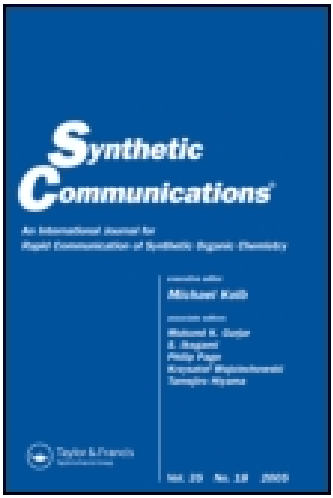

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Cyanosilylation of Prochiral Ketones Catalyzed by Lanthanide Complexes

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Cyanosilylation of Prochiral Ketones Catalyzed by Lanthanide Complexes

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Abstract: A new series of silylene-bridged rare-earth complexes involving fluorenyl are shown to be the very efficient Lewis acid catalysts, giving some cyano trimethylsilyl ethers of ketones in >99% yields.

Keywords: Cyano trimethylsilyl ethers of ketones, Lewis acid catalysts, silylene-bridged rare-earth complexes involving fluorenyl

Rare-earth organometallic complexes are the most important catalysts in polymerization of alkenes[1–3] and organic reactions.[4–6] Chiral cyanohydrins from aldehydes and ketones are highly versatile synthetic intermediates that can be easily converted into a wide variety of important synthetic intermediates including chiral α-hydroxyacids, α-amino acids, and β-amino alcohols. They are very important in medical synthesis and natural product synthesis, such as (S)-oxybutynin[7] and (20S)-camptothecin[8] synthesis. In recent years there has been intense research activity in this area. Shibasaki,[9–11] Deng,[12] Snapper and Hoveyda,[13] and Feng[14–16] have developed many catalysts in cyanosilylation of ketones.

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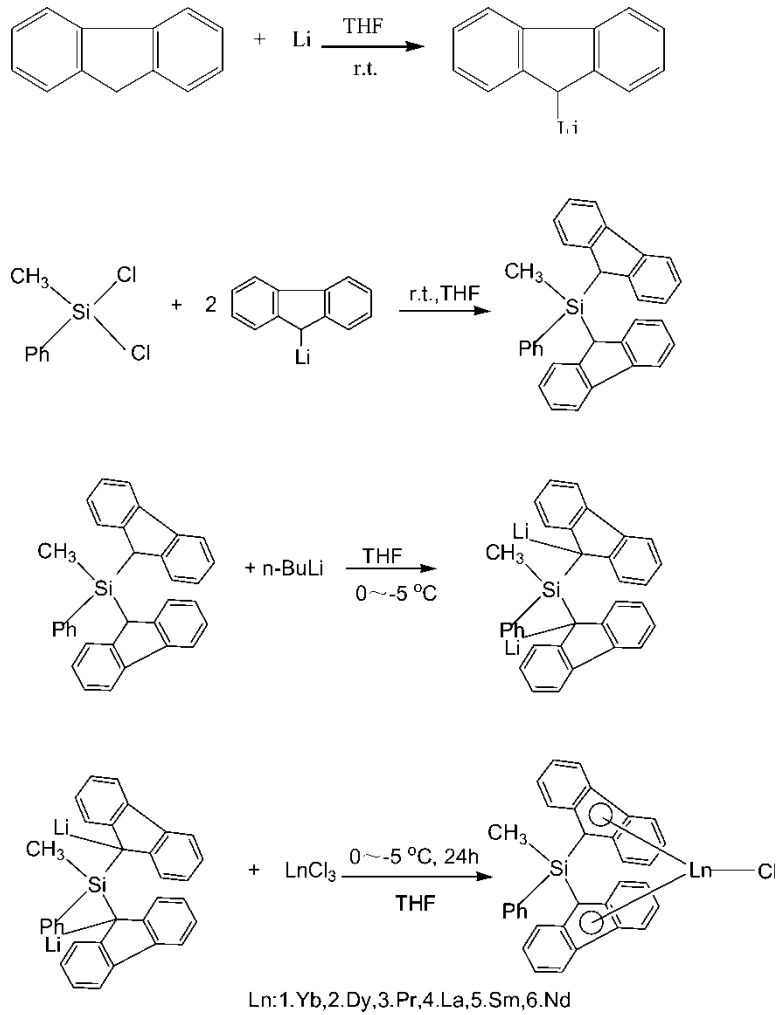
Recently, I was inspired by Jacobsen,[17] who developed a series of rare-earth trichlorides as Lewis acidic catalysts in cyanosilylation of imines. Using six rare-earth organometallic complexes as catalysts for similar cyanosilylation reactions of many cyano trimethylsilyl ethers of ketones, I obtained >99% yields.

