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Direct Synthesis of Nitriles from Alcohols with Trialkylsilyl Cyanide Using Brønsted Acid Montmorillonite Catalysts

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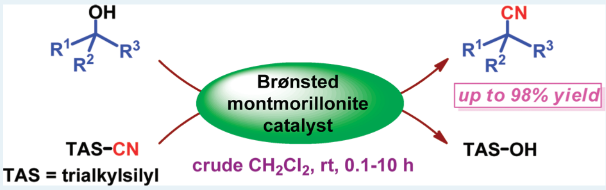
S Supporting Information



ABSTRACT: We reported a simple protocol for nitrile synthesis by the direct cyanation of various secondary/tertiary benzylic and allylic alcohols with trialkylsilyl cyanide (TASCN) with moderate to excellent yields as well as high regioselectivities and turnover numbers/frequencies catalyzed by solid Brønsted acids of metal ion-exchanged montmorillonites (M-Mont; M = Sn and Ti). The easily prepared montmorillonites demonstrated a significant catalytic performance for the cyanation of various alcohols that is far superior to those by control catalysts, such as proton ion-exchanged zeolites, homogeneous Lewis acids, and homogeneous Brønsted acids. The water-tolerant character of the montmorillonites led to high catalytic activities, even in a crude solvent. In addition, they were easily recovered from the reaction mixtures by filtration and reused without any loss of activity. The corresponding trimethylsilyl (TMS) ethers of alcohols were also found transformable into the nitriles using TASCN in the presence of the montmorillonite catalysts. However, the conversions of alcohols with TASCN were faster than those of the corresponding TMS ethers with TASCN, indicating that the activity of the TMS ethers was lower than that of alcohols. It was determined that the cyanation of allylic alcohols having a conjugated polyene structure afforded a single isomer among the possible regioisomers. Interestingly, the use of *tert*-butyldimethylsilyl cyanide is superior in the cyanation of alcohols and their TMS ethers to that of TMSCN.

KEYWORDS: nitriles, cyanation, alcohols, montmorillonite, heterogeneous catalysis, ion-exchange, Brønsted acid

INTRODUCTION

Although substitution reactions of alcohols with nucleophiles are generally far more difficult to perform than those of the corresponding halides due to the poor ability of a hydroxyl group as a leaving unit, substitution is still a fascinating protocol in synthetic organic chemistry in terms of both the greater availability and better economics of alcohols over halides. Thus, much attention has been paid to the direct substitution of alcohols with different nucleophiles, such as allylsilanes,[1−6] indoles,[7,8] 1,3-dicarbonyls,[7,9−13] amines,[14] amides,[15−21] 2-chloroethanol,[22] linear thiols,[22] trimethoxybenzene,[22] enolsilane,[23] and silyl ketene acetal.[23]

Especially, the replacement of a hydroxyl group in alcohols with a cyanide has been extensively studied[24−33] because nitriles are valuable precursors for the preparation of drugs such as indoprofen, cicloprofen, naproxen, etc.[34−37] There are also a variety of methods for nitrile syntheses, such as the substitution of aryl halides with a stoichiometric amount of copper(I) cyanide;[38] the dehydration of amides;[39,40] the hydrocyanation of olefins;[41−43] the acylation of silyl ketene imines;[44] the coupling of nitriles with aryl halides;[45,46] the transformation of carbonyl compounds with cyano phosphate;[47] and the cyanation of allylic carbonates, acetates, or methyl ethers with trialkylsilyl cyanide.[48,49]

Although alcohols can be converted into nitriles by the Mitsunobu reaction,[50] the protocol has a fatal drawback in that a stoichiometric amount of a condensation agent, dicyclohexyl carbodiimide, is required.[32,50,51] Recently, homogeneous Lewis acids, such as indium halides[52] and $B(C_6F_5)_3$,[53] were found to be efficient for the direct transformation of α-aryl alcohols with trimethylsilyl cyanide into nitriles. However, the Lewis acid InX_3 (X = Cl or Br) and $B(C_6F_5)_3$ are so moisture-sensitive that they are difficult to recover and reuse because a part of the acids is easily decomposed and deactivated by the water that comes from the substitution. The post-treatment of the Lewis acids is often a troublesome process, producing inorganic wastes. Therefore, to surmount these problems, the development of a heterogeneous as well as moisture-tolerant catalytic system instead of a homogeneous one is in high demand for the direct conversion of various benzylic alcohols as well as allylic ones to nitriles.

During the past two decades, montmorillonites as solid acids have aroused extensive interest in catalytic organic transformations.[54−56] Montmorillonite, an abundant naturally occurring clay, is composed of stacked, negatively charged, two-dimensional aluminosilicate layers that hold exchangeable cationic species, mostly sodium ions, in the interlayers. Once multivalent metal cations or protons are substituted for the sodium ions in the montmorillonite, the clay becomes acidic and has been utilized in various acid-catalyzed organic reactions. For instance, Kaneda has used metal ion-exchanged montmorillonites (M-Mont) for various organic transformations.[9,57−63] We have also

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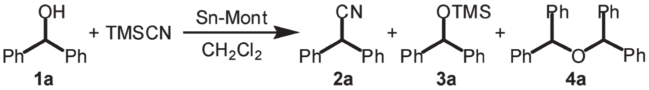
Scheme 1. Direct Transformation of Alcohols or their TMS Ethers with Trialkylsilyl Cyanide (TASCN) to Nitriles

Table 1. Optimization of the Reaction Conditions for the Cyanation of 1a with TMSCN Catalyzed by Sn-Mont[a]



entry	weight (mg)	T (°C)	t (h)	method[c]	conv (%)[b]	yield (%)[b] 2a	3a	4a
1	10	rt	0.1	A	100	27	5	68
2	10	40	1.5	A	100	31	1	68
3	20	60	4	A	100	33	3	64
4	20	rt	0.1	B	99	79	20	0
5	20	rt	1.5	B	100	88	12	0
6	20	rt	3	B	100	92	8	0

[a] **1a** (1 mmol), TMSCN (2 mmol), CH_2Cl_2 (2 mL). [b] Determined by GC based on **1a**. [c] Method A: TMSCN was added to the suspension of **1a** and Sn-Mont; method B: **1a** dissolved in CH_2Cl_2 was dropwise added to the suspension of Sn-Mont and TMSCN.

