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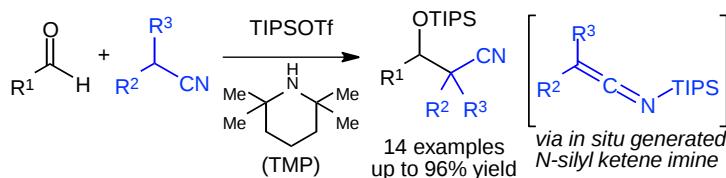


Nucleophilic Addition of Alkanenitriles to Aldehydes via *N*-Silyl Ketene Imines Generated In Situ

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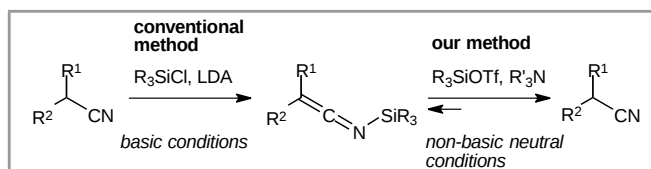
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Abstract Upon treatment with triisopropylsilyl trifluoromethanesulfonate and 2,2,6,6-tetramethylpiperidine, alkanenitriles undergo direct addition to aldehydes under mild non-basic neutral conditions to provide triisopropylsilyl ethers of β -hydroxy nitriles in good yield. The reaction proceeds via in situ generation of an *N*-silyl ketene imine intermediate from the alkanenitrile followed by nucleophilic addition of the intermediate to the aldehyde.

Key words nitriles, nitrile aldol reaction, nucleophilic addition, *N*-silyl ketene imines, aldehydes

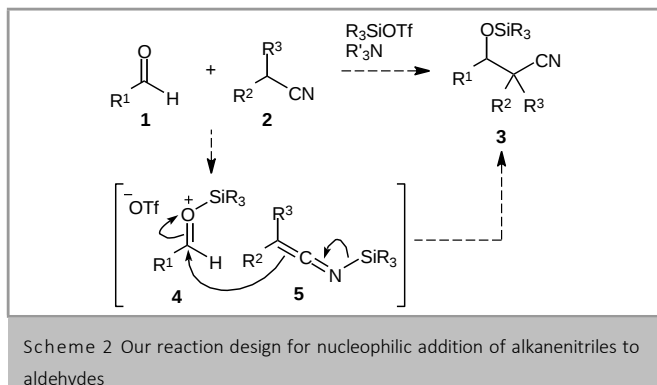
Nucleophilic addition of nitriles to carbonyl compounds (i.e., the nitrile aldol reaction) is a useful transformation in organic synthesis because of the high synthetic utility of β -hydroxynitrile products owing to the versatile convertibility of the nitrile functionality.^{1,2} Traditionally, the reaction is carried out through deprotonation of nitriles followed by addition to carbonyl compounds.³ However, the generation of α -cyano carbanions from simple unactivated alkanenitriles (e.g., pK_a 31.3 in dimethyl sulfoxide for acetonitrile)⁴ requires a stoichiometric amount of a strong base such as lithium diisopropylamide (LDA), which is incompatible with base-sensitive substrates. In addition, strongly basic conditions sometimes cause undesirable reactions, including β -elimination by dehydration to give the corresponding α,β -unsaturated nitriles and retro-additions. Recently, several types of catalytic activation of nitriles as nucleophiles have been established, which has led to successful metal-catalyzed nucleophilic additions of unactivated alkanenitriles to aldehydes.⁵ However, these catalytic reactions still have some drawbacks, for which excess amounts of nitrile (>5 equiv) are generally required. Thus, a new methodology that allows the nucleophilic addition of unactivated alkanenitriles to carbonyl compounds under mild reaction conditions without requiring excess substrates would be highly valuable.



