# Magnesium Chloride-Promoted Michael Addition of Dimethylsilyl Enolates to α-Enones

Katsukiyo Miura,* Takahiro Nakagawa, Akira Hosomi*

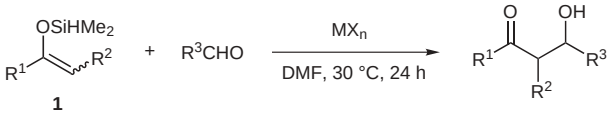
Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, and CREST, Japan Science and Technology Corporation (JST), Tsukuba, Ibaraki 305-8571, Japan
Fax +81(29)8536503; E-mail: hosomi@chem.tsukuba.ac.jp

*Received 10 July 2003*

**Abstract:** In the presence of $MgCl_2$, dimethylsilyl (DMS) enolates **1** smoothly reacted with α-enones in DMF to form 1,5-diketones **3** in moderate to high yields. The Michael addition proceeded with moderate to high *anti*-diastereoselectivity.

**Key words:** diastereoselectivity, enones, Michael additions, magnesium, silicon

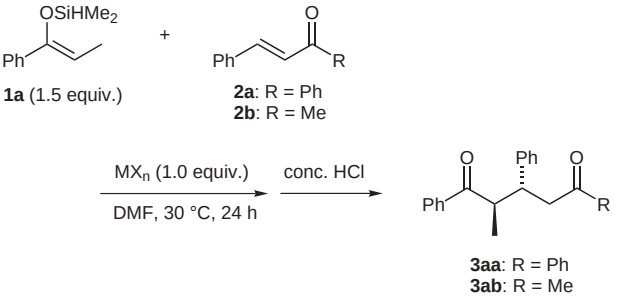
The Mukaiyama–Michael reaction of silyl enolates with α-enones is one of the most important processes for efficient and stereocontrolled carbon-carbon bond formation.[1–6] Similar to the Mukaiyama-aldol reaction of silyl enolates, this process is accelerated by Lewis acids[1–4] or nucleophiles (Lewis bases).[5,6] We have previously reported that aldol reactions of dimethylsilyl (DMS) enolates proceed efficiently in the presence of alkali earth or alkali metal chlorides ($CaCl_2$, $MgCl_2$, LiCl etc.) (Scheme 1).[7] These metal salts would serve to activate DMS enolates by nucleophilic attack of the chloride ion. Here we describe the metal chloride-promoted Mukaiyama-Michael reaction of DMS-enolates with α-enones under the same conditions. The present study discloses that the metal ions as well as the counterions strongly affect the reaction rate.




**Scheme 1**

DMS enolate **1a**, derived from propiophenone, was selected for the initial study. In the presence of a stoichiometric or catalytic amount of $CaCl_2$, **1a** smoothly added to (*E*)-1,3-diphenyl-2-propen-1-one (chalcone, **2a**) to give the Michael adduct **3aa** in a high yield with high *anti*-selectivity (entries 1 and 2 in Table 1).[8] $MgCl_2$ as well as $CaCl_2$ was quite effective in the Michael addition, while LiCl and $Bu_4NCl$ were almost ineffective (entries 3–5). The catalytic activity of $MgBr_2$ is not as high as that of $MgCl_2$ (entry 6). In the case with (*E*)-4-phenyl-3-buten-2-one (benzalacetone, **2b**), however, the $CaCl_2$-promoted reaction resulted in a low conversion (entry 7). The use of $MgCl_2$ achieved good yields of **3ab** with high *anti*-selectivity (entries 8 and 9). The other metal halides and $Bu_4NCl$ have a reduced or no ability to promote the Michael addition to **2b** (entries 10–13).

