Lithium Alkoxide-promoted Michael Reaction between Silyl Enolates and α,β-Unsaturated Carbonyl Compounds

Teruaki Mukaiyama,*[†,††] Takashi Tozawa,[†,††] and Hidehiko Fujisawa[†,††]
[†]*Center for Basic Research, The Kitasato Institute (TCI), 6-15-5 Toshima, Kita-ku, Tokyo 114-0003*
[††]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

(Received August 2, 2004; CL-040905)

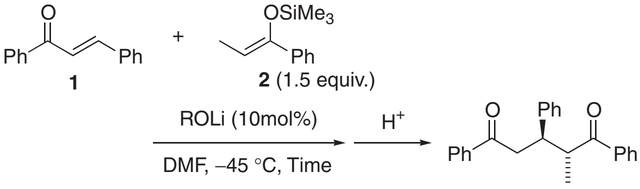
Michael reaction between silyl enolates and α,β-unsaturated carbonyl compounds by using a catalytic amount of Lewis base such as lithium alkoxide in DMF proceeds smoothly to afford the corresponding Michael-adducts in good yields with moderate to high diastereoselectivities. This reaction can be reasonably explained by considering an alkoxide anion-initiated autocatalytic process.

In our preceding paper, new possibilities of various Lewis base catalysts in synthetic reactions were demonstrated.[1] There, nitrogen- or oxygen-containing organic anions generated from amines, amides, imides, and carboxylic acids were found to work effectively as Lewis base catalysts for the activation of commonly used trimethylsilyl (TMS) enolates. For example, Lewis bases such as lithium benzamide,[1g] lithium succimide,[1g] or lithium acetate[1j] efficiently catalyzed the Michael reaction of TMS enolates with α,β-unsaturated carbonyl compounds in *N*,*N*-dimethylformamide (DMF).

Then, in the course of our continuous investigations on the usefulness of oxygen-containing organic anions for Lewis bases in organic reactions, the use of alkoxide anions was focused upon. It was reported in the previous report that the catalytic aldol reaction between TMS ketene acetals and aldehydes by using alkoxide anion proceeded smoothly to afford the corresponding aldol in DMF.[2] It was demonstrated there that the in situ formed aldolate anion worked as a useful catalyst of the above reaction. Now, we would like to describe on Michael reaction between silyl enolates and α,β-unsaturated carbonyl compounds by using a catalytic amount of alkoxide anion in DMF at low temperatures.

In the first place, various lithium alkoxides were screened by taking the Michael reaction of chalcone **1** with TMS enolate **2** in DMF at −45 °C as a model (Table 1). In the case of lithium alkoxides generated from primary alcohols, the reactions proceeded smoothly to afford the corresponding Michael-adducts in good yields with high *anti*-diastereoselectivities even when 5 mol % of lithium benzylate was used (Entries 1–4). When the reaction was carried out at 0 °C, the Michael-adduct was obtained in quantitative yield, virtually without losing diastereoselectivity (Entry 5). The desired Michael-adduct was not formed when the reaction was tried in THF different from the cases attempted in DMF (Entry 6). These results indicate that the alkoxide anions promoted the catalytic Michael reaction as effective Lewis bases and the solvent also played an important role on this reaction. On the other hand, the use of lithium alkoxides generated from sterically hindered secondary or tertiary alcohols was found to give the products while the diasteroselectivities were lost (Entries 7 and 8). It was thought then that the sterically hindered alkoxide anions would not only serve as Lewis bases to activate TMS enolates by a nucleophilic attack, but also behave as Brønsted bases to promote the epimerization of the formed adducts.

