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Selective aldol reactions of acetals on mesoporous silica catalyst

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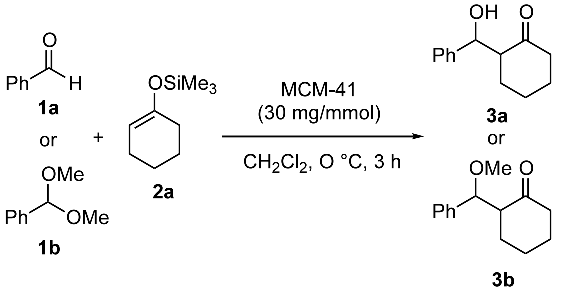
Abstract—Mukaiyama-aldol reactions of carbonyl compounds with silyl enol ethers were well catalyzed on siliceous mesoporous materials (MCM-41). The reactivity of acetals was much higher than that of aldehyde. The reactions proceeded selectively at 273–298 K on the catalyst of 30 mg per mmol of the substrate. © 2002 Published by Elsevier Science Ltd.

Heterogeneous catalyses are powerful methods for realizing environmentally benign organic reactions.[1] The use of solid acids, for example, can minimize waste emission and formation of toxic substances. While clay and zeolites are preferentially employed as solid acid catalysts, the present and the other groups have recently found novel acid catalyses on siliceous mesoporous material such as MCM-41 and FSM-16 toward organic syntheses.[2] It is well known that MCM-41 possesses well-ordered hexagonal arrays of uniform channels and high surface area: however, its acidic property is not widely accepted and it is rather believed that its surface would be neutral or slightly acidic due to its amorphous silica wall. If MCM-41 showed indeed effective acidity in heterogeneous catalyses, it would be one of the most promising candidates of solid acid catalysts because of its homogeneous and broad surface.[3]



Scheme 1. MCM-41-catalyzed Mukaiyama-aldol reactions.

Mukaiyama-aldol reaction of silyl enol ethers with carbonyl compounds[4] is one of the most important carbon–carbon bond-forming reactions to afford β-oxy-carbonyl compounds. This reaction can be catalyzed by Lewis acid in homogeneous and heterogeneous phases.[5] Generally, the reactivity of aldehydes as electrophiles in homogeneous phase is higher than that of acetals,[6] and the selective activation of acetals has been disclosed on only a few catalysts such as trimethylsilyl trifluoromethanesulfonate (TMSOTf)[7] and organotin complexes.[8] In the latter reactions, low reaction temperature of 173–195 K is required to prevent the progress of side reactions and to obtain corresponding products in high yields.

With heterogeneous catalysts, Onaka et al. showed that clay montmorillonite K10 promoted Mukaiyama-aldol reactions of aldehydes and acetals with silyl enol ethers.[9] They employed relatively large amount of clay (200–250 mg/mmol) and the reaction temperature as low as 178–223 K. On this catalyst the reactivity of acetals are comparable with that of aldehydes. In the present study we have examined the effectiveness of MCM-41 as an acid catalyst for Mukaiyama-aldol reactions and found that the reactions are well catalyzed under mild conditions[10] and the reactivity of acetals are much higher than that of aldehyde. These findings would be useful for the progress of environmentally benign organic reactions.

MCM-41 was synthesized from colloidal silica and dodecyltrimethyl-ammonium bromide by the method reported previously.[11] The MCM-41 obtained was calcined at 873 K for 6 h in air to remove organic compounds, and stored in a desiccator without any further treatment. The hexagonal structure of resulting MCM-41 was confirmed from the XRD pattern, and

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Keywords: solid acid; MCM-41; aldol reaction; acetal.

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the surface area and pore diameter determined by N_2 adsorption–desorption measurements were 1003 m^2/g and 2.12 nm, respectively. The elemental analysis showed that the Si/Al atomic ratio of the present MCM-41 was ca. 200.

