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A mild and efficient cyanosilylation of ketones catalyzed by a Lewis acid–Lewis base bifunctional catalyst

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Abstract—A new family of bifunctional catalysts (*N*-oxides–Ti(O^iPr)$_4$ (2:1)) containing a Lewis acid and a Lewis base was developed and applied to the catalytic cyanosilylation of ketones. Utilizing *rac*((1*R*,2*S*) and (1*S*,2*R*))-1-(2′-pyridylmethyl)-2-diphenylhydroxymethylpyrrolidine *N*-oxide–titanium (2:1) complex and *N*-benzyl-diethanolamine *N*-oxide–titanium (2:1) complex as catalysts, the cyanosilylation products were obtained in 42–97% yield. Based on experimental phenomena and kinetic studies, a catalytic cycle was proposed to explain the remarkable activities of these catalysts. Investigations indicated that *rac*((1*R*,2*S*) and (1*S*,2*R*))-1-(2′-pyridylmethyl)-2-diphenylhydroxymethylpyrrolidine *N*-oxide–titanium (2:1) complex and *N*-benzyl-diethanolamine *N*-oxide–titanium (2:1) complex should promote the reaction via a dual activation of the ketone by the titanium and TMSCN by the *N*-oxide.

1. Introduction

Cyanohydrins are highly versatile synthetic intermediates, which can easily be converted into a wide variety of important synthetic intermediates including α-hydroxy acids, α-amino acids, and β-amino alcohols.[1] The importance of the cyanosilylation for the synthesis of cyanohydrins has stimulated considerable interest in the development of catalysts. Despite numerous and significant advances in this area,[2] the overall scope of this reaction remains limited. A conceptually direct and attractive approach is to transform ketones to chiral or achiral building blocks containing a quaternary carbon center by a catalytic C–C bond formation. The reaction of this approach, however, has proven to be a formidable task.[3] In fact, before Shibasaki's bifunctional catalyst concept was put forward, relative few studies on cyanosilylation of ketones, especially on asymmetric cyanosilylation of ketones was reported due to relatively low reactivity of ketones. A number of recent studies have shown that multifunctional ligands possessed useful characteristics for catalysis and asymmetric synthesis.[4] For example, ligands have been reported in which one portion engaged a Lewis acid moiety that coordinated an electrophilic substrate while another portion of the ligand coordinated to the nucleophilic substrate partner. Dual coordination by such catalyst assemblies further enables the reaction by simultaneously enhancing the electrophilic character of one portion and the nucleophilic character of the other.[5]

Examples of this motif can be found in the heterobimetallic complexes[4] and the phosphine oxide-derived catalysts developed by Shibasaki and co-workers.[6] Other bifunctional ligands that operate along these lines have also been discovered.[7] Inspired by the pioneering work of Shibasaki on asymmetric cyanosilylation using chiral titanium[8] and aluminum[6] phosphane oxide-derived complexes as bifunctional catalysts, we initiated a project to develop *N*-oxide–titanium complexes as bifunctional catalysts for the addition of cyanide to ketones. Early results of using the oxygen atom of a N–O group to activate TMSCN demonstrated the feasibility of our approach.[9] In a recent preliminary communication, we reported studies of the cyanosilylation of ketones promoted by achiral *N*-oxide–titanium complex.[10] In this paper, full details of the preparation and use of **1a**-**1d**–titanium (2:1) complexes are reported, along with further studies on the relationship of catalyst structure, reactivity, substrate generality, dual activity mechanism of catalyst, and limitations of the reaction.

2. Results and discussion

The goal of the present work was to construct scaffolds in which the Lewis acid and base elements can be independently manipulated. In particular, new compounds can be

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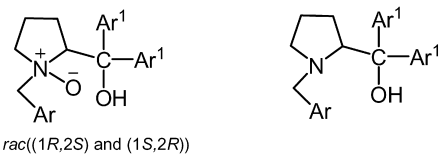


rac((1*R*,2*S*) and (1*S*,2*R*))

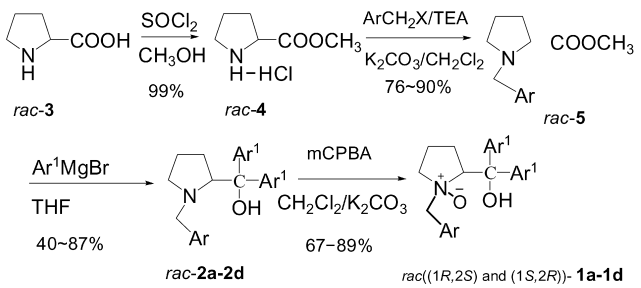
1a: Ar=2-pyridyl ; Ar^1=Ph
1b: Ar=2-$MeOC_6H_4$; Ar^1=Ph
1c: Ar=3-pyridyl ; Ar^1=Ph
1d: Ar=Ph ; Ar^1=Ph

2a: Ar=2-pyridyl ; Ar^1=Ph
2b: Ar=2-$MeOC_6H_4$; Ar^1=Ph
2c: Ar=3-pyridyl ; Ar^1=Ph
2d: Ar=Ph ; Ar^1=Ph

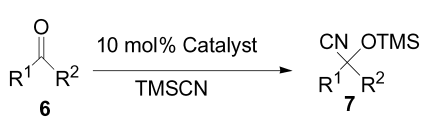
Figure 1. Structure of the designed ligands **1**-**2**.

envisioned with functional groups specifically tailored to the nucleophile and electrophile of a given reaction and with the optimal spacing and orientation between groups. The structurally well-defined and rigid Corey reagent was chosen as a starting point, leading to general structures **1**-**2** (Fig. 1). An apical coordination metal at the *N*-oxide metal center could act as the docking site for a Lewis basic substrate. In addition, the ease of preparation and derivation on of the Corey backbone was ideal for the rapid construction of many ligands.

To optimize the catalytic activity of *N*-oxides **1**–titanium (2:1) complexes, the effect of varying each aspect of its structure was investigated, starting with the substituents attached to the nitrogen atom at the 1-position. Ligands **1a**-**1d** were prepared in four steps[11] as shown in Scheme 1 to determine whether the effective coordinating atom on the aryl ring at the 1-position is the key feature controlling the catalytic activity. At first, combinations of $Ti(O^iPr)_4$ and different *N*-oxides were optimized by the model reaction of TMSCN with acetophenone. The catalyst was in situ prepared by stirring a solution of ligand (20 mol%) and $Ti(O^iPr)_4$ (10 mol%) in CH_2Cl_2. Without catalyst isolation, acetophenone was added to a cooled catalyst solution at 0°C, followed by dropwise addition of TMSCN, to afford the O-TMS cyanohydrin (Scheme 2). Each catalyst was evaluated for its ability to catalyze the addition of trimethylsilyl cyanide to acetophenone as shown in Scheme 2. The results shown in Table 1 illustrate that **1a**–titanium (2:1) was the best catalyst in terms of reactivity and the product was obtained in 80% isolated yield. In terms

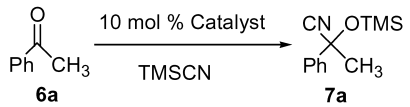


Scheme 1. Synthesis of ligands **1** and **2**.