reported the efficient use of solid acid catalysis of M-Mont for typical organic reactions, such as the trimethylsilylation/allylation of alcohols,[64,65] the cyanosilylation of carbonyl compounds,[66−68] the reduction of carbonyl compounds with hydrosilanes,[69] the Michael reactions,[70] and the one-pot Strecker synthesis of α-amino nitriles.[71]

As a continuation of our study of the montmorillonite-catalyzed transformations for fine chemicals synthesis, we now describe the unique water-tolerant catalysis of Brønsted acid montmorillonite for the direct synthesis of nitriles from not only a wide variety of benzylic and allylic alcohols but also their trimethylsilyl (TMS) ethers with trialkylsilyl cyanide (TASCN) without additives under mild conditions (Scheme 1). It is notable that all the reactions on the montmorillonites smoothly proceeded in a crude solvent with a better catalytic performance than homogeneous Lewis acid catalysts, such as metal chlorides. It is also interesting that both heterogeneous Brønsted acids of proton-exchanged zeolites (H−Y and H-Beta) and homogeneous ones, such as sulfuric acid and p-toluenesulfonic acid, are ineffective for the reactions.

RESULTS AND DISCUSSION

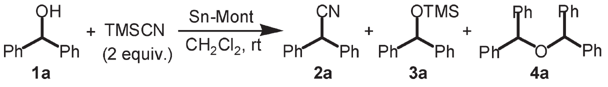
Optimization of Reaction Conditions. Initially, we tested the reaction of benzhydrol (**1a**) with trimethylsilyl cyanide (TMSCN, 2 equiv) in the presence of tin ion-exchanged montmorillonite (Sn-Mont) in crude CH_2Cl_2. It was found that the desired diphenylethanenitrile (**2a**) was accompanied by a large amount of side products, diphenylmethyl trimethylsilyl ether (**3a**) and bis(diphenylmethyl) ether (**4a**), when simultaneously the starting reagents and Sn-Mont were mixed at room temperature (rt) (eq 1). To improve the yield of **2a**, various reaction conditions, such as the reaction temperatures, reaction times, catalyst amounts, and the addition order of the starting reagents and the catalyst, were investigated, as shown in Table 1.

Table 2. Cyanation of 1a with TMSCN Using Various Catalysts[a]

$$\mathbf{1a} + \mathrm{TMSCN} \xrightarrow[\mathrm{CH_2Cl_2,\ rt}]{\mathrm{cat.}} \mathbf{2a} + \mathbf{3a} + \mathbf{4a}$$

entry	catalyst	t (h)	conv (%)[b]	yield (%)[b] 2a	3a	4a
1	no catalyst	8	96	0	96	0
2	Na-Mont	3	31	0	31	0
3	Ti-Mont	1.5	100	98	2	0
4	Sn-Mont	3	100	92	8	0
5	Mont K10	3	94	87	7	0
6	H-Mont	3	99	83	16	0
7	Al-Mont	3	100	72	28	0
8	Fe-Mont	3	99	67	32	0
9	Al-MCM-41	3	59	0	59	0
10	H−Y	3	28	0	28	0
11	H-Beta	3	27	0	27	0
12	Sn-MCM-41	3	46	0	46	0
13	$Sn(OH)_4$	3	29	0	29	0
14	SnO_2	3	35	0	35	0
15[c]	p-TsOH·H_2O	3	97	0	97	0
16[c]	H_2SO_4	3	77	0	77	0
17[d]	$SnCl_4·5H_2O$	3	96	53	0	43
18[d]	$InCl_3$	3	94	32	0	62
19[e]	$B(C_6F_5)_3$	3	42	4	8	30

[a] **1a** (1 mmol), TMSCN (2 mmol), catalyst (20 mg), CH_2Cl_2 (2 mL), rt, method B. [b] Determined by GC based on **1a**. [c] 10 mol %. [d] 5 mol %. [e] 2 mol %.



(1)

To improve the yield of **2a**, various reaction conditions, such as the reaction temperatures, reaction times, catalyst amounts, and the addition order of the starting reagents and the catalyst, were investigated, as shown in Table 1.

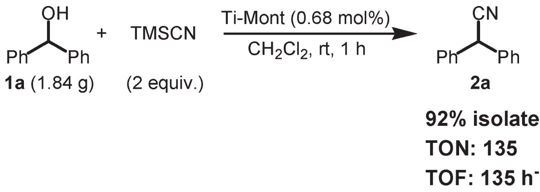
In the presence of 10 mg of Sn-Mont, which contained 1.9 mol % of tin ions, **1a** was entirely consumed in 0.1 h at rt, but the yield of **2a** was only 27% along with **3a** (5%) and **4a** (68%) when TMSCN was added to a suspended mixture of **1a** and Sn-Mont (Table 1, entry 1). This addition procedure was called method A in the paper (see the Materials and Methods section). The byproduct **3a** was further transformable into **2a**, whereas **4a** was intact when the mixture was heated at 40 °C for the prolonged time of 1.5 h (entry 2). Compound **4a** was still the dominant product, even if the amount of Sn-Mont was doubled (20 mg; 3.8 mol %) at the much higher temperature of 60 °C for the much longer time of 4 h (entry 3). To suppress the intermolecular condensation of **1a** to **4a**, another addition procedure, called method B, was employed (see the Materials and Methods section), in which a CH_2Cl_2 solution of **1a** was slowly added to a suspended mixture of Sn-Mont and TMSCN. Following this method, the yield of **2a** was dramatically improved to 79% in only 0.1 h at rt (entry 4). Compound **3a** was also formed in 20% yield, but the formation of **4a** was completely inhibited. By prolonging the reaction time, **3a** was gradually changed into **2a** (entries 4−6), and the yield finally reached 92% after 3 h (entry 6). Method B was also found optimal for the cyanation of **1a** using other montmorillonite catalysts, such as Ti-Mont (see Table S1 in the Supporting Information).