Rare-earth organometallic complexes were prepared from bis (9-fluorenyl) (methyl)(phenyl) silylene lithium with $LnCl_3$ in THF under argon. They were characterized by MS, IR, and elemental analysis; the concrete procedure and data can be seen in another article.[18,19] The synthesis routes are shown in Scheme 1.



Ln:1.Yb,2.Dy,3.Pr,4.La,5.Sm,6.Nd

Scheme 1.

By applying these complexes to the cyanosilylation of ketones, it was found that the complex **3** works the best in freshly purified chloroform (0.015 M). After 0.5 h it gave excellent yields. When rare-earth trichloride was employed, no reaction occurred because of its poor solubility. Silylene-bridged ligands and no catalysts in this reaction will lead to a slow reaction or even no reaction after 1 h. Results are listed in Table 1.

The following mechanism of cyanosilylation of ketones can be proposed: one pair of isolated electrons in the oxygen atom of the C═O bond complexes with Ln^{3+}, so the catalysts greatly activate the substrates. The reactivity become very high and leads to a smooth reaction.

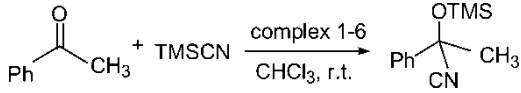
A range of ketones underwent efficient reactions under these conditions, including electron-deficient and electron-rich substrates. They all displayed different reactivity. The results are shown in Table 2 (entries 1–10).

The four-position aromatic ketones and the electron-deficient substrates have poor reactivity after 15 h, except entry 10; its electron-rich counterparts have better reactivity. The conversion of two-position substitution substrates are better than that of four-position substitution substrates. Other substrates display less reactivity (entries 2 and 3).

All in all, no matter the electron and deficient and electron-rich substrates, the steric factor is the main reason for reactivity.

In summary, this is the first example of Lewis acid catalysts in cyanosilylation of ketones to give stable cyano trimethylsilyl ethers in excellent yields at room temperature and with broad substrate generality. Additionally, these lanthanide complexes have been applied to the cyanosilation of aldehydes. Further efforts are being directed toward separating planar chiral

Table 1. Effect of different Ln^{3+} to cyanosilylation of acetophone[a]

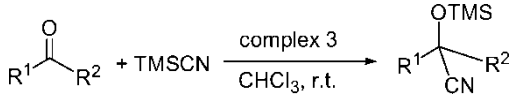


Entry	Complex	Time (h)	Conversion (%)[b]
1	$CH_3PhSi(C_{13}H_9)_2YbCl$	0.5	10
2	$CH_3PhSi(C_{13}H_9)_2DyCl$	0.5	64
3	$CH_3PhSi(C_{13}H_9)_2PrCl$	0.5	>99
4	$CH_3PhSi(C_{13}H_9)_2LaCl$	0.5	>99
5	$CH_3PhSi(C_{13}H_9)_2SmCl$	0.5	79
6	$CH_3PhSi(C_{13}H_9)_2NdCl$	0.5	16
7	$PrCl_3$	1	0
8	$CH_3PhSi(C_{13}H_9)_2$	1	0
9	No	5	0

[a]The temperature is at 25°C, $CHCl_3$ solvent.

[b]The conversion (%) was given by ^1H NMR (300 MHz, $CDCl_3$).

Table 2. Cyanosilylation of ketones catalyzed by rare-earth complex 3[a]



Entry	R^1	R^2	Time (h)	Conversion (%)[b]
1	C_6H_5	CH_3	0.5	>99
2	C_6H_5	CH_2CH_3	15	32
3	C_6H_5	$CH(CH_3)_2$	15	28
4	2-$OCH_3C_6H_4$	CH_3	15	>99
5	2-$CH_3C_6H_4$	CH_3	15	>99
6	4-$CH_3C_6H_4$	CH_3	15	52
7	4-$OCH_3C_6H_4$	CH_3	15	48
8	4-BrC_6H_4	CH_3	15	20
9	4-ClC_6H_4	CH_3	15	56
10	4-$NO_2C_6H_4$	CH_3	15	79

[a]The temperature is at 25°C, $CHCl_3$ solvent.
[b]The conversion (%) was given by ^{1}H NMR (300 MHz, $CDCl_3$).

complexes, and application to cyanosilylation of prochiral ketones, aldehydes, and some other asymmetric catalytic reactions.

