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ABSTRACT
Trimethylsilyl trifluoromethanesulfonate (TMSOTf) and a trialkylamine base promote both in situ enol silane/silyl ketene acetal formation and Mukaiyama aldol addition reactions between a variety of reaction partners in a single reaction flask. Isolation of the required enol silane or silyl ketene acetal is not necessary. For example, crossed aldol reactions between α-disubstituted aldehydes and non-enolizable aldehydes yield β-hydroxy aldehydes in good yield. In a related reaction, the common laboratory solvent ethyl acetate functions as both an enolate precursor and a green reaction solvent. When thioesters are employed as enolate precursors, high yields for additions to non-enolizable aldehydes are routinely observed.

\[ \begin{align*}
\text{R}^1 & = \text{H, alkyl, OR, SR, NR}_2 \\
\text{R}^2 & = \text{H, alkyl} \\
\text{R}^3 & = \text{aryl, alkenyl}
\end{align*} \]
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In memory of Teruaki Mukaiyama (1927-2018)

Keywords: enol silane; Mukaiyama aldol; silyl triflate; aldehyde-aldehyde coupling

The Mukaiyama aldol addition is one of the most powerful carbon-carbon coupling reactions in the field of organic synthesis.1 As first described by Mukaiyama,2 the Lewis acid-catalyzed addition of an enol silanes to an aldehyde (eq 1) remains a subject of scrutiny, both in terms of the development of new variants and in its application to the art of total synthesis.3 The Mukaiyama aldol reaction avoids one of the key weaknesses of traditional aldol chemistry, the reliance on a strong base for the enolization of the nucleophile. Because of its relatively mild reaction conditions, the Mukaiyama aldol reaction has come to be important both in the generation of building blocks for organic synthesis and in complex fragment coupling.

\[ \text{OTMS} \quad \text{H} \quad \text{R} \quad \text{OTMS} \quad \text{R'} \quad \text{TiCl}_4 \rightarrow \text{OTMS} \quad \text{R} \quad \text{O} \quad \text{R'} \quad \text{O} \quad \text{TiCl}_4 \]  

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Consequently, our own work in the field of one-pot enol silane formation-α-substitution reactions is heavily inspired by the work of Mukaiyama. For the past decade, we have studied the ability of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to play two roles in Mukaiyama-like processes: first, as a silylating agent to promote the in situ formation of nucleophilic enol silanes and silyl ketene acetals, and second, to act as a Lewis acid for the activation of electrophiles. Notable precedents for our work include elegant intramolecular aldol addition reactions as designed by Casiraghi4 and Hoye,5 each of which is mediated by a silyl trifluoromethanesulfonate and an amine base. Earlier reports from our laborabory focused on enol silane formation-Mukaiyama aldol reactions of ketones and carboxylic acids with non-enolizable aldehydes to yield β-hydroxy carbonyl products (eq 2).6 Later reports described on related enolate reactions,7 including aldol condensation reactions to form chalcone and cinnamate products.8 We now report a significant expansion of the one-pot enol silane formation-α-substitution system to include crossed aldehyde-aldehyde coupling reactions, aldol reactions of thioester substrates, and the employment of esters as both solvents and enolate precursors.

Crossed aldehyde-aldehyde aldol coupling is an enduring problem in organic synthesis.9,10 Challenges stem from the fact that the two aldehyde reactants and the product, which is also an aldehyde, are all potent electrophiles, which can lead to various undesired side reactions. In order to achieve a selective and high-yielding crossed aldol reaction, each of
the aldehydes present in the reaction mixture must fall into a strictly defined role (Figure 1). That is, only one aldehyde can serve as the enolate precursor; only one aldehyde can serve as the electrophile; and the product aldehyde must be unreactive under the reaction conditions. Moreover, dehydration of the aldol products to yield the α,β-unsaturated carbonyl compound must be avoided.

**Figure 1.** Design of a crossed aldehyde-aldehyde aldol addition reaction

![Diagram](image1)

In the course of our study of the TMSOTf/R₃N system and its ability to promote the addition of indoles to aldehydes, we observed a side reaction wherein isobutyraldehyde was efficiently converted to its enol silane but did not undergo self-aldol reaction. When a solution of this in situ-generated enol silane was treated with benzaldehyde, addition to yield the crossed aldol product occurred. Further additions to the formyl group in the product were not observed. Notably, the trial reaction appears to meet all the criteria for the ideal crossed aldol reaction described in Figure 1. In the observed reaction, the non-enolizable aromatic aldehyde can only play the role of the electrophile (Figure 2). Only the isobutyaldehyde possesses the α hydrogen necessary to achieve enolization, so it must act as the pronucleophile. Finally, the quaternary center at the α carbon in the product renders dehydration impossible, and effectively blocks additional enol silanes from attacking the adjacent formyl group, preventing unwanted oligomerization.