Scheme 2. Cyanosilylation of ketones catalysed by *N*-oxides–titanium (2:1) complexes.

Table 1. Effects of ligands on the cyanosilylation of acetophenone with TMSCN



Entry	Ligand	*T* (°C)	Time (h)	Isolated yield (%)
1	**1a**	0	48	80
2	**1b**	0	48	56
3	**1c**	0	48	75
4	**1d**	0	48	40

Reaction conditions: ligand–$Ti(O^iPr)_4$=2:1; concentration of substrate is 0.34 M.

Table 2. Effects of solvent on the cyanosilylation of acetophenone with TMSCN

Entry	Solvent	*T* (°C)	Time (h)	Isolated yield (%)
1	CH_2Cl_2	0	62	82
2	THF	0	72	40
3	Et_2O	0	72	48
4	Toluene	0	76	35
5	CH_3CN	0	72	Trace

Reaction conditions: ligand **1a** (20 mol%)–$Ti(O^iPr)_4$=2:1; concentration of substrate is 0.34 M.

of yield, **1b** and **1d** were the worst ligands (Table 1, entries 2 and 4).

The solvent effect was investigated by using the standard procedure. The solvent survey revealed that CH_2Cl_2 was the best solvent, providing the product of the cyanosilylation in high isolated yield (Table 2). In solvents containing coordinate oxygen or nitrogen atoms, such as THF, Et_2O, CH_3CN, the reactions gave the product in lower yields. It was noteworthy that the product was trace when the reaction proceeded in CH_3CN. This result was different from that reported by Saravanan.[2] Toluene afforded a similar result to ether-type solvents.

In order to optimize the reaction conditions for a higher isolated yield, the effect of the molar ratio of ligand **1a** to $Ti(O^iPr)_4$ was carefully examined. The molar ratio of ligand **1a** to $Ti(O^iPr)_4$ dramatically influenced the isolated yield. When the molar ratio of ligand **1a** to $Ti(O^iPr)_4$ was 2:1, the best isolated yield was obtained. The isolated yield increased with the molar ratio of ligand **1a** to $Ti(O^iPr)_4$ (Table 3, entries 3 and 4). The concentration of substrate and catalyst was also an important factor to obtain a high isolated yield. The optimized concentration of substrate was 0.34 M when 10 mol% amount of catalyst **1a**–titanium

Table 3. Effects of ratio of ligand to metal ion on the cyanosilylation of acetophenone with TMSCN

Entry	Catalyst (**1a**–$Ti(O^iPr)_4$)	Time (h)	Isolated yield (%)
1	2:1	62	82
2	1.25:1	72	69
3	1:1	72	56
4	1:1.25	72	40

Reaction conditions: concentration of substrate is 0.34 M; in CH_2Cl_2; at 0°C.

Table 4. Effects of concentration of substrate and catalyst on the cyanosilylation of acetophenone with TMSCN

Entry	Concentration of substrate (M)	Concentration of catalyst (M)	Isolated yield (%)
1	0.68	0.068	68
2	0.34	0.034	80
3	0.17	0.017	72
4	0.11	0.011	53
5	0.085	0.0085	37

Reaction conditions: **1a** (20 mol%)–$Ti(O^iPr)_4$=2:1; in CH_2Cl_2; at 0°C; reaction time: 48 h.

Table 5. Cyanosilylation of ketones (R^1COR^2) catalyzed by **1a**–$Ti(O^iPr)_4$ (2:1) complex

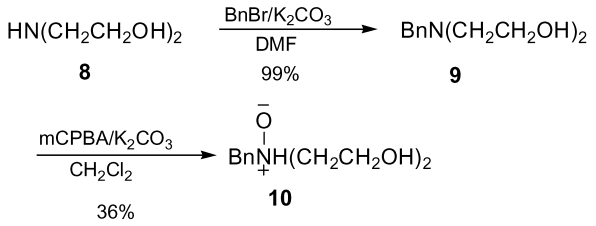
Entry	R^1	R^2	Time (h)	Isolated yield (%)[a]
1	C_6H_5	CH_3	62	82
2	2-FC_6H_4	CH_3	68	85
3	4-FC_6H_4	CH_3	68	84
4	$C_6H_5(CH_2)_2$	CH_3	96	93
5	C_6H_5	C_2H_5	72	87
6	4-$CH_3C_6H_4$	CH_3	92	79
7	β-Naphthyl	CH_3	98	79
8	4-$NO_2C_6H_4$	CH_3	80	86
9	$C_6H_5CH{=}CH$	CH_3	96	80
10	*n*-C_5H_{11}	CH_3	51	97
11	4-$NH_2C_6H_4$	CH_3	98	54
12	2-Thiophenyl	CH_3	76	42

All the reactions were carried out according to the experimental procedure.
[a] The isolated yields were given on the isolated O-TMS cyanohydrins after chromatographic purification, satisfactory spectral data (^1H NMR, ^{13}C NMR, IR) and elemental analysis were obtained for the new compounds.

(2:1) was used. If the concentrations of substrate and catalyst decreased to 2 and 4-fold lower than the optimal concentration, the reaction catalyzed by **1a**–Ti(IV) complex proceeded slowly and afforded the product in lower isolated yields (Table 4, entries 4 and 5). At a higher concentration, the formation of titanium multinuclear aggregates might compress the catalytic activity, and the isolated yield was decreased to 68% (Table 4, entry 1).

With the optimized catalyst structure and reaction conditions, the addition of trimethylsilyl cyanide to a range of aromatic and aliphatic ketones catalyzed by 10 mol% **1a**–titaniun (2:1) catalyst was investigated. The results shown in Table 5 indicated that the aromatic, conjugated and aliphatic ketones afforded the corresponding products in good to excellent isolated yields (Table 5, entries 1–10) and substituents on the aromatic ring had a slight influence on the conversions. Especially, less reactive ketones such as 2-acetylthiophen gave the product in moderate isolated yield (Table 5, entry 12) by our procedure. To the best of our knowledge, this was the first example of cyanosilylation of 2-acetylthiophen. As a matter of fact, the low conversion of 2-acetylthiophen (Table 5, entry 12) was probably due to the coordination between the sulfur atom on the thiophen ring and titanium, which restricted coordination between the carbonyl group and the titanium.

