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Rapid additions of bulky *tert*-butyldimethylsilyl cyanide to hindered ketones promoted by heterogeneous tin ion-exchanged montmorillonite catalyst

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ABSTRACT

Tin ion-exchanged montmorillonite (Sn-Mont) was found to be a powerful heterogeneous catalyst for the cyanosilylation of various ketones including congested ones with a bulky cyanide source, *tert*-butyldimethylsilyl cyanide (TBDMSCN), giving the corresponding cyanohydrin *tert*-butyldimethylsilyl ethers in good (85%) to excellent (>98%) yields at room temperature. Compared to the previously reported catalysts, Sn-Mont is easy to prepare, environmentally benign, nontoxic, noncorrosive, and recyclable.

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The cyanosilylation of aldehydes and ketones with trialkylsilyl cyanide is the most straightforward way not only to form a new C-C bond, but also to simultaneously protect an alcohol with a trialkylsilyl group. The as-formed cyanohydrin trialkylsilyl ethers can be further transformed into a wide range of important intermediates, such as α -hydroxy acids, α -amino acids, and β -amino alcohols.^{1,2} To date, there have been innumerable reports on the cyanosilylation of aldehydes and ketones with the most compact cyanide source, trimethylsilyl cyanide (TMSCN), along with the aid of various homogeneous and heterogeneous catalysts, such as metal organic frameworks (MOFs),³ metal complexes,⁴ Lewis acids,^{5,6} base catalysts,^{7–9} ionic liquids,¹⁰ organic catalysts,^{11–16} inorganic mesoporous materials,^{17,18} etc. Recently, we also found that tin ion-exchanged monmorillonite (Sn-Mont) was a highly active solid catalyst for the addition of TMSCN to sterically congested. less reactive ketones under mild conditions.¹⁹ Compared to the number of successes of the cyanosilylation of aldehydes and ketones with TMSCN, the cyanosilylation with much bulkier cyanides, such as tert-butyldimethylsilyl cyanide (TBDMSCN), was very few. For example, an organic base of P(RNCH₂CH₂)N²⁰ or a Lewis acid of ZnI₂²¹ was successfully applied to cyanosilylation,

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but these methods have disadvantages concerning their slow reaction rates and some difficulties in separating and reusing the homogeneous catalysts.

Our group developed tin ion-exchanged montmorillonite (Sn-Mont), which was easily prepared through the ion-exchange of Na-Mont with an SnCl₄ solution.²² Sn-Mont was proved to be the most powerful for the trimethylsilylation of alcohols among the various metal ion-exchanged montmorillonites.²³ We have further applied Sn-Mont as the effective acid catalyst for the Michael reactions,²⁴ and the reduction of carbonyl compounds with hydrosilanes,²⁵ the one-pot synthesis of α -aminonitriles from ketones,²⁶ and the direct substitution of alcohols with some carbon nucleophiles.²⁷⁻²⁹

In order to further demonstrate the great potential of Sn-Mont for organic syntheses, we now report that *tert*-butyldimethylsilyl cyanide (TBDMSCN) as a hindered cyanide source can conduct the rapid cyanosilylation of various ketones including congested ones catalyzed by a catalytic amount of environmentally benign Sn-Mont.³⁰ A series of cyanohydrin *tert*-butyldimethylsilyl ethers were obtained in good to excellent yields. After the reaction, Sn-Mont was easily recovered by filtration and reused without an appreciable loss of activity.

Sn-Mont, prepared through the ion-exchange of Na-Mont (Kunimine Industries Co., Ltd, Japan) with an SnCl₄ solution according to our previous report,¹⁹ possessed 1.9 mmol of tin ions per gram of Sn-Mont and the exchange percentage of sodium ions



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for tin ions in Sn-Mont was 97.1% determined by an inductively coupled plasma (ICP) analysis. Transmission electron microscopy (TEM) analysis indicated that Sn-Mont was a composite of SnO_2 nanoparticles surrounded by delaminated montmorillonite silicate layers.³¹ The specific surface area of Sn-Mont was as high as 280 m²/g, which was about 23 times that of the pristine Na-Mont (12 m²/g).