**Figure 2.** Effective crossed aldol system

![Diagram](image2)

A brief survey of the reaction scope for this crossed aldehyde-aldehyde coupling reaction is presented in Table 1. Performance of this reaction in CH₂Cl₂ at 0 °C was optimal for most of the examples studied, including when cyclohexanecarboxaldehyde was employed as pronucleophile. For the electron-rich anisaldehyde, however, room temperature was required for full conversion, and the use of 2,6-lutidine instead of Hunig’s base was found to be slightly superior. In general, the reaction worked well for the addition of α-
disubstituted aldehyde enolates to aromatic aldehydes, but attempted reactions involving additions to aliphatic aldehydes resulted in no conversion to the aldol products. When the α-monosubstituted propionaldehyde was employed as the enolate precursor, it was rapidly consumed but no desired products were observed.

Evidence suggests that α-monosubstituted aldehydes are poor reaction partners for this one-pot enol silane formation-Mukaiyama aldol reaction, which makes α-monosubstituted β-hydroxy aldehyde synthons inaccessible through this method. Indirectly, however, these building blocks are accessible from carboxylic acid esters\textsuperscript{13} or through the Fukuyama reduction of thioesters.\textsuperscript{14} Accordingly, we targeted thioesters as convenient pronucleophiles based on their performance in related reactions under similar conditions.\textsuperscript{7} Our study of these substrates began with a survey of the reactivity of various thioesters with benzaldehyde (Table 2). First, several thioacetates were examined, including various thiophenol derivatives (entries 1-3). A benzyl mercaptan-derived thioester also reacted in superior yield (entry 4). A propionate derivative was also studied, providing product 2e as a mixture of diastereomers in high yield (entry 5). Enolization of this substrate appeared to be significantly less efficient than was the case with thioacetates, however, which may be attributable to increased hindrance at the α carbon. When Hunig’s base was completely replaced by the less hindered Et\textsubscript{3}N, conversion also suffered, possibly because of competing attack by the Et\textsubscript{3}N upon TMSOTf itself. In order to circumvent these difficulties, a catalytic amount of Et\textsubscript{3}N was added to the Hunig’s base in the reaction mixture, which smoothly afforded the desired product.
Table 2. Thioester scope for reactions with benzaldehyde

<table>
<thead>
<tr>
<th>entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>product</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>2a</td>
<td>93</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4-BrPh</td>
<td>H</td>
<td>2b</td>
<td>91</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2-naphthyl</td>
<td>H</td>
<td>2c</td>
<td>86</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>H</td>
<td>2d</td>
<td>96</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>4-MePh</td>
<td>Me</td>
<td>2e</td>
<td>91&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.1:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 1. CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL), thioester (1.00 mmol), i-Pr<sub>2</sub>NEt (1.40 mmol), TMSOTf (1.20 mmol), RCHO (1.10 mmol), rt, 2h. 2. MeOH (10 mL), TFA (2 drops), rt, 5 min.
<sup>b</sup> Isolated yield after chromatography
<sup>c</sup> Diastereoselectivity determined by <sup>1</sup>H NMR spectroscopy.
<sup>d</sup> Both i-Pr<sub>2</sub>NEt (1.20 mmol) and Et<sub>3</sub>N (0.30 mmol) were included in the reaction mixture.

After the establishment of the thioester scope, various non-enolizable aldehydes were treated with a standard thioester, S-phenyl thioacetate, to good effect (Table 3). Both electron-rich and electron-poor benzaldehydes reacted in high yield, as did the sterically encumbered 2-naphthaldehyde. The sensitive heterocycle 2-furanaldehyde also proved amenable to the reaction conditions, and the convenient alkenyl substrate cinnamaldehyde provided an excellent yield of the desired product.