Although **1a** was easily synthesized, Grignard reaction conditions are severe in the process of preparation. We attempted to employ more easily prepared and inexpensive



Scheme 3. Synthesis of ligand **10**.

Table 6. Cyanosilylation of ketones (R^1COR^2) catalyzed by *N*-oxide (**10**)–$Ti(O^iPr)_4$ (2:1) complex

Entry	R^1	R^2	Time (h)	Isolated yield (%)[a]
1	Ph	CH_3	68	80
2	4-FC_6H_4	CH_3	68	84
3	C_6H_5	C_2H_5	80	87
4	$C_6H_5(CH_2)_2$	CH_3	96	93
5	4-$NO_2C_6H_4$	CH_3	80	76

All the reactions were carried out according to experimental procedure, but **1a** was replaced by *N*-oxide (**10**).
[a] The isolated yields were given on the isolated O-TMS cyanohydrins after chromatographic purification, satisfactory spectral data (^1H NMR, ^{13}C NMR, IR) and elemental analysis were obtained for the new compounds.

N-oxide instead of **1a**. For this purpose, *N*-oxide (**10**) was synthesized (Scheme 3) and employed for cyanosilylation of ketones according to the procedure described above. The results of representative substrates were shown in Table 6. Gratifyingly, the results indicated that catalytic activity of *N*-oxide (**10**)–$Ti(O^iPr)_4$ was similar to that of **1a**–$Ti(O^iPr)_4$ for this reaction. So *N*-oxide (**10**), as an inexpensive ligand, could be employed in the cyanosilylation of ketones, and made this method more practical.

To confirm that **1a**–titanium (2:1) complex was a bifunctional catalyst, we performed the following studies. First, the activation ability of *N*-oxide toward TMSCN was evaluated. The reaction of acetophenone with TMSCN in the presence or absence of 20 mol% *N*,*N*-dimethylphenylamine *N*-oxide was carried out, employing 20 mol% $Ti(O^iPr)_4$ as Lewis acid at 0°C in CH_2Cl_2. In the case without *N*,*N*-dimethylphenylamine *N*-oxide, 20 mol% $Ti(O^iPr)_4$ was used as a catalyst for this reaction, but no product could be detected after 48 h. However, in the presence of 20 mol% *N*,*N*-dimethylphenylamine *N*-oxide, the product was obtained in 9% yield under the same conditions. Lewis acidity of $Ti(O^iPr)_4$ and *N*,*N*-dimethylphenylamine *N*-oxide complex was lower than that of $Ti(O^iPr)_4$. If the complex, as a catalyst, derived from the oxygen atom of the N–O group of *N*,*N*-dimethylphenylamine *N*-oxide coordinated with $Ti(O^iPr)_4$ would promote cyanosilylation of ketones, $Ti(O^iPr)_4$, as a catalyst, would also catalyze the cyanosilylation of ketones. However, the cyanosilylation product of the ketone was not obtained. So from these results we reckoned that the N–O group of *N*,*N*-dimethylphenylamine *N*-oxide was not coordinated with $Ti(O^iPr)_4$ and activated trimethylsilyl cyanide as a Lewis base. Further evidence that the N–O moiety of the *N*-oxide was increasing nucleophilicity of trimethylsilyl cyanide was obtained by employing a complex of 20 mol% $Ti(O^iPr)_4$ and 20 mol% triethanolamine *N*-oxide as a catalyst in the reaction, and the yield of the reaction was raised to 37%.

Because the oxygen atom of the N–O group of triethanolamine *N*-oxide was at the top of molecular tetrahedron configuration and 'naked', it activated TMSCN as a Lewis base. This also suggests that the internal Lewis basic oxygen donor of **1a** would activate TMSCN if the *N*-oxide was at the defined position close to the activated ketones.

A preliminary evidence of the bifunctional catalysis by the complex of **1a** and $Ti(O^iPr)_4$ was obtained by the following experiment. When 20 mol% **2a**–$Ti(O^iPr)_4$ (2:1) complex was used to catalyze the cyanosilylation of acetophenone at 0°C in CH_2Cl_2, no product was obtained after 76 h. This showed that, although the center metal of the catalyst could activate the ketone, the reaction proceeded with difficulty. This revealed that the *N*-oxide moiety played a crucial role in the reaction. On the other hand, Lewis bases can catalyze the addition of TMSCN to a carbonyl compound.[12] However, in the absence of $Ti(O^iPr)_4$, when 20 mol% **1a** was used as a catalyst, the reaction did not proceed even after 70 h. This result indicated that $Ti(O^iPr)_4$ was also necessary for this reaction. To further explore the bifunctional catalysis of **1a**–$Ti(O^iPr)_4$ complex, the reaction of a Lewis acid ligating ketone and N–O group as Lewis base activating TMSCN was carried out, but the Lewis acid and Lewis base center was not the same molecule. Employing 20 mol% **2a**–$Ti(O^iPr)_4$ (1:1) complex as Lewis acid activating acetophenone and 20 mol% *N*,*N*-dimethylphenylamine*N*-oxide as a Lewis base activating TMSCN, the reaction proceeded by mixing the two portions at 0°C in CH_2Cl_2, the product was obtained in 51% yield after 48 h. From this result, it could be postulated that TMSCN activated by *N*,*N*-dimethylphenylamine *N*-oxide should attack the activated ketone.

To elucidate the origin of the excellent isolated yield with wide generality as a bifunctional catalysis of **1a**–$Ti(O^iPr)_4$ (2:1) complex, we designed kinetic studies to compare the reaction rate using **1a**–$Ti(O^iPr)_4$ (1:1) and **1a**–$Ti(O^iPr)_4$ (2:1) catalysts containing more N–O groups (Fig. 2). The initial reaction rate using **1a**–$Ti(O^iPr)_4$ (2:1) (20 mol%) as a catalyst was faster than that using **1a**–$Ti(O^iPr)_4$ (1:1) (20 mol%) as a catalyst, reflecting the higher basicity or with more Lewis basic oxygen donor of *N*-oxide activating trimethylsilyl cyanide in the reaction. The increased reaction rate by **1a**–$Ti(O^iPr)_4$ (2:1) complex was consistent with the dual activation mechanism of this catalyst. Much more Lewis basic oxygen donor of *N*-oxide should activate TMSCN more efficiently, thus facilitating the desired dual activation pathway.

