# Lithium Acetate-catalyzed Crossed Aldol Reaction between Aldehydes and Trimethylsilyl Enolates Generated from Other Aldehydes

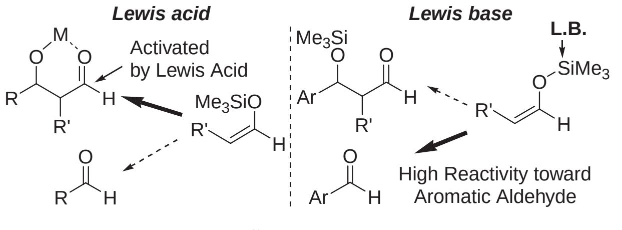
Yoshikazu Kawano,[†,††] Hidehiko Fujisawa,[†,††] and Teruaki Mukaiyama*[†,††]
[†]*Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003*
[††]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641*

(Received February 3, 2005; CL-050156)

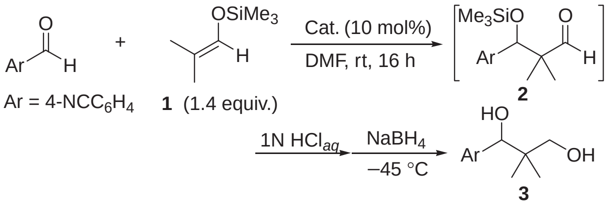
Crossed aldol reaction between aromatic aldehydes having an electron-withdrawing group and trimethylsilyl enolates generated from several aldehydes proceeded smoothly in dry or water-containing DMF in the presence of a catalytic amount of a Lewis base such as lithium acetate or lithium benzoate. Successive reduction of the produced aldehydes with sodium borohydride ($NaBH_4$) afforded the corresponding 1,3-diols in good to high yields in one-pot.

Aldol reaction is one of most important and useful tools for the carbon–carbon bond formation in synthetic organic chemistry. It is mostly carried out between carbonyl compounds and enolates generated from a ketone, ester, or amide. However, only a few examples have been reported on the crossed-aldol reaction between an aldehyde and an enolate derived from various other aldehydes.[1] The crossed aldol reactions by using Lewis acidic-metal enolates such as titanium enolates generated from aldehydes were independently reported by Mahrwald[2a–c] and Oshima.[2d,e] There are a few reports on the aldol reactions by using a catalytic amount of an activator; for example, MacMillan et al. reported a direct catalytic crossed-aldol reaction of aldehydes by using L-proline as a catalyst.[4] Denmark et al. described the reaction using Lewis acidic-trichlorosilyl enolates of aldehydes in the presence of a phosphoramide as a Lewis base catalyst.[3] However, the catalytic aldol reaction of an aldehyde enolate by using a commonly employed silyl enolate such as TMS enolate is not yet reported since the produced aldehyde is very reactive to form an adduct faster than a starting aldehyde in the presence of a Lewis acid (Scheme 1).

In our previous papers, it was reported that lithium 2-pyrrolidone or lithium acetate (AcOLi) was an effective Lewis base catalyst for the activation of trimethylsilyl (TMS) enolate in aldol reaction.[5] In order to extent the utilities of this reaction, aldol reaction by using silyl enolates of aldehydes in the presence of a catalytic amount of a Lewis base was attempted. The advantages of a Lewis base catalyst for this reaction are considered as follows: i) silylation of the formed lithium aldolate takes place rapidly to form *O*-silyl ether that is not activated by a lithium cation. ii) In the case when aromatic aldehyde was employed, the reactivities between starting aldehydes and the formed aliphatic aldehydes are differentiated since Lewis base catalyzed reaction occasionally exhibits the higher reactivity toward aromatic aldehyde than that of aliphatic one. iii) Formation of $\alpha,\beta$-unsaturated carbonyl compounds by successive dehydration of the aldol adducts is prevented when weak Lewis base catalysts such as AcOLi are used. In this communication, we would like to report on the crossed aldol reaction between aldehydes and TMS enolates generated from other aldehydes in the presence of AcOLi.



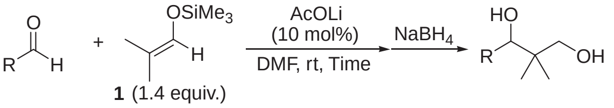
Scheme 1.



Yield of **3** : AcOLi (90), $PhCO_2Li$ (91), $CF_3CO_2Li$ (29), $CF_3SO_3Li$ (27), AcONa (86), AcOK (85), AcON*n*-$Bu_4$ (93), AcON*n*-$Bu_4$ (81[a])
[a]Reaction was carried out in THF.

Scheme 2.