Comparing the Catalytic Activity between Various Heterogeneous and Homogeneous Catalysts. Following the optimal addition procedure, various heterogeneous and homogeneous catalysts were compared in the cyanation of **1a** with TMSCN. As presented in Table 2, **2a** was not produced without a catalyst or with pristine Na-Mont (entries 1−2). In both cases, trimethylsilyl ether **3a** was an exclusive product. Not only Sn-Mont (entry 4), but also Ti-Mont (entry 3) showed excellent activities to give **2a** in 92% and 98% yields, respectively. Other montmorillonites, such as proton ion-exchanged montmorillonite (H-Mont), Al-Mont, Fe-Mont, and the commercially available K10, offered fair to good yields of 67−87% (entries 5−8). Compound **2a** was not obtained in the presence of the typical solid acids, such as Al-containing ordered mesoporous material with a high specific surface area,[72,73] and proton ion-exchanged zeolites (H−Y and H-Beta, entries 9−11). Other Sn-containing catalysts (such as Sn-MCM-41 with an ordered mesoporous structure,[74,75] $Sn(OH)_4$ prepared from $SnCl_4$ with aqueous NH_3, and crystalline SnO_2) did not promote the formation of **2a** (entries 12−14). To our surprise, homogeneous strong Brønsted acids, H_2SO_4 and *p*-toluenesulfonic acid monohydrate (*p*-$TsOH \cdot H_2O$) were useless, giving only **3a** (entries 15−16).

Although the reaction was also attempted with metal halides, such as $SnCl_4 \cdot 5H_2O$, which was a precursor for the preparation of Sn-Mont and $InCl_3$, the yields of **2a** were only 53% and 32%, respectively, together with **4a** as the main product (Table 2, entries 17−18). Curiously, the Lewis acid, $B(C_6F_5)_3$, afforded **2a** in a very low yield (4%) under our conditions. Such a low activity of $B(C_6F_5)_3$ would be caused by the small amount of water produced by the self-condensation of **1a** and included in the crude solvent, which makes $B(C_6F_5)_3$ decompose. In sharp contrast, the montmorillonite catalysts efficiently promoted the reaction, even in crude CH_2Cl_2.

The water-tolerant character of the montmorillonites should be highlighted. Sn-Mont is a nanoporous composite with Brønsted acidity composed of tin oxide nanoclusters and delaminated montmorillonite silicate layers.[71] Ti-Mont is also a Brønsted acid montmorillonite intercalating chainlike titanium hydroxide polymers.[60] The presence of Brønsted acid sites on Ti-Mont and Sn-Mont was confirmed by FT-IR spectroscopy after pyridine adsorption on Ti-Mont and Sn-Mont (see Figure S5 in the Supporting Information). Compared with the various control catalysts, it became clear that the montmorillonite catalysts, Ti-Mont and Sn-Mont, were much more efficient for the direct cyanation of alcohols with TMSCN to form the nitriles, and that this is the first example of the cyanation performed by Brønsted acid catalysts.[9,61]

Cyanation of Various Alcohols with TMSCN. Ti-Mont and Sn-Mont were used for the cyanation of various benzylic alcohols to survey the scope and limitations of the protocol (Table 3). Most reactions gave the desired nitriles with good to excellent yields in the presence of Sn-Mont (20 mg; 3.8 mol %) or Ti-Mont (20 mg; 1.36 mol %) under the optimized reaction conditions. Diarylmethanols (**1a**−**c**) underwent the cyanations with more than 90% isolated yields in 1.5 h (entries 1−3). α-Aryl alkanols with an electron-donating alkoxy group quickly afforded the corresponding nitriles with excellent yields in very short reaction times (0.1−0.5 h) (entries 5−10).[76] However, in the case of 1-(4′-methylphenyl)ethanol (**1g**), the cyanation moderately occurred (entries 11−12). Sterically hindered alcohols (**1 h**−**j**) were also proper substrates for affording the corresponding cyanated products in fair to high yields (75−92%) after longer reaction times (entries 13−16). To our delight, a far more sterically congested tertiary alcohol, triphenylmethanol (**1k**), afforded triphenylethanenitrile (**2k**) with very excellent yields (92−94%) in very short reaction times (0.3−0.5 h) (entries 17−18).



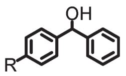
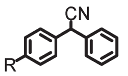
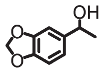
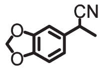
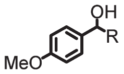
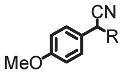
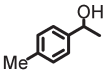
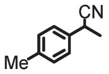
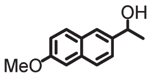
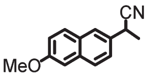
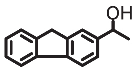
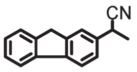
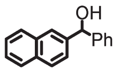
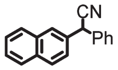
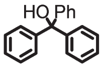
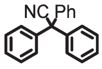
(2)

Even when 10 mmol of **1a** was applied for the reaction, the cyanation was smoothly completed within 1 h at rt with Ti-Mont (0.68 mol %). The recrystallization of the filtrate after removing the catalyst and solvent afforded **2a** in a 92% isolated yield with a high turnover number (TON) of 135 and an average turnover frequency for the reaction period (TOF) of 135 h^{-1} (eq 2). These data are definitely superior to those of the preceding methods for the cyanation of **1a** to **2a** using PPh_3/DDQ/*n*-Bu_4NCN (0.35, 0.02 h^{-1})[27] and TsIm/TBAI/TEA (0.59, 0.1 h^{-1} based on TsIm).[32] No significant changes in the structure of Sn-Mont were detected by XRD or nitrogen sorption measurements before and after the reactions (see the Supporting Information). The recovered Sn-Mont was capable of reuse without significant loss of its high catalytic performance (Table 3, entry 4).

Inspired by these findings, we extended our interest to the direct synthesis of unsaturated nitriles from the corresponding alcohols. The allylic nitriles were previously prepared by the hydrocyanation of 1,3-dienes, which required the use of highly toxic hydrogen cyanide as well as long reaction times or high temperatures, giving isomeric mixtures of nitriles.[42,77,78] As seen in Table 4, (*E*)-4-phenylbut-3-en-2-ol (**1l**) was quickly converted to (*E*)-2-methyl-4-phenylbut-3-enenitrile (**2l**) with good yields (88−90%) in the presence of a catalytic amount of Sn-Mont or Ti-Mont at rt (entries 1−2). The reaction was completed within 0.2 h with Ti-Mont (20 mg, 1.36 mol %), and the calculated TON (66) and TOF (331 h^{-1}) were definitely far higher than those for the Ni(0)-catalyzed hydrocyanation of 1,3-diene (8.7, 0.435 h^{-1})[42] and $InBr_3$-promoted cyanation (8.4, 42 h^{-1}).[52] An electron-donating group at the benzene ring of **1l** significantly increased the reaction rate (entries 3−4), whereas the introduction of an electron-withdrawing chlorine group to the para position resulted in a fair yield of 65% within 3 h (entry 5). Both Sn-Mont and Ti-Mont promoted the cyanation of a tertiary unsaturated alcohol (**1p**) with the good yields of 80−83% (entries 6−7). (*E*)-1,3-Diphenylprop-2-en-1-ol (**1q**) was also a suitable substrate to give the desired product **2q** in 94−98% yields (entries 8−9).

