One-Pot Enol Silane Formation-Mukaiyama Aldol-Type Addition to Dimethyl Acetals Mediated by TMSOTf

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One-Pot Enol Silane Formation-Mukaiyama 
Aldol-Type Addition to Dimethyl Acetals 
Mediated by TMSOTf 

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Various ketones, esters, amides, and thioesters add in high 
yield to dimethyl acetal in the presence of silyl trifluorome-
thanesulphonates and an amine base. Acetals derived from 
aryl, unsaturated, and aliphatic aldehydes are all effective 
substrates. The reaction proceeds in a single reaction flask, 
with no purification of the intermediate enol silane necessary.

The Mukaiyama aldol reaction continues to garner great inter-
est among organic chemists because of its versatility and mild 
reaction conditions.1 We recently reported a modification of 
the Mukaiyama aldol reaction wherein the requisite enol silane for-
mation was achieved in situ, achieving high yields with nonenoliz-
able aldehyde acceptors (eq 1).2 The key to this process was the 
ability of a silyl trifluoromethanesulphonate to act as both a silylat-
ing agent and a Lewis acid catalyst. To further expand the scope 
of this reaction to include enolizable aldehyde surrogates, we 
turned to dimethyl acetal electrophiles. We now report the 
successful development of a one-pot enol silane formation-
Mukaiyama aldol-type addition to dimethyl acetal, where tri-
 methylsilyl trifluoromethanesulphonate (TMSOTf) acts as both a 
silylating agent and a Lewis acidic activator of the acetal 
electrophile.3

In the course of our study of the in situ enol silane formation-
Mukaiyama aldol reaction, we discovered that enolizable alde-
hydes were incompatible with the reaction conditions, presum-
ably because enolization of the aldehyde electrophile competed 
with the desired ketone enolization. We speculated that if the 
effective concentration of the enolizable electrophile could be 
lowered, this competition could be greatly reduced. Alterna-
tively, a highly electrophilic aldehyde surrogate might prefer enol 
silane addition over enolization. Accordingly, we began to 
explore the catalytic activation of dimethyl acetals as a 
source of oxocarbenium ions, a class of electrophiles well 
documented to undergo Mukaiyama-type addition.3 As a proof 
of principle, we first investigated the addition of acetophenone 
to benzaldehyde dimethyl acetal. We were gratified to find that 
in the presence of 1.2 equiv of TMSOTf and 1.2 equiv of i-Pr2-
NEt, aldol-type addition occurs in exceptional yield in less than 
2 h (eq 2).

Based on our previous work with the Mukaiyama aldol 
reaction,2 we hypothesize that the mechanism involves the in 
situ formation of an enol silane derived from acetophenone, 
effecting stoichiometric amounts of TMSOTf and i-Pr2NEt (Scheme 1). The remaining unreacted TMSOTf then activates 
the dimethyl acetal, leading to the formation of a highly 
electrophilic oxocarbenium intermediate.4 Mukaiyama-type ad-
dition of the enol silane to the oxocarbenium ion, followed by 
silicon transfer to another acetal, provides the product. Although 
a stoichiometric amount of silylating agent is necessary to 
produce the enol silane, the carbon—carbon bond-forming event 
is catalytic in TMSOTf.6b

Table 1 shows the addition reactions of acetophenone and a 
wide range of acetal electrophiles, including acetals derived from 
enolizable aldehydes. As evidenced by entry 1, addition may 
be mediated by either TMSOTf or triethylsilyl trifluoromethane-
sulphonate (TESOTf) with comparable yield. Electron-rich aro-
matic acetals react extremely well (entry 2).5 Several other 
and heteroaromatic substrates were excellent electrophiles (entries 3–5). Importantly, versatile styrenyl product 6 
was synthesized in near-quantitative yield.6 Although enolizable 
aldol-type aldehydes were completely incompatible with our original aldol 
conditions, we were gratified to find that their acetal derivatives 
were outstanding substrates (entries 7–9). These results, which 
include the extremely unhindered and enolization-prone acetal-
dehyde dimethyl acetal, greatly expand the scope of our in situ 
enol silane formation strategy. Finally, even relatively unreactive 
dimethoxy methane provided good yield of the addition product 
(entry 10). Despite this success with acetals, ketal electrophiles 

96, 7503–7509. For a review, see: (b) Carreira, E. M. In Comprehensive 
Asymmetric Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; 
Springer-Verlag: Berlin, Germany, 1999; Vol. 3, pp 997–1065. For more 
recent examples, see: (c) Rech, J. C.; Floreancig, P. E. Org. Lett. 2005, 7, 
(2) (a) Downey, C. W.; Johnson, M. W. Tetrahedron Lett. 2007, 48, 
3559–3562. For intramolecular precursors for this reaction, see: (b) Hoye, 
T. R.; Dvorinikovs, V.; Sizova, E. Org. Lett. 2006, 8, 5191–5194. (c) Rassu, 
8075.
derived from acetone and cyclohexanone provided no desired product under similar reaction conditions. In addition to dimethyl acetals, other acetal electrophiles were examined in the course of this study. When 2-methoxy pyran was subjected to the reaction conditions, a glycosidation-type reaction occurred in 48% yield (eq 3). Analysis of the unpurified reaction mixture by $^1$H NMR spectroscopy revealed multiple unidentified side products, perhaps due to competing enolization of the cyclic oxocarbenium intermediate. Side products also complicated initial attempts to add acetophenone to the diethyl acetal of acetaldehyde. Fortunately, the use of mildly basic 2,6-lutidine suppressed the side reactions for this case, possibly by inhibiting competitive deprotonation of the oxocarbenium intermediate (eq 4).

