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Sequential Mukaiyama–Michael reaction induced by carbon acids

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In the presence of strong carbon acid, sequential Mukaiyama–Michael reaction using two different Michael acceptors proceeded; the reaction of ketene silyl acetal derived from ETOAc with α-pyrones as primal acceptors yielded the corresponding cyclic ketene silyl acetics, which were enough reactive to undergo the following reaction with second acceptors.

Discovery of the Mukaiyama aldol reaction in 1973 has motivated further investigations on organic reactions using silicon enolates such as enol silyl ethers (ESEs) and ketene silyl acetics (KSAs) until today. In particular, sequential reactions using silicon enolates recently attract much attention to construct complex molecular architecture in a one pot manner. For example, Yamamoto reported sequential Mukaiyama aldol reaction using tris(trimethylsilyl)silyl enol ethers (Eqn. 1). In the presence of Tf2NH (Tf = SO2CF3), the reaction of aldehyde with the ESE produced β-silyloxyaldehydes, which could be subjected in one pot to the second Mukaiyama aldol reaction with another ESE. The 1,4-addition of silicon enolates to α,β-unsaturated carbonyls, so-called the Mukaiyama–Michael reaction, is also a fundamental method for C–C bond formation. However, its sequential version using two or more different Michael acceptors is not common (Eqn. 2). The difficulties come from undesired overreactions of the intermediates, which possess both of the nucleophilic ESE or KSA moiety and the electrophilic carbonyl moiety, with the unreacted Michael acceptors or nucleophilic species. If the in situ-generated silicon enolates have higher nucleophilicity than the starting one, competitive polymerization of the Michael acceptor will occur. Actually, group transfer polymerization (GTP) of (meth)acrylic acid esters using KSAs as initiators is a well-established living polymerization technique. In addition, some successful examples of the sequential reactions initiated by the Mukaiyama–Michael reaction suggest that intramolecular trapping of the intermediates is necessary to obtain the desired products.

The (4+2) or (2+2) cycloadditions of silicon (di)enolates with α,β-unsaturated carbonyls are categorized into such reaction systems. Herein we describe that, by using strongly acidic carbon (C=H) acid catalysts, the sequential, one-pot reactions triggered by the Mukaiyama–Michael reaction occur in a controlled manner; the carbon acid nicely promoted the 1,4-addition of a KSA to α,β-unsaturated lactones giving rise to the corresponding cyclic KSA intermediates, which were enough reactive to be engaged in the following the Mukaiyama aldol or Mukaiyama–Michael reaction.

In designing desired sequential reactions triggered by the Mukaiyama–Michael reaction, we referred to the Mayr’s nucleophilicity parameter N as a guiding principle. The N value of A, a KSA derived from butyl acetate, is higher than that of C derived from acetone (Figure 1). More importantly, the value of phenylated derivative B lies midway between A and C. Keeping this in mind, we first examined the reaction of isocoumarin 3a, which was a cyclic analogue of phenyl acrylate, with a KSA 4 derived from ethyl acetate in the presence of triple carbon acid 1a (Eqn. 3). In previous work, the (4+2) or (2+2) cycloadditions of silicon (di)enolates with α,β-unsaturated carbonyls are categorized into such reaction systems. Herein we describe that, by using strongly acidic carbon (C=H) acid catalysts, the sequential, one-pot reactions triggered by the Mukaiyama–Michael reaction occur in a controlled manner; the carbon acid nicely promoted the 1,4-addition of a KSA to α,β-unsaturated lactones giving rise to the corresponding cyclic KSA intermediates, which were enough reactive to be engaged in the following the Mukaiyama aldol or Mukaiyama–Michael reaction.

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this acid demonstrated higher catalytic activity over usual acids such as TfOH and Tf$_2$NH in some C–C bond forming reactions. Upon treatment with 1.2 equiv of the KSA and 1 mol% of 1a at –78 °C, 3a was rapidly consumed to give the Mukaiyama–Michael product 6a in 91% yield after acidic workup. $^1$H NMR analysis revealed quantitative formation of the intermediate 5a before the workup. Similar result was obtained by using zwitterion 213 instead of 1a. Unfortunately, 5,6-dihydro-2H-pyran-2-one just gave a complex mixture and phenyl acrylate did not react with 4.14

Next we tried trapping the in situ-generated KSA 5a with cyclohexanone as the second electrophile (Table 1).15 When the reaction mixture obtained from 3a and 4 was treated with 2.0 equiv of cyclohexanone in a one pot manner, the desired reaction took place to give 3,4-anti product 7a in 99% yield (entry 1). Under similar conditions, lower loading of 1a resulted in selective formation of simple Mukaiyama–Michael product 6a along with recovery of a small amount of 3a (entry 2). This indicated that carbon acid 1a promoted not only initial Mukaiyama–Michael step but also the following Mukaiyama aldol reaction with cyclohexanone. In this case, less acidic zwitterion 2 was ineffective (entry 3). Tf$_2$CHCH$_2$CHTf$_2$, 1b, Tf$_2$CHC$_6$F$_5$, 1c, and Tf$_2$NH could be used, while a considerable amount of 6a was also obtained (entries 4-6). In contrast, TfOH and some Lewis acids such as Ph$_3$P$^+$PF$_6^-$ and TBSOTf did not show acceptable catalysis (entries 7-9).

