

The Mukaiyama Aldol Reactions for Congested Ketones Catalyzed by Solid Acid of Tin(IV) Ion-exchanged Montmorillonite

Satoshi Takehira,¹ Yoichi Masui,² and Makoto Onaka*²

¹Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033

²Department of Chemistry, Graduate School of Arts and Sciences, The University of Tokyo, 3-8-1 Komaba, Meguro-ku, Tokyo 153-8902

(E-mail: conaka@mail.ecc.u-tokyo.ac.jp)

Tin(IV) ion-exchanged montmorillonite (Sn-Mont) was found to be an excellent solid acid catalyst for the Mukaiyama aldol reactions of congested ketones with silicon enolates from ketones as well as esters. It was disclosed that Sn-Mont was far more active than other metal ion- or proton-exchanged montmorillonites and typical homogeneous acid catalysts such as TMSOTf and $\text{BF}_3 \cdot \text{OEt}_2$.

The Mukaiyama aldol reactions are Lewis acid-promoted nucleophilic additions of silicon enolates to carbonyl acceptors, specifically, most of which are aldehydes. On the other hand, the use of less reactive ketones is limited as the acceptor¹ because the additions to ketones are much more sluggish than those to aldehydes.² Therefore, the Mukaiyama aldol reactions between ketones and ketone enolates are still a challenge yet to explore.

Our previous study has shown that the Mukaiyama aldol reactions of aldehydes with silicon enolates from ketones are effectively catalyzed by aluminum ion-exchanged montmorillonite (Al-Mont).³ Montmorillonite is a naturally occurring layered clay which is composed of lamellar aluminosilicate layers and interlayer metal ions.⁴ Especially, montmorillonites exchanged with multivalent metal ions, such as Al^{3+} and Fe^{3+} (M-Mont), act as solid acids.⁵ In a series of our studies of clay-based solid acid catalysis for various organic reactions, we discovered that tin(IV) ion-exchanged montmorillonite (Sn-Mont) possessing a unique and delaminated silicate layer structure, different from other laminated metal ion-exchanged montmorillonites, showed much higher catalytic activities for the cyanotrimethylsilylation and the Strecker reactions of congested ketones than the conventional clay catalysts.⁶ Thus it is envisaged that Sn-Mont would work as an effective solid acid catalyst for more impracticable aldol reactions between ketones and ketone enolates.

Initially, Sn-Mont⁷ was applied to the reaction of acetophenone (**1a**) with a ketone enolate **2a**,⁸ and compared to various solid and homogeneous acid catalysts (Table 1). The model reaction of **1a** with **2a** was limited to fewer precedents^{9,10} than those of **2a** with aldehydes (Table S1).¹¹

Among the M-Monts, Sn-Mont showed the highest yield of 81% for aldol products **3aa** and **4aa** together with dehydrated product **5aa** (16% yield) in the shortest reaction time (Entry 3),¹² while Ti-Mont and Al-Mont gave only poor yields (Entries 5 and 6). Although H-Mont also afforded **3aa** and **4aa** in a good combined yield (73%), it required a longer reaction time than Sn-Mont (Entry 7). The homogeneous acid catalysts,¹³ TMSOTf and TfOH, afforded only desilylated aldol product **4aa**

Table 1. The Mukaiyama aldol reaction of acetophenone (**1a**) with silicon enolate **2a**

| Entry | Catalyst | Time/h | Yield/% ^{a,b} | | |
|-------|---|------------------|------------------------|------------|------------|
| | | | 3aa | 4aa | 5aa |
| 1 | No catalyst | 15 | 0 | 0 | 0 |
| 2 | Na-Mont | 3 | 0 | 0 | 0 |
| 3 | Sn-Mont | 0.75 | 75 | 6 | 16 |
| 4 | Sn-Mont ^c | 3 | 88 | 2 | 0 |
| 5 | Ti-Mont | 3 | 26 | 0 | 0 |
| 6 | Al-Mont | 3 | 2 | 0 | 0 |
| 7 | H-Mont | 3 | 64 | 9 | 17 |
| 8 | H-Mont ^c | 3 | 43 | 10 | 17 |
| 9 | TMSOTf ^d | 3 | 0 | 45 | 0 |
| 10 | TfOH ^d | 3 | 0 | 30 | 0 |
| 11 | $\text{BF}_3 \cdot \text{OEt}_2$ ^d | 4.5 ^e | 0 | 0 | 0 |