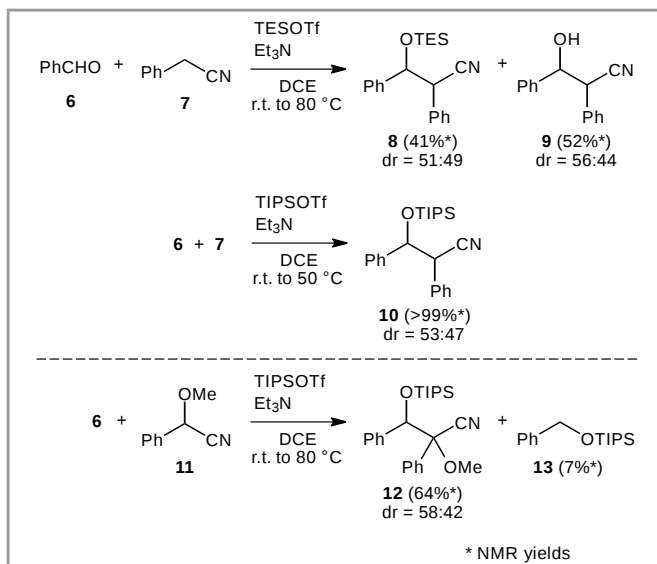
Scheme 1 Generation of *N*-silyl ketene imines from alkanenitriles

N-Silyl ketene imines, which are typically prepared by lithiation of alkanenitriles with a strong base such as LDA followed by trapping with a bulky trialkylsilyl chloride, have recently attracted much attention as a competent α -cyano carbanion equivalent (Scheme 1).⁶ Although *N*-silyl ketene imines show synthetic potential, considerable drawbacks remain in their handling and storage instability because they are rapidly hydrolyzed with water. In this context, we reported that *N*-silyl ketene imines could be generated in equilibrium by treatment of alkanenitriles with trialkylsilyl triflate (R_3SiOTf) and a tertiary amine (Scheme 1).^{7,8} These mild and non-basic generation conditions allowed the development of several C–C bond forming reactions that do not require isolation of the labile *N*-silyl ketene imines.⁷

Motivated by our interest in new reaction development by using in situ generated *N*-silyl ketene imines, we expected that treatment of a mixture of aldehydes **1** and alkanenitriles **2** with R_3SiOTf and tertiary amine would directly yield *O*-trialkylsilyl β -hydroxy nitriles **3** (Scheme 2).^{9,10} The reaction would proceed through in situ formation of the highly electrophilic silyl oxonium intermediate **4** and *N*-silyl ketene imine **5**, followed by addition of **5** to **4**. We report herein trialkylsilyl triflate and alkylamine promoted novel nucleophilic addition reactions of nitriles to aldehydes, which offer an efficient synthetic method for β -hydroxy nitrile derivatives under non-basic mild conditions. This new method does not require preformation of the labile *N*-silyl ketene imine nucleophile or excess substrates. This is the nitrile analogue of a formal one-pot Mukaiyama aldol reaction.



To ascertain the feasibility of the proposed addition reaction, we initially tested the reaction of benzaldehyde (**6**) with phenylacetonitrile (**7**; Scheme 3). When **6** (1 equiv) and **7** (1 equiv) were treated with triethylsilyl trifluoromethanesulfonate (TESOTf; 2 equiv) and triethylamine (2 equiv) in 1,2-dichloroethane (DCE), the expected *O*-TES β -hydroxynitrile **8** was obtained in 41% yield as a 51:49 diastereomeric mixture; however, a considerable amount (52% yield) of the corresponding desilylated product **9** was also obtained due to the instability of the TES ether in the reaction medium. To suppress this desilylation product, we next tested the ability of a more robust silyl group in the reaction. Happily, the use of triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) led to quantitative formation of *O*-TIPS β -hydroxynitrile **10**. However, the reaction of **6** with the sterically hindered nitrile **11** gave inferior results with the TIPSOTf/Et₃N system, and addition product **12** was obtained in 64% yield along with TIPS ether **13** (7% yield), which is derived from hydrosilylation of **6** as a side reaction product.¹¹



Scheme 3 Preliminary results in nucleophilic additions

To prevent the competitive hydrosilylation reaction, the effects of amine bases were evaluated in the reaction of nitrile **11** with benzaldehyde (**6**; Table 1), which revealed that the choice of amine was of critical importance for this type of reaction. In contrast to the results with triethylamine, significant amounts of TIPS ether **13** were obtained when sterically hindered tertiary alkylamines, such as diisopropylethylamine (DIPEA) and

