

Lithium Acetate-catalyzed Michael Reaction between Trimethylsilyl Enolate and α,β -Unsaturated Carbonyl Compound

Takashi Nakagawa,^{†,††} Hidehiko Fujisawa,^{†,††} Yuzo Nagata,^{†,††} and Teruaki Mukaiyama^{*,†,†}

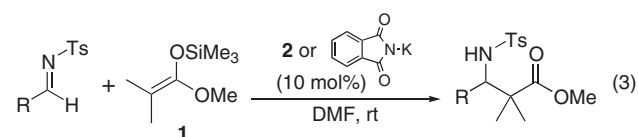
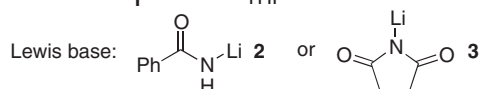
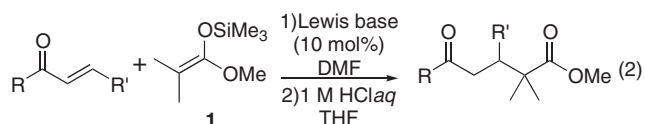
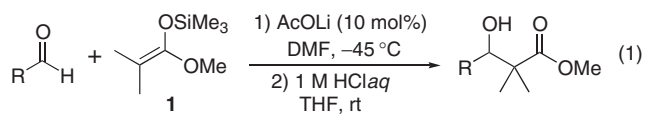
[†]Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003

^{††}Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641

(Received May 21, 2004; CL-040583)

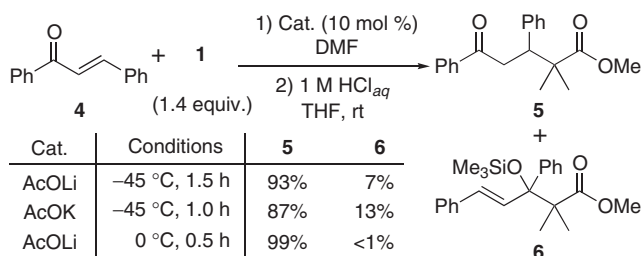
Lithium acetate-catalyzed Michael reaction between trimethylsilyl enolates and α,β -unsaturated carbonyl compounds in DMF proceeded smoothly to afford the corresponding Michael-adducts in good to high yields. Hindered α,β -unsaturated ketones also behaved as an excellent Michael-acceptor in the above reaction at room temperature.

Several effective Lewis base catalysts for the activation of simple silyl enolates such as trimethylsilyl (TMS) enolate were recently introduced from our laboratory, which were employed successfully in aldol,¹ Michael,² and Mannich-type reactions³ via the formation of active hypervalent silicate (Eqs 1–3).



It is interesting to note that the TMS enolate was activated either by lithium succinimide **3** or by lithium acetate (AcOLi) that is a weaker nucleophile toward silicon atom compared with lithium benzamide **2**. From the synthetic point of view, AcOLi has such advantages as easy availability, low cost and could be used under mild conditions because of its weak basicity. Also, the acetate can be prepared from AcOH by using weak bases such as lithium carbonate (Li_2CO_3) while preparation of **2** or **3** from amide or imide require strong bases such as alkyl lithium. In addition, from the environmental points of view, they would be very useful for its low toxicity and is disposable without any special treatment. In this communication, we would like to report on AcOLi-catalyzed Michael reaction between TMS enolates and α,β -unsaturated carbonyl compounds in order to demonstrate the usefulness of AcOLi as a Lewis base catalyst.

In the first place, reaction of chalcone **4** and TMS enolate **1** in DMF was tried by using 10 mol % of AcOLi at -45°C , and the Michael-adduct **5** was obtained in 93% yield together with 1,2-addition product, silyl ether **6**, in 7% yield. In the above reaction, the amount of 1,2-adduct increased when AcOK was



Scheme 1. AcOLi catalyzed Michael reaction between TMS enolate **1** and chalcone.

used instead of AcOLi. Next, the reaction conditions were carefully screened using AcOLi so as to reduce the amount of 1,2-adducts and the desired 1,4-addition proceeded at 0°C to afford **5** exclusively in high yield (Scheme 1).⁴ In the absence of the catalyst, on the other hand, **5** was not obtained at all, which indicated that AcOLi worked as an efficient Lewis base catalyst in this Michael reaction.

Next, reactions of TMS enolate **1** with various Michael-acceptors were tried by using AcOLi as a catalyst (Table 1).⁵ Then, the enolate **1** reacted smoothly with various Michael-acceptors to give the corresponding Michael-adducts in high yields. In the case when 3-nonene-2-one **9** was used, AcOLi worked more effectively than the previously-reported **3** (Entry 3). One of the

Table 1. AcOLi catalyzed Michael reaction using various Michael acceptors

Entry	Michael Acceptor	Temp / $^\circ\text{C}$	Time /h	Yield ^a /%	
1	cyclopentenone	7	0	0.5	98
2	4-hexene-3-one	8	0	0.5	98
3	3-nonene-2-one	9	rt	0.5	99 (83 ^b)
4	mesityl oxide	10	rt	3	85 (34 ^c)
5	3-methyl-cyclohexenone	11	rt	6	83 (44 ^c)
6	4-NMe ₂ -C ₆ H ₄ -CH=CH-Ph	12	0	0.5	91 ^d
7	methyl acrylate	13	rt	6	64 ^e