^a**1a** (1.0 mmol), **2a** (1.1 mmol), catalyst (20 mg), CH_2Cl_2 (2 mL), 0 °C. ^bDetermined by ¹H NMR. ^cCatalyst was activated at 150 °C. ^dFive mol % of the catalyst was used. ^ePerformed at 0 °C for 1.5 h and then at RT for 3 h.

in low yields after the normal workup (Entries 9 and 10), while $\text{BF}_3 \cdot \text{OEt}_2$ promoted no reaction (Entry 11).

Generally, the clay catalysts can be easily removed from the reaction mixture by filtration without any workup with aqueous bases, thus silylated aldol product **3aa** was obtained as the main product. However, in the cases of Sn-Mont and H-Mont, a part of **3aa** was hydrolyzed by some residual water included in the clay to afford **4aa**, which was further dehydrated to **5aa**.¹⁴ In order to improve the selectivity for **3aa**, Sn-Mont was activated at the higher temperature of 150 °C rather than 120 °C,¹⁵ and almost exclusively afforded **3aa**, thus suppressing the formation of **4aa** and **5aa** (Entry 4), but slightly retarding the reaction. On the contrary, the same thermal treatment on H-Mont only led to a rather poor yield of **3aa** along with the formation of both **4aa** and **5aa** (Entry 8). It should be emphasized that the acid catalysis of Sn-Mont for the aldol reaction between **1a** and **2a** is quite superior to those of the precedent heterogeneous acid catalysts.¹⁰

Next, the Sn-Mont-catalyzed Mukaiyama aldol reactions of **2a** were examined with various congested ketones (Table 2). As

Table 2. The Mukaiyama aldol reaction of congested ketones **1** with silicon enolates **2** catalyzed by Sn-Mont

| Entry | Ketone 1 | Silicon enolate 2 | Time /h | Yield/% ^{a,b} |
|-------|-----------------|--------------------------|---------|--|
| 1 | | | 3 | 88 ^{c,d} |
| 2 | | | 2 | 98 |
| 3 | | | 2 | 97 |
| 4 | | | 3 | 35 |
| 5 | | | 10 | 0 |
| 6 | | | 3 | 72 |
| 7 | | | 5 | 35 ^d |
| 8 | 1a | | 1 | 96 |
| 9 | 1b | | 1.5 | 97 |
| 10 | 1c | | 1.5 | 99 |
| 11 | 1d | 2b | 6 | 35 |
| 12 | 1e | | 7 | 96 |
| 13 | 1a | | 2 | 95 (62:38) ^c |
| 14 | 1b | | 3 | 96 (43:57) ^c |
| 15 | 1c | | 3 | 51 |
| 16 | 1d | | 7 | 58 (70:30) ^c |
| 17 | 1e | | 8 | 79 |
| 18 | 1a | | 4 | 99 ^f |
| 19 | 1b | | 5 | 76 ^{f,g} |
| 20 | 1c | | 5 | 92 ^{f,h} (34 ^{a,f}) |
| 21 | 1d | 2d | 10 | 0 ^f |
| 22 | 1e | | 12 | 0 ^f |
| 23 | 1a | | 3 | 96 ⁱ |
| 24 | 1b | | 4 | 92 ⁱ |

^a**1** (1.0 mmol), **2** (2.0 mmol), catalyst (40 mg), CH₂Cl₂ (2 mL), 0 °C. ^bDetermined by ¹H NMR. ^cSn-Mont was activated at 150 °C. ^d**1** (1.0 mmol), **2** (1.1 mmol), catalyst (20 mg). ^eThe molar ratio of threo and erythro diastereomers. ^fPerformed under reflux conditions. ^gDehydrated product **5bd** was also formed (23%). ^hCatalyst (100 mg). ⁱPerformed at RT.

