Lewis Base Catalyzed Michael Reaction between Ketene Silyl Acetals and α,β-Unsaturated Carbonyl Compounds

Teruaki Mukaiyama,* Takashi Nakagawa, and Hidehiko Fujisawa#
The Kitasato Institute, Center for Basic Research, TCI, 6-15-5 Toshima, Kita-ku, Tokyo 114-0003

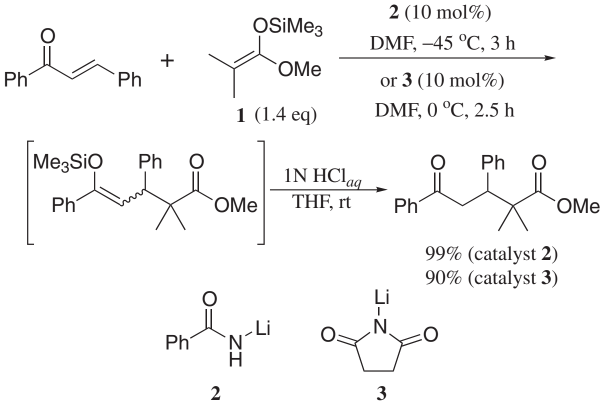
(Received October 4, 2002; CL-020853)

Catalytic Michael reaction between trimethylsilyl enolates and α,β-unsaturated carbonyl compounds by using a Lewis base such as lithium benzamide or lithium succimide in a DMF solvent proceeded smoothly to afford the corresponding Michael adducts.

Silyl enolates are stable enolate equivalents and can be isolated by distillation. However, their utility in synthetic organic chemistry has not fully been developed because of their weakly nucleophilic character. Since a crossed aldol reaction between aldehydes and silyl enolates promoted by Lewis acids such as titanium tetrachloride was reported from our laboratory,[1] silyl enolates are recognized as convenient and useful nucleophiles and have frequently been employed in constructing carbon skeleton. Recently, activation of silyl enolates under neutral or nonacidic conditions is studied intensively: for example, Denmark et al. and Hosomi and co-workers reported methods of using silyl enolates having an enhanced Lewis acidic silicon atom, by which the interaction between Lewis bases is increased.[2] In our previous paper, it was reported that the lithium diphenylamide or lithium pyrrolidone was an effective Lewis base catalyst for the activation of a simple silyl enolate such as trimethylsilyl enolate in a dimethylformamide (DMF) or pyridine solvent under nonacidic conditions.[3] In this communication, we would like to report a catalytic Michael reaction between trimethylsilyl enolates and α,β-unsaturated carbonyl compounds by using Lewis base catalysts in order to prove the usefulness of the Lewis base catalysts.

Although the Michael reaction is one of the most important methods for carbon–carbon bond formation, side reactions such as self-condensations of substrates, proton transfers, and concomitant 1,2-additions often occur in conventional Michael reactions which are carried out under basic conditions.[4] Such undesired reactions can be conquered by using silyl enol ethers as the functional equivalents of Michael donors. This type of reaction has become very popular ever since the Michael reaction between α,β-unsaturated ketones and silyl enolates promoted by Lewis acid was reported from our laboratory.[5] Also, fluoride ion catalyzed reactions of sily enol ethers[6] or silyl ketene acetals,[7] and a reaction of dimethyl(trifloxy)silyl enol ethers with α,β-unsaturated ketones[8] have been shown. In the latter case, silyl enolates smoothly reacted with α,β-unsaturated ketones even in the absence of catalysts. In addition, reactions of silyl ketene acetals with α,β-unsaturated carbonyl compounds have been carried out in DMSO[9] or nitromethane[7] at room temperature and in acetonitrile at 55 °C[10] or under high pressure.[11] Some of these methods, however, were found to have synthetic limitations: i.e., when trimethylsilyl enolate derived from methyl isopropionate **1** was used, the reactivity decreased and, therefore, reaction temperature must be elevated.[11]