As shown in Figure 2, under the optimized conditions, cyclopentanone and acetone were found to be excellent as the second electrophile (8a, 87% yield; 9a, 97% yield). Likewise, 2-methylcyclohexanone gave the product 10a in 82% yield as a mixture of two diastereomers in a ratio of 8:1:1.15 Substituted isocoumarins 3b-3e reacted cleanly as the primal electrophile to yield the corresponding products 9b-9e with perfect 3,4-anti selectivity by the trapping with acetone. α-Pyrones 3f and 3g also worked well and the desired products 9f and 9g were isolated in 90% and 87% yields, respectively. Here it should be noted that acid-sensitive vinyl ester moiety of these products were tolerant to acid 1a.

Next, we conducted the reactions with α,β-unsaturated ketones as the second Michael acceptor (Figure 3). Our initial effort using isocoumarin 3a and methyl vinyl ketone, as the primal and second Michael acceptors, respectively, gave the desired product 11a in 59% yield without any overreactions (6a was also isolated in 21% yield). Under the similar conditions, phenyl vinyl ketone was a better reaction partner. For instance, the reaction of 3a, 4, and phenyl vinyl ketone gave the desired 3,4-anti product 12a in 83% yield after desilylation with TfOH. Mesityl oxide also worked as second acceptor to give 13a in 61% yield with the Mukaiyama aldol product (not shown) in 12% yield. By using phenyl vinyl ketone as the second acceptor, the reactions of substituted isocoumarins 3b-3e as the first ones were examined. In all cases, the desired products 12b-12e were isolated in good to excellent yields. Likewise, the sequential reaction of α-pyrones 3f and 3g was successful; the corresponding products 12f and 12g were obtained in 84% and 72% yields, respectively. Cyclic enones were also suitable second Michael acceptors. 5-, 6-, and 7-Membered enones smoothly reacted with KSA 5a generated from 3a

![Diagram](attachment:diagram.png)

Figure 2. Sequential Mukaiyama–Michael/Mukaiyama aldol reaction

Table 1: Effects of acids in sequential Mukaiyama–Michael/Mukaiyama aldol reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid catalyst</th>
<th>Yield (%)</th>
<th>Recovery of 3s (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbon acid 1a</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>2*</td>
<td>Carbon acid 1a</td>
<td>2</td>
<td>68</td>
</tr>
<tr>
<td>3*</td>
<td>Zwitterion 2</td>
<td>4</td>
<td>87</td>
</tr>
<tr>
<td>4*</td>
<td>Tf$_2$CHCH$_2$CHTf$_2$ 1b</td>
<td>87</td>
<td>&lt;5*</td>
</tr>
<tr>
<td>5*</td>
<td>Tf$_2$CHC$_6$F$_5$ 1e</td>
<td>69</td>
<td>11*</td>
</tr>
<tr>
<td>6*</td>
<td>Tf$_2$NH</td>
<td>59</td>
<td>12*</td>
</tr>
<tr>
<td>7</td>
<td>TfOH</td>
<td>0</td>
<td>7*</td>
</tr>
<tr>
<td>8</td>
<td>Ph$_3$P$^+$PF$_6^-$</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td>9</td>
<td>TBSOTf</td>
<td>3</td>
<td>40</td>
</tr>
</tbody>
</table>

*a isolated yield, ^b 0.25 mol% of acid was used, ^c 3 mol% of acid was used, ^d 1.5 mol% of acid was used.

*a Determined by $^1$H NMR of crude mixture.
to be converted to the ketones 14a-16a in excellent yields with moderate to good diastereoselectivity. Under the similar conditions, the sequential Mukaiyama–Michael products 14b-16b were isolated by the reaction of 6-bromoisocoumarin 3b. In these cases using cyclic enones, the perfect 3,4-anti selectivity was preserved and only two diastereomers (3,3'-syn and anti) were obtained.

