Self-promoted Aldol Reaction between Aldehyde Having Lewis Base Moiety and Trimethylsilyl Enolate

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Self-promoted aldol reaction between aldehydes having Lewis base moieties and trimethylsilyl enolates proceeded smoothly to afford the corresponding aldols in good to high yields. It is noted that various functionalized aldols can be directly obtained without protection of functional groups in the above reaction.

Recently, new Lewis base-catalyzed aldol reactions between trimethylsilyl (TMS) enolates and aldehydes in a N,N-dimethylformamide (DMF) solvent were reported from our laboratory, which afforded the corresponding aldols in high yields by using Lewis bases such as lithium dihydridamide, lithium pyrrolidone or lithium acetate (AcOLi). In addition, an effective aldol reaction was established in water-containing DMF by using AcOLi catalyst. One of the most characteristic points of this reaction is that the aldol having acidic hydrogen such as carboxylic acid smoothly reacted to afford the desired aldol in moderate yield (Eq. 1).

\[
\begin{align*}
RCHO + \overset{\text{Me}_{3}Si}{\overset{\text{O}}{\overset{\text{OSiMe_{3}}}{\text{Me}_{3}Si}}}
\rightarrow \overset{\text{H}}{\overset{\text{O}}{\overset{\text{O}}{\text{R}}}}
\end{align*}
\]

(1.4 equiv.)

In order to improve the yield, this reaction was examined under non-aqueous condition at −45 °C for 3 h. However, the aldol adduct was obtained only in 23 and 35% yields, while 10 and 140 mol% of AcOLi were used, respectively. It was assumed that the proton transfer from 4-formylbenzoic acid to AcOLi took place rapidly to let aldolize 2a behave as Lewis base (Eq 2). The aldol 2a did not effectively activate TMS enolate 1, which was derived from methyl isobutyrate at −45 °C because of its low nucleophilic ability compared to that of AcOLi. The enolate 1 was decomposed by free carboxylic acids before the aldol reaction and thus the yield of this reaction lowered under non-aqueous condition at −45 °C.

\[
\text{HOOC-C}_7\text{H}_5\text{CHO} \xrightarrow{\text{AcOLi}} \text{LiOOC-C}_7\text{H}_5\text{CHO + ACOH}(2)
\]

Next, the aldol reaction between TMS enolate 1 and an equivalent molar amount of 2a was planned. It was considered that the aldol 2a having metallated lithium carboxylate would behave as a Lewis base catalyst and decomposition of 1 would be prevented by using an equivalent molar amount of 2a. From a synthetic point of view, this aldol reaction excels in affording the corresponding aldol without protecting functional groups of various substrates when the metallation is carried out in situ. In this communication, we would like to report on self-promoted aldol reaction between aldehydes having Lewis base moieties and TMS enolates.

In the first place, aldol 2a was generated in situ and its reaction with TMS enolate 1 was tried at −45 °C in DMF. Expectedly, 2a did not effectively activate 1 at −45 °C and the reaction was very slow whereas the aldol adduct was obtained in high yield at −20 °C. On the other hand, the aldol reaction proceeded smoothly at −45 °C to afford the corresponding aldol in high yield when tetrabutylammonium salt 2b was used instead of 2a (Scheme 1).

Scheme 1. Self-promoted aldol reaction between silyl enolate 1 and aldehydes having carboxylic acid salt moieties.

Next, the reactions of TMS enolate 1 with aldehydes having various Lewis base moieties were tried (see Table 1). Similarly, 2-formylbenzoic acid salts 2c and 2d reacted smoothly to afford the corresponding γ-lactones (Entries 1 and 2). When the nucleophilic abilities of anions in aldehydes were higher than that of carboxylate anion, lithium or sodium salts such as 2e–2h activated 1 effectively at −45 °C and the reactions proceeded smoothly to afford the aldol adducts in high yields (Entries 3–6). The most characteristic point of the present reaction is that various functionalized aldols having acetamide, sulfonamide and indole moieties were obtained in high yields by one pot reaction without protecting their functional groups (Entries 4–6).

This aldol reaction can be performed smoothly by using other TMS enolates. For example, TMS enolates derived from S-tert-butyl isobutanethioate and acetophenone afforded the corresponding aldols in good to high yields. Moreover, the present reaction can also be applied to that in water-containing DMF by using 2b and the desired aldol was obtained in good yield (Scheme 2).

