Lithium Acetate-Catalyzed Aldol Reaction between Aldehyde and Trimethylsilyl Enolate

Takashi Nakagawa[†,††], Hidehiko Fujisawa,[#†,††] 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*

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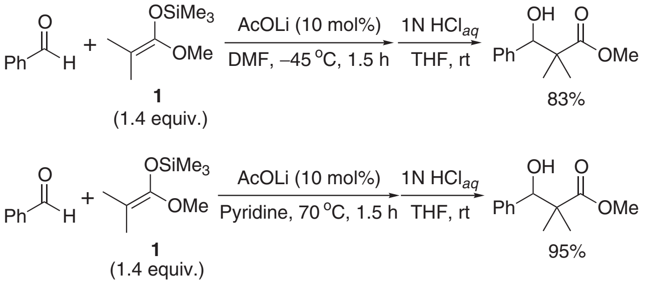
Lithium acetate-catalyzed aldol reaction between trimethylsilyl enolates and aldehydes proceeded smoothly in a DMF or pyridine solvent to afford the corresponding aldols in good to high yields under weakly basic conditions.

A new method for a catalytic aldol reaction between silyl enolates and aldehydes was recently reported from our laboratory: that is, simple and commonly employed trimethylsilyl (TMS) enolates reacted with aldehydes smoothly to afford the corresponding aldols by using a catalytic amount of lithium diphenylamide or lithium pyrrolidone as Lewis base in a *N*,*N*-dimethylformamide (DMF) or pyridine solvent.[1] In order to extend the scope of this reaction, lithium acetate, a milder and readily available Lewis base, was chosen in place of the above mentioned lithium salts. In our previous paper, lithium succimide was shown to have effectively been employed in a catalytic Michael reaction between TMS enolates and α,β-unsaturated carbonyl compounds.[2] It is interesting to note that the TMS enolate was activated by the nucleophilic attack of lithium succimide on silicon atom though the p*K*a value of N–H bond of succimide was much lower than that of diphenylamine or pyrrolidone.[3] In order to examine the possibility of using lithium carboxylates in these types of reactions as catalysts, carboxylic acids such as acetic acid were tried considering the advantages of their availability, inexpensiveness and p*K*a values of their O–H bonds which were relatively close to that of N–H bond of succimide.[3] In this communication, we would like to report on the lithium acetate (AcOLi) catalyzed aldol reaction between TMS enolates and aldehydes.

In the first place, reaction of benzaldehyde and TMS enolate (**1**) derived from methyl isobutyrate was tried in the presence of 10 mol% of AcOLi at −45 °C in DMF, and the aldol adduct was obtained in 83% yield.[4] Since AcOLi is a weak nucleophile, the reaction did not proceed at 0 °C in pyridine although the same reaction went on smoothly when lithium diphenylamide or lithium pyrrolidone was used.[1] However, the corresponding aldol was obtained in high yield when the reaction was carried out at 70 °C in pyridine (Scheme 1). In the absence of the catalyst, on the other hand, the aldol adduct was obtained only in 14% yield even when the reaction was carried out at 70 °C in pyridine. These results indicated the capability of AcOLi that behaved as an effective Lewis base catalyst in this aldol reaction.



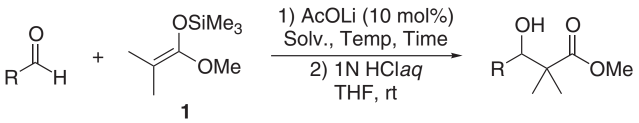
Scheme 1.

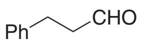
Next, the reactions of TMS enolate **1** with various aldehydes were tried by using 10 mol% of AcOLi in DMF or pyridine (see Table 1).[5] Aromatic aldehydes having an electron-donating group reacted smoothly to afford the desired aldols in high yields (Entries 1–4). On the other hand, aromatic aldehydes having an electron-withdrawing group and aliphatic aldehyde as 3-Phenylpropionaldehyde gave the corresponding aldols in moderate yields in DMF while the aromatic aldehydes gave the aldol adducts in high yields when the reactions were carried out in pyridine at 70 °C.

The present Lewis base catalyzed reaction has a remarkable advantage of forming aldols especially when the aldehydes having basic functions in the same molecules were used: that is, the reactions proceeded smoothly at −45 °C in DMF and the corresponding aldols were afforded in high yields (Table 2, Entries 1–4).

The AcOLi-catalyzed aldol reaction was further examined using several other silyl enolates (see Table 3). When the enolate generated from *S*-ethyl ethanethioate was employed, the aldol adduct was obtained in high yield (Entry 1) while no effective activation took place at −45 °C when the enolate generated from acetophenone was used. The above reaction proceeded smoothly at 0 °C to afford the aldol adduct in good yield (Entry 2). Next, it was observed that the corresponding aldol adduct was obtained only in 4% yield when sterically hindered triethyl-

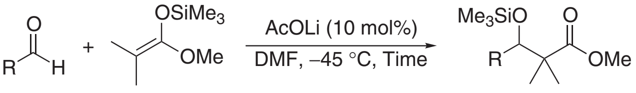
Table 1.