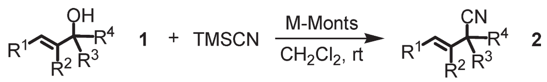
Table 3. Cyanation of Benzylic Alcohols with TMSCN Using Sn-Mont or Ti-Mont[a]

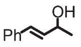
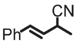
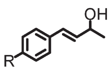
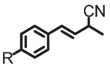
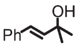
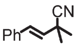
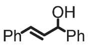
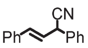
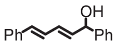
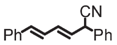
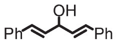
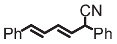
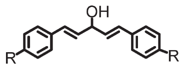
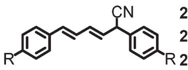
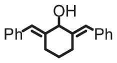
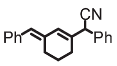
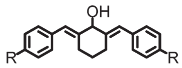
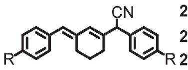
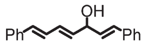
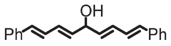
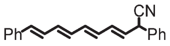
$$\mathbf{1} + \text{TMSCN} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt}]{\text{M-Monts}} \mathbf{2}$$

Entry	Alcohol **1**	R		M-Mont	*t* (h)	Nitrile **2**		Yield (%)[b]
1		H	**1a**	Ti	1.5		**2a**	91
2		Me	**1b**	Ti	1.5		**2b**	93
3		OMe	**1c**	Ti	1.5		**2c**	95
4	**1a**			Ti	1.5	**2a**		92[c] 91[d]
5			**1d**	Sn	0.5		**2d**	93
6			**1d**	Ti	0.2		**2d**	92
7		Me	**1e**	Sn	0.1		**2e**	98
8		Et	**1f**	Sn	0.1		**2f**	96
9	**1e**			Ti	0.1	**2e**		98
10	**1f**			Ti	0.1	**2f**		98
11			**1g**	Ti	1		**2g**	62
12			**1g**	Sn	1		**2g**	57
13[e]			**1h**	Sn	10		**2h**	85
14[e]			**1h**	Ti	10		**2h**	92
15[e]			**1i**	Ti	10		**2i**	79
16[e]			**1j**	Ti	6		**2j**	75
17[e]			**1k**	Ti	0.3		**2k**	94
18[e]			**1k**	Sn	0.5		**2k**	92

[a] Alcohol (1 mmol), TMSCN (2 mmol), M-Mont (20 mg), CH_2Cl_2 (2 mL), rt, method B. [b] Isolated yields. [c] The first reuse of Ti-Mont. [d] The second reuse of Ti-Mont. [e] Alcohol (0.5 mmol).

Table 4. Cyanation of Various Unsaturated Alcohols with TMSCN Using Sn-Mont or Ti-Mont[a]



Entry	Alcohol **1**	R		M-Mont	*t* (h)	Nitrile **2**		Yield (%)[b]
1			**1l**	Sn	0.3		**2l**	88
2			**1l**	Ti	0.2		**2l**	90
3		Me	**1m**	Sn	0.2		**2m**	95
4		OMe	**1n**	Sn	0.1		**2n**	98
5		Cl	**1o**	Sn	3		**2o**	65
6			**1p**	Sn	1		**2p**	80
7			**1p**	Ti	1		**2p**	83
8			**1q**	Sn	0.1		**2q**	98
9			**1q**	Ti	0.1		**2q**	94
10			**1r**	Sn	0.5		**2r**	85
11			**1s**	Sn	0.5		**2r**	84
12			**1s**	Ti	0.5		**2r**	81
13		Me	**1t**	Sn	0.5		**2t**	89
14		OMe	**1u**	Sn	0.5		**2u**	85
15		Cl	**1v**	Sn	0.5		**2v**	71
16			**1w**	Sn	1		**2w**	85
17			**1w**	Ti	1		**2w**	84
18		Me	**1x**	Sn	1		**2x**	89
19		OMe	**1y**	Sn	1		**2y**	93
20		F	**1z**	Sn	1		**2z**	82
21		Cl	**1aa**	Sn	1		**2aa**	79
22			**1bb**	Ti	1		**2bb**	91
23			**1cc**	Ti	1		**2cc**	63

[a] Alcohol (1 mmol), TMSCN (2 mmol), M-Mont (20 mg), CH_2Cl_2 (2 mL), rt, method B. [b] Isolated yields.

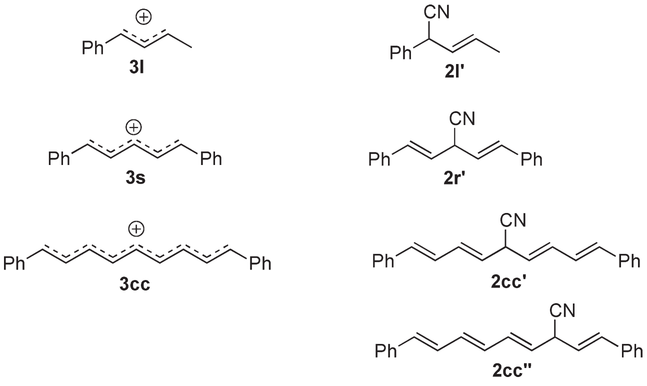


Figure 1. Possible carbocation intermediates and regioisomers of cyanation products.