**Table 1.** AcOLi-catalyzed aldol reaction of various aldehydes



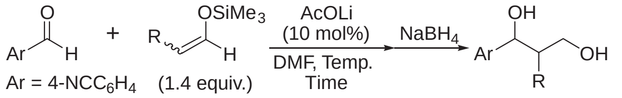
| Entry | R | Time /h | Yield[a] /% | Entry | R | Time /h | Yield[a] /% |
|---|---|---|---|---|---|---|---|
| 1 | 4-$MeOC_6H_4$ | 41 | trace[b] | 6 | 4-$MeO_2CC_6H_4$ | 16 | 83 |
| 2 | $C_6H_5$ | 40 | 40[b] | 7 | 4-$NO_2C_6H_4$ | 16 | 87 |
| 3 | 4-$ClC_6H_4$ | 40 | 76[b] | 8 | 2-Furyl | 16 | 73 |
| 4 | 4-$NCC_6H_4$ | 16 | 90 | 9 | 2-Quinolyl | 17 | 83 |
| 5 | 4-$CF_3C_6H_4$ | 16 | 87 | 10 | $PhCH_2CH_2$ | 41 | 24[c] |

[a]Yield was determined by $^1H$ NMR analysis (270 MHz) using $Cl_2HCCHCl_2$ as an internal standard. [b]2.0 equiv. of **1** were used. [c]Isolated yield.

In the first place, the reaction of 4-cyanobenzaldehyde and TMS enolate **1** derived from 2-methylpropionaldehyde was tried in the presence of 10 mol % of AcOLi at room temperature in DMF and the successive reduction of the formed aldehyde with $NaBH_4$ in situ gave the corresponding 1,3-diol in 90% yield.[6] Next, the effects of various lithium carboxylates or sulfonates were examined as shown in Scheme 2. The acetate and benzoate anions turned out to be effective promoters for the acceleration of this reaction. The acetates having such counter cations as sodium, potassium or ammonium ion also worked effectively and the desired 1,3-diols were obtained in good yields. Also, the reaction was performed smoothly in THF by using AcON*n*-$Bu_4$ as a catalyst. In all cases, the products were isolated and analyzed as 1,3-diols after the reduction of thus formed aldehydes with $NaBH_4$ because the 3-hydroxyaldehydes are unstable and decomposed rapidly.[3]

Next, the reaction of TMS enolate **1** with various aldehydes was tried by using AcOLi in DMF (Table 1). Aromatic aldehydes having electron-donating groups or aliphatic aldehydes afforded the corresponding 1,3-diols in low yields (Entries 1, 2, and 10). On the other hand, when the aromatic aldehydes having electron-withdrawing groups were used as acceptors, the reactions proceeded smoothly and the corresponding 1,3-diols were afforded in good yields (Entries 3–9). It is noteworthy to point out that the corresponding 1,3-diol was also obtained in good yield when an aldehyde having a basic function in the same molecule was used (Entry 9).

**Table 2.** Aldol reaction using various silyl enolates



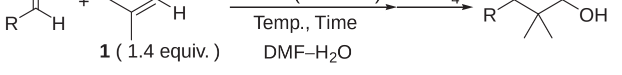
| Entry | R | Temp./°C | Time/h | Yield[a]/% | *syn*:*anti*[b] |
|---|---|---|---|---|---|
| 1 | Me ($E$:$Z$ = 1:4) | 0 | 16 | 84 | 57:43 |
| 2 | Et ($E$:$Z$ = 1:3) | 0 | 17 | 82 | 51:49 |
| 3 | Bn ($E$:$Z$ = 1:2) | 0 | 17 | 87 | 50:50 |
| 4 | *i*-Pr ($E$:$Z$ = 1:4) | 0 | 16 | 72 | 33:67 |
| 5 | H | −45 | 16 | 79 | — |

[a] Yield was determined by $^1H$ NMR analysis (270 MHz) using $Cl_2HC$-$CHCl_2$ as an internal standard. [b] Determined by $^1H$ NMR analysis (270 MHz).

The lithium acetate-catalyzed aldol reaction was further examined by using various silyl enolates (Table 2). The reactions proceeded smoothly at 0 °C in DMF to afford the corresponding 1,3-diols in good yields while the diastereoselectivities were low (Entries 1–4). Interestingly, when vinyloxytrimethylsilane giving highly reactive primary aldehyde was employed, the reaction proceeded smoothly at −45 °C without accompanying any byproducts (Entry 5).

It was reported that the acetate anion worked as an effective catalyst of aldol reaction in water-containing organic solvent. However, the reaction by using silyl enolate derived from an aldehyde has not been tried in aqueous media yet. Then, reaction in water-containing DMF was tried and it was found that the yield of 1,3-diols increased a little more than that in dry DMF (Table 3). When the reactions were carried out in DMF–$H_2O$ (50:1) and the following by reduction afforded the corresponding 1,3-diols in high yields (Entries 1–3 and 6). The reaction proceeded to afford the adduct in a moderate yield even when the reaction was carried out in DMF–$H_2O$ (2:1) (Entry 5).