Generally, solvents used in heterogeneous catalytic reactions often have significant influences on the yields and selectivities of the reactions. Thus, the reaction of 9-fluorenone (1a, 1 mmol) with a slight excess amount of TBDMSCN (1.05 mmol) at room temperature was selected as the model reaction in order to investigate the solvent effects on the yield of the desired product **2a** catalyzed by Sn-Mont (20 mg, 3.8 mol %). Among the solvents tested as shown in Table 1. the non-polar solvents, such as dichloromethane (CH_2Cl_2) and toluene, gave **2a** in excellent yields of >98 and 97%. respectively. (entries 1 and 2). In polar solvents, such as tetrahydrofuran (THF), 1,4-dioxane, and acetonitrile, 2a was produced in very poor to moderate yields (8-66%) (entries 3-5). Especially, almost no reaction proceeded in dimethylformamide (DMF), probably because the basic character of DMF hindered the acid catalysis of Sn-Mont (entry 6). Accordingly, performing the reaction in dichloromethane is optimal for the addition of bulky TBDMSCN to ketones in the presence of Sn-Mont.

Inspired by the above results, we further compared Sn-Mont with other heterogeneous catalysts for the same reaction in CH_2Cl_2 to highlight the high performance of Sn-Mont: As presented in Table 2, no reaction took place in the absence of a catalyst or in the presence of pristine Na-Mont (entries 1 and 2). A catalytic amount of Sn-Mont (20 mg, 3.8 mol %) showed the highest catalytic activity for cyanosilylation to give the corresponding 2a in more than 98% yield in only 8 min (entry 3). The recovered Sn-Mont was usable for the reaction without any loss in catalytic activity (>98% yield, entry 4). Other acidic montmorillonites, such as Al-Mont and H-Mont, also gave excellent yields of 93-95%, while a commercially available K10 resulted in the moderate yield (78%) of 2a (entries 5-7). In contrast, Cu-Mont only afforded a very poor yield (7%) (entry 8). When the reaction was performed with crystalline SnO_2 , no reaction occurred (entry 9). Interestingly, mesoporous silicates of Sn- and Al-MCM-41 as well as microporous proton-exchanged zeolites of H-Beta and H-USY also showed no activity (entries 10-13), although they have been employed in a wide range of acid-catalyzed reactions.^{32,17,33-36}

To investigate the possibility of a homogeneous catalysis by the tin species leaching into the solution during the cyanosilylation of **1a**, the following experiments were carried out: The cyanosilylation of **1a** with TBDMSCN was performed as shown in entry 3 of Ta-

Table 1

Sn-Mont-catalyzed addition of TBDMSCN to 9-fluorenone (1a) in various solvents^a

+	TBDMSCN	NC OTBDMS
1a	8 min	2a
Entry	Solvent	Yield ^b (%)
1	CH_2Cl_2	>98
2	Toluene	97
3	THF	66
4	1,4-Dioxane	51
5	Acetonitrile	8
6	DMF	<1

^a Reaction conditions: Sn-Mont (20 mg, 3.8 mol %), 9-fluorenone (**1a**, 1 mmol), TBDMSCN (1.05 mmol), solvent (2 mL), rt.

^b Determined by GC using dodecane as the internal standard.

Table 2

Comparing different heterogeneous catalysts^a

	1a + TBDMSCN CH ₂ Cl ₂ 2a 8 min 8	
Entry	Catalyst	Yield ^b (%)
1	No catalyst	0
2	Na-Mont	0
3	Sn-Mont	>98
4 ^c	Sn-Mont	>98
5	H-Mont	95
6	Al-Mont	93
7	K10	78
8	Cu-Mont	7
9	SnO ₂	0
10	Sn-MCM-41	0
11	Al-MCM-41	0
12	H-Beta	0
13	H-USY	0

 a Reaction conditions: catalyst (20 mg), 1a (1 mmol), TBDMSCN (1.05 mmol), CH_2Cl_2 (2 mL), rt.