These studies described above led to several key observations. (1) The presence of the N–O moiety of *N*-oxide was critical to reactivity (compare **2a** with **1a**); (2) the presence of a more Lewis basic N–O moiety influenced the rate of cyanide addition. For instance, the initial rate of reaction (within 10 h) with the **1a**–$Ti(O^iPr)_4$ (2:1) catalyst was almost two (1.8) times faster than that for **1a**–$Ti(O^iPr)_4$ (1:1). The importance of the presence of the N–O moiety and the significant influence on the reaction rate suggest that the N–O moiety of **1a** might participate actively in the cyanosilylation of ketones.

To further prove interaction between the oxygen atom of the N–O moiety of *N*-oxide and trimethylsilyl cyanide, a simple spectroscopic study of **1a**–titanium complex was carried out. First, a solution of trimethylsilyl cyanide in CH_2Cl_2 was prepared, and the infrared spectrum was recorded, with the infrared absorption associated with C≡N bond observed at 2190 and 2306 cm^{-1}; then a solution of TMSCN and *N*,*N*-dimethylphenylamine *N*-oxide in CH_2Cl_2 was prepared for the IR spectrum. It was found that the infrared absorption at 2190 cm^{-1} disappeared. The same phenomenon was observed during the process of cyanosilylation of acetophenone catalyzed by **1a**–$Ti(O^iPr)_4$ (2:1). The spectral changes strongly revealed that interaction between the oxygen atom of the N–O moiety of *N*-oxide and TMSCN really existed and the N–O group was likely coordinated to Si with respect to the cyanide to increase its nucleophilicity.

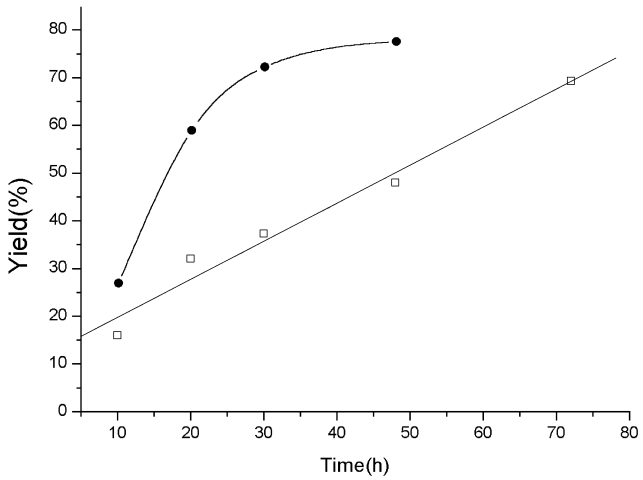


Figure 2. Initial reaction rate in the absence of catalysts **1a**–$Ti(O^iPr)_4$ (2:1) (20 mol%) (●) and **1a**–$Ti(O^iPr)_4$ (1:1) (20 mol%) (□).

From these mechanistic studies, the cyanosilylation of ketones promoted by **1a**–$Ti(O^iPr)_4$ (2:1) may be explained by the working model depicted as **13** in Figure 3. Significantly, the center titanium metal in complex **11** was already six coordinate similar to that of Salen-titanium, so the formation of a complex between titanium and acetophenone would presumably only be possible if an existing bond in the complex was broken first.[13] Thus, combination of complex **12** (obtained from complex **11** and ketone) with TMSCN generated the key intermediate complex **13**, which comprised both an activated ketone and an activated TMSCN. Intramolecular transfer of cyanide within complex **13** generated a complex **14** containing a titanium bound cyanohydrin. Subsequent intramolecular trimethylsilylation would give the product and catalyst **11**. Ketone coordinated to catalyst **11** would regenerate complex **12**.

3. Conclusion

A new strategy was devised to catalyze the addition of trimethylsilyl cyanide to ketones using **1a** and *N*-oxide (**10**)–titanium (2:1) as catalysts. It was demonstrated that, **1a**–titanium (2:1) and *N*-oxide (**10**)–titanium (2:1) complexes can serve as bifunctional catalysts to deliver appreciable reactivity. A possible mechanistic cycle and

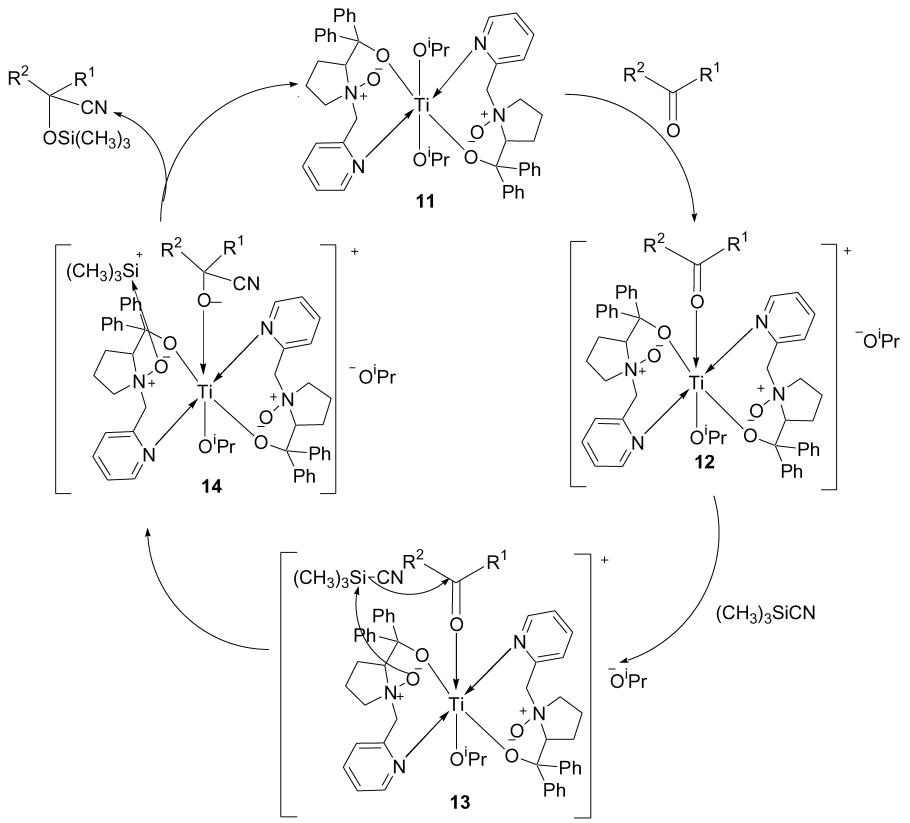


Figure 3. Proposed catalytic cycle.

transition state structure for the addition of trimethylsilyl cyanide to ketones promoted by catalyst **1a**–titanium (2:1) was presented. It must be noted that, although the above catalytic cycle offered a plausible and consistent rationale that accounted for numerous features of the titanium-catalyzed cyanide addition, it failed to explain the more subtle attributes of this class of transformation. The remarkable activity of **1a**–titanium (2:1) catalyst was also explained by its ability to simultaneously activate both the ketone and cyanide components of the reaction. Ongoing work is aimed at the development of new catalysts for asymmetric cyanosilylation of ketones and other asymmetric C–C bond forming reactions.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker-200, 300 and 400 spectrometer, at 300, 400 MHz for ^{1}H NMR, 75 MHz, 100 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (δ=0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm for ^{13}C NMR as an internal reference). Infrared spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer. Column chromatography was performed with silica gel H 60. In general, reactions were carried out in dry solvents under a nitrogen atmosphere, unless noted otherwise. Melting points are uncorrected. Elemental analyses were performed on a Carlo-1106 analyzer. Tetrahydrofurn (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Other reagents were purified by usual methods.