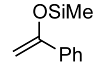
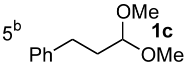
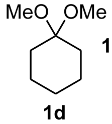
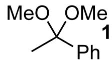
We first examined the reaction of benzaldehyde (**1a**: 0.5 mmol) with silyl enol ether of cyclohexanone (**2a**: 0.6 mmol) on 15 mg of MCM-41 which was pre-evacuated at 373 K for 1 h before use (Scheme 1). The reaction proceeded at 273 K but the yield of *syn*/*anti* mixture of the corresponding β-hydroxy ketone was only 18%, as shown in Table 1. In contrast, the reaction of benzaldehyde dimethylacetal (**1b**)[12] and silyl enol ether **2a** smoothly proceeded under the same conditions to afford the corresponding product in 65%. The higher reactivity of acetal than that of aldehyde is clearly distinct from the reactivity on typical homogeneous Lewis acids[4] or on montmorillonite K10[9] and thus the detailed reactivity of various acetals for Mukaiyama-aldol reactions was studied hereafter.

The wall of MCM-41 is made of amorphous silica and can adsorb a lot of water. There is the possibility that pretreatment of catalyst materials affects their activities. The effect of evacuation treatment (<0.1 mmHg) at elevated temperatures for 2 h was therefore investigated (Scheme 2). As shown in Figure 1, the catalytic activity of MCM-41 evacuated at 298 K was low (42%). At or above 373 K the yield of **3b** gradually increased and the best yield of **3b** (81%) was attained when MCM-41 was evacuated at 673 K. The results would indicate that physisorbed water molecules inhibit the reaction. On the basis of the results, the following aldol-type reactions of various acetals with silyl enol ethers were carried out after the evacuation of MCM-41 at 673 K.

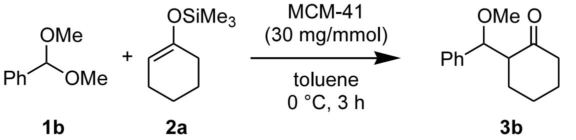
The reactivity of several kinds of acetals with enolates is summarized in Table 1 (runs 3–9). All reactions smoothly proceeded to yield the corresponding products as diastereo-mixtures[13] in good to high yields by using 30 mg/mmol of MCM-41. Toluene as well as dichloromethane was applicable solvent to the reactions. Not only acetals derived from aldehydes, but also those from ketones well reacted to afford the aldol-type products with quaternary carbon center at β-position in high yields; only a few examples had been known in homogeneous catalyses.[14] Run 9 shows that the MCM-41 catalyst recycled by simple filtration could be reused four times without losing its catalytic activity.

Chemoselective aldol reactions of acetals over aldehydes were demonstrated. As clearly listed in Table 2, MCM-41 selectively catalyzed the reaction of acetal among benzaldehyde, benzaldehyde dimethylacetal, and silyl enolate **2a** to give **3b** in 63% yield with trace amount of **3a**. Similar results were observed on the other acetals.

Table 1. MCM-41-catalyzed aldol reactions of various acetals with silyl enolates[a]

run	electrophile	Si enolate	solvent	time (h)	yield (%)
1[b]	**1a**	**2a**	CH_2Cl_2	3	18
2[b]	**1b**	**2a**	CH_2Cl_2	3	65
3[b]	**1b**	**2a**	toluene	6	84
4[b]	**1b**	 **2b**	toluene	5	91
5[b]	 **1c**	**2b**	toluene	5	73
6[c]	 **1d**	**2a**	toluene	12	90
7[b]	**1d**	**2b**	toluene	12	99
8[c,]	 **1e**	**2a**	CH_2Cl_2	3	88
9[c, d]	**1e**	**2a**	CH_2Cl_2	3	93 97[e], 85[f], 87[g]
10[c, h]	**1e**	**2a**	CH_2Cl_2	12	Trace
11[c, i]	**1e**	**2a**	CH_2Cl_2	12	Trace

[a] Thirty mg/mmol of MCM-41 was used except for Runs 9-11.
[b] The reaction was carried out at 0 °C. [c] The reaction was carried out at 25 °C. [d] Fifty mg/mmol of MCM-41 was used.
[e] Recoverd catalyst was used. (2nd run). [f] 3rd run. [g] 4th run.
[h] Silica gel A[15] (120 mg/mmol) was used. [i] Silica gel B[16] (250 mg/mmol) was used.



Scheme 2.