EXPERIMENTAL

General Procedures[18]

All cyanosilylation reactions were performed using chloroform as solvent. Ligands and lanthanum complexes were synthesized, and reactions were monitored by thin-layer chromatography using 0.25-mm E. Merck silica gel–coated glass plates (60F-254) with UV light to visualize the course of the reaction. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.02–0.03 mm). Chemical conversions were obtained by ^{1}H NMR and ^{13}C NMR. ^{1}H and ^{13}C NMR spectra were obtained using either a Bruker AM-200 or AM-300 spectrometer. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, and m = multiplet. Infrared spectra were recorded on a Mattson Galaxy Series FTIR 3000 spectrometer. High-resolution mass spectra were obtained on a MASPEC.

Preparation of Bis(9-fluorenyl)(methyl)(phenyl) Silane[19]

10 g (60.24 mmol) of dry fluorene and 2 g (288.18 mmol) of lithium were added under free-water and free-oxygen conditions in a dry 100-ml Schlenk flask.

They were dissolved in 100 ml of dry THF. The yellow mixture was stirred for 48 h. 4.9 mL (30.12 mmol) of dichloro(methyl)(phenyl) silane was added dropwise at room temperature to the flask containing a THF solution of fluorenyllithium. After the condition was complete, the reaction mixture was stirred for an additional 24 h. The solvent was removed under vacuum and the residue was treated with 30 ml of n-hexane. The crude product was washed with n-hexane to afford a white solid. Mp (208–212°C), $C_{33}H_{26}Si$ found (calc, %): C, 88.02% (88.00%); H, 5.79% (5.78%). ^{1}H NMR (500 MHz, $CDCl_3$, 27°C), δ (ppm) = 7.71–7.77 (d, 6H, aromH), 7.30–7.33 (t, 8H, aromH), 7.15–7.18 (t, 2H, aromH), 7.09–7.10 (t, 1H, aromH), 6.85–6.88 (t, 2H, aromH), 6.49–6.51 (t, 2H, aromH), 4.64 (s, 2H, H-9, Flu), −0.32 (s, 3H, CH_3). ^{13}CNMR, −10.001, 39.623, 120.109, 120.186, 124.603, 125.700, 125.750, 126.262, 126.295, 126.773, 129.266, 134.076, 141.044, 141.159, 144.397, 144.440. MS: m/z 450 (M^+, 4.66%).

Preparation of (Methyl)(phenyl) Silylene-bis(9-fluorenyl) Lithium

A certain amount of 2 g (288.18 mmol) of lithium and 1 g (2.22 mmol) of bis (9-fluorenyl)(methyl)(phenyl) silane were diluted with 30 ml of dry THF under argon in a 100-ml Schlenk flask. The stirred solution was cooled to between 0 and 5°C. The resulting green solution was stirred for 48 h.

Preparation of (Methyl)(phenyl) Silylene-bis(9-fluorenyl) Yatterium Chloride

Bis (9-fluorenyl)(methyl)(phenyl) silylene lithium was added dropwise to a solution of rare-earth trichlorine, and the mixture was cooled down to between 0 and 5°C and under argon. The resulting yellow mixture was stirred for 48 h and then was allowed to warm up to room temperature. The resulting solution was concentrated in vacuum to about 20 ml. After adding 30 ml of n-hexane, the solid precipitated out and was recrystallized in THF/n-hexane. It was washed twice with THF/n-hexane and dried in vacuum to give complex **1** as white crystals (72% yield). HRMS (EI): 657.1306, Yb% 25.98 (26.33%); IR (KBr, cm^{-1}): υ 3065.4, 2962.6, 2925.9, 2835.2, 1632.1, 1457.3, 1428.7, 1261.3, 790.0, 737.7, 403.3, 390.7. Anal. calc. for CH_3-$PhSi(C_{13}H_9)_2YbCl$: C, 59.97%; H, 3.64%. Found: C, 60.32%; H, 3.68%.

(Methyl)(phenyl) Silylene-bis(9-fluorenyl) Dysprosium Chloride

Following the procedure described earlier, complex **2** as a white crystals was obtained (80% yield); HRMS (EI): 646.6505, Dy% 25.98 (25.13%); IR (KBr, cm^{-1}): υ 3069.1, 2961.1, 2924.1, 2851.2, 1634.6, 1476.3, 1428.2, 1260.9,

1098.0, 1028.2, 872.9, 798.6, 1098.0, 1028.2, 872.9, 798.6, 437.4. Anal. calc. for $CH_3PhSi(C_{13}H_9)_2DyCl$: C, 60.97%; H, 3.67%. Found: C, 61.30%; H, 3.71%.