The montmorillonite catalysts were also highly active for the reactions of various unsaturated alcohols conjugating with a phenyl group. The alcohols have not been used for the nitrile synthesis: (2*E*, 4*E*)-1,5-diphenyl-penta-2,4-dien-1-ol (**1r**) was transformed into (3*E*, 5*E*)-2,6-diphenylhexa-3,5-dienenitrile (**2r**) in 85% yield within 0.5 h (Table 4, entry 10). Interestingly, the cyanation of **1s**, which is a regioisomer to **1r**, took place at the benzylic carbon to exclusively afford **2r** (Table 4, entries 11–12; 81–84%). The same regioselective cyanation was observed for **1t**, **1u**, and **1v**, regardless of the substituent on the benzene rings (entries 13–15). The reactions of **1w**, **1x**, **1y**, **1z**, and **1aa** with TMSCN exclusively underwent the cyanation at the benzylic position in 79–93% yields (entries 16–21). To our delight, the triene alcohol **1bb** and the tetraene alcohol **1cc** also underwent the regioselective cyanation to afford the corresponding cyanides **2bb** and **2cc**, respectively (entries 22–23).

We postulated that the cyanation of **1l** would proceed via a stabilized carbocation intermediate **3l**, as shown in Figure 1, which could then react with a cyanide. Thus, we compared the difference in the Gibbs free energy (*G*) between **2l** and its regioisomer **2l′** calculated by Gaussian 03[79] at the B3LYP/6-31+G(d,p) level.[80,81] According to our calculation, **2l** is more stable by 4.0 kcal mol^{-1} than **2l′**. Therefore, we propose that the transition energy from **3l** to **2l** would be lower than that from **3l** to **2l′**, according to the Bell–Evans–Polanyi (BEP) principle, explaining why **2l** is exclusively produced by the cyanation of **1l** with TMSCN (Table 4, entries 1–2).

Similarly, the difference in *G* between **2r** and its regioisomer **2r′** shows that **2r** is more stable by 3.7 kcal mol^{-1} than **2r′**, ensuring the regioselective formation of **2r** rather than **2r′** from

Table 5. Cyanation of Benzylic and Allylic Alcohols with Sterically Bulky TBDMSCN Using Ti-Mont[a]

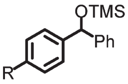
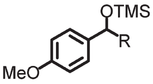
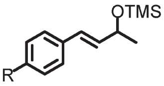
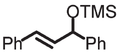
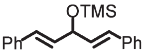
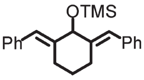
$$\mathbf{1} + \text{TBDMSCN} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt}]{\text{Ti-Mont}} \mathbf{2}$$

entry	alcohol **1**	*t* (h)	nitrile **2**	yield (%)[b]
1	**1a**	0.5	**2a**	95
2	**1b**	0.5	**2b**	98
3	**1c**	0.5	**2c**	98
4[c]	**1h**	1	**2j**	96
5[c]	**1i**	1	**2k**	92
6[c]	**1j**	1	**2l**	93
7[d]	**1e**	0.1	**2e**	77
8	**1l**	0.2	**2l**	91
9	**1o**	1	**2o**	68
10	**1q**	0.2	**2q**	98
11	**1s**	0.2	**2r**	83
12	**1bb**	0.3	**2bb**	89

[a] Alcohol (1 mmol), TBDMSCN (2 mmol), Ti-Mont (20 mg; 1.36 mol %), CH_2Cl_2 (2 mL), rt, method B. [b] Isolated yields. [c] Alcohol (0.5 mmol). [d] The symmetric ether **4e** derived from the condensation of **1e** was obtained in 20% yield.

Table 6. Conversion of Various TMS Ethers with TASCN to Nitriles Catalyzed by Ti-Mont[a]

$$\mathbf{3} + \text{TASCN} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt}]{\text{Ti-Mont}} \mathbf{2}$$

Entry	Ether **3**	R		TASCN	*t* (h)	Nitrile **2**	Yield (%)[b]
1		H	**3a**	TMSCN	10	**2a**	76
2		Me	**3b**	TMSCN	8	**2b**	83
3		OMe	**3c**	TMSCN	8	**2c**	88
4		Me	**3e**	TMSCN	0.2	**2e**	95
5		Et	**3f**	TMSCN	0.2	**2f**	97
6		H	**3l**	TMSCN	0.5	**2l**	85
7		Cl	**3o**	TMSCN	6	**2o**	72
8		Me	**3m**	TMSCN	0.5	**2m**	95
9		OMe	**3n**	TMSCN	0.5	**2n**	98
10			**3q**	TMSCN	0.5	**2q**	92
11			**3s**	TMSCN	3	**2r**	85
12			**3w**	TMSCN	3	**2w**	89
13	**3a**			TBDMSCN	1	**2a**	96
14	**3b**			TBDMSCN	1	**2b**	96
15	**3c**			TBDMSCN	1	**2c**	98

[a] TMS ether (1 mmol), TASCN (1.5 mmol.), Ti-Mont (20 mg, 1.36 mol %), CH_2Cl_2 (2 mL), rt, method B. [b] Isolated yields.

the intermediate **3s** (Table 4, entries 11−12). Compared with **2cc**, regioisomers **2cc**′ and **2cc**″ were calculated to be less stable in *G* by 15.5 kcal mol^{-1} and 16.6 kcal mol^{-1}, respectively.[82] These large energy differences prove the exclusive formation of **2cc**.

Cyanation of Various Alcohols with *tert*-Butyldimethylsilyl Cyanide (TBDMSCN). Because we discovered the facile cyanation of alcohols with TMSCN on Sn-Mont and Ti-Mont, we further investigated the cyanation using a bulkier alkylsilyl cyanide, such as *tert*-butyldimethylsilyl cyanide (TBDMSCN, Table 5). Surprisingly, in most cases, the cyanations of benzylic alcohols with TBDMSCN proceeded faster, and the yields significantly improved with Ti-Mont (20 mg, 1.36 mol %), compared with those with TMSCN. For example, **1a** and its derivatives gave the corresponding nitriles with almost quantitative yields in 0.5 h (entries 1−3). Other congested alcohols (**1h**−**j**) underwent the cyanations with excellent yields (92−96%) in 1 h (entries 4−6). Only the cyanation of **1e** with TBDMSCN gave **2e** in the moderate yield of 77% together with the symmetric ether **4e** in 20% yield (entry 7). Several unsaturated alcohols were also investigated for the cyanations using TBDMSCN (entries 8−12). The reactions were completed with short reaction times compared with the reactions with TMSCN, and the corresponding unsaturated nitriles were produced in good yields.