1,2,2,6,6-pentamethylpiperidine (PMP),^{12,13} were used (entries 1 and 2). Less hindered bicyclic tertiary amines, such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and 2,6-lutidine, did not give addition product **12**, even if the mixture was heated to 80 °C. To our delight, the best result was obtained when 2,2,6,6-tetramethylpiperidine (TMP) was used as the amine base, which provided **12** in 85% yield after isolation (dr = 55:45) with stirring at room temperature for 22 h (entry 5). Other sterically hindered secondary amines, such as hexamethyldisilazane (HMDS), did not promote the nucleophilic addition (entry 6). Control experiments revealed that the reaction did not proceed in the absence of either TIPSOTf or TMP. In addition, reduction in the amounts of TIPSOTf and TMP to 1.1 equivalents each resulted in the formation of **12** in only 47% yield (dr = 56:44), as well as recovery of **11** in 22% yield, after stirring the reaction mixture at room temperature for 23 h. Therefore, the use of two equivalents of both reagents is important for full conversion in this reaction. When TMP was used as the amine base, other silyl triflates, such as trimethylsilyl trifluoromethanesulfonate, TESOTf, and *tert*-butyldimethylsilyl trifluoromethanesulfonate, also induced nucleophilic additions of hindered nitriles (see Scheme S1 in the supporting information for details). Unfortunately, although the reaction proceeds with a high yield, diastereoselectivity was not induced, probably due to a low level of stereodiscrimination in the addition step.

Table 1 Optimization of Amines for Addition of Nitrile **11** to Benzaldehyde (**6**)^a

Reaction scheme showing the conversion of **6** (PhCHO) and **11** (1-methoxy-2-phenylethanenitrile) to **12** (1-methoxy-2-phenyl-2-(phenylthio)propanenitrile) and **13** (1-(phenylthio)propan-2-ol) using TIPSOTf and an amine in DCE at Temp.

Entry	Amine	Temp. (°C)	Yield (%) ^b
			<u>12 (dr)^c</u> <u>13</u>
1	DIPEA	50 to 80	6 (55:45) 35
2	PMP	50 to 80	0 70
3	DABCO	50 to 80	0 0
4	2,6-lutidine	50 to 80	trace 0
5	TMP	r. t.	85 (55:45) ^d 0
<u>6</u>	<u>HMDS</u>	<u>50 to 80</u>	<u>0</u> <u>trace</u>

^a Reaction conditions: aldehyde **6** (0.4 mmol), nitrile **11** (0.4 mmol), TIPSOTf (0.8 mmol), amine (0.8 mmol), DCE (2 mL), 80 min–22 h.

^b Yield determined by ¹H-NMR spectroscopic analysis of the crude product mixture by using pyrazine as an internal standard.

^c Diastereomeric ratios of **12** are given in parentheses. The relative configuration was not assigned.

^d Yield of isolated product after purification by silica gel column chromatography.

With the optimized reaction conditions using the TIPSOTf/TMP system in hand, we next investigated the reactions of benzaldehyde (**6**) with a series of nitriles (Table 2). The results show that the reaction has broad applicability to nitriles including simple unactivated alkanenitriles (i.e., **14a**, **14b**, and **14e**). The α -alkyl nitriles **14a,b**, α -aryl nitriles **7** and **14c,d**, acetonitrile (**14e**), and α -halo nitrile **14f** afforded the corresponding *O*-TIPS β -hydroxy nitriles in good to excellent yields (entries 1–7). Note that the reactions of unactivated nitriles **14a** and **14b** with **6** under the TIPSOTf/Et₃N system provided no addition products **15a,b**, which clearly indicated the unique and remarkable reactivity of TMP as an amine base.¹⁴ α,α -Disubstituted nitriles including isobutyronitrile (**14b**), 2-phenylpropanenitrile (**14c**), and diphenylacetoneitrile (**14d**)

gave addition products with a newly formed quaternary carbon atom in good yields, indicating the advantage of the sterically unhindered nitrile group (entries 3–5). When an equimolar amount of acetonitrile was used in this addition, an inseparable mixture of the desired product **15e**, the double aldol type addition product (not shown), and the *C*-silylation product, i.e., 2-(triisopropylsilyl)acetonitrile, was obtained. Thus, excess amounts of nitrile were used in the case of acetonitrile (**14e**) to prevent these side reactions (entry 6). Although chloroacetonitrile (**14f**) produced the desired product in good yield (entry 7),¹⁵ fluoroacetonitrile (**14g**) remained unreactive (entry 8). The diastereomeric ratio of addition products **15**, however, remained low (68:32–50:50).