Table 1. Michael reaction of chalcone **1** with TMS enolate **2** in the presence of a catalytic amount of lithium alkoxides



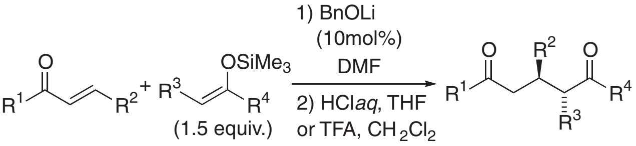
Entry	ROLi[a]	Time /h	Yield[b] /%	*anti*:*syn*[c]
1	MeOLi	10	64	90:10
2	EtOLi	6	91	90:10
3	BnOLi	4	93	92:8
4	BnOLi	5	88[d]	91:9
5	BnOLi	0.5	quant.[e]	89:11
6	BnOLi	6	0[f]	
7	*i*-PrOLi	6	65	60:40
8	*t*-BuOLi	4	90	60:40

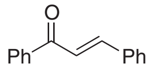
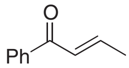
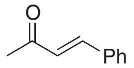
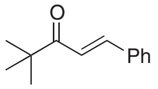
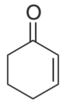
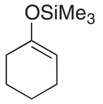
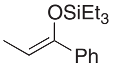
[a]Lithium alkoxides were prepared from alcohol and MeLi. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis (270 MHz). [d]5 mol % of BnOLi was used. [e]Reaction was carried out at 0 °C. [f]Reaction was carried out in THF.

Several examples of Michael reactions by using 10 mol % of lithium benzylate in DMF are summarized in Table 2.[3] This Lewis base-promoted reaction was more effective than the previously reported lithium acetate-catalyzed reaction[1j] when TMS enolates derived from ketones were used. Actually, it was observed that TMS enolates derived from ketones smoothly reacted with various Michael-acceptors to give the corresponding products in good to high yields with moderate to high diastereoselectivities at low temperatures. On the other hand, higher reaction temperature was still required in the lithium acetate-catalyzed Michael reaction. It is noteworthy to point out that the Michael-adducts were also obtained in good yields when α,β-unsaturated carbonyl compounds having active hydrogen atoms at α-position of carbonyl moiety or having sterically hindered group were applied to this catalytic system (Entries 3 and 4). In addition, the desired product was obtained in good yield without diminution of the diastereoselectivity when triethylsilyl (TES) enolate derived from propiophenone was employed in place of the above TMS enolate **2** (Entry 7).

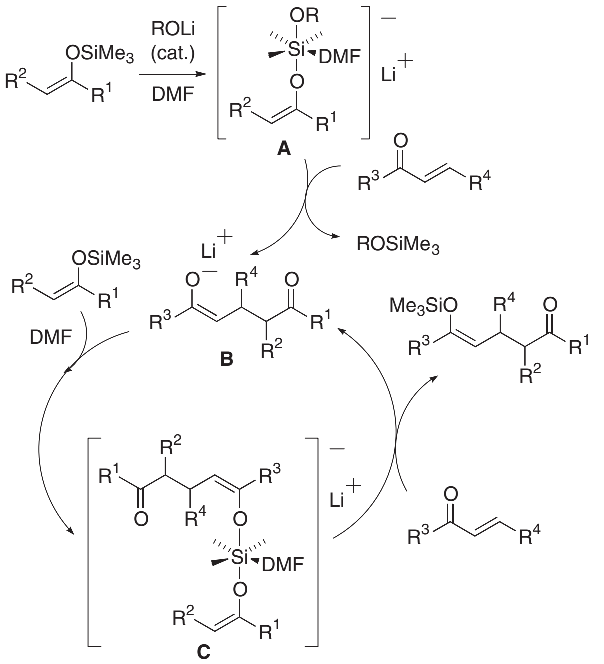
The present catalytic Michael reaction is assumed to proceed by a pathway similar to the previously reported product-

Table 2. Lithium alkoxide-promoted Michael reaction using various Michael acceptors and silyl enolates



Entry	Acceptor	Enolate	Conditions	Yield[a] /%	*anti*:*syn*[b]
1	 **1**	**2**	–45 °C, 4 h	93	92:8
2		**2**	–20 °C, 4 h	88	75:25
3		**2**	–20 °C, 6 h	92	96:4
4		**2**	–20 °C, 8 h	70	96:4
5		**2**	–10 °C, 10 h	60[c]	nd[d]
6	**1**		0 °C, 10 h	86	75:25[e]
7	**1**		0 °C, 10 h	72	90:10

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis (270 MHz). [c] 2 equivalents of **2** were used. [d] nd = not determined. [e] The relative configuration was not determined.