Cyanation of TMS Ethers 3 with TASCN. In entry 4 of Table 1, **1a** was promptly consumed in only 0.1 h in the cyanation with TMSCN to form nitrile **2a** (79%) and diphenylmethyl TMS ether **3a** (20%). After the prolonged reaction time, **3a** was gradually transformed into **2a**, as shown in entries 5−6 of Table 1, indicating that **3a** was one of the possible intermediates to nitrile **2a**. Therefore, we examined the conversion of various TMS ethers **3** with TASCN to nitriles in the presence of Ti-Mont (20 mg, 1.36 mol %). As shown in Table 6, when the benzhydrol TMS ethers (**3a**−**c**) were allowed to react with 1.5 equiv of TMSCN, the corresponding diarylethanenitriles (**2a**−**c**) were formed in 76−88% yields (entries 1−3). The cyanations of **3e** and **3f** quickly proceeded in very excellent yields of 95−97% in 0.2 h (entries 4−5). The TMS ethers from **1l** and its substituted derivatives also readily produced the corresponding unsaturated nitriles in good to excellent yields (entries 6−9), although an extended reaction time (6 h) was required for the ether having a chlorine substituent at the benzene ring. The TMS ether of **1q** easily afforded the corresponding nitrile **2q** with a 92% yield (entry 10). The cyanation of the TMS ethers **3s** and **3w** exclusively proceeded to afford nitriles **2r** and **2w** in 85% and 89%, respectively (entries 11−12). The regioselective formation of **2r** and **2w** from the allylic TMS ethers **3s** and **3w** suggested that the reactions also proceeded via stabilized carbocation intermediates.

It should be highlighted again that the cyanation of the TMS ethers **3a**−**c** with bulkier TBDMSCN was far more quickly completed in almost quantitative yields than that with TMSCN (Table 6, entries 13−15). In all cases, the symmetric ethers **4**, which could be derived from TMS ether, were not detected.[83]

Investigation of Why TBDMSCN Was More Effective for the Cyanation of Alcohols and Their Trimethylsilyl Ethers in the Presence of Ti-Mont than TMSCN. It is interesting and curious that in the presence of Ti-Mont, the cyanation of alcohols and their trimethylsilyl (TMS) ethers with TBDMSCN having a bulkier *tert*-butyldimethylsilyl (TBDMS) group proceeded more rapidly than that with TMSCN. Then, we performed the following experiments.

The reaction of **1a** with TMSCN proceeded even in the absence of Ti-Mont, as shown in eq 3, yielding TMS ether **3a**

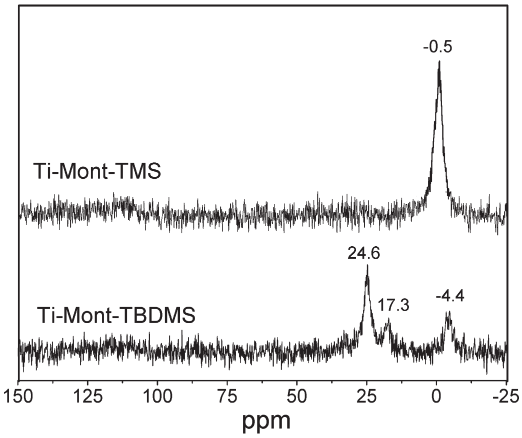


Figure 2. ^{13}C DDMAS NMR spectra of Ti-Mont-TMS and Ti-Mont-TBDMS.

in 96% yield within 8 h. In contrast, the use of TBDMSCN gave no corresponding TBDMS ether **3x**, even after 24 h, and **1a** was completely recovered in eq 4. These results indicate the use of TBDMSCN suppresses the formation of the side product, TBDMS ether **3x**. Ether **3x** would be a much less reactive and undesired intermediate for the nitrile formation during the cyanation of alcohols because even less sterically hindered **3a** took a long time of 10 h to convert to **2a** (entry 1, Table 6).

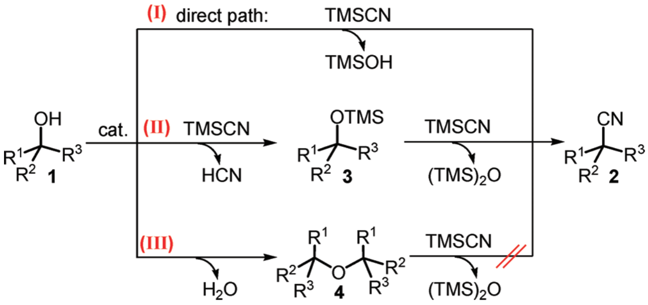
$$\mathbf{1a} + \underset{(1.5\ \text{equiv.})}{\text{TMSCN}} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt}]{\text{no cat.}} \mathbf{3a} \quad \textbf{(8 h, yield: 96\%)} \tag{3}$$

$$\mathbf{1a} + \underset{(1.5\ \text{equiv.})}{\text{TBDMSCN}} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt}]{\text{no cat.}} \mathbf{3x} \quad \textbf{(24 h, yield: 0\%)} \tag{4}$$

In the Ti-Mont-catalyzed cyanation of **1a** with TMSCN, **1a** was almost quantitatively consumed in only 0.1 h to yield nitrile **2a** (75%) and diphenylmethyl TMS ether **3a** (24%). After 1.5 h, the yield of **3a** decreased to 2%, while that of **2a** increased to 98%, as shown in entries 4−6 of Table S1 of the Supporting Information, indicating that **3a** was one of the intermediates to nitrile **2a**. On the other hand, no **3x** was detected in the Ti-Mont-catalyzed cyanation of **1a** with TBDMSCN (entry 1, Table 5).

Compared with TBDMSCN, TMSCN is considered not only to be a more reactive alkylsilylating agent of OH groups in alcohols, as mentioned above, but also more easily to convert Brønsted acid sites (H^+) on the surface of Ti-Mont into a trialkylsilyl group. Therefore, we investigated the surface of TASCN-treated Ti-Mont by solid NMR as follows: After the treatment of Ti-Mont with TASCN at room temperature (see the Supporting Information), the resulting reddish brown clay was washed with CH_2Cl_2, dried in a vacuum, and analyzed by ^{13}C DDMAS NMR. As shown in Figure 2, ^{13}C NMR spectra confirmed that the trialkylsilyl groups were successfully attached on Ti-Mont upon treatment with TASCN. The signal at −0.5 ppm due to the trimethylsilyl groups in the spectrum of TMSCN-treated Ti-Mont (Ti-Mont−TMS) is far stronger than that at 24.6 ppm corresponding to three methyls in the *tert*-butyl substituent in the spectrum of TBDMSCN-treated Ti-Mont (Ti-Mont−TBDMS). This fact indicates that the density of the trimethylsilyl groups attached on Ti-Mont−TMS is far higher than that of the *t*-butyldimethylsilyl ones on Ti-Mont−TBDMS; in other words, more acidic protons (Brønsted acid sites) survive on Ti-Mont−TBDMS than on Ti-Mont−TMS. The higher density of the Brønsted acid sites should result in the higher catalytic activity caused by the acid sites. Thus, TBDMSCN demonstrated the higher activity in the cyanation of alcohols and their trimethylsilyl ethers catalyzed by Brønsted acid Ti-Mont than TMSCN.

