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C. Wade Downey

University of Richmond, wdowney@richmond.edu

Miles W. Johnson

Kathryn J. Tracy

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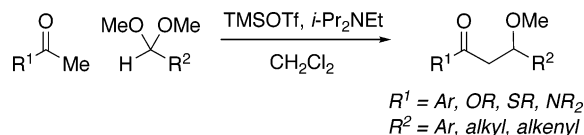
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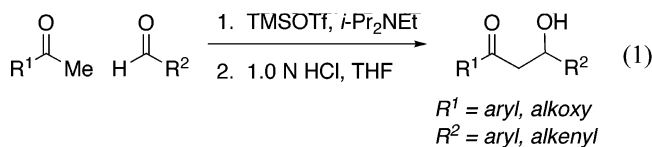
One-Pot Enol Silane Formation-Mukaiyama Aldol-Type Addition to Dimethyl Acetals Mediated by TMSOTf

C. Wade Downey,* Miles W. Johnson, and Kathryn J. Tracy
 Gottwald Center for the Sciences, University of Richmond,
 Richmond, Virginia 23173
 wdowney@richmond.edu
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Various ketones, esters, amides, and thioesters add in high yield to dimethyl acetals in the presence of silyl trifluoromethanesulfonates 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.

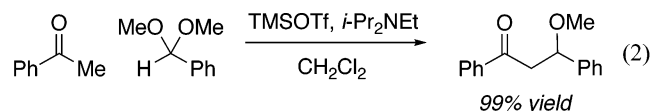
The Mukaiyama aldol reaction continues to garner great interest among organic chemists because of its versatility and mild reaction conditions.¹ We recently reported a modification of the Mukaiyama aldol reaction wherein the requisite enol silane formation was achieved in situ, achieving high yields with nonenolizable aldehyde acceptors (eq 1).² The key to this process was the



ability of a silyl trifluoromethanesulfonate to act as both a silylating 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 acetals, where trimethylsilyl trifluoromethanesulfonate (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 aldehydes 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. Alternatively, a highly electrophilic aldehyde surrogate might prefer enol silane addition over enolization. Accordingly, we began to examine 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*-Pr₂NEt, 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, effected by 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 addition 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.^{3a,b}

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 trifluoromethanesulfonate (TESOTf) with comparable yield. Electron-rich aromatic acetals react extremely well (entry 2).⁵ Several other aromatic and heteroaromatic substrates were excellent electrophiles (entries 3–5). Importantly, versatile styrenyl product **6** was synthesized in near-quantitative yield.⁶ Although enolizable 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 acetaldehyde 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

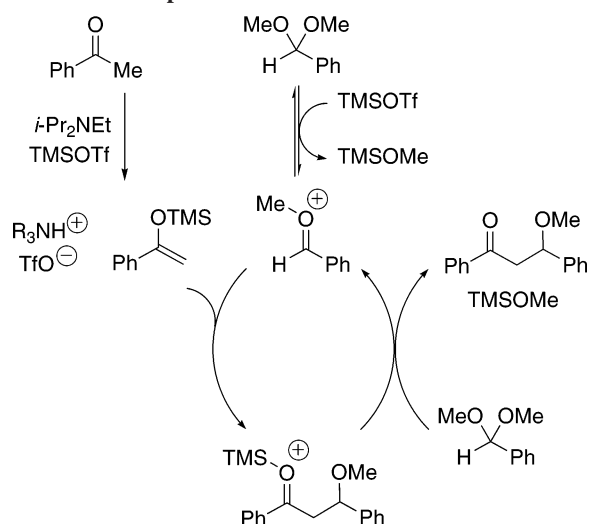
(3) For the use of silyl trifluoromethanesulfonates as Lewis acids in Mukaiyama-type addition to acetals, see: (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248–3249. (b) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259–4275. For a strategy similar to the one reported here, but with a boron Lewis acid, see: (c) Li, L.-S.; Das, S.; Sinha, S. C. *Org. Lett.* **2004**, *6*, 127–130.

(4) Similar conditions (TESOTf/2,6-lutidine) have been used to convert symmetric acetals to mixed acetals via a similar oxocarbenium intermediate. See: Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930–5938.

(5) Synthesis of the dimethyl acetal derived from *p*-nitrobenzaldehyde proved nontrivial, preventing its inclusion in this study.

(6) Styrenyl bonds are easily cleaved by ozonolysis to yield an aldehyde. For example, see: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.