**Table 1** Michael Addition of DMS Enolate **1a** to a-Enones in the Presence of Metal Salts or $Bu_4NCl$[a]



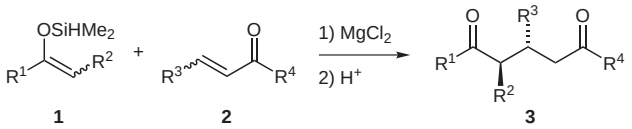

| Entry | Enone | $MX_n$ | Yield (%) | *anti*:*syn*[b] |
|---|---|---|---|---|
| 1 | **2a** | $CaCl_2$ | 93 | 96:4 |
| 2 | **2a** | $CaCl_2$[c] | 97 | 97:3 |
| 3 | **2a** | $MgCl_2$[c] | quant. | 98:2 |
| 4 | **2a** | LiCl | < 9 | nd |
| 5 | **2a** | $Bu_4NCl$ | 0 | |
| 6 | **2a** | $MgBr_2$ | 68 | 98:2 |
| 7 | **2b** | $CaCl_2$ | 31 | 99:1 |
| 8 | **2b** | $MgCl_2$ | 78 | 95:5 |
| 9 | **2b** | $MgCl_2$[c] | 84 | 95:5 |
| 10 | **2b** | $BaCl_2$ | 0 | |
| 11 | **2b** | LiCl[d] | < 5 | nd |
| 12 | **2b** | $Bu_4NCl$ | 0 | |
| 13 | **2b** | $MgBr_2$ | 6 | nd |

[a] Unless otherwise noted, all reactions were carried with **1a** (*Z*:*E* = >98:2, 0.75 mmol), an enone **2** (0.5 mmol), and a promoter (0.5 mmol) in DMF (1 mL) at 30 °C for 24 h. The resultant mixture was treated with 35% HCl (1 mL) for 5 min and neutralized with saturated aqueous $NaHCO_3$. See ref.[8]
[b] Determined by 270 MHz $^1H$ NMR or GC-MS analysis. nd = not determined.
[c] $MgCl_2$ or $CaCl_2$ (0.13 mmol) was used.
[d] LiCl (2.0 mmol) was used.

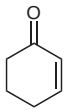
*SYNLETT* 2003, No. 13, pp 2068–2070
Advanced online publication: 08.10.2003
DOI: 10.1055/s-2003-41467; Art ID: U13203ST

With the initial results in hand, we examined the applicability of the $MgCl_2$-promoted Michael reaction by using various DMS enolates and α-enones.[9] The results are summarized in Table 2. (*E*)-1-Phenyl-2-buten-1-one (**2c**), 2-cyclohexenone (**2d**), and 3-buten-2-one (**2e**) underwent the Michael addition of **1a** to afford the corresponding 1,5-diketones **3ac**–**ae** in moderate to good yields (entries 3–5). In the case with **2d** (entry 4), hydrolysis of the reaction mixture with 35% HCl was accompanied by reduction of the cyclohexanone moiety of **3ad**. The hydrolysis with pure water suppressed the unfavorable reaction. In entry 5, the cyclized product **4** consisting of one molecule

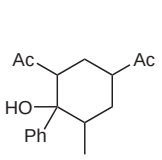
**Table 2** $MgCl_2$-Promoted Michael Addition of Various DMS Enolates[a]



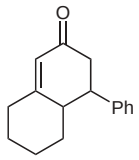

**1** **2** **3**

| Entry | DMS Enolate[b] | Enone | Time (h) | Yield (%) | *anti*:*syn*[c] |
|---|---|---|---|---|---|
| 1[d] | **1a**: $R^1$ = Ph, $R^2$ = Me | **2a** | 24 | quant. | 98:2 |
| 2[d] | | **2b** | 24 | 84 | 95:5 |
| 3[d] | | **2c**: $R^3$ = $CH_3$, $R^4$ = Ph | 4 | 91 | 94:6 |
| 4[e] | |  **2d** | 4 | 82 | nd |
| 5[d,f] | | **2e**: $R^3$ = $CH_3$, $R^4$ = $CH_2$ | 1 | 58 [h] | |
| 6 | **1b**: $R^1$, $R^2$ = $(CH_2)_4$ | **2a** | 24 | 92 | 77:23[k] |
| 7 | | **2b** | 24 | 46 [i] | nd |
| 8[e] | | **2d** | 24 | 42 | nd |
| 9[f] | **1c**: $R^1$ = Et, $R^2$ = Me | **2a** | 4 | 87 | 87:13 |
| 10[f,g] | | **2b** | 24 | 54 | 99:1 |
| 11[e,f] | | **2d** | 4 | 68 | nd |
| 12 | **1d**: $R^1$ = Ph, $R^2$ = H | **2a** | 24 | 80 | |
| 13[e,f] | | **2d** | 4 | 31 | |
| 14[f] | **1e**: $R^1$ = *i*-Pr, $R^2$ = H | **2a** | 24 | 69 | |
| 15[f] | | **2b** | 24 | 0[i] | |