a result, the reactions of 2-acetonaphthone (**1b**) and nonan-5-one (**1c**) afforded excellent yields of the corresponding products **3ba** and **3ca** (Entries 2 and 3). However, the reaction with more congested isopropyl phenyl ketone (**1d**) gave **3da** in only 35% yield (Entry 4), and that of benzophenone (**1e**) with **2a** did not occur (Entry 5).¹⁶ In contrast, benzophenone derivative bearing an electron-withdrawing chlorine substituent **1f** reacted with **2a** to give the product in 72% yield (Entry 6), and benzophenone dimethyl acetal (**1g**) also reacted with **2a** (Entry 7).

It is well known that the silicon enolates of esters are more nucleophilic than those of ketones, and that the free energy difference of the aldol reaction of a ketone with the ester enolate is smaller than that with the ketone enolate.¹⁷ Some silicon enolates of esters were then employed. As shown in Table 2, the reactions of ketones **1a–1e** with ester enolate **2b** afforded the corresponding silylated aldol products **3** in excellent yields except for **1d** (Entries 8–12). Similar results were achieved for the reactions with cyclic ester enolate **2c** (Entries 13–17). In addition, the reactions of ketones **1a–1c** with more congested but less nucleophilic disubstituted ester enolate **2d** afforded good to excellent yields of the products (Entries 18–20), but no reactions took place using **1d** and **1e** (Entries 21 and 22). In the reactions of **1c** with enolates **2c** and **2d**, the aldol products were obtained in only 51 and 34% yields, respectively (Entries 15 and 20), and some **2c** and **2d** remained intact under the standard conditions, indicating that the catalyst became inactive. Therefore, the amount of Sn-Mont was increased from 40 to 100 mg, and the yield of **3cd** rose to 92% from 34% as expected, while that of **3cc** only slightly changed.

The aldol reactions of the silicon enolates from thioesters have been mainly applied to aldehydes. The reactions of ketones **1a** and **1b** with enolate **2e** successfully occurred to yield products **3ae** and **3be** in over 90% yields (Entries 23 and 24).

The high catalytic activity of Sn-Mont for the aldol reactions is ascribed not only to the intrinsic strong acidic character of Sn-Mont, but also to its unique porous structure. Sn-Mont is composed of delaminated aluminosilicate layers holding Sn(OH)₄ nanoparticles, thus providing a high specific surface area and a large pore volume.^{6c} The water molecules coordinating to Sn(OH)₄-based nanoparticles are considered to be dissociated to form acidic protons (Sn_x(OH)_y(OH)⁻...H⁺), which is promoted by the neighboring montmorillonite silicate anions, and thus show an efficient acid catalysis for the aldol reactions. In addition, inside the characteristic voids of Sn-Mont, the bulky reactants and products are allowed to diffuse more easily and contact with the acid sites on the solid Sn-Mont to promote the aldol reactions.

The natural clay-derived Sn-Mont is stable to moisture and air so that it can be stored for a long period in air. Before use as the solid acid, it is only necessary to be activated at 120 or 150 °C under reduced pressure.

In summary, it was demonstrated that the solid acid Sn-Mont catalyzed the Mukaiyama aldol reactions of silicon enolates from ketones and esters with congested ketone acceptors much more effectively than the other M-Monts and typical homogeneous acid catalysts. It should be emphasized that various congested ketones are applicable as the acceptors of this reaction, and that the products can be isolated as moisture-sensitive trimethylsilylated aldols which are apt to be hydrolyzed.

This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction.