Table 3. Aldehyde scope for reactions with S-phenyl thioacetate

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-(NO&lt;sub&gt;2&lt;/sub&gt;)Ph</td>
<td>2f</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOPh</td>
<td>2g</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>2-naphthyl</td>
<td>2h</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>2-furyl</td>
<td>2i</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>cinnamyl</td>
<td>2j</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 1. CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL), thioester (1.00 mmol), i-Pr<sub>2</sub>NEt (1.40 mmol), TMSOTf (1.20 mmol), RCHO (1.10 mmol), rt, 2h. 2. MeOH (10 mL), TFA (2 drops), rt, 5 min.
<sup>b</sup> Isolated yield after chromatography

Earlier work established that carboxylic acid esters are good substrates for one-pot silyl ketene acetal formation-Mukaiyama aldol reactions in CH<sub>2</sub>Cl<sub>2</sub>. More recently, we became intrigued by the possibility that a ubiquitous ester like ethyl acetate could act as both
solvent and enolate precursor in these reactions. When a solvent-like quantity of ethyl acetate was treated with TMSOTf and Hunig’s base, precipitate formation was observed but no Claisen condensation products were detectible. When benzaldehyde was added to that mixture, successful aldol addition was observed to yield product 3a. Examination of a wide range of benzaldehydes followed, generally resulting in very high yield (Table 4). Somewhat lower yields were observed with the sensitive 2-furanaldehyde, and employment of cyclohexanecarboxaldehyde as a potential electrophile resulted only in conversion to its enol silane.

**Table 4. Aldehyde scope with EtOAc as reactant and solvent**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield (%)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>3a</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>4-(NO₂)Ph</td>
<td>3b</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>4-(CF₃)Ph</td>
<td>3c</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>4-FPh</td>
<td>3d</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>4-BrPh</td>
<td>3e</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>4-MePh</td>
<td>3f</td>
<td>92</td>
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<tr>
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<td>4-MeOPh</td>
<td>3g</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>2-naphthyl</td>
<td>3h</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>2-furyl</td>
<td>3i</td>
<td>63</td>
</tr>
<tr>
<td>10</td>
<td>2-thienyl</td>
<td>3j</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>cinnamyl</td>
<td>3k</td>
<td>80</td>
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<tr>
<td>12</td>
<td>Cy</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

^a Conditions vary by substrate. See Supplementary Data for details.

^b Isolated yield after chromatography

Expansion of this reaction to other enolizable esters followed. Results for isopropyl acetate mirrored those of ethyl acetate, and are illustrated in Table 5. Reactions performed in methyl acetate proved capricious in our hands, but when methyl acetate was employed as an enolate precursor in CH₂Cl₂, the product was provided in good yield. Table 5 also includes a number of other results for related one-pot reactions, including those where tertiary amides have been employed as enolate precursors. Although primary and secondary amides did not yield desired products under these conditions, entries 3-5 demonstrate that tertiary amides are very good substrates. Likewise, expansion of the reaction scope to include the wholly aliphatic ketone pinacolone demonstrates a breadth of scope not previously communicated. Finally, tolerance of strained rings was confirmed when acetylcyclopropane underwent efficient aldol reaction to yield the desired product. Another unsymmetrical aliphatic ketone, 2-butanone, was also suitably reactive under the standard conditions but did not react with satisfactory regio- or stereochemical control, providing a 1:0.7:0.6 mixture of three isomeric products.
Table 5. Reaction of various enolate precursors with benzaldehyde

\[
\begin{array}{cccc}
\text{entry} & \text{R} & \text{solvent} & \text{product} & \text{yield (%)}^b \\
1 & i-\text{PrO} & i-\text{PrOAc} & 3l & 95 \\
2 & \text{MeO} & \text{CH}_2\text{Cl}_2 & 3m & 84 \\
3 & \text{Ph}_2\text{N} & \text{CH}_2\text{Cl}_2 & 4a & 88 \\
4 & \text{Ph(Me)N} & \text{CH}_2\text{Cl}_2 & 4b & 86 \\
5 & \text{N-morpholiny} & \text{CH}_2\text{Cl}_2 & 4c & 81 \\
6 & t-\text{Bu} & \text{CH}_2\text{Cl}_2 & 5a & 72 \\
7 & \text{cyclopropyl} & \text{CH}_2\text{Cl}_2 & 5b & 92 \\
\end{array}
\]

\(^a\) Conditions vary by substrate. See Supplementary Data for details.
\(^b\) Isolated yield after chromatography

In conclusion, in situ formation of silyl ketene acetals or enol silanes with TMSOTf and an amine base provides an opportunity for one pot reactivity when the electrophile is also activated by residual TMSOTf. This report describes the application of this one-pot method to aldol addition additions of aldehydes, thioesters, esters, amides, and ketones to non-enolizable aldehydes. Notable advances include the development of crossed aldehyde-aldehyde coupling, the use of esters as both solvent and reactant, and the employment of thioester substrates.

Acknowledgments
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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at xxx. These data include MOL files and InChiKeys of the most important compounds described in this article.

References


For a similar strategy that results in the dehydration of the aldol adduct, see reference 8.