4.1.1. *rac*-*N*-Arylmethyl proline methyl ester (5). To a solution of D,L-proline methyl ester hydrochloride **4** (1.66 g, 10 mmol) in dry DMF (10 mL) was added triethylamine (2.0 mL, 15.3 mmol) at room temperature and the mixture was stirred at room temperature for a few minutes. The mixture was then filtrated to give a solution of D,L-proline methyl ester in dry DMF.

The solution of D,L-proline methyl ester was added dropwise to a mixture of halomethyl aromatic compound (6.67 mmol), anhydrous K_2CO_3 (0.78 g, 5.65 mmol) and NaI (44 mg, 0.29 mmol) in dry DMF (50 mL). The mixture was kept at 50°C, and monitored by TLC after 2 h until halomethyl aromatic compound disappeared. Then the mixture was poured into water and extracted with CH_2Cl_2 (3×20 mL). Organic layer was washed with water (100 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent under the reduced pressure and purification of the residue by a silica gel column chromatography (50% AcOEt–petroleum ether) afforded the title compounds **5a**-**5d**, which were used for next reaction without further purification.

4.2. General procedure for the preparation of *rac*-1-arylmethyl-2-diphenylhydroxymethyl pyrrolidine (2a-2d)

A dry, three-necked, round-bottomed flask was equipped

with a pressure-equalizing dropping funnel, a condenser, a rubber septum and a magnetic stirrer. The contents of the flask were placed under nitrogen, and 40 mL (8 mmol) of phenylmagnesium bromide in THF solution (0.2 M) was added. A solution of *rac*-*N*-arylmethyl proline methyl ester **5** (1 mmol) in dry THF (20 mL) was added to the phenylmagnesium bromide solution over 1 h at 0 to −10°C with ice–salt bath cooling. After the addition, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 1 day. Sat. NH_4Cl solution (20 mL) was added to the reaction mixture. The resulted mixture was concentrated under reduced pressure to remove THF and the resultant aqueous mixture was extracted with ethyl ether (3×10 mL). The ethereal extract was washed with brine (20 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a solid, which was purified by silica gel column chromatography and recrystallized to give the title compounds **2a**-**2d**.

4.2.1. *rac*-1-(2′-Pyridylmethyl)-2-diphenylhydroxymethylpyrrolidine (2a). Purification of the residue by silica gel column chromatography (50% AcOEt–petroleum ether) afforded a solid, which was recrystallized from ethyl ether to give the title compound **2a** (137.9 mg, 40%) as colorless crystals, mp 120–123°C. [Found: C, 80.02; H, 6.91; N, 8.08. $C_{23}H_{24}N_2O$ requires C, 80.23; H, 6.98; N, 8.14%]; R_f (50% AcOEt–petroleum ether) 0.47; ν_{max} (KBr) 3332, 2954, 1620, 1590, 1478, 1186, 1100, 750, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.42 (1H, d, J=4 Hz, C_5H_4N), 7.84 (2H, d, J=1.2 Hz, C_5H_4N), 7.57 (3H, m, C_5H_4N, Ph), 7.16–7.31 (5H, m, Ph), 7.05–7.14 (3H, m, Ph), 4.98 (1H, s, O*H*), 4.09 (1H, d, J=4.8 Hz, $NCH_2C_5H_4N$), 4.06 (1H, d, J=4.8 Hz, $NCH_2C_5H_4N$), 3.35 (1H, m, C_4H_7N), 2.97 (1H, m, C_4H_7N), 2.48–2.55 (1H, m, C_4H_7N), 1.93–2.01 (1H, m, C_4H_7N), 1.74–1.79 (1H, m, C_4H_7N), 1.63–1.68 (2H, m, C_4H_7N); δ_C (100 MHz, $CDCl_3$) 159.69, 148.58, 147.71, 146.36, 136.31, 128.11, 128.01, 126.37, 126.24, 125.59, 125.55, 122.44, 121.79, 78.01, 70.89, 62.23, 55.71, 29.61, 24.38.

4.2.2. *rac*-1-(2′-Methoxyphenylmethyl)-2-diphenylhydroxymethylpyrrolidine (2b). Purification of the residue by silica gel column chromatography (9% AcOEt–petroleum ether) afforded a solid, which was recrystallized from ethyl ether to give thetitle compound **2b** (176.1 mg, 47%) as colorless crystals, mp 112–113°C. [Found: C, 80.27; H, 7.27; N, 3.78. $C_{25}H_{27}NO_2$ requires C, 80.43; H, 7.24; N, 3.75%]; R_f (9% AcOEt–petroleum ether) 0.43; ν_{max} (KBr) 3260, 2956, 1514, 1445, 1252, 1178, 750, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, J=8 Hz, Ph), 7.57 (2H, d, J=8.4 Hz, Ph), 7.28 (4H, m, Ph), 7.13 (2H, m, Ph), 6.86 (4H, m, Ph) 4.94 (1H, s, O*H*), 3.95 (1H, m, C_4H_7N), 3.76 (3H, s, OCH_3), 3.13 (1H, d,J=12.8 Hz, NCH_2Ph), 2.96 (1H, d,J=12.8 Hz, NCH_2Ph), 2.90 (1H, m, C_4H_7N), 2.34 (1H, dd,J=9.2, 15.6 Hz, C_4H_7N), 1.95 (1H, m, C_4H_7N), 1.74 (1H, m, C_4H_7N), 1.62 (2H, m, C_4H_7N); δ_C (100 MHz, $CDCl_3$) 158.43, 148.05, 146.63, 131.77, 129.70, 128.14, 128.06, 126.35, 126.19, 125.59, 125.53, 113.40, 77.93, 70.43, 59.81, 55.39, 55.18, 29.82, 24.13.

