# Mukaiyama Aldol Reaction Catalyzed by Mesoporous Aluminosilicate

Suguru Ito, Hitoshi Yamaguchi, Yoshihiro Kubota, and Masatoshi Asami*
*Department of Advanced Materials Chemistry, Graduate School of Engineering, Yokohama National University,*
*79-5 Tokiwadai, Hodogaya-ku, Yokohama 240-8501*

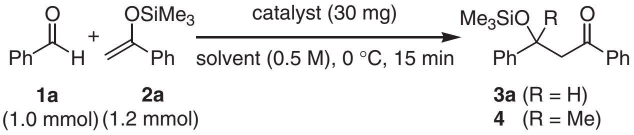
(Received April 24, 2009; CL-090411; E-mail: m-asami@ynu.ac.jp)

In the presence of a mesoporous aluminosilicate Al–MCM-41, aldol reaction of various silyl enol ethers with both aromatic and aliphatic aldehydes proceeded under mild reaction conditions to afford the corresponding O-silylated aldol adducts in high yields. The solid acid catalyst was easily recovered and reusable three times.

The Mukaiyama aldol reaction has been recognized as a facile and valuable method for the synthesis of $\beta$-hydroxy carbonyl compounds, and a wide variety of catalysts are known to catalyze the reaction.[1] Along with increasing attention to the development of environmentally benign heterogeneous catalytic systems, several heterogeneous catalysts have also been reported to promote the reaction.[2] For example, ordered mesoporous silica MCM-41 was found to catalyze the reaction of silyl enol ethers with acetals.[2d] Since MCM-41 possesses large uniform pores (2–10 nm) and high surface area,[3] it has been applied to many synthetic transformations as a solid catalyst. Moreover, it is well known that the catalytic activity of MCM-41 increases by incorporating metals, such as Ti, Sn, and Al, into its structure.[4] Although titanium- or tin-containing MCM-41 has been reported to catalyze the Mukaiyama aldol reaction of aldehydes,[2g,2i] they required relatively long reaction time and high reaction temperature even using ketene silyl acetals as nucleophiles. The reactions promoted by metal-incorporated MCM-41 were thus carried out under rather severe reaction conditions usually,[5] whereas aluminium-incorporated MCM-41 (Al–MCM-41) has begun to be used for some synthetic reactions under mild reaction conditions, recently.[6] Herein, we wish to report a remarkable acceleration of the aldol reaction of silyl enol ethers with aldehydes by using Al–MCM-41 as a solid acid catalyst.

According to a literature procedure with slight modification,[7] Al–MCM-41 (Si/Al = 26) was synthesized[8] and dried at 120 °C for 1 h under vacuum prior to use. Initially, the reaction of benzaldehyde (1.0 mmol) with 1-phenyl-1-trimethylsiloxyethene (**2a**) (1.5 mmol) was carried out in dichloromethane at 30 °C in the presence of Al–MCM-41 (30 mg). The reaction was complete within 15 min and afforded the corresponding $\beta$-siloxy ketone, 1,3-diphenyl-3-trimethylsiloxypropan-1-one (**3a**), in 99% yield (Table 1, Entry 1). In this case, the activity of the catalyst was so high that the reaction of **2a** with acetophenone, generated in the reaction mixture from silyl enol ether **2a**, also occurred, and undesired self-aldol adduct **4** (0.1 mmol) was detected in the crude product. When the reaction was carried out in acetonitrile at 0 °C using 1.2 equiv of **2a**, $\beta$-siloxy ketone **3a** was obtained in 99% yield without the formation of **4** (Entry 2). Next, the reaction was examined in the presence of aluminium-free MCM-41 or amorphous silica–alumina ($SiO_2$–$Al_2O_3$, Si/Al = 31) in acetonitrile at 0 °C (Entries 3 and 4). In either case, **3a** was not detected after 15 min. From these results, it is suggested that high catalytic activity of Al–MCM-41 is attributed to the presence of aluminium sites and ordered mesoporous structure. Similar results were observed in the case of Al–MCM-41-catalyzed cyanosilylation and allylation of carbonyl compounds.[6b,6d]

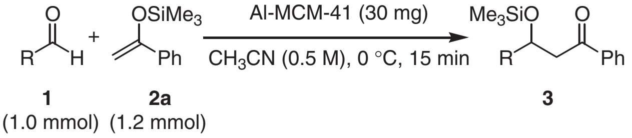
**Table 1.** Aldol reaction of benzaldehyde with **2a**



| Entry | Solvent | Catalyst | Yield of **3a**/%[a] |
|---|---|---|---|
| 1[b,c] | $CH_2Cl_2$ | Al–MCM-41 | 99 |
| 2 | $CH_3CN$ | Al–MCM-41 | 99 |
| 3 | $CH_3CN$ | MCM-41 | N.D.[d] |
| 4 | $CH_3CN$ | $SiO_2$–$Al_2O_3$ | N.D.[d] |

[a]Determined by $^1$H NMR analysis of the crude product using nitromethane as an internal standard. [b]Silyl enol ether **2a** (1.5 mmol) was used and the reaction was carried out at 30 °C. [c]Small amount (0.1 mmol) of 1,3-diphenyl-3-trimethylsiloxybutan-1-one (**4**) was detected. [d]Not detected.