Entry	Aldehyde	Solv.	Temp /°C	Time /h	Yield[a] /%
1	4-MeOC$_6$H$_4$CHO	DMF	–45	1	94[b]
2	4-MeOC$_6$H$_4$CHO	Pyridine	rt	2	96[b]
3	4-MeC$_6$H$_4$CHO	DMF	–45	2	84
4	4-MeC$_6$H$_4$CHO	Pyridine	70	2	98
5	4-ClC$_6$H$_4$CHO	DMF	–45	3	63
6	4-ClC$_6$H$_4$CHO	Pyridine	70	4.5	93
7	4-NO$_2$C$_6$H$_4$CHO	DMF	$-45 \rightarrow$ rt	2 d	69
8	4-NO$_2$C$_6$H$_4$CHO	Pyridine	70	3	82
9	 Ph CHO	DMF	–45	2	65[b]
10		Pyridine	70	4.5	54[b]

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b] Isolated yields.

Table 2.



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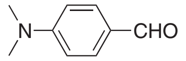
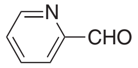
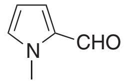
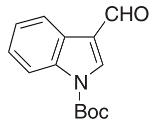
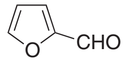
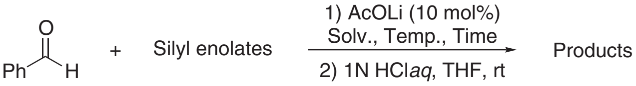
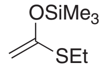
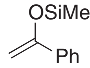
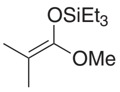
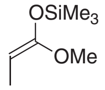
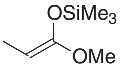
Entry	Aldehyde	Time /h	Yield[a] /%
1[b]		1	99
2		1.5	84
3		1.5	91[c]
4		2.5	99
5		1	90

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]5 mol% of AcOLi was used. [c]Isolated yield after desilylation.

Table 3.



Entry	Silyl enolates	Solv.	Temp /°C	Time /h	Yield[a] /%	*syn* : *anti*
1		DMF	–45	2	91	–
2		DMF	0	2	85	–
3		DMF	–45	1.5	4	–
4	 (*E*:*Z* =5:1)	DMF	–45	3	87	1.8 : 1
5		Pyridine	70	2	86	1.5 : 1
6	 (*E*:*Z* =1:9)	DMF	–45	3	79	2.7 : 1
7		Pyridine	70	2	94	1.9 : 1

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

silyl enolate derived from methyl isobutyrate was employed in place of the above TMS enolate **1** (Entry 3). This result showed that the reaction proceeded via the activation of TMS enolate by forming hypervalent silicate between AcOLi and silicon atom of the enolate.[1] Further, the aldol adducts were obtained in high yields with moderate *syn*-diastereoselectivity irrespective of geometry of the two isomeric silyl enolates derived from methyl propionate (Entries 4–7). Both reactivities of *E* and *Z* enolates were nearly the same when AcOLi was used as a catalyst while the reactivity of *E* enolate was lower than that of *Z* enolate when the previously mentioned Lewis bases such as lithium diphenylamide or lithium pyrrolidone were used.[1] The *syn*-diastereoselectivity of the AcOLi-catalyzed aldol reaction indicated that the reaction proceeded mostly via acyclic transition states.[4b,6]

This catalytic aldol reaction can also be performed smoothly by using other lithium carboxylates that are prepared easily in situ by treating carboxylic acids with lithium carbonate (Li_2CO_3) while Lewis bases employed in the previous studies needed strong bases such as alkyl lithium.[1] For example, aldol reaction of 4-methoxybenzaldehyde with silyl enolate **1** gave the aldol adduct in 92% yield by using 10 mol% of lithium isobutyrate prepared from isobutyric acid and Li_2CO_3 in DMF.

Thus, lithium acetate-catalyzed aldol reaction between TMS enolates and aldehydes under weakly basic conditions in a DMF or pyridine solvent was established. This method is practically applicable for the synthesis of various aldols because it uses such a mild, readily-available, and inexpensive Lewis base catalyst. Further extension of this reaction is now in progress.

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References and Notes

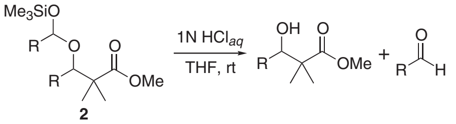
\# A doctor course student of Science University of Tokyo.

1 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*, **85**, 4518 (2002).

2 T. Mukaiyama, T. Nakagawa, and H. Fujisawa, *Chem. Lett.*, **32**, 56 (2003).

3 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).

4 Although a small amount of acetal **2** was co-produced, it was easily converted to normal aldol and starting aldehyde on treatment with 1 N HCl.



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See: a) E. Nakamura, M. Shimizu, I. Kuwajima, J. Sakata, K. Yokoyama, and R. Noyori, *J. Org. Chem.*, **48**, 932 (1983). b) S. Matsukawa, N. Okano, and T. Imamoto, *Tetrahedron Lett.*, **41**, 103 (2000).

5 Typical experimental procedure is as follows (Table 1, Entry 1): 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-methoxybenzaldehyde (54.5 mg, 0.4 mmol) in DMF (1.5 mL) at −45 °C. The mixture was stirred for 1 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 N, 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 aldol (89.6 mg, 94%) as a white powder.

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

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