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Highly Efficient Cyanosilylation of Sterically Bulky Ketones Catalyzed by Tin Ion-Exchanged Montmorillonite

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Abstract: Tin ion-exchanged montmorillonite (Sn-Mont) was found to be a powerful catalyst for the cyanosilylation of aromatic and aliphatic ketones having a carbonyl group in sterically congested circumstances with cyanotrimethylsilane, giving the corresponding cyanohydrin trimethylsilyl ethers in excellent yields.

Keywords: clays; cyanosilylation; heterogeneous catalysis; ketones; tin

The cyanosilylation of carbonyl compounds with trimethylsilyl cyanide (TMSCN) is the most straightforward way to form cyanohydrin trimethylsilyl ethers, which can be further transformed into a wide range of valuable polyfunctionalized building blocks including α-hydroxy acids, β-amino alcohols, and other biologically active compounds.[1] Because of its importance in organic synthesis, different catalysts have been developed for the cyanosilylation reaction of carbonyl compounds with TMSCN, such as noble metal nanoparticles,[2] a metal complex,[3] Lewis acids,[4] base catalysts,[5] organic salts,[6,7] an ionic liquid,[8] and various organic catalysts.[9] Most of these catalysts are successful in the cyanosilylation of aldehydes and simple ketones under mild conditions. However, their catalytic activities obviously decrease, and even disappear in the case of the cyanosilylation of sterically bulky ketones like aromatic ketones owing to the congestion around the carbonyl groups. Thus, the reaction time has to be prolonged to several or tens of hours, or the reaction must be performed under heating. Even so, the resultant yields are unsatisfactory in most cases. Therefore, to realize the efficient cyanosilylation of sterically congested ketones in high yields is a big challenge in the field of current organic synthesis.

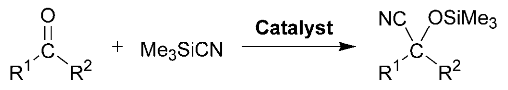
Montmorillonite, a naturally-occurring clay, is composed of stacked, negatively-charged aluminosilicate layers that hold exchangeable cationic species in the interlayers.[10]

Normally, multivalent metal cations are introduced into the interlayer space of Na ion-exchanged montmorillonite (Na-Mont),[11,12,13,14] forming the acidic montmorillonites which have been utilized as solid acids in various acid-catalyzed organic reactions because of the environmental compatibility, reusability, operational simplicity, innocuousness, absence of corrosion, low cost, and easy isolation. Among metal ion-exchanged montmorillonites (M-Monts),[15] we have found that Sn-Mont possesses quite a high surface area and very strong acidicity suitable for the Michael reaction,[11a] the silylation of alcohols,[15] and the reduction of carbonyl compounds with hydrosilanes.[16]

We have also revealed the catalysis of Sn-Mont for the cyanosilylation of aldehydes and ordinary ketones.[13] And unique catalysts have still been developed for the reaction during the last decade.

In this communication, we address the powerful catalysis of Sn-Mont especially for the cyanosilylation of ketones congested with sterically bulky substituents around the carbonyl group, comparing the catalytic effectiveness between Sn-Mont and the recently developed catalysts (Scheme 1).

Sn-Mont was prepared through ion-exchange of Na-Mont (Kunimine Industries Co. Ltd., Japan) with



Scheme 1. Cyanosilylation of sterically congested ketone with Me_3SiCN.

an $SnCl_4$ solution. Elemental analysis of Sn-Mont by inductively coupled plasma (ICP) showed a 97.1% exchange of Na^+ for Sn^{4+}, indicating that 0.0019 mol of tin ions are included in one gram of the as-prepared Sn-Mont. The nitrogen sorption data showed that the specific surface area greatly increased from $12\,m^2g^{-1}$ of pristine Na-Mont to $280\,m^2g^{-1}$ of Sn-Mont with a porous structure (see the Supporting Information).