(Methyl)(phenyl) Silylene-bis(9-fluorenyl) Praseodymium Chloride

Following the procedure described earlier, complex **3** was obtained yellow as crystals (75% yield); HRMS(EI): 625.0642, Pr% 21.98 (22.54%), IR (KBr, cm^{-1}): υ 3066.0, 3047.7, 2956.6, 2923.2, 2852.1, 1646.2, 1615.9, 1516.7, 1448.7, 1427.8, 1114.8, 1020.2, 983.7, 738.5, 484.2, 442.7. Anal. calc. for $CH_3PhSi(C_{13}H_9)_2PrCl$: C, 63.23%; H, 3.77. Found: C, 63.42%; H, 3.87%.

(Methyl)(phenyl) Silylene-bis(9-fluorenyl) Lanthanum Chloride

Following the procedure described earlier, complex **3** was obtained as yellow crystals (83% yield); HRMS(EI):623.0036, Pr% 21.86 (22.35%); IR (KBr, cm^{-1}): υ 3065.3, 3046.2, 2952.4, 2923.2, 2851.8, 1611.3, 1601.1, 1505.8, 1476.8, 1115.2, 984.8, 781.8, 738.2, 484.2, 456.3. Anal. calc. for $CH_3PhSi(C_{13}H_9)_2PrCl$: C, 63.62%: H, 3.89. Found: C, 63.52%; H, 3.87%.

(Methyl)(phenyl) Silylene-bis(9-fluorenyl) Samarium Chloride

Following the procedure described earlier, complex **4** was obtained as yellow crystals (90% yield); HRMS (EI): 634.0565, Sm% 23.59 (23.70%); IR (KBr, cm^{-1}): υ 3068.1, 2962.7, 1635.3, 1475.6, 1446.8, 1260.9, 1098.8, 1027.7, 790.6, 484.3, 443.5. Anal. calc. for $CH_3PhSi(C_{13}H_9)_2SmCl$: C, 62.51%; H, 3.62%. Found: C, 62.47%; H, 3.81%.

(Methyl)(phenyl) Silylene-bis(9-fluorenyl) Neodymium Chloride

Following the procedure described earlier, complex **5** was obtained as yellow crystals (86% yield); HRMS(EI): 627.9565, Nd% 22.31 (22.96%); IR (KBr, cm^{-1}): υ 3067.9, 2961.2, 2923.5, 1634.7, 1476.7, 1260.6, 1049.1, 1028.1, 789.1, 789.8, 737.8, 481.8, 430.5. Anal. calc. for $CH_3PhSi(C_{13}H_9)_2$ NdCl: C, 62.98%; H, 3.79%. Found: C, 63.08%; H, 3.84%.

2-(Trimethylsilyloxy)-2-phenyl-propanenitrile

$CH_3PhSi(C_{13}H_9)_2$ LnCl (0.015 mmol) was dissolved in 1 M $CHCl_3$ acetophone (1 mmol) and TMSCN (297 μl, 2.23 mmol) was successively added at room temperature. After 0.5 h, the reaction was quenched. Further

purification was performed by silica gel (petroleum/dichloromethane: 4/1). The title compound was obtained as a colorless oil (0.22 g, conversion >99%). The physical and spectral data were identical to those previously reported for this compound.[20] ^{1}H NMR (300 MHz, $CDCl_3$): 7.44–7.47 (m, 3H), 7.24–7.32 (m, 2H), 1.76 (s, 1H), 0.079 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 0.98 (×3), 22.56, 33.51, 71.53, 121.54, 124.53 (×2), 128.57 (×2), 141.92.

2-(Trimethylsilyloxy)-2-phenylbutanenitrile

The title compound was obtained as a colorless oil (74.56 mg, conversion 32%). The physical and spectral data were identical to those previously reported for this compound.[20] 1H NMR (300 MHz, $CDCl_3$): 7.36–7.39 (m, 2H), 7.21–7.29 (m, 3H), 1.80–1.92 (q, $J = 12.6$ Hz, 2H), 0.79–0.88 (t, $J = 9.9$ Hz, 3H), −0.052 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 1.35 (×3), 22.58, 30.87, 69.96, 120.67, 126.88, 128.58, 128.75, 129.51, 130.95, 135.11.