Table 2 Substrate Scope of Nitriles^a

Entry	Nitrile 14 or 7	Product 15 or 10	Yield (%) ^b	dr ^c	
1	14a	EtCN	15a	83	50:50
2	7	PhCH ₂ CN	10	88	50:50
3	14b	<i>i</i> -PrCN	15b	64	–
4	14c	PhMeCHCN	15c	88	52:48
5	14d	Ph ₂ CHCN	15d	89	–
6	14e	MeCN ^d	15e	71	–
7	14f	ClCH ₂ CN ^e	15f	82	68:32
8	14g	FCH ₂ CN ^f	15g	trace	–

^a Reaction conditions: aldehyde **6** (0.4 mmol), nitrile **14** or **7** (0.4 mmol), TIPSOTf (0.8 mmol), TMP (0.8 mmol), DCE (2.0 mL), r.t., 30 min–140 min.

^b Yield of isolated product after purification by silica gel column chromatography. ^c

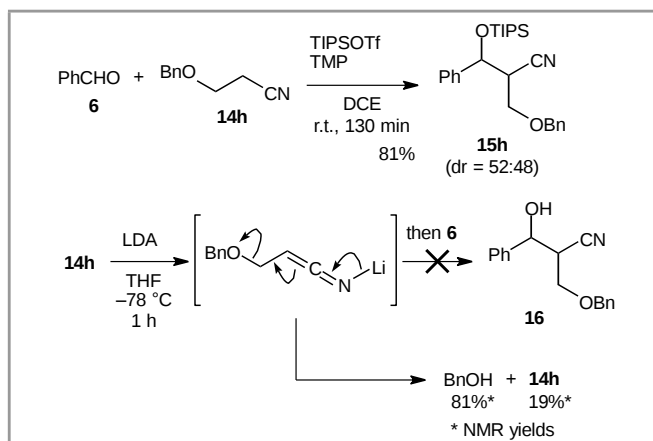
Determined by ¹H-NMR spectroscopic analysis of the crude product; relative stereochemistry not assigned.

^d Acetonitrile was used as the solvent (0.2 M). Two equivalents of TIPSOTf and TMP were used.

^e Toluene was used as the solvent. Reaction temperature was 100 °C.

^f Reaction temperature was 80 °C.

The synthetic advantage of our new method over the standard method under anionic conditions³ is clearly demonstrated in Scheme 4. Namely, our addition reaction of base-sensitive 3-(benzyloxy)propanenitrile (**14h**) to benzaldehyde (**6**) with TIPSOTf and TMP gave addition product **15h** in 81% yield. By contrast, β-hydroxy nitrile **16** was not obtained under the conventional anionic conditions with LDA as a base because competitive β-elimination of the benzyloxy group from the resulting α-cyano carbanion occurred even at –78 °C.



Scheme 4 Comparison with the conventional method

The scope of applicable aldehydes was then examined with phenylacetonitrile (**7**; Table 3). Addition of nitrile **7** to aromatic aldehydes **17a–c** with either electron-donating or -withdrawing substituents proceeded smoothly to afford *O*-TIPS β-hydroxy nitriles **18a–c** in high yields (entries 1–3). An ester functionality survived intact under these conditions (entry 3). The reaction of sterically hindered 2,6-dimethylbenzaldehyde (**17d**) efficiently provided addition product **18d** (entry 4). The new addition reaction was also applicable to an aliphatic aldehyde without an acidic α-proton (entry 5). However, the reaction with enolizable aliphatic aldehyde **17f** gave addition product **18f** as a minor product (35% yield) along with silyl enol ether **19**, which is derived from **17f** (51% yield; entry 6 and Figure 1). α,β-Unsaturated aldehyde **17g** underwent both 1,2- and 1,4-addition, with 1,4-addition favored, to produce a mixture of TIPS ether **18g** (18% yield, entry 7), silyl enol ether **20** (46% yield, Figure 1), and aldehyde **21** (22% yield, Figure 1); this indicates a similar tendency to the uncatalyzed solvent-free reaction of preformed *N*-silyl diphenylketene imine.⁹

Table 3 Substrate Scope of Aldehydes^a

Entry	Aldehyde 17	18	Yield (%) ^b	dr ^c	
1	17a	18a	87	50:50	
2	17b	18b	93	51:49	
3	17c	18c	82	50:50	
4	17d	18d	96	58:42	
5	17e	18e	72	50:50	
6	17f	18f	35 ^{d,e}	57:43	
7	17g	18g	18 ^{d,f}	62:38	

^a Reaction conditions: aldehyde **17** (0.4 mmol), nitrile **7** (0.4 mmol), TIPSOTf (0.8 mmol), TMP (0.8 mmol), DCE (2.0 mL), r.t., 10 min to 4 h.