Our studies started with benzophenone as a test substrate to compare the catalysis between the different catalysts in the cyanosilylation with TMSCN, because benzophenone is much less reactive than aldehydes and ordinary, simple ketones. The results are summarized in Figure 1 and Table 1. No reaction proceeded in the absence of a catalyst (Table 1, entry 1). Firstly, various heterogeneous catalysts were used in entries 2–9. Although Na-Mont gave almost no catalysis (Table 1, entry 2), Sn-Mont (10 mg) showed the highest catalytic activity for the cyanosilylation to give the corresponding cyanohydrin trimethylsilyl ether in 99% yield in only 6 min (Figure 1; Table 1, entry 3). It should be emphasized that merely filtering and condensing the reaction mixture gave the product in greater than 98% purity without further purification. In contrast, $Sn(OH)_4$ which was prepared from $SnCl_4$ with aqueous NH_3 and crystalline SnO_2 were ineffective for the reaction (Table 1, entries 4 and 5). Sn-MCM-41, which was prepared from silica MCM-41 and aqueous $SnCl_4$, or by hydrothermal sol-gel synthesis from $Si(OEt)_4$ and tin oxalate (see Supporting Information), did not promote the reaction (Table 1, entry 6). Although the other metal ion-exchanged montmorillonites such as Ti-Mont and Fe-Mont were also efficient for the cyanosilylation, affording the product in more than 90% yield in 30 min, their catalytic activity is definitely inferior to that of Sn-Mont (Figure 1; Table 1, entries 7 and 8).[14] More recently, Yasuda et al. found that mesoporous aluminosilicate Al-MCM-41 catalyzed the cyanosilylation of various aldehydes and ketones with TMSCN under mild reaction conditions.[17] However, it was found that Al-MCM-41 had almost no activity for the cyanosilylation of benzophenone (Figure 1; Table 1, entry 9).

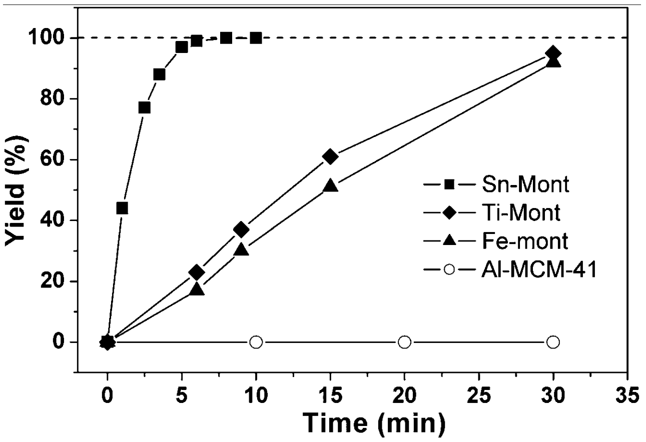
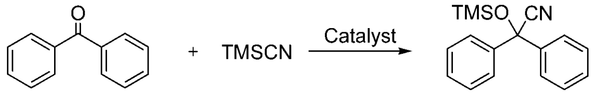


Figure 1. Time-course of the cyanosilylation of benzophenone using Sn-Mont and control heterogeneous catalysts. *Reaction conditions:* benzophenone (1 mmol); TMSCN (1.2 mmol); CH_2Cl_2 (2 mL); catalyst (10 mg); room temperature.

Table 1. Cyanosilylation of benzophenone with TMSCN using different catalysts.[a]



Entry	Catalyst	Time (min)	Yield[b] (%)
1	No catalyst	30	0
2	Na-Mont	30	< 0.5
3	Sn-Mont	6	99
4	SnO_2	30	< 0.5
5	$Sn(OH)_4$	30	< 0.5
6[c]	Sn-MCM-41	30	< 0.5
7	Ti-Mont	30	92
8	Fe-Mont	30	95
9	Al-MCM-41	90	< 1
10[d]	LiCl	90	11
11[d]	ZnI_2	60	0
12[d]	LiOMe	6	84 (98[e])

[a] *Reaction conditions*: benzophenone (1 mmol); TMSCN (1.2 mmol); CH_2Cl_2 (2 mL); catalyst (10 mg); room temperature.

[b] GC yields using *n*-dodecane as an internal standard.

[c] Sn-MCM-41 prepared by the ion-exchange method or the direct hydrothermal method (see the Supporting Information).