References and Notes

- 1 a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, 1011. b) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503. c) T. Mukaiyama, *Organic Reactions*, John Wiley & Sons, New York, **1982**, Vol. 28, pp. 203–331. doi:10.1002/0471264180.or028.03.
- 2 Based on our calculations using Gaussian 03W¹⁸ at the B3LYP/6-31+G(d) level, the free energy difference, ΔG , of the Mukaiyama aldol reaction of a silicon enolate, 2-(trimethylsilyloxy)propene, with acetone is much lower than that with acetaldehyde (-4.9 kcal mol⁻¹ vs. -11.4 kcal mol⁻¹). The higher the ΔG , the higher the activation energy ΔG^\ddagger , according to the Bell–Evans–Polanyi principle: S. Roy, S. Goedecker, V. Hellmann, *Phys. Rev. E: Stat., Nonlinear, Soft Matter Phys.* **2008**, *77*, 056707. In fact, it was calculated that the ΔG^\ddagger of the reaction with protonated acetone was higher than that with protonated acetaldehyde (17.4 kcal mol⁻¹ vs. 15.9 kcal mol⁻¹).
- 3 M. Kawai, M. Onaka, Y. Izumi, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1237.
- 4 a) T. J. Pinnavaia, *Science* **1983**, *220*, 365. b) P. Laszlo, *Science* **1987**, *235*, 1473.
- 5 a) K. Higuchi, M. Onaka, Y. Izumi, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2016. b) J. M. Adams, *Appl. Clay Sci.* **1987**, *2*, 309. c) K. Kaneda, *Synlett* **2007**, 999.
- 6 a) J. Wang, Y. Masui, K. Watanabe, M. Onaka, *Adv. Synth. Catal.* **2009**, *351*, 553. b) J. Wang, Y. Masui, M. Onaka, *Eur. J. Org. Chem.* **2010**, 1763. c) Y. Masui, J. Wang, K. Teramura, T. Kogure, T. Tanaka, M. Onaka, submitted.
- 7 Sn-Mont was prepared as follows: Na-Mont (cation-exchange capacity: 1.19 mequiv g⁻¹, 8 g) was ion-exchanged with aq. SnCl₄·5H₂O (0.30 M, 80 mL) at room temperature (RT) for 2 h, and this exchange process was repeated. The clay was collected, and successively washed twice with water (80 mL), six times with a mixture of water (40 mL) and methanol (40 mL), and finally once with absolute methanol (80 mL). The clay was dried in a 0.5 Torr vacuum at RT for 12 h, followed by being ground in a mortar with a pestle and passed through a 60-mesh screen. Sn-Mont contained 2.1 mmol of tin atom per gram of Sn-Mont determined by inductively coupled plasma (ICP) analysis. The specific surface area of Sn-Mont was as high as 380 m² g⁻¹, which was about 17 times that of the pristine Na-Mont (22 m² g⁻¹).
- 8 Ketone **1a** (1.0 mmol) was added to a CH₂Cl₂ (2 mL) suspension of Sn-Mont (20 mg) which had been activated under vacuum at 120 °C for 1 h, then ketone enolate **2a** (1.1 mmol) was added. The mixture was stirred at 0 °C under a nitrogen atmosphere. After the reaction was completed, the catalyst was filtered off and washed with cold CH₂Cl₂. The product yields were determined by ¹H NMR analysis of the filtrate using mesitylene as the internal standard.