We also found that the sequential Mukaiyama–Michael reaction nicely proceeded with chromones as the second Michael acceptors (Scheme 1). For example, the reaction of 3a, 4, and chromone itself produced the corresponding ketone 17 in 85% yield as a 1:8:5 mixture of 3,2'-syn- and anti-diastereomers after acidic workup. This diastereoselectivity closely reflected the ratio of the ESE intermediate. Although bromination was forming reaction in a linear fashion using one reactio

Regarding catalytic pathway for the sequential Mukaiyama–Michael reaction, we propose the in situ-generated silicon Lewis acid as a catalytically active species (Figure 4). That is, loosely contact ion pair D is generated by protonation of starting KAS 4 by triple carbon acid 1a and it activates the primal Michael acceptor 3 through O-silylation reaction giving rise to the intermediate E and ethyl acetate. In this context, ion pair D can be depicted as an equivalent of Lewis acid “R3Si+.” Recent theoretical study on the conjugate base [1a]+ of the acid 1a confirmed its unexpected stability through two-point hydrogen bonding between sulfonic oxygens and proximal phenolic hydroxyl groups on the benzene ring. Therefore, it would be unlikely to generate the C-silylated species through further attack of [1a]+ on the silicon atom. The following nucleophile attack of unreacted 4 on E produces the intermediate F. After that, silyl transfer reaction from F, which also works as the “R3Si+” equivalent, to unreacted acceptor 3 results in regeneration of E along with formation of the 1,4-adduct 5 bearing silicon enolate moity.

In the sequential reaction, the second Michael acceptor is activated in a similar way by “R3Si+” equivalents existing in the reaction system. In our case, no overreactions were observed. The present outcome can be rationalized by considering relative nucleophilicity of each silicon enolates. As mentioned above, we carefully chose each Michael acceptors on the basis of the Mayr’s nucleophilicity, which was determined by reaction rate of silicon enolates with stabilized carbocations. To avoid undesired overreactions including the GTP, it is necessary to evaluate the nucleophilicity of each intermediates.
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![Sequential reaction products](image)

**Fig. 4.** Plausible reaction pathway

rigorously. Our results demonstrate that the Mayr’s nucleophilicity $N$ is helpful as a practical guiding principle for such sequential reaction systems. The nucleophilicity of 5, which is generated by the primal Mukaiyama–Michael reaction, is lower than that of starting one 4 (Figure 4). Therefore, relatively faster reaction rate of activated lactone E with 4 over 5 brings about preferential formation of 5. We managed similar reactivity difference in the second Mukaiyama–Michael reaction by using $\alpha,\beta$-unsaturated ketones.

Satisfactory correlation between the nucleophilicity and the reaction outcome in such sequential systems implies that the Michael acceptors, not but the donors, are one-sidedly activated. If $\text{RSi}^+$ equivalents activate the acceptor, at the same time, their counter anions activate the donor through attacking on the silicon atom, we will not find good correlation. Obviously, some features of triple carbon acid 1a, e.g. its low loading and no nucleophilicity of [1a]$^-$, work to suppress undesired overreactions. Unexpected lower catalyst activity of 1a in GTP of methyl methacrylate 19a would support this thing. Our work suggests that one-sided, strong activation of Michael acceptors becomes a promising approach to such sequential reactions.

In summary, we found that triple carbon acid 1a was remarkably effective for the 1,4-addition chemistry of silicon enolates. The Mukaiyama–Michael reaction of carboxylic acid derivatives is used as an excellent polymerization method producing well-controlled polymers. In contrast, we successfully arranged some different electrophiles in an order by linear, stepwise bond formations without any overreactions; the results presented herein are the first examples for a practical level of sequential Mukaiyama–Michael reaction using two different $\alpha,\beta$-unsaturated carbonyls. The present sequential reactions also provide an effective methodology to make covalent bonds between sterically hindered substrates.

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Notes and references

4. To the best of our knowledge, only one example was reported; by the reaction of KSA, a cyclohexanone derivative, and methyl vinyl ketone, desired product was obtained in low yield due to competitive polymerization of methyl vinyl ketone and undesired overreactions. See: S. Marczak, K. Michalak, Z. Urbaničzyk–Ipikowska, J. Wicha, *J. Org. Chem.* 1998, 63, 2218.
14. In the most successful examples of the Mukaiyama–Michael reaction, $\alpha,\beta$-unsaturated ketones or aldehydes were used as Michael acceptors. The Mukaiyama–Michael reaction with unsaturated esters is limited. See, ref. 5 and cited therein.
18. Under these conditions, 1b rapidly decomposed to give a mixture of Tf$_2$CH$_2$ and Tf$_2$C=CH$_2$. For this reason, this GTP was likely to be triggered by protonation of the KSA by Tf$_2$CH$_2$.