**Table 3.** Aldol reaction using AcOLi in DMF–$H_2O$



| Entry | R | DMF:$H_2O$[a] | Temp./°C | Time/h | Yield[b]/% |
|---|---|---|---|---|---|
| 1 | 4-$NCCC_6H_4$ | 50:1 | rt | 16 | 91 |
| 2 | 4-$MeO_2CC_6H_4$ | 50:1 | 0 | 16 | 90 |
| 3 | 4-$NO_2C_6H_4$ | 50:1 | rt | 16 | 94 |
| 4 | 4-$NO_2C_6H_4$ | 5:1 | rt | 16 | 95[c] |
| 5 | 4-$NO_2C_6H_4$ | 2:1 | rt | 16 | 58[c] |
| 6 | 2-Quinolyl | 50:1 | 0 | 17 | 87 |

[a] Volume ratio. [b] Yield was determined by $^1H$ NMR analysis (270 MHz) using $Cl_2HCCHCl_2$ as an internal standard. [c] 2.0 equiv. of **1** were used.

Thus, it is noted that the AcOLi-catalyzed aldol reaction using TMS enolates derived from aldehydes proceeded smoothly under weakly basic conditions in dry DMF or water-containing DMF, and the subsequent reduction of the formed aldehydes with $NaBH_4$ afforded the corresponding 1,3-diols in good to high yields. This method is practically applicable for the synthesis of various 1,3-diols in a one-pot procedure. 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 Using Lewis acid: a) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974). b) T. Mukaiyama and T. Inoue, *Chem. Lett.*, **1976**, 559. Via metal enolate: c) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980). d) E. Nakamura, S. Yamago, D. Machii, and I. Kuwajima, *Tetrahedron Lett.*, **29**, 2207 (1988). Via enamine: e) G. Wittig and A. Hesse, *Org. Synth.*, Coll. Vol. **VI**, 526 (1988). f) C. F. Barbas, III, Y.-F. Wang, and C.-H. Wong, *J. Am. Chem. Soc.*, **112**, 2013 (1990). g) H. J. M. Gijsen and C.-H. Wong, *J. Am. Chem. Soc.*, **116**, 8422 (1994).

2 Via titanium enolate: a) R. Mahrwald, B. Costisella, and B. Gündogan, *Tetrahedron Lett.*, **38**, 4543 (1997). b) R. Mahrwald, B. Costisella, and B. Gündogan, *Synthesis*, **1998**, 262. c) R. Mahrwald and B. Gündogan, *Chem. Commun.*, **1998**, 2273. d) K. Yachi, H. Shinokubo, and K. Oshima, *J. Am. Chem. Soc.*, **121**, 9465 (1999). e) Z. Han, H. Yorimitsu, H. Shinokubo, and K. Oshima, *Tetrahedron Lett.*, **41**, 4415 (2000).

3 Catalytic enantioselective crossed aldol reaction: S. E. Denmark and S. K. Ghosh, *Angew. Chem., Int. Ed.*, **40**, 4759 (2001).

4 Direct enantioselective crossed aldol reaction: A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **124**, 6798 (2002).

5 Aldol reaction: 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. Nakagawa, H. Fujisawa, Y. Nagata, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **77**, 1555 (2004). h) H. Fujisawa, T. Nakagawa, and T. Mukaiyama, *Adv. Synth. Catal.*, **346**, 1241 (2004).

6 A typical experimental procedure is as follows (Table 1, Entry 1); to a stirred solution of AcOLi (2.6 mg, 0.04 mmol) in DMF (0.4 mL) were added successively a solution of TMS enolate **1** (80.8 mg, 0.56 mmol) in DMF (0.6 mL) and a solution of 4-cyanobenzaldehyde (52.5 mg, 0.4 mmol) in DMF (1.5 mL) at room temperature. The mixture was stirred for 16 h at room temperature and quenched with aqueous HCl (1.0 M, 0.3 mL) at −45 °C and stirred an additional 1 h. Then saturated aqueous $NaHCO_3$ (0.6 mL), MeOH (2.0 mL) and $NaBH_4$ were added. The reaction mixture was warmed slowly to room temperature and after stirring for 16 h at the same temperature, and it was quenched with saturated aq $NH_4Cl$. The mixture was extracted with EtOAc and organic layer was washed with brine and dried over anhydrous $Na_2SO_4$. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to afford the corresponding 1,3-diol (74.0 mg, 90%) as an colorless oil.

Published on the web (Advance View) March 25, 2005; DOI 10.1246/cl.2005.614