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Practical Carbonyl-Ene Reactions of α-Methylstyrenes with Paraformaldehyde Promoted by a Combined System of Boron Trifluoride and Molecular Sieves 4A

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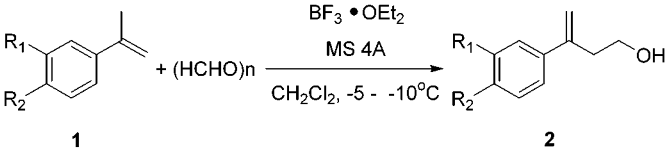
ABSTRACT



A combined system of boron trifluoride and molecular sieves is an efficient promoter for the carbonyl-ene reaction of α-methylsyrenes with paraformaldehyde. The coexistence of $BF_3 \cdot OEt_2$ and molecular sieves 4A is essential for obtaining high yields of ene products.

The carbonyl-ene reaction promoted by Lewis acid is a powerful tool for the preparation of various homoallylic alcohols.[1,2]However, there have been few practical synthetic methods to promote efficiently the carbonyl-ene reaction of α-methylstyrene derivatives. This is partly because a homoallylic alcohol product (ene adduct) forms a complex (**A**) with a Lewis acid promoter to generate a strongly acidic proton. This acidic proton migrates intramolecularly to a double bond of the ene adduct or intermolecularly to a starting styrene derivative to produce a labile cationic intermediate, which triggers various side reactions as shown in Figure 1.[1d] Therefore, the key to success in the carbonyl-ene reaction is to find how to activate a carbonyl group and scavenge the acidic proton effectively.

In 1997, Uemura et al. reported carbonyl-ene reactions catalyzed by metal-cation-exchanged montmorillonites.[2d] By use of their method, α-methylstyrene and its methylated derivative produced homoallylic alcohols in moderate yields, but styrenes with electron-withdrawing groups gave poor results.

Here we propose a new practical method for the carbonyl-ene reaction of α-methylstyrenes **1** with paraformaldehyde using a combination of $BF_3 \cdot OEt_2$ and molecular sieves 4A (MS 4A).

Initially we tested the reaction of 3,4-dichloro-α-methylstyrene **1a** with paraformaldehyde using acids shown in Table 1. There is a single precedent[2a] in which the reaction was catalyzed by H_2SO_4 to afford the corresponding ene adduct **2a** in 46% yield (entry 1). Although alkylaluminum halides

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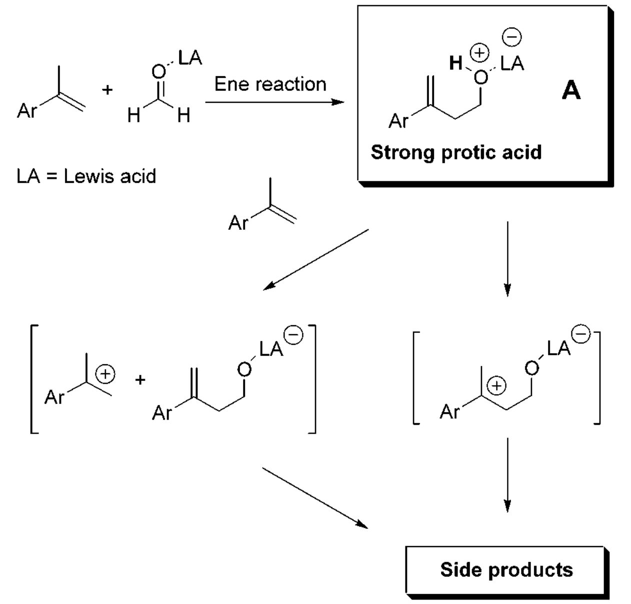
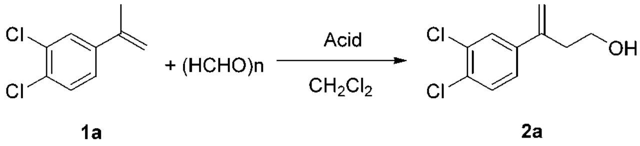


Figure 1. Conceivable paths to side products via an ene-adduct.