Concurrent with the investigation of various acetal reaction partners, we probed the ability of a range of enolate precursors to add to benzaldehyde dimethyl acetal under similar reaction conditions (Table 2). As expected, aromatic methyl ketones reacted exceptionally well, providing high yields of $\beta$-methoxy

**TABLE 1.** Addition of Acetophenone to Various Dimethyl Acetals

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>1</td>
<td>99 (98)$^b$</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>2</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
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<td>4</td>
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<td>99</td>
</tr>
<tr>
<td>6</td>
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</tr>
<tr>
<td>9</td>
<td>12</td>
<td>9</td>
<td>90</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield after chromatography. $^b$ Reaction performed with TESOTf instead of TMSOTf. $^c$ See the Supporting Information for experimental procedures.

**TABLE 2.** Addition of Various Substrates to Benzaldehyde Dimethyl Acetal

<table>
<thead>
<tr>
<th>entry</th>
<th>RCOMe</th>
<th>product</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>11</td>
<td>48% yield</td>
</tr>
<tr>
<td>2</td>
<td>PhEt</td>
<td>12</td>
<td>88% yield</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield after chromatography. $^b$ TESOTf was used instead of TMSOTf. $^c$ Product contaminated with <5% starting amide. $^d$ See the Supporting Information for experimental procedures.
ketones (entries 1–3). Attempts to employ alkyl–alkyl ketones as nucleophiles resulted in many side reactions and intractable product mixtures. Ester substrates generally suffered from poor yields when TMSOTf was employed as the silylating agent; analysis of the reaction mixture suggested that the β-methoxy group in the product was being eliminated to yield a cinnamate ester. Similarly, N,N-diphenylacetamide suffered from low conversion, and the product was chromatographically inseparable from the starting material (entry 5). Furthermore, when one of the phenyl groups on the amide was removed, the resultant secondary amide underwent N-alkylation rather than aldol-type addition (eq 5).

Given the success of this one-pot addition procedure with simple nucleophiles, we next investigated the diastereoselectivity of the reaction. Propiophenone was reacted with both benzaldehyde dimethyl acetal and acetaldehyde dimethyl acetal. The yield for both reactions was 82%, with a modest but promising syn:anti ratios of 3.1:1 and 3.7:1, respectively (eq 6).

In conclusion, the use of dimethyl acetal electrophiles has expanded the scope of our one-pot enol silane formation-Mukaiyama aldol process to include aliphatic aldehyde surrogates. A wide range of dimethyl acetals is compatible with the reaction conditions. Future work in this area includes the use of chiral auxiliaries to achieve greater control of the stereochemical outcome of these promising reactions.

### Experimental Section


To an oven-dried 10 mL round-bottomed flask under N₂ was added CH₂Cl₂ (2.5 mL). The flask was cooled to 0 °C, and acetophenone

(10) Analysis by 500 MHz ¹H NMR suggests that enolization of ester and amide substrates is slow under the reaction conditions, typically less than 10% after 15 min at ambient temperature. In contrast, conversion of aromatic ketones to enol silanes under identical conditions is >90% complete after 15 min.

(11) Product structure assigned on the basis of ¹H NMR spectrum. No yield was determined. Methoxymethyl protection of amides is known to occur under similar conditions. For example, see: Szmigielśki, R.; Danikiewicz, W. Synlett 2003, 372–376.

(12) Assignment of relative stereochemistry for product 26 is based on literature precedent (ref 3b). Assignment for product 27 is by analogy.

(117 μL, 1.00 mmol), i-Pr2NEt (210 μL, 1.21 mmol), and TMSOTf (217 μL, 1.20 mmol) were added sequentially. After 15 min, benzaldehyde dimethyl acetal (210 μL, 1.40 mmol) was added, and the reaction was removed from the ice bath and allowed to warm to room temperature. After 2 h, the reaction mixture was filtered through a plug of silica (2 cm × 5 cm) with Et2O, and the solvent was removed by rotary evaporation. Silica gel chromatography (2–10% EtOAc/Hexanes) provided the product as a colorless oil (99% yield): IR (film) 3055, 3023, 2925, 2822, 1681, 1595, 1459, 1356, 1269, 1198, 1095, 992, 749, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) ð 8.00–7.95 (m, 2H), 7.59–7.55 (m, 1H), 7.49–7.37 (m, 6H), 7.35–7.30 (m, 1H), 4.91 (dd, J = 4.5, 8.6 Hz, 1H), 3.62 (dd, J = 8.5, 16.8 Hz, 1H), 3.26 (s, 3H), 3.41 (dd, J = 4.4, 16.2 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) ð 197.7, 141.5, 137.3, 133.1, 128.6, 128.5, 128.2, 127.9, 126.1, 79.6, 56.9, 47.2; HRMS (ESI): Exact mass calcd for C₁₆H₁₆O₂Na [M + Na]⁺, 263.1043. Found 263.1040.

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Supporting Information Available: Experimental procedures, compound characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.