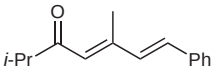
[a] See footnote a in Table 1.
[b] Substrate **1a**, *Z*:*E* = >98:2; **1b**, *E* only; **1c**, *Z*:*E* = 37:63.
[c] See footnote b in Table 1.
[d] $MgCl_2$ (0.13 mmol) was used.
[e] The reaction mixture was quenched with $H_2O$.
[f] Substrate **1** (1.00 mmol) was used.
[g] The reaction mixture was quenched with 2 M HCl.
[h] Cyclohexanol **4** was obtained as a byproduct in 16% yield.
[i] Enone **5** was obtained as a byproduct in 30% yield.
[j] Dienone **6** was formed as the major product in 40% yield.
[k] The relative configuration was not determined.




**4**




**5**




**6**

of **1a** and two molecules of **2e** was obtained as a by-product. Other DMS enolates **1b**–**e** were available for the $MgCl_2$-promoted Michael addition although they were not as reactive as **1a** (entries 6–14). The reaction of **1b** with **2b** provided the Michael adduct **3bb** along with the Robinson annulation product **5** (entry 7). In entry 15, dienone **6** was mainly formed by an aldol reaction and subsequent dehydration.

As shown in Table 1, the reaction rate was strongly affected by the metal chloride used. In addition, $Bu_4NCl$ had no rate-accelerating ability. These results imply that the Lewis acidity of the metal center effects the Michael addition. However, the fact that $MgBr_2$ is not so effective as $MgCl_2$ indicates that the chloride ion also provides a positive effect for the rate-acceleration. We have previously proposed that, in the metal chloride-promoted aldol reaction of DMS enolates, the chloride ion rather than the Lewis acidic metal cation plays a crucial role as the promoter.[7] In the present case, $MgCl_2$ may activate both reactants by the metal center coordinating to the enone and by aiding nucleophilic attack of the chloride ion at the silicon of DMS enolates.

In conclusion, we have demonstrated that, in the presence of $MgCl_2$, DMS enolates add to α-enones efficiently to give the Michael adducts stereoselectively. The present study has disclosed that the behavior of metal halides in the Michael reaction of DMS enolates is slightly different from that observed in the aldol reaction.[7]

## Acknowledgment

This work was partly supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Government of Japan. We thank Dow Corning Toray Silicone Co. Ltd. and Shin-Etsu Chemical Co. Ltd. for a gift of organosilicon compounds.

## References

(1) Pioneer works: (a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223. (b) Narasaka, K.; Soai, K.; Aikawa, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779.

(2) Reviews: (a) Oare, D. A.; Heathcock, C. A. In *Topics in Stereochemistry*, Vol. 20; Eliel, E. L.; Wilen, S. H., Eds.; Wiley: New York, **1991**, 124. (b) Lee, V. J. In *Comprehensive Organic Synthesis*, Vol. 4; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, Chap. 1.3, 139.

(3) (a) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 953. (b) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797. (c) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1990**, *31*, 1581. (d) Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Tetrahedron Lett.* **1991**, *32*, 4665. (e) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815. (f) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472. (g) Ishihara, K.; Hanaki, N.; Funahashi, M.; Miyata, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1721. (h) Chen, J.; Sakamoto, K.; Orita, A.; Otera, J. *Tetrahedron* **1998**, *54*, 8411. (i) Marx, A.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2000**, *39*, 178.

(4) For Lewis acid-catalyzed asymmetric Michael reactions, see; (a) Kobayashi, S.; Suda, S.; Yamada, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 97. (b) Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921. (c) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568. (d) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

(5) (a) RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083. (b) Génisson, Y.; Gorrichon, L. *Tetrahedron Lett.* **2000**, *41*, 4881. (c) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2001**, *3*, 639.

(6) Mukaiyama, T.; Nakagawa, T.; Fujisawa, H. *Chem. Lett.* **2003**, *32*, 56.

(7) Miura, K.; Nakagawa, T.; Hosomi, A. *J. Am. Chem. Soc.* **2002**, *124*, 536.

(8) Propiophenone TMS enolate was much less reactive toward the Michael addition to **2a** even in the presence of an equimolar amount of $MgCl_2$ (7% yield of **3aa**, 30 °C, 24 h).