^b Yield of isolated product after purification by silica gel column chromatography. ^c Determined by ¹H-NMR spectroscopic analysis of the crude product; relative stereochemistry not assigned.

^d For side products, see Figure 1.

^e Slow and dropwise addition of aldehyde **17f** over 2.5 h to the reaction mixture did not improve the yield of addition product **18f**.

^f Two-step yield after treatment of the crude product with silica gel in CH₂Cl₂.

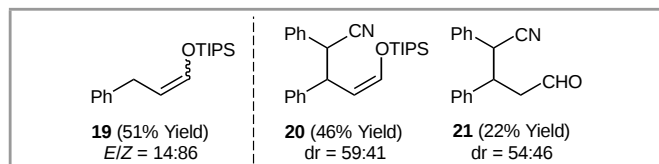
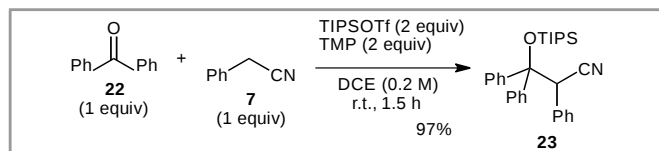


Figure 1 Side products for entries 6 and 7 in Table 3

Finally, nucleophilic addition to a ketone was briefly examined to evaluate the synthetic potential of this reaction (Scheme 5). Thus, upon treatment with TIPSOTf and TMP at room temperature, nitrile **7** underwent an efficient addition reaction with benzophenone (**22**) to afford adduct **23** in 97% yield.



Scheme 5 Nucleophilic addition to a ketone

In conclusion, we have developed a novel method for nucleophilic addition reactions of alkanenitriles, including simple unactivated nitriles, to aldehydes promoted by TIPSOTf and TMP under mild silylation conditions.¹⁶ The reaction appears to proceed via in situ *N*-silyl ketene imine formation followed by a Mukaiyama aldol-type reaction.¹⁷ The synthetic benefits of the reaction include the avoidance of preformation and isolation of labile *N*-silyl ketene imines. The non-basic mild reaction conditions mean that the present method tolerates many functional groups and provides β -hydroxy nitrile products with a high yield without β -elimination and retro-additions, which sometimes occur with conventional anionic conditions. The new method does not require excess substrates and will offer an efficient route to β -hydroxy nitrile derivatives, which serve as useful intermediates in the synthesis of natural products and biologically active substrates. Further studies will focus on the reaction of in situ generated *N*-silyl ketene imines to other classes of electrophiles.

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We acknowledge Dr. Eri Fukushi and Mr. Yusuke Takata (GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University) for performing mass spectral measurements. This work was supported by a Grant for Basic Science Research Projects from The Sumitomo Foundation (to F.Y.) and JSPS KAKENHI Grant Numbers JP15K01795 (to F.Y.), JP15H03806 (to K.T.), and JP15H05842 in Middle Molecular Strategy (to K.T.).

Supporting Information

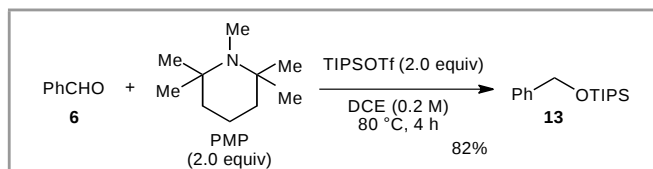
YES

Primary Data

NO

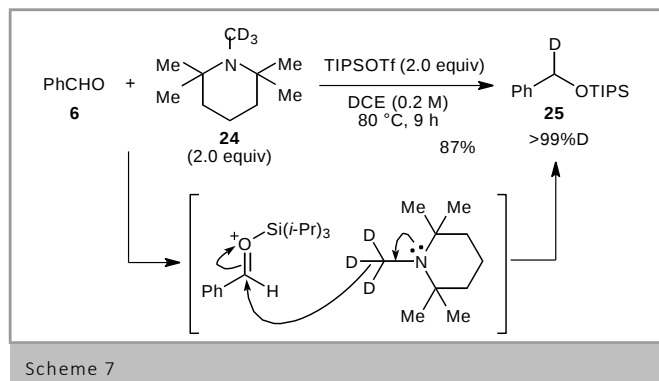
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- (12) The combination of TIPSOTf and PMP smoothly promoted hydrosilylation of benzaldehyde (**6**) to afford TIPS ether **13** in 82% yield (Scheme 6).