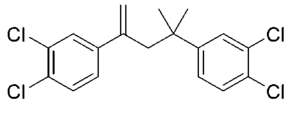
have been known as good promoters for the carbonyl-ene reaction,[1] Me_2AlCl gave very low yield in this case (entry 2). The reaction using BF_3·OEt_2 also afforded complex mixtures (entry 3). Interestingly, when MS 4A was added to the reaction system with BF_3·OEt_2, the ene adduct **2a** was obtained in good yield (entry 4). MS 4A and commercially available solid acid K-10 independently did not promote the reaction (entries 5 and 6). By the combined use of K-10 and MS 4A, an undesired dimeric product **3** was the sole product in 70% yield (entry 7). Therefore, a combination of BF_3·OEt_2 and MS 4A turned out to be essential for obtaining the ene product in good yield.[3]

Table 1. Acid-Promoted Carbonyl-Ene Reactions[a]



entry	acid (equiv)	conditions	yield (%)^d
1	H_2SO_4 (0.2)^b	35 °C, 1.0 h	46
2	Me_2AlCl (1.0)	−10 to −5 °C, 3.0 h	28
3	BF_3·OEt_2 (1.2)	−30 to −10 °C, 0.5 h	tr^e
4	BF_3·OEt_2 (1.2)/MS 4A^c	−20 to −5 °C, 5.0 h	72
5	MS 4A^c	−20 °C to reflux, 5.0 h	0^f
6	K-10^c	0 °C to rt, 24.0 h	0^f
7	K-10/MS 4A^c	0 to 5 °C, 3.0 h	0^g

[a] (HCHO)*n*, 1.0 equiv. [b] Solvent = Ac_2O. [c] One weight equivalent of MS 4A (K-10) to **1a** was used. [d] Determined by ^{1}H NMR using chloroacetone as internal standard. [e] Complex mixtures were formed. [f] Styrene **1a** was recovered. [g] Dimeric product **3** was formed.



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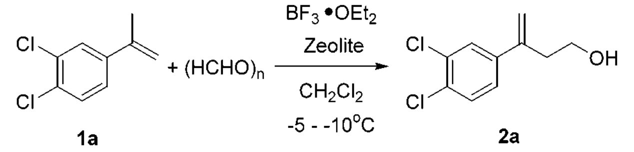
At first we speculated that MS 4A would scavenge water from incompletely dried reagents, solvents, or equipment that coordinated to the Lewis acid to produce strong Brønsted acids and that these strong acids would cause the polymerization or isomerization of alkenes as side reactions. However, the use of a dehydrating agent, $MgSO_4$, instead of MS 4A resulted in a low yield (22%) of **2a**.

Another potential role of molecular sieves (zeolites) is to trap acidic protons of the coordinated allylic alcohol (**A**) and to retard the side reactions in Figure 1.[4] We applied several sodium ion exchanged zeolites with different Si/Al ratios such as X- and Y-type zeolites and mordenite as well as MS 4A (A-type zeolite) to the ene reaction (Table 2). Zeolites are crystalline aluminosilicates with intrinsic pore structures and generally function as acid and base.[5] Roughly speaking, the total number of base sites on a zeolite is proportional to the Al content in the zeolite framework. In other words, the smaller the Si/Al ratio is, the more base sites exist in the zeolite. Therefore, the order of base site amounts on the zeolites is estimated as follows: MS 4A (NaA, Si/Al = 1.0) > NaX (1.5) > NaY (2.7) > Na-mordenite (9.2).

Table 2. Carbonyl-Ene Reactions in the Presence of Zeolites Having Various Amounts of Base Sites[a]



entry	zeolites	pore size^6 (nm)	Si/Al^c	yield (%)^d
1^b	MS 4A (NaA)	0.41	1.0	72
2	NaX	0.74	1.5	69
3	NaY	0.74	2.7	46
4	Na-mordenite	0.65 × 0.70	9.2	35

[a] Zeolite (0.5 wt equiv to **1a**), BF_3·OEt_2 (2.0 equiv), (HCHO)*n* (2.0 equiv). [b] MS 4A (1.0 wt equiv), BF_3·OEt_2 (1.2 equiv), (HCHO)*n* (1.0 equiv). [c] The Si/Al ratios of zeolite. [d] Determined by ^{1}H NMR using chloroacetone as internal standard.

Table 2 clearly shows that the yield of **2a** was increased with an increase in the number of base sites on the zeolite.

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(3) Trioxane, which is more easily soluble in CH_2Cl_2 than paraformaldehyde, was unusable as formaldehyde precursor in this carbonyl-ene reaction.