(9) **General Procedure for the $MgCl_2$-promoted Michael Addition of DMS Enolates**: Under $N_2$ atmosphere, dry DMF (1 mL) was added to $MgCl_2$ (12 mg, 0.13 mmol). The mixture was stirred for 10 min at 30 °C, and a DMS enolate (0.75 mmol) and an α-enone (0.50 mmol) were introduced into the resultant solution. After the reaction was completed, concd HCl (1 mL) was added to the reaction mixture. After being stirred for 5 min, the mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over $Na_2SO_4$ and evaporated. The crude product was purified by silica gel column chromatography. Compound *anti*-**3aa**: CAN [40794-93-2] (ref.[10]). $^1$H NMR (270 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.8 Hz, 3 H), 3.36–3.53 (m, 2 H), 3.89–4.00 (m, 2 H), 7.06–7.27 (m, 5 H), 7.35–7.55 (m, 6 H), 7.83–7.89 (m, 4 H). $^{13}$C NMR (68 MHz, $CDCl_3$) δ 14.10 ($CH_3$), 39.87 ($CH_2$), 42.76 (CH), 45.93 (CH), 126.51 (CH), 127.91 (CH × 2), 127.95 (CH × 2), 128.12 (CH × 2), 128.34 (CH × 2), 128.46 (CH × 2), 128.58 (CH × 2), 132.86 (CH), 132.88 (CH), 136.72 (C), 137.07 (C), 142.79 (C), 198.43 (C), 203.23 (C). The signal for the methyl group of the minor isomer appears at 1.01 ppm (d, *J* = 6.6 Hz). According to the report by Heathcock et al., the major isomer was determined to be *anti*. See ref.[11] Compound *anti*-**3ab**: CAN [111873-77-9] (ref.[12]). $^1$H NMR (270 MHz, $CDCl_3$) δ 1.21 (δ, *J* = 6.9 Hz, 3 H), 2.00 (s, 3 H), 2.89 (d, *J* = 7.1 Hz, 2 H), 3.72 (q, *J* = 7.1 Hz, 1 H), 3.83 (quint., *J* = 6.9 Hz, 1 H), 7.09–7.26 (m, 5 H), 7.38–7.54 (m, 3 H), 7.80–7.83 (m, 2 H). $^{13}$C NMR (68 MHz, $CDCl_3$) δ 14.19 ($CH_3$), 30.42 ($CH_3$), 42.71 (CH), 45.08 ($CH_2$), 45.79 (CH), 126.64 (CH), 127.86 (CH × 2), 128.06 (CH × 2), 128.43 (CH × 2), 128.54 (CH × 2), 132.86 (CH), 136.68 (C), 142.54 (C), 203.20 (C), 207.12 (C). Compound *anti*-**3ac**: CAN [95741-11-0] (ref.[13]). $^1$H NMR (270 MHz, $CDCl_3$) δ 1.07 (δ, *J* = 6.4 Hz, 3 H), 1.23 (δ, *J* = 6.9 Hz, 3 H), 2.17–2.79 (m, 2 H), 3.12 (d, *J* = 14.5, 2.5 Hz, 1H), 3.62 (qd, *J* = 6.9, 4.9 Hz, 1 H), 7.37–7.58 (m, 6 H), 7.85–8.06 (m, 4 H). $^{13}$C NMR (68 MHz, $CDCl_3$) δ 12.94 ($CH_3$), 18.57 ($CH_3$), 31.91 (CH), 41.24 ($CH_2$), 44.92 (CH), 128.00 (CH × 2), 128.21 (CH × 2), 128.47 (CH × 2), 128.66 (CH × 2), 132.89 (CH), 132.94 (CH), 136.91 (C), 137.05 (C), 199.60 (C), 203.89 (C).

(10) Gorrichon-Guigon, L.; Maroni-Barnaud, Y. *Bull. Soc. Chim. Fr.* **1973**, 263.

(11) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.

(12) Bernardi, A.; Dotti, P.; Poli, G.; Scolastico, C. *Tetrahedron* **1992**, *48*, 5597.

(13) Inokuchi, T.; Kurokawa, Y.; Kusumoto, M.; Tanigawa, S.; Takagishi, S.; Torii, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3739.