[d] The reaction was conducted in freshly distilled tetrahydrofuran (THF, 2 mL) using 1.9 mol% of a catalyst.

[e] Reaction time was 10 min.

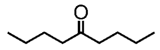
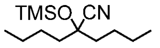
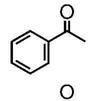
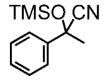
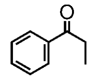
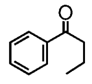
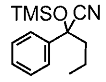
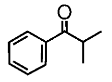
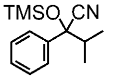
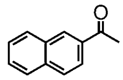
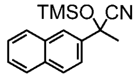
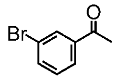
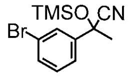
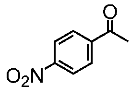
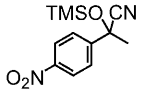
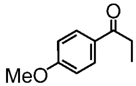
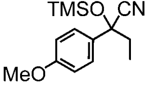
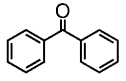
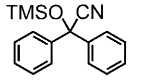
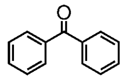
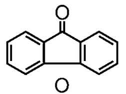
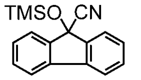
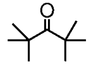
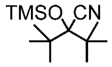
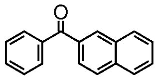
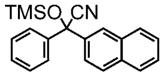
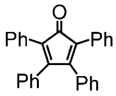
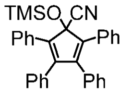
Secondly, representative homogeneous catalysts were applied for the cyanosilylation (entries 10–12): LiCl was active for the cyanosilylation of aldehydes and ketones under a high molar ratio of substrate to LiCl in THF.[18] However, the cyanosilylation of benzophenone in the presence of LiCl (1.9 mol%) gave a very poor yield of 11% in 90 min (Table 1, entry 10). Although ZnI_2 was also reported to be highly efficient,[19] in our experiment no cyanohydrin trimethylsilyl ether was obtained by use of 1.9 mol% of ZnI_2 in 60 min (Table 1, entry 11). Among the homogeneous catalysts, LiOMe[20] (1.9 mol%) turned out to give the highest yields of 84% and 98% in 6 and 10 min, respectively (Table 1, entry 12). LiOMe is not only basic, but also moisture- and CO_2-sensitive so that it requires special care for handling and storage, and is not reusable.

Recently, benzyltriphenylphosphonium chloride was proposed in the cyanosilylation of benzophenone

(0.5 mmol) at 50 °C for a long reaction period of 48 h to obtain the corresponding product in 94% yield.[7] Subsequently, Olah et al. reported that the cyanosilylation of benzophenone with 5 mol% of K_2CO_3 or phosphate salts in dimethylformamide (DMF) efficiently proceeded to give the cyanosilylated product in 88–100% yield in 1–2 h at room temperature,[21] whereas with our catalyst system, use of only 10 mg of Sn-Mont is enough to complete the reaction in just 6 min with 99% yield (Figure 1; Table 1, entries 1–3). It can be concluded that the activity of Sn-Mont for the cyanosilylation of benzophenone is clearly higher than that of the known catalysts, such as Al-MCM-41, ZnI_2, LiOMe, LiCl, K_2CO_3, phosphonium salts and phosphates.