Scheme 1.

catalyzed aldol reaction[2] (Scheme 1), that is; an alkoxide anion and a solvent coordinated to the silicon atom of TMS enolate to form a highly nucleophilic hexacoordinated hypervalent silicate **A**. Thus, the enolate became more reactive and attacked smoothly the α,β-unsaturated carbonyl compounds to form lithium enolate **B** and TMS ether of alcohol. The alkoxide anion just served as an initiator of the reaction and was not involved in the catalytic cycle. In the next step, lithium enolate **B** similarly activated TMS enolate to form a silylated Michael-adduct via a hexacoordinated hypervalent silicate **C** and then regenerated the lithium enolate (enolate anion) **B** that behaved as a key species in the above catalytic cycle.

Thus, Michael reaction between silyl enolates and α,β-unsaturated carbonyl compounds by using a catalytic amount of Lewis base such as lithium alkoxide in DMF at low temperatures proceeded smoothly to afford the corresponding Michael-adducts. This reaction is induced by a readily available alkoxide anion and then is further catalyzed by the in situ formed enolate anion. It is noted that these two oxygen-containing anions work effectively as Lewis base for the promotion of silyl enolates. Further investigation on 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.

References and Notes

1 a) H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, **2002**, 182. b) H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, **2002**, 858. c) T. Mukaiyama, H. Fujisawa, and T. Nakagawa, *Helv. Chim. Acta*, **85**, 4518 (2002). d) T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 462 (2003). e) T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 696 (2003). f) T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **33**, 92 (2004). g) T. Mukaiyama, T. Nakagawa, and H. Fujisawa, *Chem. Lett.*, **32**, 56 (2003). h) H. Fujisawa, E. Takahashi, T. Nakagawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 1036 (2003). i) E. Takahashi, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **33**, 936 (2004). j) T. Nakagawa, H. Fujisawa, Y. Nagata, and T. Mukaiyama, *Chem. Lett.*, **33**, 1016 (2004).

2 H. Fujisawa, T. Nakagawa, and T. Mukaiyama, *Adv. Synth. Catal.*, (2004), in press.

3 Typical experimental procedure is as follows (Table 2, Entry 1): a) Preparation of lithium benzylate; To a solution of benzyl alcohol (227 mg, 2.1 mmol) in Et$_2$O (18 mL) was added methyllithium in Et$_2$O (0.98 M, 2.0 mL, 2.0 mmol) at 0 °C and the mixture was stirred for 30 min. b) General procedure of lithium alkoxide-promoted Michael reaction; An etheral solution containing lithium benzylate (0.6 mL, 0.06 mmol) was concentrated under reduced pressure and residual lithium reagent was dissolved in DMF (1.2 mL). The resulting solution was cooled to −45 °C and then solutions of silyl enolate **2** (186 mg, 0.9 mmol) in DMF (0.6 mL) and chalcone (125 mg, 0.6 mmol) in DMF (1.2 mL) were added. The mixture was stirred for 4 h at the same temperature, and quenched with saturated aqueous NH$_4$Cl. The mixture was extracted with EtOAc and the residue was dissolved in a mixture of HCl (1.0 M, 2 mL) and THF (8 mL) after evaporation of the solvent. The mixture was stirred for 30 min and was extracted with EtOAc. Organic layer was washed with brine and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvent, the crude product was purified by silica gel column chromatography to give the corresponding Michael-adduct (190 mg, 93%).

Published on the web (Advance View) September 29, 2004; DOI 10.1246/cl.2004.1410