- 9 Catalyzed by homogeneous catalysts: a) W. Odenkirk, J. Whelan, B. Bosnich, *Tetrahedron Lett.* **1992**, *33*, 5729. b) T. K. Hollis, N. P. Robinson, B. Bosnich, *Tetrahedron Lett.* **1992**, *33*, 6423. c) T. K. Hollis, W. Odenkirk, N. P. Robinson, J. Whelan, B. Bosnich, *Tetrahedron* **1993**, *49*, 5415. d) K. Ishihara, Y. Hiraiwa, H. Yamamoto, *Synlett* **2001**, 1851. e) K. Hara, R. Akiyama, M. Sawamura, *Org. Lett.* **2005**, *7*, 5621. f) C. H. Cheon, H. Yamamoto, *Tetrahedron Lett.* **2009**, *50*, 3555. g) C. H. Cheon, H. Yamamoto, *Tetrahedron* **2010**, *66*, 4257. h) G. Onodera, T. Toeda, N.-n. Toda, D. Shibagishi, R. Takeuchi, *Tetrahedron* **2010**, *66*, 9021. i) A. C. S. Reddy, Z. Chen, T. Hatanaka, T. Minami, Y. Hatanaka, *Organometallics* **2013**, *32*, 3575.
- 10 Catalyzed by heterogeneous catalysts: a) H. Ohki, M. Wada, K.-y. Akiba, *Tetrahedron Lett.* **1988**, *29*, 4719. b) M. Wada, E. Takeichi, T. Matsumoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 990. c) C. L. Roux, H. Gaspard-Iloughmane, J. Dubac, J. Jaud, P. Vignaux, *J. Org. Chem.* **1993**, *58*, 1835. d) J. W. Faller, L.-L. Gundersen, *Tetrahedron Lett.* **1993**, *34*, 2275. e) C. Le Roux, L. Ciliberti, H. Laurent-Robert, A. Laporterie, J. Dubac, *Synlett* **1998**, 1249.
- 11 Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.
- 12 The plausible reaction pathways are shown in Figure S1.
- 13 Twenty milligrams of Sn-Mont contain 0.042 mmol of tin atom which corresponds to 4.2 mol % of **1a**. Therefore, 5 mol % of each homogeneous acid was employed for the control reactions.
- 14 This is the first example of the formation of **5aa** by dehydration from **4aa**. It is plausible that the less stable **5aa** rather than the α,β -unsaturated ketone product is mainly formed through the stable 6-membered transition state in the dehydration step (See Figure S2). The other synthetic methods for **5aa**: a) M.-K. Zhu, J.-F. Zhao, T.-P. Loh, *J. Am. Chem. Soc.* **2010**, *132*, 6284. b) M. Okabe, T. Osawa, M. Tada, *Tetrahedron Lett.* **1981**, *22*, 1899. c) H. Grund, V. Jäger, *Liebigs Ann. Chem.* **1980**, *80*. d) A. I. Kovalev, Y. I. Lyakhovetskii, M. M. Teplyakov, A. L. Rusanov, P. V. Petrovskii, S. O. Yakushin, *Russ. Chem. Bull.* **1993**, *42*, 1529. e) X. Yu, L. Wang, X. Feng, M. Bao, Y. Yamamoto, *Chem. Commun.* **2013**, *49*, 2885.
- 15 The TG analysis showed that the residual water in Sn-Mont was removed over 150 °C. See Figure S3.
- 16 There have been no successful examples of the aldol reactions of **1e** with ketone enolates to the best of our knowledge, but only a few examples were reported for the reactions of **1e** with ester enolates. Use of Lewis bases: a) M. Hatano, E. Takagi, K. Ishihara, *Org. Lett.* **2007**, *9*, 4527. b) M. Hatano, S. Suzuki, E. Takagi, K. Ishihara, *Tetrahedron Lett.* **2009**, *50*, 3171. Use of Lewis acid: c) R. Nagase, J. Osada, H. Tamagaki, Y. Tanabe, *Adv. Synth. Catal.* **2010**, *352*, 1128.
- 17 According to our calculations, the free energy difference ΔG of the Mukaiyama aldol reaction of acetone with a ketone enolate, 2-(trimethylsilyloxy)propene, is greater than that of acetone with an ester enolate, 1-methoxy-2-(trimethylsilyloxy)propene (-4.9 kcal mol⁻¹ vs. -19.4 kcal mol⁻¹), and the ΔG^\ddagger of the reaction of protonated acetone with the ketone enolate was higher than that with the ester enolate (17.4 kcal mol⁻¹ vs. 11.2 kcal mol⁻¹).
- 18 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03 (Revision D.01)*, Gaussian, Inc., Wallingford CT, **2004**.