4.2.3. *rac*-1-(3′-Pyridylmethyl)-2-diphenylhydroxymethylpyrrolidine (2c). Purification of the residue by silica gel column chromatography (50% AcOEt–petroleum ether) afforded a solid, which was recrystallized from ethyl ether to give the title compound **2c** (218.4 mg, 64%) as colorless crystals, mp 125–127°C. [Found: C, 80.21; H, 6.88; N, 7.85. $C_{23}H_{24}N_2O$ requires C, 80.23; H, 6.98; N, 8.14%]; R_f (50% AcOEt–petroleum ether) 0.54; ν_{max} (KBr) 3255, 2967, 1683, 1578, 1480, 1166, 749, 709 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.43 (1H, dd,J=1.6, 4.8 Hz, C_5H_4N), 8.25 (1H, d, J=1.6 Hz, C_5H_4N), 7.71 (2H, m, C_5H_4N), 7.56–7.59 (2H, m, Ph), 7.26–7.35 (5H, m, Ph), 7.09–7.19 (3H, m, Ph), 4.66 (1H, s, O*H*), 4.00 (1H, dd, J=4.4, 9.6 Hz, C_4H_7N), 3.16 (1H, d, J=12.8 Hz, $NCH_2C_5H_4N$), 3.07 (1H, d, J=12.8 Hz, $NCH_2C_5H_4N$), 2.88–2.92 (1H, m, C_4H_7N), 2.32–2.38 (1H, m, C_4H_7N), 1.95–2.03 (1H, m, C_4H_7N), 1.80–1.83 (1H, m, C_4H_7N), 1.63–1.69 (2H, m, C_4H_7N); δ_C (100 MHz, $CDCl_3$) 149.86, 148.36, 147.72, 146.21, 136.11, 134.89, 128.26, 128.13, 126.52, 126.35, 125.55, 125.52, 123.20, 78.12, 70.75, 57.95, 55.63, 29.67, 24.30.

4.2.4. *rac*-1-Benzyl-2-diphenylhydroxymethylpyrrolidine (2d). Purification of the residue by silica gel column chromatography (5% AcOEt–petroleum ether) afforded solid, which was recrystallized from ethyl ether to give the title compound **2d** (299.1 mg, 87%) as colorless crystals, mp 120–122°C. [Found: C, 83.79; H, 7.16; N, 4.07. $C_{24}H_{25}NO$ requires C, 83.96; H, 7.29; N, 4.08%]; R_f (5% AcOEt–petroleum ether) 0.57; ν_{max} (KBr) 3436, 2967, 1492, 1447, 1128, 1100, 766, 703 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.75 (2H, m, Ph), 7.63 (2H, m, Ph), 7.06–7.36 (11H, m, Ph), 4.98 (1H, s, O*H*), 3.98–4.04 (1H, m, C_4H_7N), 3.26 (1H, d, J=12.6 Hz, NCH_2Ph), 3.08 (1H, d, J=12.6 Hz, NCH_2Ph), 2.93–2.96 (1H, m, C_4H_7N), 2.37–2.40 (1H, m, C_4H_7N), 1.97–2.01 (1H, m, C_4H_7N), 1.62–1.80 (3H, m, C_4H_7N); δ_C (100 MHz, $CDCl_3$) 147.99, 146.63, 139.65, 128.58, 128.17, 128.09, 128.07, 126.83, 126.37, 126.23, 125.58, 125.54, 77.94, 70.59, 60.57, 55.52, 29.79, 24.15.

4.2.5. *N*-Benzyl-diethanolamine (9). To a solution of diethanolamine (8.40 g, 80.0 mmol) and TEA (13.4 mL, 96 mmol) in dry DMF (20 mL) was added benzyl bromide (10.5 mL, 88.0 mmol) at room temperature and at same temperature stirred for 1 h, then the resulting mixture was poured into water. The resulting mixture was extracted with CH_2Cl_2 (3×20 mL), organic layer was washed with water (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound **9**, which was used in next step without further purification.

4.2.6. *rac*((1*R*,2*S*) and (1*S*,2*R*))1-Arylmethyl-2-diphenylhydroxymethylpyrrolidine *N*-oxide (1a-1d). Synthesis of aminoalcohol *N*-oxide proceeded according to Ref. 7. To a solution of aminoalcohol (3.0 mmol) and anhydrous K_2CO_3 (621 mg, 4.5 mmol) in CH_2Cl_2 (25 mL) was added 70–74% *m*CPBA (718.8 mg, 3.0 mmol) under nitrogen atmosphere at −78°C. The resulting mixture was stirred for 5 h at same temperature, then the mixture was warmed slowly to room temperature, filtrated and evaporated under reduced pressure. The residue was purified by silica gel column chromatography.

4.2.7. *rac*((1*R*,2*S*) and (1*S*,2*R*))-1-(2′-Pyridylmethyl)-2-diphenylhydroxymethylpyrrolidine *N*-oxide (1a). The residue was purified by silica gel column chromatography

(17% CH_3OH–AcOEt) to give the title compound **1a** (922.0 mg, 85%) as white solid, mp 167–168°C. [Found: C, 76.44; H, 6.66; N, 7.82. $C_{23}H_{24}N_2O_2$ requires C, 76.67; H, 6.67; N, 7.78%]; R_f (17% CH_3OH–AcOEt) 0.45; ν_{max} (KBr) 3423, 2963, 1592, 1488, 1177, 1050, 845, 750, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.81 (1H, s, O*H*), 8.51 (1H, d, *J*=4 Hz, C_5H_4N), 7.86 (2H, d, *J*=7.2 Hz, C_5H_4N), 7.58–7.64 (3H, m, Ph, C_5H_4N), 7.14–7.41 (8H, m, Ph), 4.68 (1H, t,*J*=8.8 Hz, C_4H_7N), 3.86 (1H, d, *J*=12.4 Hz, $NCH_2C_5H_4N$), 3.78 (1H, d, *J*=12.4 Hz, $NCH_2C_5H_4N$), 3.53–3.60 (1H, m, C_4H_7N), 2.85–2.90 (1H, m, C_4H_7N), 2.47–2.55 (1H, m, C_4H_7N), 2.22–2.31 (1H, m, C_4H_7N), 1.99–2.09 (1H, m, C_4H_7N), 1.75–1.82 (1H, m, C_4H_7N); δ_C (100 MHz, $CDCl_3$) 151.96, 148.68, 147.48, 146.74, 136.35, 128.20, 127.69, 126.84, 126.56, 126.40, 124.76, 123.67, 78.01, 77.21, 73.07, 69.40, 26.32, 20.16.