Scheme 6

- (13) A deuterium-labeling experiment proved that PMP acts as the hydride source (Scheme 7).



- (14) The reason for the superior reactivity of TMP is not clear yet. Very low solubility of 2,2,6,6-tetramethylpiperidinium triflate (TfOH·TMP) in DCE might cause the equilibrium shifts slightly toward the *N*-silyl ketene imine.
- (15) When DCE was used as the solvent, a significant amount of inseparable double aldol type addition product accompanied **15f**. Solvent screening revealed that toluene could suppress such side reactions, although it required heating of the reaction mixture to 100 °C.
- (16) **General Procedure (Table 1, Entry 5):** To a mixture of benzaldehyde (**6**; 40.8 μ L, 0.400 mmol), 2-methoxy-2-phenylacetonitrile (**11**; 55.5 μ L, 0.400 mmol), and 2,2,6,6-tetramethylpiperidine (136 μ L, 0.800 mmol) in DCE (2.0 mL) was added TIPSOTf (215 μ L, 0.800 mmol), and the mixture was stirred at room temperature for 22 h, at which point the consumption of starting materials **6** and **11** was complete (as determined by TLC analysis, hexane:EtOAc = 4:1). After cooling to 0 °C, the reaction was quenched by slow addition of saturated

aqueous NaHCO₃ (1 mL), and the resulting mixture was filtered through a cotton plug to remove the precipitate (rinsed with CH₂Cl₂). The filtrate was extracted with CH₂Cl₂ (1 mL $\times$ 3). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1) to give nitrile **12** (139.6 mg, 0.341 mmol, 85% yield) as an inseparable 55:45 mixture of diastereomers.

Compound **12**: Colorless oil; ¹H-NMR (500 MHz, CDCl₃) δ 7.53–7.51 (1H, m), 7.40–7.36 (3H, m), 7.31–7.27 (2H, m), 7.22 (1H, t, *J* = 7.4 Hz), 7.13–7.04 (2H, m), 6.92 (1H, m), 4.98 (0.55H, s), 4.97 (0.45H, s), 3.34 (0.45 $\times$ 3H, s), 3.18 (0.55 $\times$ 3H, s), 1.15–1.09 (0.45 $\times$ 3H, m), 1.06 (0.45 $\times$ 9H, d, *J* = 6.9 Hz), 1.00 (0.45 $\times$ 9H, d, *J* = 7.5 Hz), 0.81–0.74 (0.55 $\times$ 21H, m); ¹³C NMR (125 MHz, CDCl₃) δ 139.08, 137.95, 134.79, 133.93, 129.21, 128.99, 128.51, 128.45, 128.18, 128.09, 127.96, 127.86, 127.76, 127.41, 127.20, 127.07, 117.15, 116.89, 88.12, 86.64, 81.44, 81.06, 54.03, 53.97, 17.87, 17.82, 17.70, 17.63, 12.44, 12.40; IR (ATR) ν 2943, 2867, 2365, 1122, 1069 cm⁻¹; HRMS (FD) calcd for C₂₅H₃₆NO₂Si ([M+H]⁺): 410.2515, found: 410.2484.

- (17) Attempts to detect *N*-silyl ketene imine intermediates by ¹H- or ¹³C-NMR were unsuccessful, suggesting that these reactive species in equilibration with the corresponding nitriles are existing only in low concentration. The reaction of **6** with **11** did not proceed in the absence of either TIPSOTf or TMP. The alkanenitrile underwent isomerization at the α -position of the cyano group by treatment with TIPSOTf/TMP (i.e., nitrile **28** in Scheme S2). These results support that the nucleophilic addition should proceed via the *N*-silyl ketene imine intermediate. For details, see Scheme S2 in the Supporting Information.