In the first place, a reaction of chalcone and **1** in DMF was tried in the presence of a catalytic amount of lithium diphenylamide or lithium pyrroridone, and the Michael adduct was afforded in 52% or 68% yield, respectively. Of the amides screened, lithium benzamide **2** then turned out to be the most effective Lewis base for the acceleration of the reaction. Surprisingly, the lithium succimide **3** also catalyzed the reaction and the Michael adduct was obtained in high yield even though pKa value of N–H bond of its precursor was much lower than that of above three precursors, which was measured in DMSO[12] (Scheme 1). In the absence of the catalyst, on the other hand, the Michael adduct was not obtained at all.

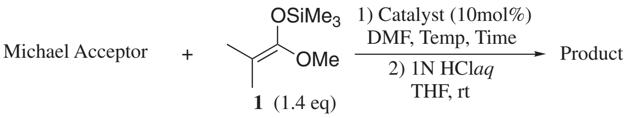


Scheme 1.

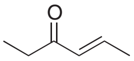
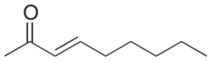
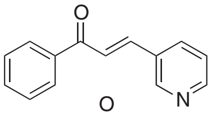
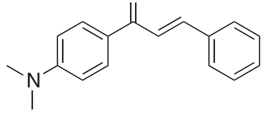
Next, the reactions of trimethylsilyl enolate with various Michael acceptors were tried by using **2** or **3** as a catalyst. The results are summarized in Table 1. Bulky silyl enolate **1** smoothly reacted with various Michael acceptors to give the corresponding Michael adducts in high yields at low temperature. When the acceptors having active hydrogens at the α position of carbonyl moiety were used, **3** proved to be a very effective Lewis base catalyst; that is, the reaction proceeded smoothly by using such weak base catalyst **3** and gave the corresponding Michael adducts in high yield (Entry 9), while the yield was very poor when the same reaction was carried out by using **2** at room temperature because **2** behaved as a brønsted base in DMF (Entry 8). From a synthetic point of view, the present Lewis base catalyzed reaction has a remarkable advantage in forming Michael adducts especially when Michael acceptors of having basic functions in the same molecules were used. Expectedly, reactions proceeded smoothly and the corresponding Michael adducts were afforded in high yields in the above cases (Entry 10–13).

The lithium benzamide **2** catalyzed Michael reaction was further tried by using several silyl enolates (see Table 2). When sterically hindered triethylsilyl enolate derived from methyl

Table 1.

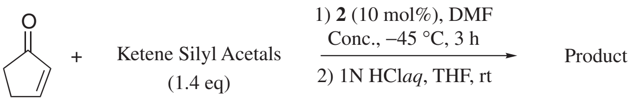


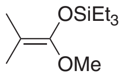
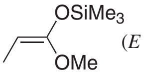
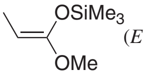
1 (1.4 eq)

Entry	Michael acceptor	Catalyst	Temp /°C	Time /h	Yield^a /%
1	cyclopentenone	**2**	–45	3	91
2	cyclopentenone	**3**	–45	3	88
3	cyclohexenone	**2**	–45	3	94
4	methyl vinyl ketone	**2**	–45	3	90
5		**2**	0	3	85
6		**2**	–45	3	42
7		**2**	0	3	75
8		**2**	rt	3	40
9		**3**	rt	3	83
10		**2**	–45	3	83
11		**3**	–45	4	97
12		**2**	0	3	92
13		**3**	0	3.5	91
14	methyl acrylate	**2**	–45 → 0	5	65

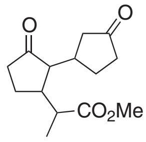
All reactions were carried out at 0.11 mol dm^{-3}. ^{a}Yield was determined by ^{1}H-NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

Table 2.