Finally, it would be worthy to note that the regular mesopore structure is essential to the present catalysis. Here two types of silica gel were used as the catalyst for the reaction; silica gel 60 of Merck[15] (silica gel A) and silica gel prepared by using the same starting materials as those used for the preparation of MCM-41 (silica gel B).[16] Both of them did not show any catalytic activity even when much amounts of silica gel were used for the reaction, as shown in runs 10 and 11 of Table 1. No activity suggests that the catalysis of MCM-41 does not result from impurities in the wall such as aluminum ions, and that the surface area is not an important factor controlling the catalytic activity. The origin of the catalysis of MCM-41 should be studied in the near future.

In conclusion, we have discovered novel catalytic activity of metal-free MCM-41. Mukaiyama-aldol reactions of acetals and silyl enol ethers proceeded on a little amount of MCM-41 at around room temperature to afford the corresponding products in good to high yields. Acetal-selective reactions in the co-existence of

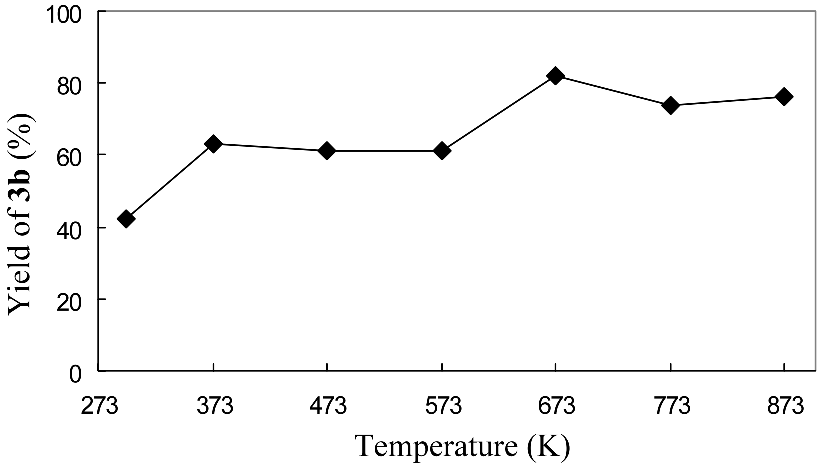
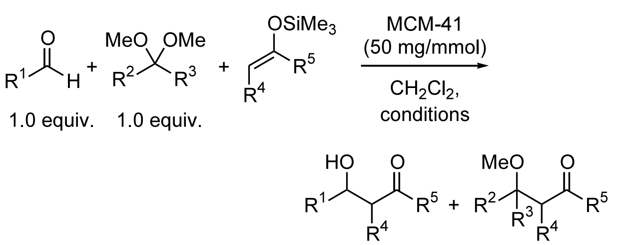
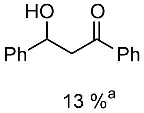
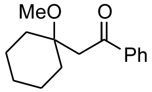
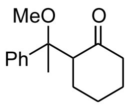


Figure 1. Effect of thermal pretreatment under evacuation conditions.

Table 2. Aldol reactions of acetals in the presence of aldehydes



run	electrophiles	conditions	products	
1	**1a/1b**	**2a (1.2 equiv.),** 0 °C, 3 h	**3a**: trace	**3b**: 63 %[b]
2	**1a/1d**	**2b (1.0 equiv.),** 0 °C, 12 h	 13 %[a]	 44 %[b]
3	**1a/1e**	**2a (1.2 equiv.),** 0 °C, 12 h	**3a**: 9 %[a]	 65 %[b]

[a] Based on aldehyde. [b] Based on acetal.

aldehyde were also clarified. The catalyst was reusable without significant loss of activity.

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15. Silica gel 60 (silica gel A) was purchased from Merck. The BET surface area was 480–540 m^2/g.
16. Non-ordered silica gel (silica gel B) was prepared by using the same colloidal silica and dodecyltrimethyl-ammonium bromide as those used for the preparation of MCM-41. Instead of the hydrothermal treatment in the latter preparation, the raw materials were vigorously stirred to avoid the formation of micelles of surfactant molecules. The BET surface area of silica gel B was 220 m^2/g.