2-(Trimethylsilyloxy)-2-phenyl-i-pentanenitrile

The title compound was obtained as a colorless oil (69.65 mg, conversion 28%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.46–7.51 (m, 2H), 7.34–7.42 (m, 3H), 2.02–2.08 (m, 1H), 1.06–1.08 (d, $J = 6.6$ Hz, 3H), 0.79–0.82 (d, $J = 6.9$ Hz, 3H), 0.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 0.80 (×3), 17.15, 17.26, 41.48, 80.09, 120.19, 125.74 (×2), 128.23 (×2), 128.52, 140.19. HRMS: calcd. for $C_{13}H_{19}SiNO$: 247.13924, found: 247.13812.

2-(Trimethylsilyoxy)-(2′-methyloxylphenyl) Propanenitrile

The title compound was obtained as a colorless oil (0.25 g, conversion >99%), the physical and spectral data were identical to those previously reported for this compound. ^{1}H NMR (300 MHz, $CDCl_3$): 7.44–7.48 (m, 1H), 7.23–7.29 (m, 1H), 6.85–6.95 (m, 2H), 3.83 (s, 3H), 1.83 (s, 3H), 0.229 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 1.28 (×3), 30.09, 55.53, 68.53, 111.63, 120.56, 125.72, 129.80 (×2), 157.9. HRMS: calcd. for $C_{13}H_{19}SiNO_2$: 249.11851, found: 249.11720.

2-(Trimethylsilyoxy)-2-(2′-methylphenyl) Propanenitrile

The title compound was obtained as a colorless oil (0.23 g, conversion >99%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.53–7.58 (m, 1H), 7.18–7.27 (m, 3H), 2.55 (s, 3H), 1.94 (s, 3H), 0.077 (s, 9H). ^{13}C NMR (75 MHz,

$CDCl_3$): 1.09 (×3), 20.68, 30.51, 71.68, 121.62, 125.29, 125.97, 128.66, 132.64, 135.50, 138.41. HRMS: calcd. for $C_{13}H_{19}SiNO$: 233.12359, found: 233.12213.

2-(Trimethylsilyoxy)-2-(4′-methylphenyl) Propanenitrile

The title compound was obtained as a colorless oil (0.12 g, conversion 52%). The physical and spectral data were identical to those previously reported for this compound.[21] ^{1}H NMR (300 MHz, $CDCl_3$): 7.33–7.37 (m, 2H), δ 7.09–7.17 (m, 2H), 2.28 (s, 3H), 1.18 (s, 3H), 0.068 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 1.00 (×3), 20.98, 33.45, 71.44, 121.67, 124.51 (×2), 129.19 (×2), 138.43, 139.03.

2-(Trimethyloxy)-2-(4′-methyloxylphenyl) Propanenitrile

The title compound was obtained (0.12 g, conversion 48%). The physical and spectral data were identical to those previously reported for this compound.[21] ^{1}H NMR (300 MHz, $CDCl_3$), 7.33–7.36 (d, $J = 9$ Hz, 2H), δ 6.78–6.81 (d, $J = 9$ Hz, 2H), δ 3.71 (s, 3H), 1.73 (s, 3H), −0.024 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 1.00 (×3), 33.40, 55.32, 71.25, 113.85 (×2), 121.78, 126.03 (×2), 134.02, 159.75.

2-(Trimethylsilyoxy)-2-(4′-bromophenyl) Propanenitrile

The title compound was obtained (69.20 mg, conversion 20%). The physical and spectral data were identical to those previously reported for this compound.[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.46 (d, $J = 13.5$ Hz, 2H), 7.31–7.35 (d, $J = 12.6$ Hz, 2H), 1.74 (s, 3H), −0.002 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 1.00 (×3), 33.42, 71.02, 115.87, 121.07, 122.66, 126.30 (×2), 131.73 (×2), 141.19. HRMS: calcd. for $C_{12}H_{16}SiNOBr$: 297.01845, found: 297.1875.

2-(Trimethylsilyoxy)-2-(4′-chlorophenyl) Propanenitrile

The title compound was obtained (0.14 g, conversion 56%). The physical and spectral data were identical to those previously reported for this compound.[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13–8.16 (m, 2H), 7.61–7.64 (m, 2H), 7.33–7.36 (m, 2H), 1.75 (s, 3H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 0.96 (×3), 33.42, 70.96, 121.12, 126.00, 128.75 (×2), 134.50 (×2), 140.64.

2-(Trimethyloxy)-2-(4′-nitrophenyl) Propanenitrile

The title compound was obtained (0.21 g, conversion 79%). The physical and spectral data were identical to those previously reported for this compound.[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.49 (m, 2H), 7.29–7.33 (m, 2H), 1.78 (s, 3H), 0.09 (s, 9H).

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