**Table 2.** Aldol reaction of various aldehydes with **2a** catalyzed by Al–MCM-41

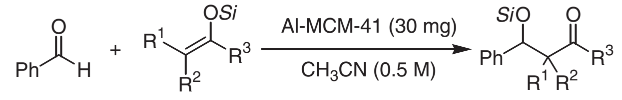


| Entry | R | Yield/%[a] |
|---|---|---|
| 1 | 4-$NO_2C_6H_4$ | 90 |
| 2 | 4-$ClC_6H_4$ | 92 |
| 3 | 4-$MeC_6H_4$ | 87 |
| 4 | 3-$MeC_6H_4$ | 95 |
| 5 | 2-$MeC_6H_4$ | 94 |
| 6 | 4-$MeOC_6H_4$ | 86 |
| 7 | 2-Naphthyl | 92 |
| 8 | (*E*)-PhCH=CH | 80 |
| 9 | $PhCH_2CH_2$ | 74 |
| 10 | *c*-$C_6H_{11}$ | 81 |
| 11[b] | *t*-Bu | 67 |

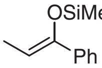
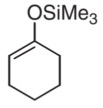
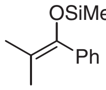
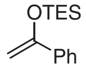
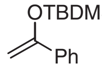
[a]Isolated yield. [b]Reaction was carried out for 2 h.

The catalytic system was then applied to the reaction of various aldehydes with **2a**. The results are summarized in Table 2. Aromatic aldehydes, bearing electron-withdrawing or -donating groups, gave the corresponding $\beta$-siloxy ketones **3** in high yields (Entries 1–7). The reaction of **2a** with (*E*)-cinnamaldehyde, 3-

**Table 3.** Aldol reaction of benzaldehyde with various silyl enol ethers catalyzed by Al–MCM-41



**1a** (1.0 mmol) **2** (1.2 mmol) **3**

| Entry | Silyl enol ether | Temp/°C | Time/h | Yield/%$^a$ |
|---|---|---|---|---|
| 1 |  **2b** | 30 | 0.5 | 88$^b$ |
| 2 |  **2c** | 0 | 0.25 | 86$^b$ |
| 3 |  **2d** | 30 | 24 | 69 |
| 4 |  **2e** | 0 | 0.25 | 94 |
| 5 |  **2f** | 0 | 0.25 | 87 |

$^a$Isolated yield. $^b$Syn/anti = 3:2.

**Table 4.** Reuse of Al–MCM-41 in the reaction of benzaldehyde with **2a**$^a$

| Run | PhCHO /mmol | Al–MCM-41 /mg | Time /min | Yield/%$^b$ |
|---|---|---|---|---|
| 1 | 2.0 | 60 | 15 | 99 |
| 2 | 1.6 | 47 | 15 | 99 |
| 3 | 1.1 | 32 | 15 | 86 |
| 4 | 0.6 | 18 | 60 | 85 |

$^a$The reaction of benzaldehyde with 1.2 equiv of **2a** was carried out in acetonitrile (0.5 M) at 0 °C. $^b$Isolated yield.

phenylpropanal, or cyclohexanecarboxaldehyde under the same reaction conditions gave the corresponding adduct in good yields (Entries 8–10). The reaction of pivalaldehyde with **2a** was relatively slow and the yield of the product was 67% even after the reaction mixture was stirred for 2 h probably due to the steric hindrance of pivalaldehyde (Entry 11).

The reaction of various silyl enol ethers with benzaldehyde was also examined (Table 3). The reaction with **2b** at 30 °C for 30 min afforded the product in 88% yield as a diastereomeric mixture (Entry 1). Cyclic silyl enol ether **2c** also reacted with benzaldehyde to give a diastereomeric mixture of the corresponding adduct in 86% yield (Entry 2). When sterically hindered silyl enol ether **2d** was used, the reaction was sluggish even at 30 °C and the corresponding $\beta$-siloxy ketone was obtained in 69% yield after 24 h (Entry 3). Triethylsilyl (TES) ether and *tert*-butyldimethylsilyl (TBDMS) ether are often synthetically useful for the protection of hydroxy groups. Thus, the reactions of TES ether **2e** and TBDMS ether **2f** with benzaldehyde were also examined. In both cases, the reaction proceeded at 0 °C for 15 min to afford the corresponding silyl ethers in 94 and 87% yields, respectively (Entries 4 and 5).