The reaction mechanism of the present self-promoted aldol reaction using aldehydes having Lewis base moiety is assumed to proceed by a pathway similar to that of previously reported Lewis base-catalyzed aldol reactions. Namely, Lewis base moieties of the substrates and DMF coordinated to silyl enolates to proceed the reaction via a hexacoordinated hypervalent silicate to afford lithium aldolate. Subsequent silylation of lithium aldo-
Table 1. Aldol reactions using aldehydes having various Lewis Base moieties.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Time /h</th>
<th>R'</th>
<th>Yield /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>CHO</td>
<td>2c 1</td>
<td>NaNH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>99&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>2d 1</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;H</td>
<td>91&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>CHO</td>
<td>2e 1</td>
<td>HO-Ph</td>
<td>94&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>CHO</td>
<td>2f 0.5</td>
<td>AcHN-Ph</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>CHO</td>
<td>2g 0.5</td>
<td>96&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CHO</td>
<td>2h 0.5</td>
<td>PhO&lt;sub&gt;2&lt;/sub&gt;S-Na</td>
<td>93&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were carried out with molar ratio of aldehyde:metallating reagent = 1:0.9:1.4. See refs. 3, 5 and 6 for preparations of Lewis base moieties. <sup>b</sup>Yield was determined by <sup>1</sup>H-NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. <sup>c</sup>Reaction was carried out at -20 °C. <sup>d</sup>Product was obtained as a γ-lactone. <sup>e</sup>Isolated yield. <sup>f</sup>Product was obtained as a silyl ether without carrying out a desilylation step.

Scheme 2. Self-promoted aldol reaction using various silyl enolates.

\[
\begin{align*}
\text{2e} + \text{SiMe}<sub>3</sub>\text{Bu} & \quad \text{DMF, -20 °C, 1 h} \\
\text{H}^+ & \\
\text{2c} + \text{SiMe}<sub>3</sub>\text{Ph} & \quad \text{DMF, rt, 2 h} \\
\text{2b} + \text{OMe} & \quad \text{DMF-H<sub>2</sub>O (Volume ratio 50:1), -45 °C, 2 h} \\
\text{1} & \\
\end{align*}
\]

Scheme 3. Three component coupling reaction.

The reaction by TLC, alklylation was found to proceed smoothly at acetamide moiety and the three-component-coupling product was obtained in high yield, as expected (Scheme 3).

Thus, self-promoted aldol reaction between aldehydes having Lewis base moieties and TMS enolates was established. This method is quite practical to the syntheses of various functionalized aldos as it proceeded conveniently without protecting their functional groups and can be applied to one-pot three-component-coupling reactions. Further development of this reaction is now in progress.

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References and Notes


3. Lithium salt was prepared from carbonyl chloride (0.4 mmol) and lithium ethoxide (freshly prepared from dry EtOH and n-BuLi) (0.36 mmol) in THF. After solvent was removed under reduced pressure, the residue was used without further purification.

4. In the case of aldol reaction between silyl enolate 1 and benzaldehyde in DMF at -19 °C for 1 h, 2 was activated by DMF and the corresponding aldol was obtained in 43% yield without adding any catalyst (See Ref. 1a). The result of present reaction clearly indicates that 2 was activated effectively by 2a in DMF at -20 °C.

5. Tetra-n-butyrammonium salt was prepared by treating carbonyl chloride (0.4 mmol) with methanol solution of tetra-butyrammonium hydroxide (0.36 mmol) in THF. After solvent was removed under reduced pressure, the residue was azeotroped with toluene (1.0 mL, twice) and was used without further purification.

6. Typical experimental procedure is as follows (Table 1, Entry 6: to a stirred suspension of NaH (55% in oil, 15.7 mg, 0.36 mmol) in DMF (0.2 mL) was added a solution of N-(4-formylphenyl)benzenesulfonamide (104.5 mg, 0.4 mmol) in DMF (0.6 mL) at 0 °C and the mixture was stirred for 0.5 h. After the mixture was cooled to -45 °C, a solution of silyl enolate 1 (97.6 mg, 0.56 mmol) in DMF (1.0 mL) was added and the mixture was stirred for 0.5 h at the same temperature. The mixture was quenched with saturated aqueous NH<sub>4</sub>Cl, extracted with EtO<sub>2</sub> 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 EtO<sub>2</sub>. 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 (134.8 mg, 93%) as a white powder.