In order to reveal the scope of the Sn-Mont-catalyzed cyanosilylation, not only common aromatic ketones, but also congested aromatic and aliphatic ketones with a carbonyl group surrounded by phenyl or *tert*-butyl substituents were applied (Table 2). In general, the cyanosilylation of various ketones (1 mmol) with TMSCN (1.2 mmol) proceeded efficiently to provide the desired products in high yields and >98% purities with only 10 mg of Sn-Mont after filtering and condensing the reaction mixture (entries 1–10 and 12–14): A simple ketone, 5-nonanone reacted with TMSCN rapidly in only 30 seconds. Alkyl aryl ketones underwent the cyanosilylation at room temperature with high yields in very short reaction periods of 1–6 min, depending on the size of the alkyl groups (entries 2–5) or the properties of the aromatic rings (entries 6–9) with an electron-withdrawing or electron-releasing substituent. It is noteworthy that all the known catalysts in the literature required several to tens of hours to complete the cyanosilylation of alkyl aryl ketones, while Sn-Mont completed the cyanosilylation in very short periods. In addition to the cyanosilylation of benzophenone (entry 10), we also investigated the cyanosilylation of ketones with a carbonyl group under extraordinarily congested circumstances (entries 12–15). Excellent yields for the desired adducts were obtained for the cyanosilylation of 9-fluorenone, di-*tert*-butyl ketone and 2-benzoylnaphthalene, although slightly longer reaction times were required (entries 12–14). In contrast, of note is that the cyanosilylation of 9-fluorenone by Amberlite XAD resin needed more than 20 h at 60 °C.[22] Toward a further hindered ketone, tetraphenylcyclopentadienone, the cyanosilylation proceeded with Sn-Mont for 1.5 h under heating to obtain a high yield of 93% (entry 15). Unsurprisingly, no cyanosilylation of tetraphenylcyclopentadienone with TMSCN took place without Sn-Mont even at high temperatures (entry 15). To the best of our knowledge, the cyanosilylation of congested ketones such as 2-benzoylnaphthalene, di-*tert*-butyl ketone, and tetraphenylcyclopen-

Table 2. Cyanosilylation of various ketones with TMSCN using Sn-Mont as the catalyst.[a]

Entry	Ketones	Time [min]	Products	Yield [%][b]
1		0.5		> 98
2		1		> 98
3		2		> 98
4		2		> 98
5		2		> 98
6		2		> 98
7		2		> 98
8		3		94
9		5		98
10		6		> 98
11		6		64[c] 64[d]
12		7		> 98
13		10		> 98
14[e]		35		> 98
15[f]		90		93 0[g]

[a] *Reaction conditions*: ketone (1 mmol), TMSCN (1.2 mmol), Sn-Mont (10 mg), CH_2Cl_2 (2 mL), room temperature.

[b] Yields were calculated based on the product weight after filtering and condensing the reaction mixture. Purity of all products was >98% by ^{1}H NMR.

[c] The reaction was carried out in the presence of Sn-Mont for 2 min, and then Sn-Mont was filtered off and the filtrate was stirred for 4 min. Yields were determined by ^{1}H NMR using an internal standard.

[d] Reaction time: 2 min.

[e] Reaction was carried out with 0.5 mmol of ketone and 0.6 mmol of TMSCN.

[f] *Reaction conditions*: ketone (0.25 mmol), TMSCN (1.25 mmol), Sn-Mont (10 mg), chlorobenzene (2.5 mL), 100 °C.

[g] Reaction was carried out without Sn-Mont.

tadienone with TMSCN represent unprecedented results.

In the course of the cyanosilylation with Sn-Mont in CH_2Cl_2, some active tin species might migrate from the solid into the liquid phase and the leached tin species in solution could be partly contributing to the catalysis. To investigate the possibility of such a homogeneous catalysis in the cyanosilylation of benzophenone, Sn-Mont was filtered off after the reaction mixture had been stirred for 2 min at room temperature, and then the filtrate was again stirred under the same conditions. No increase in the yield was observed after solid Sn-Mont was removed, proving that the cyanosilylation was catalyzed heterogeneously (Table 2, entry 11).

Thus, Sn-Mont is superior to homogeneous catalysts in the way that Sn-Mont can be easily separated from the products and can be used in fixed-bed processes. Generally, the reusability is another important aspect for a heterogeneous catalyst. Re-use of Sn-Mont was examined for the cyanosilylation of acetophenone and benzophenone. Sn-Mont was able to be easily recovered by simple filtration and re-used in at least 3 reaction cycles under the same conditions without any significant loss of the activity (Figure 2), confirming that Sn-Mont is truly reusable and highly stable. Actually, as-prepared Sn-Mont was stored in a glass vial under ambient conditions for 6 months, and showed no decrease in catalytic activity.