Scheme 2. Plausible Reaction Pathways for the Cyanation of Alcohols with TMSCN Catalyzed by the Montmorillonite Catalyst



Proposed Reaction Pathways and Mechanisms for the Cyanation of Alcohols and TMS Ethers. According to the above results, three plausible reaction pathways can be considered for the cyanation of alcohol **1** with TMSCN as in Scheme 2. The direct path, **I**, goes through an intermediate carbocation derived from the dehydration of protonated alcohols, followed by the direct cyanation with TMSCN to **2**, which was supported by the prompt formation of **2**, as shown in entry 4, Table 1.[15,84] The indirect path, **II**, via the formation of TMS ether intermediate **3**, which is then cyanated with TMSCN to **2**, has also been proved reasonable, as shown in Table 6. Another indirect path, **III**, via the formation of the symmetric ether **4**, followed by the cyanation with TMSCN to **2**, is considerable because the formation of **4** was observed by ^{1}H NMR and GC during the cyanation.

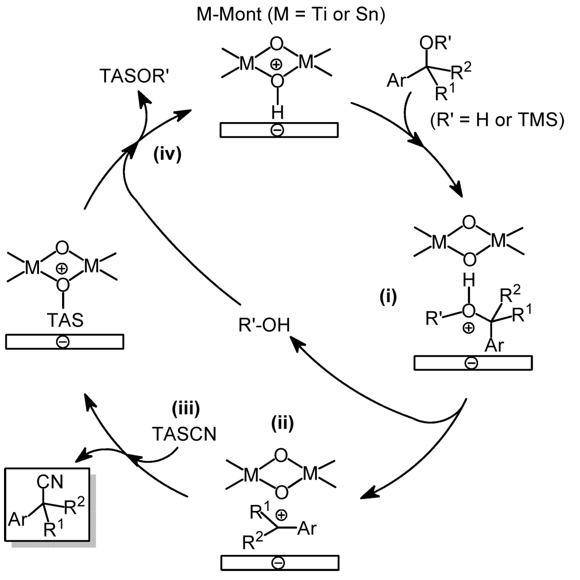
The possibility of the indirect path **III** was independently investigated in the presence of Ti-Mont. First, **4a** was prepared in a 75% isolated yield by simply mixing Ti-Mont and **1a** in CH_2Cl_2, as shown in eq 5. Second, the reaction of pure **4a** with TMSCN did not yield **2a**, even after 24 h (eq 6), indicating that indirect path **III** via the symmetric ethers **4** in Scheme 2 is not the case. Thus, the formation of symmetric ethers **4** has to be avoided for the effective cyanation of alcohols. This result is in sharp contrast to the fact that **4** is a reactive intermediate for the carbon−carbon bond-forming reactions of **1** with 1,3-dicarbonyl compounds[7] or allyltrimethylsilane.[61]

$$\mathbf{1a} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt, 1 h}]{\text{Ti-Mont (1.36 mol\%)}} \mathbf{4a} \quad \textbf{(Yield: 75 \%)} \tag{5}$$

$$\mathbf{4a} + \underset{(1\ \text{equiv.})}{\text{H}_2\text{O}} + \underset{(3\ \text{equiv.})}{\text{TMSCN}} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt, 24 h}]{\text{Ti-Mont (2.72 mol\%)}} \mathbf{2a} \quad \textbf{(Yield: 0 \%)} \tag{6}$$

A catalytic cycle is shown in Scheme 3 for the cyanation of an alcohol or its TMS ether using trialkylsilyl cyanide (TASCN) in the presence of Brønsted acid montmorillonites, Sn-Mont and Ti-Mont: (i) the protonation of an alcohol or its TMS ether by a Brønsted acid site on the montmorillonites, (ii) the formation of

Scheme 3. A Catalytic Cycle of the Cyanation of an Alcohol or Its TMS Ether with TASCN Using Brønsted Acid Montmorillonite Catalyst



a carbocation intermediate with liberation of H_2O or TMSOH, (iii) the nucleophilic attack of TASCN to the carbocation intermediate to produce the corresponding cyanide product, and (iv) the regeneration of a Brønsted acid site.

■ CONCLUSIONS

In summary, we have demonstrated the facile synthesis of nitriles by the direct cyanation of not only secondary/tertiary benzylic and allylic alcohols but also their TMS ethers using trialkylsilyl cyanide in high yields (up to 98%) with exclusive regioselectivity by use of a small amount of Brønsted acid montmorillonite catalysts in crude CH_2Cl_2 under mild conditions. The cyanation with TASCN catalyzed by the Brønsted acid montmorillonite catalysts proceeds via a stabilized carbocation intermediate derived from the protonated alcohols or their TMS ethers, followed by a nulceophilic attack of TASCN. Interestingly, TBDMSCN with a bulky *tert*-butyldimethylsilyl group was found superior in the cyanation of alcohols and their TMS ethers to TMSCN. This is because the steric effects of the TBDMS group suppress not only the formation of the TBDMS ethers but also a decrease in the active Brønsted acid sites in the montmorillonite catalysts in contact with TBDMSCN.

The present heterogeneous catalytic systems, compared with the preceding methods using homogeneous catalysts, have the significant advantages of higher activity, operational simplicity, water-tolerant character, reusability, and safe handling. Further investigation of the applications of the current catalytic system for a variety of organic transformations is now in progress.

■ MATERIALS AND METHODS

Caution: Due to the toxic nature of trimethylsilyl cyanide (TMSCN) and *tert*-butyldimethylsilyl cyanide (TBDMSCN), all experiments were carried out in a well-ventilated fume hood.

