3$, 73% ee) HRMS(M+) calcd for $C_{12}H_{16}BrNOSi$: 297.0185; found: 297.0181 HPLC (DAICEL CHIRALCEL OB-H, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 16.4 and 17.8 min.

4.1.7. 2-Trimethylsilyloxy-2-(4′-nitrophenyl)propanenitrile (3g). ^1H NMR ($CDCl_3$) δ 0.26 (s, 9H), 1.89 (s, 3H), 7.75 (d, 2H), 8.30 (d, 2H) ^{13}C NMR ($CDCl_3$) δ 1.0, 33.5, 71.0, 115.6, 121.4, 126.5, 138.0, 162.2 $[\alpha]_D^{22}$ −15.3° (*c* 1.65, $CHCl_3$, 72% ee) HRMS(M+) calcd for $C_{12}H_{16}N_2O_3Si$: 264.0930; found: 264.0933 HPLC (DAICEL CHIRALCEL OJ-H, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 51.38 and 54.61 min.

4.1.8. 2-Trimethylsilyloxy-2-(4′-methylphenyl)propanenitrile (3h). ^1H NMR ($CDCl_3$) δ 0.16 (s, 9H), 1.84 (s, 3H), 2.36 (s, 3H), 7.21 (m, 2H), 7.43 (m, 2H) ^{13}C NMR ($CDCl_3$) δ 1.1, 20.8, 33.5, 71.8, 121.9, 124.9, 128.3, 138.4, 139.8 $[\alpha]_D^{23}$ −16.1° (*c* 1.65, $CHCl_3$, 72% ee) [lit. $[\alpha]_D^{25}$ +21.3° (*c* 1.28, $CHCl_3$, for *R* enantiomer with 90% ee)]9a HRMS(M+) calcd for $C_{13}H_{19}NOSi$: 233.1236; found: 233.1240 HPLC (DAICEL CHIRALCEL OJ-H, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 51.38 and 54.61 min.

4.1.9. 2-Trimethylsilyloxy-2-(4′-methoxylphenyl)propanenitrile (3i). ^1H NMR ($CDCl_3$) δ 0.19(s, 9H), 1.87(s, 3H), 3.85(s, 3H), 6.93(m, 2H), 7.49(m, 2H) ^{13}C NMR ($CDCl_3$) δ 1.1, 33.41, 55.33, 71.28, 113.89, 121.81, 126.06, 134.04, 159.80 $[\alpha]_D^{23}$ −17.0° (*c* 1.44, $CHCl_3$, 71% ee) HRMS(M+) calcd for $C_{13}H_{19}NO_2Si$: 249.1185; found: 249.1182 HPLC (DAICEL CHIRALCEL OJ-H, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 23.61 and 25.54 min.

4.1.10. 2-(Trimethylsilyloxy)indane-1-carbonitrile (3j). ^1H NMR ($CDCl_3$) δ 0.20 (s, 9H), 2.43–2.47 (m, 1H),

2.70–2.74 (m, 1H), 2.97–3.02 (m, 1H), 3.10–3.15 (m, 1H), 7.28 (d, 1H), 7.31 (t, 1H), 7.36 (t, 1H), 7.55 (d, 1H) ^{13}C NMR ($CDCl_3$) δ 1.1, 29.4, 42.9, 76.8, 121.3, 124.5, 125.3, 127.8, 129.9, 142.7, 142.9 $[\alpha]_D^{23}$ −19.4° (*c* 1.4, $CHCl_3$, 68% ee) [lit. $[\alpha]_D^{20}$ +24.5° (*c* 2.18 CH_2Cl_2, for *R* enantiomer with 65% *ee*)][9a] HRMS(M+) calcd for $C_{13}H_{17}NOSi$: 231.1079; found: 231.1082 HPLC (DAICEL CHIRALCEL OD, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 3.27 and 3.64 min.

4.1.11. 2-Trimethylsilyloxy-2-phenyl-3-methyl-butanenitrile (3k). ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 9H), δ 1.03 (q, *J*=7.4 Hz 6H), 1.97 (m, 1H), 7.38 (m, 3H), 7.50 (m, 2H) $[\alpha]_D^{20}$ −45.9° (*c* 4.1, $CHCl_3$, 92% ee) HRMS(M+) calcd for $C_{14}H_{21}NOSi$: 247.1392; found: 247.1395 HPLC (DAICEL CHIRALCEL OD, ^{i}PrOH/hexane=1/99, flow=0.5 mL/min) 6.36 and 6.84 min.

4.1.12. 2-Trimethylsilyloxy-3-(4-methoxyphenyl)-2-methyl-propanenitrile (3l). ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 9H), δ 1.73 (s, 1H), 2.71–2.93 (m, 2H), 3.75 (s, 3H), 6.76–7.23 (m, 4H) $[\alpha]_D^{20}$ −1.2° (*c* 4.1, $CHCl_3$, 65% ee) HRMS(M+) calcd for $C_{14}H_{21}NO_2Si$: 263.1342; found: 263.1345 HPLC (DAICEL CHIRALCEL OJ-H, ^{i}PrOH/hexane=1/99, flow=0.25 mL/min) 24.72 and 27.38 min.

4.1.13. 2-Trimethylsilyloxy-2-methyl-4-phenylbutanenitrile (3m). ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9H), δ 1.61 (s, 3H), 2.02 (m, 2H), 2.78(d, 2H) 2.87 (d, 2H), 7.19–7.22 (m, 3H), 7.28–7.3 (m, 2H) ^{13}C NMR ($CDCl_3$) δ 1.3, 29.4, 30.7, 45.2, 69.4, 121.9, 126.1, 128.3, 128.5, 140.7 $[\alpha]_D^{20}$ −10.5° (*c* 4.8, $CHCl_3$, 75% ee) [lit. $[\alpha]_D^{24}$ +13.3° (*c* 1.15, $CHCl_3$, for *R* enantiomer with 81% ee)][9a] HRMS(M+) calcd for $C_{14}H_{21}NOSi$: 247.1392; found: 247.1390 HPLC (DAICEL CHIRALCEL OJ-H, ^{i}PrOH/hexane=1/99, flow=0 .5 mL/min) 13.90 and 17.34 min.

4.1.14. 2-Trimethylsilyloxy-2-methyl-4-phenyl-3-butenenitrile (3n). ^{1}H NMR ($CDCl_3$) δ 0.29 (s, 9H), δ 1.77 (s, 3H), 6.16 (d, 1H), 6.91(d, 1H) 7.31 (m, 1H), 7.39 (m, 2H), 7.44 (m, 2H) ^{13}C NMR ($CDCl_3$) δ 1.4, 30.8, 69.9, 120.6, 126.9, 128.6, 128.7, 129.5, 130.9, 135.1 $[\alpha]_D^{20}$ −17.5° (*c* 2.4, $CHCl_3$, 60% ee) [lit. $[\alpha]_D^{25}$ +21.3° (*c* 1.34, $CHCl_3$, for *R* enantiomer with 91% ee)][11] HRMS(M+) calcd for $C_{14}H_{19}NOSi$: 245.1236; found: 245.1233 HPLC (DAICEL CHIRALCEL OJ-H, ^{i}PrOH/hexane=1/99, flow=0.5 mL/min) 11.36 and 14.02 min.

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