^b Determined by GC using dodecane as the internal standard.

^c The second reuse of Sn-Mont.

ble 2. Sn-Mont was then removed from the reaction mixture by filtration after **1a** was completely consumed. The filtrate was again treated with an additional supply of **1a** (1 mmol) and TBDMSCN (1.05 mmol) while stirring at rt, and no evident increase in the amount of **2a** was observed after 1 h. This fact directly indicates that the solution phase does not include any catalytically active species and that the cyanosilylation with TBDMSCN catalyzed by Sn-Mont is truly a heterogeneous reaction.

To further validate the utility of Sn-Mont as the solid acid catalyst for the cyanosilylation with TBDMSCN at room temperature, a variety of carbonyl compounds were tested. As summarized in Table 3, various ketones (1 mmol) underwent cyanosilylation in the presence of Sn-Mont (20 mg, 3.8 mol %) with a slight excess of TBDMSCN (1.05 equiv) to promptly provide the desired products in good to excellent yields: An aliphatic ketone, 4-phenylbutan-2-one (1b), reacted with TBDMSCN in only 2 min to afford 2b in greater than 98% yield (entry 1). Alkyl phenyl ketones (1c, 1d, and 1e) underwent cyanosilylation at room temperature with high yields (>98%) in the short reaction period of 5 min (entries 2-4). Methyl 2-naphthyl ketone (1f) also yielded 2f in greater than 98% yield in 5 min (entry 5). Although the 2-fluorenyl group in 1g clearly made the reaction slower, the reaction was completed in only 15 min with a 91% yield of 2g (entry 6). Bulkier ketones, such as benzophenone (1h) and its derivatives (1i and 1j) as well as 9-fluorenone, were also able to efficiently react with the bulky TBDMSCN in 6-15 min to afford the desired cyanohydrin tertbutyldimethylsilyl ethers with high yields (entries 7-10). In addition, the cyanosilylation of ketones with a carbonyl group under extraordinarily congested circumstances was also investigated (entries 11 and 12). Excellent yields for the desired adducts (2k and 21) were obtained for the cyanosilylation of 2-benzoylnaphthalene (1k) and di-tert-butyl ketone (1l), although slightly longer reaction times (30-45 min) were required (entries 11-12). Naturally, the cyanosilylation of a simple aldehyde, benzaldehyde **1m**, with TBDMSCN in the presence of 10 mg of Sn-Mont was completed in only 1 min to afford the desired **2m** in >98%.

We also investigated the reactions of α , β -unsaturated ketones and aldehyde with TBDMSCN in the presence of Sn-Mont. Benzalacetone (**1n**) and more sterically congested cinnamyl cyclohexyl ketone (**1o**) underwent the *t*-butyldimethylsilylcyanation to exclusively afford the 1,2-addition products (**2n** and **2o**) in excellent yields (>98% and 95%, respectively). In contrast, not only more amounts of Sn-Mont and TBDMSCN as well as heating at 100 °C

Table 3

Cyanosilylation of various ketones with TBDMSCN using Sn-Mont as the catalyst^a

Entry	Ketone		Time (min)	Product		Yield ^b (%)
1	O O	1b	2	NC OTBDMS	2b	>98
2		1c	5	NC OTBDMS	2c	>98
3		1d	5	NC_OTBDMS	2d	>98
4		1e	5	NC OTBDMS	2e	>98
5		1f	5	NC OTBDMS	2f	>98
6		∖ 1g	15		MS 2g	91
7		1h	6	NC OTBDMS	2h	>98
8		1i	15	NC OTBDMS	2i	96
9		1j	6	CI	2j	92
10		1a	8	NC_OTBDMS	2a	>98
11		1k	45	NC_OTBDMS	2k	94
12	\rightarrow	11	30		21	85
13 ^c		1m	1		2m	>98
14		1n	60		2n	>98
15) ¹⁰	180		20	95
16 ^d		1p	180		2р	50
	0				2p'	47 ^e
17	H	1q	5	Н	2q	>98

^a Reaction conditions: Sn-Mont (20 mg, 3.8 mol %), substrate (1 mmol), TBDMSCN (1.05 mmol), CH₂Cl₂ (2 mL), rt.