SCHEME 1. Proposed Mechanistic Scheme

TABLE 1. Addition of Acetophenone to Various Dimethyl Acetals^c

entry	R	product	yield (%) ^a
1	X=H	1	99 (98) ^b
2	X=OMe	2	99
3		3	88
4		4	95
5		5	99
6		6	99
7		7	91
8	Me	8	89
9	Et	9	90
10	H	10	76

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

derived from acetone and cyclohexanone provided no desired product under similar reaction conditions.⁷

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

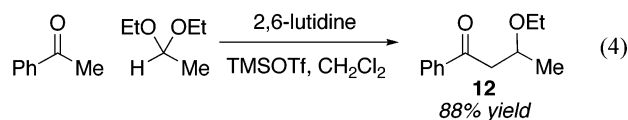
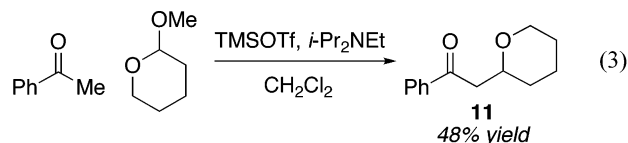
(7) Ketals were generally converted to enol ethers under the reaction conditions.

TABLE 2. Addition of Various Substrates to Benzaldehyde Dimethyl Acetal^d

entry	RCOMe	product	yield (%) ^a
1		1	99
2		13	96
3		14	94
4		15	81 ^b
5		16	76 ^b
6		17	80 ^c
7		18	94
8		19	84

^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.

occurred in 48% yield (eq 3). Analysis of the unpurified reaction mixture by ¹H 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 β -methoxy

TABLE 3. Addition of Various Substrates to Acetaldehyde Dimethyl Acetal^c

entry	R-COMe	product	yield (%) ^a
1		8	89
2		20	95
3		21	94
4		22	0
5		23	47 ^b
6		24	81
7		25	71

^a Isolated yield after chromatography. ^b Conversion as determined by 500 MHz ¹H NMR spectroscopy. ^c 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.⁸ Furthermore, elimination was observed when the ethyl acetate-derived product was resubjected to the reaction conditions. Fortunately, when TMSOTf was replaced with the bulkier TESOTf, the elimination reaction was suppressed (entries 4 and 5).

As shown in entry 6, diphenylamide product **17** was formed in good yield but was inseparable from trace amounts of the starting material. Thioesters performed very well in the reaction, providing convenient building blocks in excellent yield (entries 7 and 8).⁹

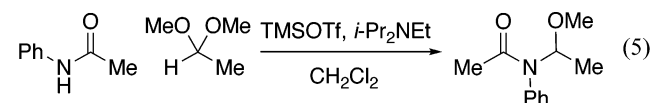
Upon completion of the benzaldehyde dimethyl acetal study, we turned to a representative and challenging substrate derived from an enolizable aldehyde, acetaldehyde dimethyl acetal

(8) β -Methoxy carbonyl compounds are known to undergo elimination under Lewis acidic conditions. See: Ramirez, F.; Rubin, M. B. *J. Am. Chem. Soc.* **1955**, *77*, 2905–2907.

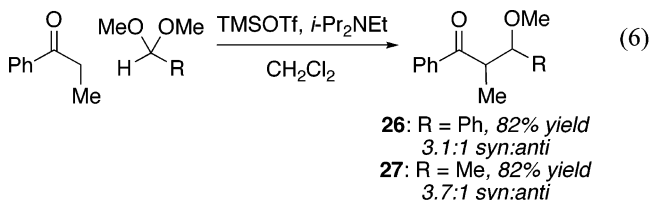
(9) For an example of a thioester aldol adduct used as a building block in the asymmetric total synthesis of pectenotoxin, see: Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4573–4576. For the direct conversion of thioesters to aldehydes by Fukuyama reduction, see: Fukuyama, T.; Lin, S.-L.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051.

(Table 3). Again, aromatic methyl ketones provided aldol-type products in high yields (entries 1–3), even though the elimination of β -methoxy adduct **20** in the presence of Lewis acids is precedented.⁸ Indeed, preliminary results indicated that if more than a 1% excess of TMSOTf relative to *i*-Pr₂NEt was present in the reaction mixture, elimination of the methoxy group became a competing reaction.

Although thioester substrates again performed well (entries 6 and 7), the less acidic ester and amide substrates proved problematic when used in conjunction with acetaldehyde dimethyl acetal. No conversion to the desired product was observed with ester nucleophiles, probably due to competing enolization of the acetal-derived oxocarbenium ion (entry 4). Similarly, *N,N*-diphenylacetamide suffered from low conversion, and the product was chromatographically inseparable from the starting material (entry 5).¹⁰ 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).¹¹



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).¹²



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

Typical Procedure for One-Pot Enol Silane-Formation Mukaiyama Aldol-Type Addition. Synthesis of Product 1.¹³ 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: Szmigielski, 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.

(13) For a literature synthesis of product **1**, see: Torii, S.; Inokuchi, T.; Takagishi, S.; Horike, H.; Kuroda, H.; Uneyama, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2173–2188.

(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 \times 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, 748, 699 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 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) δ 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>.

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