4.2.8. *rac*((1*R*,2*S*) and (1*S*,2*R*))-1-(2′-Methoxyphenylmethyl)-2-diphenylhydroxymethylpyrrolidine *N*-oxide (1b). The residue was purified by silica gel column chromatography (9% CH_3OH–AcOEt) to give the title compound**1b** (1.03 g, 89%) as white solid, mp 182–184°C. [Found: C, 76.91; H, 6.83; N, 3.59. $C_{25}H_{27}NO_3$ requires C, 77.12; H, 6.94; N, 3.60%]; R_f (9% CH_3OH–AcOEt) 0.45; ν_{max} (KBr) 3424, 2930, 1516, 1264, 1178, 746, 706 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J*=7.8 Hz, Ph), 7.15–7.36 (8H, m, Ph), 6.82 (4H, d, *J*=8.4 Hz, Ph), 4.47 (1H, t, *J*=8.8 Hz, C_4H_7N), 3.77 (3H, s, OCH_3), 3.59 (2H, dd, *J*=12.4, 32 Hz, NCH_2Ph), 3.20 (1H, m, C_4H_7N), 2.87 (1H, m, C_4H_7N), 2.51 (1H, m, C_4H_7N), 2.28 (1H, m, C_4H_7N), 2.05 (1H, m, C_4H_7N), 1.76 (1H, m, C_4H_7N); δ_C (100 MHz, $CDCl_3$) 160.14, 147.58, 146.84, 133.10, 128.20, 126.87, 126.56, 126.50, 124.83, 123.59, 113.50, 78.16, 76.68, 71.55, 68.50, 55.25, 26.88, 20.07.

4.2.9. *rac*((1*R*,2*S*) and (1*S*,2*R*))-1-(3′-Pyridylmethyl)-2-diphenylhydroxymethylpyrrolidine *N*-oxide (1c). The residue was purified by silica gel column chromatography (17% CH_3OH–AcOEt) to give the title compound **1c** (726.8 g, 67%) as white solid, mp 171–172°C. [Found: C, 76.44; H, 6.66; N, 7.82. $C_{23}H_{24}N_2O_2$ requires C, 76.67; H, 6.67; N, 7.78%]; R_f (17% CH_3OH–AcOEt) 0.51; ν_{max}(KBr) 3423, 2963, 1592, 1488, 1177, 1050, 845, 750, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.68 (1H, s, O*H*), 8.56 (1H, s, C_5H_4N), 8.43 (1H, s, C_5H_4N), 7.81–7.88 (3H, m, C_5H_4N, Ph), 7.57–7.59 (2H, d, *J*=7.6 Hz, Ph), 7.17–7.37 (7H, m, Ph), 4.53 (1H, t, *J*=8.4 Hz, C_4H_7N), 3.62 (1H, s, C_4H_7N), 3.38 (1H, d, *J*=9.6 Hz, $NCH_2C_5H_4N$), 3.22 (1H, d, *J*=9.6 Hz, $NCH_2C_5H_4N$), 2.85 (1H, m, C_4H_7N), 2.54 (1H, m, C_4H_7N), 2.32–2.25 (1H, m, C_4H_7N), 2.13–2.05 (1H, m, C_4H_7N), 1.85–1.80 (1H, m, C_4H_7N); δ_C (100 MHz, $CDCl_3$) 151.48, 150.41, 147.32, 146.65, 140.10, 128.35, 128.29, 127.52, 127.07, 126.71, 126.40, 124.76, 123.22, 78.07, 77.81, 69.11, 69.06, 26.67, 20.07.

4.2.10. *rac*((1*R*,2*S*) and (1*S*,2*R*))-1-Benzyl-2-diphenylhydroxymethylpyrrolidine *N*-oxide (1d). The residue was purified by silica gel column chromatography (5% CH_3OH–AcOEt) to give the title compound **1d** (829.3 mg, 77%) as white solid, mp 187–188°C. [Found: C, 80.06; H, 6.90; N, 4.04. $C_{24}H_{25}NO_2$ requires C, 80.22; H, 6.96; N, 3.90%]; R_f (5% CH_3OH–AcOEt) 0.46; ν_{max} (KBr) 3426, 2957, 1490, 1375, 806, 751, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 12.37 (1H, s, O*H*), 7.88 (2H, d, *J*=7.6 Hz, Ph), 7.60 (2H, d, *J*=7.6 Hz, Ph), 7.24–7.34 (11H, m, Ph), 5.05 (1H, m, C_4H_7N), 3.41 (1H, d, *J*=7.6 Hz, NCH_2Ph), 3.35 (1H, d, *J*=8 Hz, NCH_2Ph), 3.35 (1H, m, C_4H_7N), 2.45 (1H, m, C_4H_7N), 2.05–2.11 (1H, m, C_4H_7N), 1.84–1.90 (2H, m, C_4H_7N), 1.67–1.72 (1H, m, C_4H_7N); δ_C (100 MHz, $CDCl_3$) 148.68, 148.05, 132.14, 131.88, 128.69, 128.00, 127.77, 126.52, 126.21, 124.63, 79.22, 77.63, 75.12, 70.43, 67.54, 26.03, 19.33.

4.2.11. *N*-Benzyl-diethanolamine *N*-oxide (10). The residue was purified by silica gel column chromatography (33% CH_3OH–AcOEt) to give the title compound **10** (225.4 mg, 36%) as white solid, mp 135–137°C; R_f (33% CH_3OH–AcOEt) 0.41; δ_H (200 MHz, $CDCl_3$) 7.37–7.46 (5H, m, Ph), 5.15 (2H, br, O*H*), 4.61 (2H, s, NCH_2Ph), 4.12 (4H, m, CH_2OH), 3.46–3.47 (4H, t, *J*=1.6 Hz, CH_2); *m*/*z* 212 (M^++H, 81%).

4.3. A general procedure for the cyanosilylation reactions of ketones

To a solution of **1a** (12.2 mg, 0.034 mmol) in CH_2Cl_2 (1 mL) was added $Ti(O^iPr)_4$ (1 M in toluene, 17 μL, 0.017 mmol) at room temperature, and the mixture was stirred for 1 h, CH_2Cl_2 was evaporated under reduced pressure. The resulting residue was further dried in vacuum for 30 min. The residue was dissolved in CH_2Cl_2 (0.5 mL). To this solution, the ketone (0.17 mmol) was added under ice–water bath, followed by the addition of TMSCN (45 μL, 0.34 mmol) as shown in Table 5. The reaction was monitored by TLC, and after the reaction period described in Table 5, the solution was concentrated, usual workup and purification by silica gel chromatography (1.6% ether–petroleum ether) gave the title compounds **7a**-**7n**.