General: The GC analysis was performed by a 6850A GC (Agilent Technologies) using *n*-dodecane as the internal standard. The ^{1}H and ^{13}C NMR spectra were recorded using JEOL α-500/GSX-270 and Bruker Avance III 500 USPlus NMR spectrometers with the samples in $CDCl_3$. The ^{1}H NMR chemical shifts were determined relative to the internal tetramethylsilane at δ 0.0 ppm. The ^{13}C NMR chemical shifts were determined relative to the internal tetramethylsilane at δ 0.0 ppm or to the ^{13}C signal of $CDCl_3$ at δ 77.0 ppm. The coupling constants (J) are given in Hz. The ^{13}C DDMAS NMR spectra were recorded on a Bruker Avance III 400 WBUSPlus spectrometer operating at 100 MHz, rotor spin rate of 10 kHz. External standard was used for the calibration of chemical shifts. The accumulation number was fixed at 5000. The IR spectra were measured using a Jasco IR-630 spectrophotometer (NaCl film). The high-resolution mass spectra were obtained by a JEOL GCmate (EI) mass spectrometer. The melting points were measured in open capillaries with an electrothermal model IA 9100 digital melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using commercially available 60 mesh silica gel plates visualized with short-wavelength UV light (254 nm). The BET surface areas of the ion-exchanged montmorillonites were determined by the multipoint N_2 adsorption—desorption method at liquid N_2 temperature (77 K) using a Belsorp-mini instrument (Bel Japan, Inc.). Prior to the analyses, all samples were degassed at 120 °C under 10^{-4} Torr for 4 h to evacuate any physisorbed water. The X-ray powder diffraction patterns were collected by a Rigaku Multiflex instrument using Cu Kα (λ = 0.15406 nm) radiation at 40 kV and 40 mA.

Reagents: Sodium montmorillonite (Na-Mont) was supplied by Kunimine Industry Co., Ltd., as Kunipia F (Na, 2.69; Al, 11.8; Fe, 1.46; Mg, 1.97%; cation-exchange capacity = 1.19 mequiv g^{-1}). All organic chemicals were purchased from commercial sources without purification before use. All reagents were weighed and handled in the air at rt. It was unnecessary to dehydrate the solvent, CH_2Cl_2, for the montmorillonite-catalyzed reactions. Silica gel 60 (70—230 mesh, ASTM) used for column chromatography was obtained from Merck Japan, Ltd. The proton ion-exchanged zeolites (H—Y and H-Beta) were supplied by Catalysts and Chemicals Industry Co., Ltd. The trimethylsilyl ethers **4** were prepared by the silylation of the corresponding alcohols with hexamethyldisilazane (HMDS).[85,86]

Preparation of the Control Catalysts. Sn-MCM-41 (Si/Sn = 20),[72] Al-MCM-41 (Si/Al = 20),[74] and various M-Mont's, such as Sn-Mont,[67] Ti-Mont,[87] Al-Mont,[61] Fe-Mont,[64,67,69] and H-Mont,[61] were prepared according to previous reports. The detailed synthesis and characterization of Sn-Mont and Ti-Mont are described in the Supporting Information.

Two different addition orders (methods A and B) of reagents and a catalyst were employed to investigate the cyanation of benzhydrol (**1a**) with TMSCN catalyzed by Sn-Mont as follows (Tables 1 and 2):

Method A. Into a flask were placed Sn-Mont (20 mg; 3.8 mol %), **1a** (1 mmol, 184 mg), and CH_2Cl_2 (2 mL). The obtained mixture was vigorously stirred in a nitrogen atmosphere, and then TMSCN (2 mmol, 0.268 mL) was added. After stirring for a specific time at room temperature (rt), the solution was analyzed by GC to determine the yield with *n*-dodecane as the internal standard.

Method B. To a flask were added Sn-Mont (20 mg; 3.8 mol %), CH_2Cl_2 (0.5 mL), and TMSCN (2 mmol, 0.268 mL). During vigorous stirring in a nitrogen atmosphere, **1a** (1 mmol, 184 mg) dissolved in CH_2Cl_2 (1.5 mL) was then dropwise (about 5 s per drop) added using a syringe to the above reaction mixture.

After stirring for a specific time at rt as shown in Tables 1 and 2, the solution was analyzed by GC to determine the yield with *n*-dodecane as the internal standard.

A Representative Experimental Procedure for the Cyanation of Alcohols with TASCN According to Method B (Tables 3, 4, and 5). To a flask were added Ti-Mont (20 mg; 1.36 mol %), CH_2Cl_2 (0.5 mL), and TASCN (2 mmol, 0.268 mL). During vigorous stirring in a nitrogen atmosphere, benzhydrol (**1a**; 1 mmol, 184 mg) dissolved in CH_2Cl_2 (1.5 mL) was then dropwise (about 5 s per drop) added using a syringe to the above reaction mixture. After the completion of the reaction monitored by TLC, the Ti-Mont catalyst was removed by filtration through a Celite plug. The solid catalyst on the Celite was washed with CH_2Cl_2, and the combined solution was evaporated under reduced pressure to obtain the crude products. Further purification was carried out by silica chromatography using EtOAc/*n*-hexane (1:10) as the eluent to afford the corresponding nitrile **2a** (176 mg, 91% yield).

A General Procedure for the Conversion of Trimethylsilyl (TMS) Ethers 3 to Nitriles 2 Using Method B (Table 6). To a flask were added Ti-Mont (20 mg; 1.36 mol %), CH_2Cl_2 (0.5 mL), and TMSCN (1.5 mmol, 0.201 mL). During vigorous stirring in a nitrogen atmosphere, TMS ether **3a** (1 mmol, 256 mg) dissolved in CH_2Cl_2 (1.5 mL) was then dropwise (about 5 s per drop) added using a syringe to the above reaction mixture. The progress of the reaction was monitored by TLC. After the reaction was completed, the catalyst was filtered off and washed with CH_2Cl_2. Evaporation of the filtrate in a vacuum gave the corresponding crude products. Further purification was carried out by silica chromatography using EtOAc/*n*-hexane (1:10) as the eluent to afford **2a** as a light yellow solid (147 mg, 76% yield).

ASSOCIATED CONTENT

S Supporting Information. Additional experimental procedures, characterization data of the compounds, and copies of the ^1H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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