^a Reaction conditions: Sh-Mont (20 ling, 5.8 line) b), substate (1 line), 195/05Ct (1.05 line), 212/22 (2 line), 12
 ^b Isolated yields after the purification by column chromatography on silica gel.
 ^c Ten milligrams of Sh-Mont were used.
 ^d Reaction conditions: Sh-Mont (50 mg, 9.5 mol %), 1p (1 mmol), TBDMSCN (2.10 mmol), chlorobenzene (2 mL), 100 °C.
 ^e The product of 2p' is a mixture of geometric isomers with a ratio of about 4:1 by ¹H NMR.

Table	4
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Comparison of the cyanosilylation of acetophenone (1c) and benzophenone (1h) with TBDMSCN in the presence of Sn-Mont to those reported in the literature

Substrate	Catalyst (amount)	Time	Yield (%)	TOF (h^{-1})	Ref.
1c	P(RNCH ₂ CH ₂)N (7 mol %)	1 h	90	12.9	20
1c	ZnI ₂ (3 mol %)	3 h	86	9.7	21
1h	P(RNCH ₂ CH ₂)N (5 mol %)	1 h	87	17.4	20
1c	Sn-Mont (3.8 mol %)	5 min	>98	309.5	This work
1h	Sn-Mont (3.8 mol %)	8 min	>98	193.4	This work

in a chlorobenzene solvent were needed for chalcone (**1p**) to complete the reaction, but also a mixture of 1,2-addition product (**2p**) and 1,4-additon one (**2p**') were produced in 50% and 47% yields, respectively. As expected, cinnamaldehyde (**1q**) underwent exclusive 1,2-addition to quantitatively give **2q**.

It was previously reported that the homogeneous catalysts, such as $P(RNCH_2CH_2)N^{20}$ and ZnI_2 ,²¹ successfully achieved the cyanosilylation of acetophenone (**1c**) and benzophenone (**1h**) with TBDMSCN, as shown in Table 4. The average turn-over frequencies (TOF) of the cyanosilylation of **1c** with TBDMSCN catalyzed by $P(RNCH_2CH_2)N$ and ZnI_2 are 12.9 and 9.7 h⁻¹, respectively, both of which are far lower than that of 309.5 h⁻¹ by Sn-Mont. The average TOF of the cyanosilylation of **1h** by Sn-Mont was as high as 193.4 h⁻¹, which is far greater than that of 17.4 h⁻¹ for the same reaction using $P(RNCH_2CH_2)N$.³⁷ Moreover, Sn-Mont is superior to homogeneous catalysts in the way that Sn-Mont can be easily separated from the products³⁸ and can be used in the fixed-bed processes.

Compared with the cyanosilylation of various ketones with TMSCN in the presence of Sn-Mont, that with TBDMSCN proceeded slightly more slowly, but such a prompt cyanosilylation protocol is useful without question because the OH groups in the formed cyanohydrins are being protected by a *tert*-butyldimethylsilyl group and much more robust to acidic conditions which often encounter multi-step organic synthetic processes.

In conclusion, tin ion-exchanged montmorillonite (Sn-Mont) as a heterogeneous acid catalyst demonstrated a high catalytic activity for the cyanosilylation of various ketones including congested ones with a bulky cyanide source, *tert*-butyldimethylsilyl cyanide (TBDMSCN). The desired products were produced in good to excellent yields (85 to >98%) at room temperature. Compared to the previously reported catalysts, Sn-Mont is easy to prepare, environmentally benign, nontoxic, noncorrosive, and recyclable.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.026.

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