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These results suggest that MS 4A and NaX function as solid base, i.e., a competent proton scavenger in the reaction as proposed in Figure 2. A slight difference in promotion of the reaction between MS 4A and NaX is that greater amounts of BF_3·OEt_2 are needed to get the reaction completed (entries 1 and 2). This arises from the difference in pore size between the two zeolites. Since the pore size of NaX is 0.74 nm, some BF_3 (molecular size 0.44 nm) is readily adsorbed on base sites inside the pores of NaX and hence deactivated. On the other hand, MS 4A has smaller pores of 0.41 nm in diameter, and BF_3 is less able to go into the pores of MS 4A and works as an effective acid promoter for paraformaldehyde. Therefore, MS 4A would exclusively capture the acidic proton generated and stabilize the ene product (Figure 2).

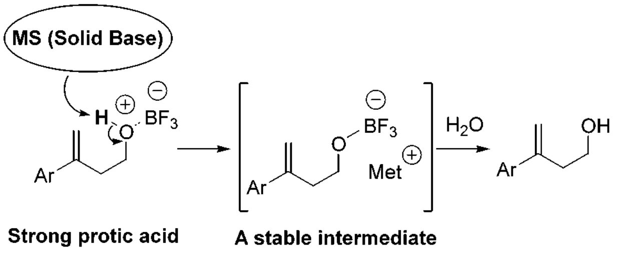


Figure 2. A proposed role of molecular sieves (zeolite).

Other typical solid and organic bases were also applied to the reaction in the presence of BF_3·OEt_2. Among the bases tested, only 2,6-di-*tert*-butylpyridine could give the product but in very low yield. On the basis of the result in Table 3, it was found that MS 4A and NaX zeolites are very unique as bases in the ene reaction.

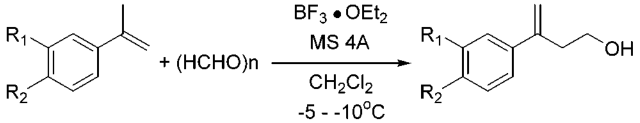
Table 3. Carbonyl-Ene Reactions of **1a** Using Various Bases[a]

entry	base	yield of **2a** (%)[c]
1	MS 4A[b]	72
2	$NaHCO_3$	tr[d]
3	Et(i-Pr)$_2$N	tr[d]
4	2,6-di-*tert*-butylpyridine	16
5	proton sponge	tr[d]

[a] Base (1.0 equiv), BF_3·OEt_2 (1.0 equiv), (HCHO)*n* (1.0 equiv). [b] MS 4A (1 wt equiv to **1a**). [c] Determined by ^1H NMR using chloroacetone as internal standard. [d] Styrene **1a** was recovered.

We applied the BF_3·OEt_2/MS 4A system to various α-methylstyrenes as shown in Table 4. The reactions of styrene derivatives **1a**–**d** afforded **2a**–**d** in moderate to good yields (entries 1–4), whereas unfortunately this system was not applicable to the styrene **1e** with an electron-donating group (entry 5). Our system is complementary to the clay-catalyzed system[2d] in the carbonyl-ene reaction of α-methylstyrenes with paraformaldehyde.

Table 4. BF_3-Promoted Carbonyl-Ene Reactions in the Presence of Molecular Sieves 4A



1 **2**

entry	**1**	R_1	R_2	conditions[a]	yield (%)[b]
1	**1a**	Cl	Cl	A	**2a** (72)
2	**1b**	F	F	A	**2b** (72)
3	**1c**	H	F	A	**2c** (59)
4	**1d**	H	H	B	**2d** (41)
5	**1e**	H	Me	B	**2e** (tr)[c]

[a] A: MS 4A (1.0 wt equiv to **1**), BF_3•·Et_2 (1.2 equiv), (HCHO)*n* (1.0 equiv). B: MS 4A (3.0 wt equiv), BF_3·OEt_2 (1.2 equiv), (HCHO)*n* (1.0 equiv). [b] Determined by ^1H NMR using chloroacetone as internal standard. [c] Polymeric products were formed as byproducts.

In summary, we have developed a practical method to promote efficiently the carbonyl-ene reaction of electron-deficient α-methylstyrene derivatives with paraformaldehyde. The key to our success was the combined use of homogeneous Lewis acid BF_3·OEt_2 and solid base MS 4A, which activate paraformaldehyde and trap acidic protons from labile intermediates, respectively. Further studies on more detailed mechanistic aspects of this system are under way.

Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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