4.3.1. 2-Trimethylsilyloxy-2-phenylpropanenitrile (7a). The title compound **7a** (30.5 mg, 82%) as a colorless oil; R_f (1.6% ether–petroleum ether) 0.43; δ_H (300 MHz, $CDCl_3$) 7.27–7.57 (5H, m, Ph). 1.87 (3H, s, CH_3), 0.19 (9H, s, $(CH_3)_3Si$).

4.3.2. 2-Trimethylsilyloxy-2-(2′-fluorophenyl)propanenitrile (7b). The title compound **7b** (34.2 mg, 85%) as a colorless oil; R_f (1.6% ether–petroleum ether) 0.50; δ_H (300 MHz, $CDCl_3$) 7.60 (1H, m, Ph), 7.36 (1H, m, Ph), 7.11–7.22 (2H, m, Ph), 1.96 (3H, s, CH_3), 0.27 (9H, s, $(CH_3)_3Si$).

4.3.3. 2-Trimethylsilyloxy-2-(4′-fluorophenyl)propanenitrile (7c). The title compound **7c** (33.8 mg, 84%) as colorless oil; R_f (1.6% ether–petroleum ether) 0.54; δ_H (300 MHz, $CDCl_3$) 7.54 (2H, m, Ph), 7.09 (2H, m, Ph), 1.86 (3H, s, CH_3), 0.20 (9H, s, $(CH_3)_3Si$).

4.3.4. 2-Trimethylsilyloxy-2-methyl-4-phenylbutanenitrile (7d). The title compound **7d** (39.2 mg, 93%) as colorless oil; R_f (1.6% ether–petroleum ether) 0.50; δ_H (300 MHz, $CDCl_3$) 7.22–7.33 (5H, m, Ph) 2.85 (2H, m, CH_2), 2.06 (2H, m, CH_2), 1.65 (3H, s, CH_3), 0.28 (9H, s, $(CH_3)_3Si$).

4.3.5. 2-Trimethylsilyloxy-2-phenylbutanenitrile (7e). The title compound **7e** (34.6 mg, 87%) as colorless oil; R_f

(1.6% ether–petroleum ether) 0.42; δ_H (300 MHz, $CDCl_3$) 7.50 (2H, m, Ph), 7.40 (3H, m, Ph), 1.92–2.23 (2H, m, CH_2), 0.99 (3H, t, J=7.2 Hz, CH_3), 0.15 (9H, s, $(CH_3)_3Si$).

4.3.6. 2-Trimethylsilyloxy-2-(4′-methylphenyl)propanenitrile (7f). The title compound **7f** (31.3 mg, 79%) as colorless oil; R_f (1.6% ether–petroleum ether) 0.44; δ_H (300 MHz, $CDCl_3$) 7.44 (2H, m, Ph), 7.20–7.28 (2H, m, Ph), 2.38 (3H, s, PhCH_3), 1.86 (3H, s, CH_3), 0.18 (9H, s, $(CH_3)_3Si$).

4.3.7. 2-Trimethylsilyloxy-2-(2′-naphthyl)propanenitrile (7g). The title compound **7h** (36.1 mg, 79%) as white solid; R_f (1.6% ether–petroleum ether) 0.60; δ_H (300 MHz, $CDCl_3$) 8.07 (1H, s, $C_{10}H_7$) 7.92 (3H, m, $C_{10}H_7$), 7.20–7.67 (3H, s, $C_{10}H_7$), 1.97 (3H, s, CH_3), 0.22 (9H, s, $(CH_3)_3Si$).

4.3.8. 2-Trimethylsilyloxy-2-(4′-nitrophenyl)propanenitrile (7h). The title compound **7h** (38.6 mg, 86%) as colorless oil; δ_H (300 MHz, $CDCl_3$) 8.30 (2H, d, J=9.0 Hz, Ph), 7.75 (2H, d, J=9.0 Hz, Ph), 1.89 (3H, s, CH_3), 0.26 (9H, s, $(CH_3)_3Si$).

4.3.9. 2-Trimethylsilyloxy-2-methyl-4-phenyl-3-butenenitrile (7j). The title compound **7j** (33.3 mg, 80%) as colorless oil; R_f (1.6% ether–petroleum ether) 0.58; δ_H (300 MHz, $CDCl_3$) 7.28–7.45 (5H, m, Ph), 6.91 (1H, d, J=15.9 Hz, CH=), 6.15 (1H, d, J=15.9 Hz, CH=), 1.77 (3H, s, CH_3), 0.27 (9H, s, $(CH_3)_3Si$); δ_C ($CDCl_3$, 100 MHz) 135.06, 130.90, 129.47, 128.71, 128.54, 126.84, 120.63, 69.92, 30.83, 1.71.

4.3.10. 2-Trimethylsilyloxy-2-methylheptanenitrile (7k). The title compound **7k** (35.1 mg, 97%) as colorless oil; R_f (1.6% ether–petroleum ether) 0.60; δ_H (300 MHz, $CDCl_3$) 1.70 (2H, m, CH_2), 1.58 (3H, s, CH_3), 1.50 (2H, m, CH_2), 1.42 (1H, m, CH_2), 1.34 (4H, m, CH_2), 0.92 (3H, t, J=6.9 Hz, CH_3), 0.25 (9H, s, $(CH_3)_3Si$).

4.3.11. 2-Trimethylsilyloxy-2-(4′-aminophenyl)propanenitrile (7m). The title compound **7m** (21.3 mg, 54%) as colorless oil; R_f (1.6% ether–petroleum ether) 0.35; δ_H (300 MHz, $CDCl_3$) 7.28–7.34 (2H, m, Ph), 6.64–6.71 (2H, m, Ph), 3.78 (2H, br, NH_2), 1.85 (3H, s, CH_3), 0.15 (9H, s, $(CH_3)_3Si$).

4.3.12. 2-Trimethylsilyloxy-2-thiophenylpropanenitrile (7n). The title compound **7n** (12.9 mg, 42%) as colorless oil. [Found: C, 53.48; H, 6.94; N, 6.43. $C_{10}H_{15}NOSiS$ requires C, 53.33; H, 6.66; N, 6.22%]; R_f (1.6% ether–petroleum ether) 0.55; δ_H (300 MHz, $CDCl_3$) 7.21–7.34 (2H, m, Ph), 7.00 (1H, m, Ph), 2.00 (3H, s, CH_3), 0.20 (9H, s, $(CH_3)_3Si$); δ_C (75 MHz, $CDCl_3$) 146.27, 126.61, 125.97, 124.70, 120.82, 68.24, 33.40, 0.78.

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