Reactions were carried out using Michael acceptor (0.4 mmol) in DMF (3 mL). ^aYield was determined by ¹H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane or 2,4,6-trimethylbenzene (Entry 3) as an internal standard. ^bBy using **3** as a catalyst at rt for 3 h (See Ref. 2). ^cBy using **3** as a catalyst under the same reaction conditions. ^dIsolated yield. ^e2 equiv. of **1** was used.

most characteristic points of the present reaction is that the hindered α,β -unsaturated ketones also behaved as an excellent Michael-acceptor to form the corresponding Michael-adduct in high yields at room temperature (Entries 4, 5). This Lewis base-catalyzed reaction is effective especially when Michael-acceptors having basic functions within the same molecule are used. Actually, the reaction proceeded smoothly and the corresponding Michael-adduct was afforded in high yield, as expected (Entry 6).

Several methods were recently reported concerning Lewis base-catalyzed Michael reaction. However, each of them had worked only with limited kinds of silyl enolates, i.e. one worked only with dimethylsilyl enolates derived from ketones,^{6,7} and another was performed only with keten silyl acetals.⁸ On the other hand, AcOLi-catalyzed Michael reaction also proceeded smoothly to afford the corresponding Michael-adducts in good to high yields even when various TMS enolates derived from esters, thioesters or ketones were employed (Table 2).

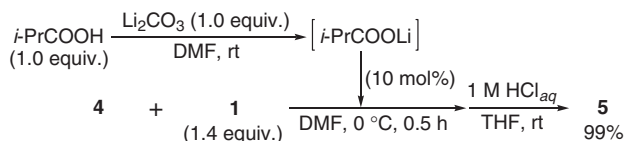
This catalytic Michael reaction was also carried out by using other lithium carboxylates that were prepared easily in situ by treating carboxylic acids with Li_2CO_3 . For example, Michael reaction of **4** with silyl enolate **1** gave the Michael-adduct **5** in high yield when 10 mol % of lithium isobutyrate prepared from isobutyric acid and Li_2CO_3 in DMF was used (Scheme 2).⁹

Thus, AcOLi-catalyzed Michael reaction between trimethylsilyl enolates and α,β -unsaturated carbonyl compounds was established. This is a useful method for the synthesis of various 1,5-dicarbonyl compounds since the reactions proceed

Table 2. AcOLi catalyzed Michael reaction using various silyl enolates

Entry	Acceptor	Silyl enolates	Temp /°C	Time /h	Yield ^a /%	syn : anti ^b
1	7		0 → rt	3	64	55:45
2 ^c	7		0 → rt	3	74	54:56
3	7		0	2	89	59:41
4 ^c	7		0	1.5	84	60:40
5	7		0	1	87	–
6	7		0	1	93	59:41
7	4		rt	10	83 ^d	26:74 ^e
8	4		70	8	75 ^d	30:70 ^{e,f}

Reactions were carried out using Michael acceptor (0.4 mmol) in DMF (3 mL). ^aIsolated yield. ^bDetermined by GC. ^cReactions were carried out using Michael acceptor (0.8 mmol) in DMF (3 mL). ^dYield was determined by ¹HNMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. ^eDetermined by ¹HNMR analysis (270 MHz). ^fRelative configurations were not determined.



Scheme 2. Michael Reaction by using *i*-PrCOOLi prepared from *i*-PrCOOH and lithium carbonate.

smoothly by using such a mild and readily-available Lewis base catalyst. Further expansion of this reaction is now in progress.

This study was supported in part by the Grant of the 21st Century COE Program from Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

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e) T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 696 (2003).
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- The Michael adduct **5** was not observed at all by treating silyl ether **6** with the reaction conditions [AcOLi (10 mol %), DMF, 30 min].
- Typical experimental procedure is as follows (Table 1, Entry 6): to a stirred solution of AcOLi (2.6 mg, 0.04 mmol) in DMF (0.5 mL) were added successively a solution of silyl enolate **1** (97.6 mg, 0.56 mmol) in DMF (1.0 mL) and a solution of 4'-(dimethylamino)chalcone¹⁰ (100.5 mg, 0.4 mmol) in DMF (1.5 mL) at 0 °C. The mixture was stirred for 0.5 h at the same temperature, and quenched with saturated aqueous NH_4Cl . The mixture was extracted with Et_2O and the residue was dissolved in a mixture of HCl (1.0 M, 0.5 mL) and THF (5 mL) after evaporation of the solvent. The mixture was stirred for 30 min and was extracted with Et_2O . Organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to give the corresponding Michael-adduct (128.7 mg, 91%) as a yellow powder.
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- When the above reaction was carried out without using the isobutyric acid, the corresponding Michael-adduct was obtained only in 10% yield. This result clearly indicates that **1** was activated effectively by lithium isobutyrate prepared from isobutyric acid and Li_2CO_3 in DMF.
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