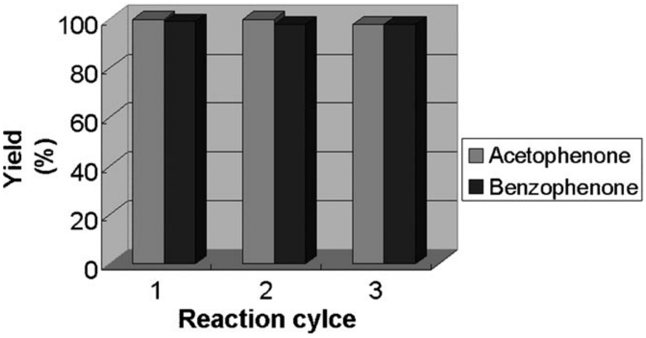


Figure 2. Reusability of Sn-Mont for the cyanosilylation of acetophenone and benzophenone, respectively.

In conclusion, Sn-Mont, easily prepared from commercially available montmorillonite clay, was found to be the most efficient heterogeneous catalyst generally applicable for the cyanosilylation of various ketones – from simple to highly congested ones. Further application of Sn-Mont as a solid strong acid catalyst to a variety of fine chemicals syntheses is now in progress.

Experimental Section

Synthesis of Sn-Mont

Sn-Mont was prepared from Na^+ ion-exchanged montmorillonite (Na-Mont) "Kunipia-F" (Kunimine Industries Co. Ltd.; Na, 2.69; Al, 11.8; Fe, 1.46; Mg, 1.97%. Cation-exchange capacity = 1.19 mequiv g^{-1}) according to our previously report.[16] Na-Mont (8 g) was ion-exchanged with aqueous $SnCl_4{\cdot}5H_2O$ (0.3 M, 80 mL) at room temperature for 2 h and then this exchange procedure was repeated again. Then the collected clay was washed with water (80 mL) twice, with a mixture of water (40 mL) and methanol (40 mL) 6 times until the washing filtrate became almost neutral. Then the solid cake was rinsed with absolute methanol (80 mL) once. Finally Sn-Mont was dried in vacuum (0.5 mmHg) at room temperature for 12 h, followed by being ground in a mortar with a pestle, passed through a 60-mesh screen and stored in a glass vial.

The synthesis and characterization of the control catalysts such as Al-MCM-41 and Sn-MCM-41 are shown in the Supporting Information.

Catalytic Reaction

Dichloromethane and 1-chlorobenzene were distilled with CaH_2 and stored in a glass bottle containing activated molecular sieves 4 A. The experimental procedures for the cyanosilylation of various ketones catalyzed by Sn-Mont are shown as follows:

The reaction procedures in entries 1–10 and 12–13 in Table 2: The ketone (1.0 mmol) was added to a CH_2Cl_2 (2 mL) suspension of Sn-Mont (10 mg) which had been pretreated under vacuum at 120 °C for 1 h, and then TMSCN (160 μL, 1.2 mmol) was added. The mixture was stirred at room temperature under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. After the reaction was complete, the catalyst was filtered off and washed with CH_2Cl_2. Evaporation of the filtrate under vacuum gave the corresponding cyanohydrin trimethylsilyl ether, the purity of which was analyzed by ^1H NMR to be more than 98%. Thus, no further purification was needed.

The recovered catalyst was separated, washed with a large amount of water and methanol, dried under vacuo, and used again in another reaction.

The reaction procedure in entry 14 in Table 2: The reaction procedure is the same as the above one except that a half amount of ketone (0.5 mmol) and TMSCN (0.6 mmol) are used.

The reaction procedure in entry 15 in Table 2: Tetraphenylcyclopentadienone (0.25 mmol) was added to a 1-chlorobenzene (2.5 mL) suspension of Sn-Mont (10 mg), which had been pretreated under vacuum at 120 °C for 1 h, and then TMSCN (1.25 mmol) was added. The mixture was stirred at 100 °C under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. After the reaction was complete, the catalyst was filtered off and washed with CH_2Cl_2. Evaporation of the filtrate under vacuum gave the corresponding crude cyanohydrin trimethylsilyl ether. The pure product was obtained by recrystallization from MeOH.

Products were characterized by spectral analysis (^1H NMR, ^{13}C NMR, and FT-IR) and HR-MS, and the spectral data and representative NMR images are included in the Supporting Information.

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