Entry	Ketene silyl acetals	Conc. / mol dm^{-3}	Yield^a / %	*syn* : *anti*
1		0.11	46	
2	 (*E* : *Z* = 5 : 1)	0.11	59	1 : 1
3		0.23	85^b	1 : 1
4	 (*E* : *Z* = 1 : 9)	0.11	60	1 : 1
5		0.23	41^{b,c}	1 : 1

^{a}Yield was determined by ^{1}H-NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. ^{b}Isolated yield. ^{c}Compound **4** was afforded as a by-product (13% yield).



4

isopropionate was employed in place of the above trimethylsilyl enolate **1**, the corresponding Michael adduct was obtained only in 46% yield (Entry 1). This result indicated that the reaction proceeded via the activation of trimethylsilyl enolate by forming hypervalent silicate between Lewis bases and the silicon atom of enolate.[3] Further, the reactivities were slightly decreased when trimethylsilyl enolates derived from methyl propionate were used as a substrate. Similar phenomenon was observed also in the Michael reaction carried out in DMSO in the absence of a catalyst.[9] When the *E* enolate was allowed to react with cyclopentenone at 0.23 mol dm^{-3}, the corresponding Michael adduct was afforded in high yield (Entry 3).

Thus, a new catalytic Michael reaction between trimethylsilyl enolates and α,β-unsaturated carbonyl compounds was established under nonacidic conditions by using lithium benzamide **2** or lithium succimide **3** in a DMF solvent. Further expansion of this reaction is now in progress.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

References and Notes

\# A doctor course student of Science University of Tokyo.

1 T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).

2 S. E. Denmark and R. A. Stavenger, *Acc. Chem. Res.*, **33**, 432 (2000); K. Miura, T. Nakagawa, and A. Hosomi, *J. Am. Chem. Soc.*, **124**, 536 (2002).

3 H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, **2002**, 182; H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, **2002**, 858; T. Mukaiyama, H. Fujisawa, and T. Nakagawa, *Helv. Chim. Acta*, **2002**, in press.

4 E. D. Bergmann, D. Ginsburg, and R. Rappo, in "Organic Reactions," ed. by R. Adams, Wiley, New York (1959), Vol. 10, pp 179–555; H. O. House, in "Modern Synthetic Reactions," 2nd ed., ed. by W. A. Benjamin, Menlo Park, California (1972), p 595; P. Perlmutter, "Conjugate Addition Reactions in Organic Synthesis," Pergamon Press, Oxford (1992).

5 K. Narasaka, K. Soai, and T. Mukaiyama, *Chem. Lett.*, **1974**, 1223; K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49**, 779 (1976); K. Saigo, M. Osaki, and T. Mukaiyama, *Chem. Lett.*, **1976**, 163.

6 J. Boyer, R. J. P. Corriu, R. Perz, and C. Reye, *J. Organomet. Chem.*, **184**, 157 (1980); J. Boyer, R. J. P. Corriu, R. Perz, and C. Reye, *Tetrahedron*, **39**, 117 (1983).

7 T. V. Rajan Babu, *J. Org. Chem.*, **49**, 2083 (1984).

8 S. Kobayashi and K. Nishio, *J. Org. Chem.*, **58**, 2647 (1993).

9 Y. Génisson and L. Gorrichon, *Tetrahedron Lett.*, **41**, 4881 (2000).

10 Y. Kita, J. Segawa, J. Haruta, H. Yasuda, and Y. Tamura, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 1099.

11 R. A. Bunce, M. F. Schlecht, W. G. Dauben, and C. H. Heathcock, *Tetrahedron Lett.*, **24**, 4943 (1983); Y. Yamamoto, K. Maruyama, and K. Matsumoto, *Tetrahedron Lett.*, **25**, 1075 (1984).

12 F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988); F. G. Bordwell, J. C. Branca, D. L. Hughes, and W. N. Olmstead, *J. Org. Chem.*, **45**, 3305 (1980).