Finally, the recovery and reuse of Al–MCM-41 was examined in the reaction of benzaldehyde with **2a** (Table 4). The catalyst was recovered from the reaction mixture by filtration. The catalyst was then washed with ether, dried at 70 °C for 15 min, treated at 120 °C for 1 h under vacuum, and used in the next reaction. Al–MCM-41 was reusable, although the catalytic activity of the recovered catalyst slightly decreased after using three times.

In summary, the aldol reaction of various aldehydes with silyl enol ethers were promoted under mild reaction conditions by using Al–MCM-41 as a solid acid catalyst. This heterogeneous catalytic system could afford silyl ethers of the $\beta$-hydroxy ketones in moderate to high yields. The catalyst was easily recovered and reusable three times.

## References and Notes

1 a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, 1011. b) T. Mukaiyama, *Org. React.* **1982**, *28*, 203. c) T. Mukaiyama, *Angew. Chem., Int. Ed.* **2004**, *43*, 5590.

2 a) M. Onaka, R. Ohno, M. Kawai, Y. Izumi, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2689. b) M. Kawai, M. Onaka, Y. Izumi, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1237. c) T.-P. Loh, X.-R. Li, *Tetrahedron* **1999**, *55*, 10789. d) H. Ishitani, M. Iwamoto, *Tetrahedron Lett.* **2003**, *44*, 299. e) M. Sasidharan, R. Kumar, *J. Catal.* **2003**, *220*, 326. f) S. Iimura, K. Manabe, S. Kobayashi, *Tetrahedron* **2004**, *60*, 7673. g) R. Garro, M. T. Navarro, J. Primo, A. Corma, *J. Catal.* **2005**, *233*, 342. h) R. Srivastava, *J. Mol. Catal. A: Chem.* **2007**, *264*, 146. i) T. R. Gaydhankar, P. N. Joshi, P. Kalita, R. Kumar, *J. Mol. Catal. A: Chem.* **2007**, *265*, 306. j) A. Heydari, S. Khaksar, M. Sheykhan, M. Tajbakhsh, *J. Mol. Catal. A: Chem.* **2008**, *287*, 5.

3 C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710.

4 a) A. Corma, H. García, *Chem. Rev.* **2002**, *102*, 3837. b) A. Corma, H. García, *Chem. Rev.* **2003**, *103*, 4307.

5 a) A. Papp, G. Galbács, Á. Molnár, *Tetrahedron Lett.* **2005**, *46*, 7725. b) K. Shanmugapriya, M. Palanichamy, V. Murugesan, *Catal. Commun.* **2006**, *7*, 47. c) S. Ajaikumar, A. Pandurangan, *J. Mol. Catal. A: Chem.* **2007**, *266*, 1. d) P. P. Samuel, S. Shylesh, A. P. Singh, *J. Mol. Catal. A: Chem.* **2007**, *266*, 11. e) C. Xie, F. Liu, S. Yu, F. Xie, L. Li, S. Zhang, J. Yang, *Catal. Commun.* **2008**, *10*, 79.

6 a) M. W. C. Robinson, R. Buckle, I. Mabbett, G. M. Grant, A. E. Graham, *Tetrahedron Lett.* **2007**, *48*, 4723. b) K. Iwanami, J.-C. Choi, B. Lu, T. Sakakura, H. Yasuda, *Chem. Commun.* **2008**, 1002. c) H. Murata, H. Ishitani, M. Iwamoto, *Tetrahedron Lett.* **2008**, *49*, 4788. d) S. Ito, H. Yamaguchi, Y. Kubota, M. Asami, *Tetrahedron Lett.* **2009**, *50*, 2967.

7 C.-Y. Chen, H.-X. Li, M. E. Davis, *Microporous Mater.* **1993**, *2*, 17.

8 The specific surface area (BET) and the average pore diameter (BJH) were 1120 m$^2$ g$^{-1}$ and 2.7 nm, respectively.

9 Typical experimental procedure: Under an atmosphere of argon, to a mixture of Al–MCM-41 (60 mg, dried prior to use at 120 °C for 1 h under vacuum) and benzaldehyde (0.213 g, 2.0 mmol) in acetonitrile (3.0 mL), 1-phenyl-1-trimethylsiloxyethene (0.462 g, 2.4 mmol) in acetonitrile (1.0 mL) was added through a syringe at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. The catalyst was removed by filtration and washed with $Et_2O$ (40 mL). After the combined organic solution was concentrated under reduced pressure, crude product was purified by silica-gel column chromatography (hexane/$Et_2O$ = 20:1) to afford 1,3-diphenyl-3-trimethylsiloxypropan-1-one[10] as a colorless oil (0.591 g, 99%). The product gave satisfactory IR and $^1H$, $^{13}C$ NMR spectra. The recovered catalyst was dried at 70 °C for 15 min. Then, the catalyst (47 mg) was dried at 120 °C for 1 h under vacuum and used in a second run.

10 S. Torii, T. Inokuchi, S. Takagishi, H. Horike, H. Kuroda, K. Uneyama, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2173.

Published on the web (Advance View) June 13, 2009; doi:10.1246/cl.2009.700