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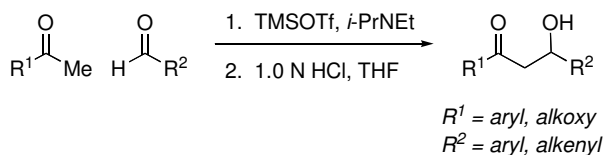
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# A Tandem Enol Silane Formation-Mukaiyama Aldol Reaction Mediated by TMSOTf

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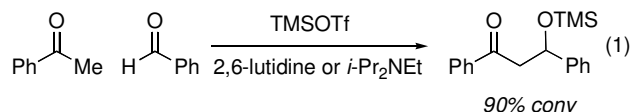
**Abstract** A slight excess of silyl trifluoromethanesulfonate mediates a tandem enol silane formation-Mukaiyama aldol reaction in the presence of Hunig's base. Preformation of the enol silane is unnecessary for efficient reactions, which proceed in 75-97% yield for the addition of aryl methyl ketones and acetate esters to non-enolizable aldehydes. Mechanistic data suggests that free amine is crucial for full conversion.

**Keywords:** Mukaiyama aldol; silyl triflate; silyl trifluoromethanesulfonate; enol silane.

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The Mukaiyama aldol reaction<sup>i</sup> has become an important tool in organic synthesis in recent decades,<sup>ii</sup> displaying utility in both fragment coupling<sup>iii</sup> and building block construction.<sup>iv</sup> One drawback, however, is the necessity of preforming the requisite enol silane nucleophile. Furthermore, cationic silicon species generated under the reaction conditions may interfere with stereoselective Mukaiyama aldol processes mediated by exogenous Lewis acids.<sup>v</sup> In our efforts to address these problems, we have discovered that under specific reaction conditions TMSOTf acts as both a silylating agent and a Lewis acid, thus mediating a tandem enol silane formation-Mukaiyama aldol reaction, which obviates the need for preformation and purification of the enol silane.

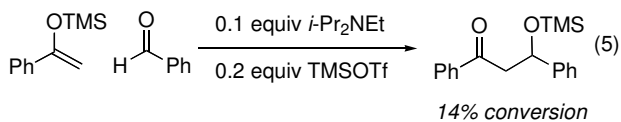
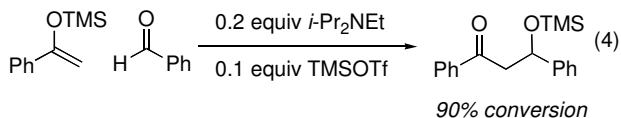
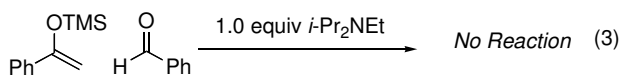
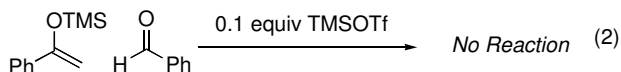
Our efforts to develop a direct aldol reaction of ester and ketone enolates led us to the investigation of a number of metal catalysts in the presence of TMSOTf and an amine base.<sup>vi</sup> After the identification of a promising reaction, we were surprised when control experiments indicated that the reaction occurred even in the absence of a metal catalyst (eq 1).<sup>vii</sup> Given the reaction conditions, we suspected that a Mukaiyama aldol pathway was a likely possibility, wherein the requisite enol silane nucleophile was formed in situ. Subsequent Mukaiyama aldol addition, catalyzed by a small amount of unreacted TMSOTf, might then explain the observed product.



Literature accounts of the ability of silyl trifluoromethanesulfonates to mediate Mukaiyama-type reactions are somewhat conflicting. Pioneering work by Noyori in 1980 described the use of TMSOTf to catalyze the addition of enol silanes to dimethyl acetals, but no reaction was observed with aldehyde electrophiles.<sup>viii</sup> A

decade later, Hanaoka reported that TMSOTf cleanly catalyzes the addition of acetophenone enol silane to benzaldehyde under conditions seemingly identical to those employed by Noyori.<sup>ix</sup> Likewise, Bosnich observed that TMSOTf was a very effective catalyst in the presence of tetrabutylammonium trifluoromethanesulfonate.<sup>v</sup> We set out to clarify this ambiguity via a mechanistic investigation of our own system, with the goal of providing synthetic chemists with a predictive model for avoiding competitive catalysis by adventitious cationic silicon during Mukaiyama aldol reactions.

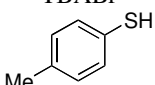
To this end, the putative acetophenone enol silane intermediate was independently synthesized and purified.<sup>x</sup> Treatment of this enol silane with benzaldehyde and 0.1 equiv TMSOTf in methylene chloride provided no aldol product, as suggested by Noyori's experiments (eq 2). Confronted by the apparent inadequacy of TMSOTf to act as a Lewis acid, we turned to the possibility that Hunig's base might act as a catalytic Lewis base under our reaction conditions, activating the nucleophile by attack upon the silicon atom of the enol silane.<sup>xi</sup> Treatment of the enol silane and benzaldehyde with Hunig's base, however, also provided no product (eq 3). Based on these results, we chose to add catalytic amounts of both TMSOTf (0.1 equiv) and Hunig's base (0.2 equiv) to the same reaction mixture, which afforded >90% conversion of the enol silane to the silylated aldol product (eq 4). Interestingly, when 0.2 equiv TMSOTf and 0.1 equiv Hunig's base were employed, only low conversion was observed (14%).<sup>xii</sup>



It is clear from these experiments that catalytic quantities of both TMSOTf and an amine base are necessary for high conversion to the Mukaiyama aldol adduct. Furthermore, an excess of Hunig's base in comparison to TMSOTf greatly increases the efficacy of the reaction conditions. Based on these findings, we suggest that TMSOTf alone is not capable of interfering with the stereoselectivity of chiral Lewis acids in Mukaiyama aldol reactions, *but in the presence of a weakly nucleophilic Lewis base, cationic silicon is a highly active achiral Mukaiyama aldol catalyst.* This data is of tremendous value to the organic chemist for whom high stereoselectivity is a paramount goal in complex fragment coupling reactions, the formation of chiral building blocks, or other related processes.

Although it is apparent that both TMSOTf and an amine must be present, the exact role of Hunig's base is not entirely clear. In the absence of aldehyde, acetophenone is converted to the enol silane as expected, regardless of whether TMSOTf or Hunig's base is in excess. Even when aldehyde is in the reaction mixture, *no aldol products are observed unless an excess of Hunig's base in comparison to TMSOTf is present*, although that excess may be as little as 0.1 equiv. It has not been determined whether this additional amine acts as a silyl transfer catalyst, as a nucleophilic activator of the enol silane, or as a nucleophilic activator of TMSOTf. In each of these scenarios, however, the amine must act as a Lewis base, which prompted us to survey the effects of other potential Lewis basic catalysts upon the TMSOTf-catalyzed Mukaiyama aldol reaction (Table 1).

**Table 1.** Nucleophilic Additives in the Mukaiyama Aldol Reaction<sup>a</sup>

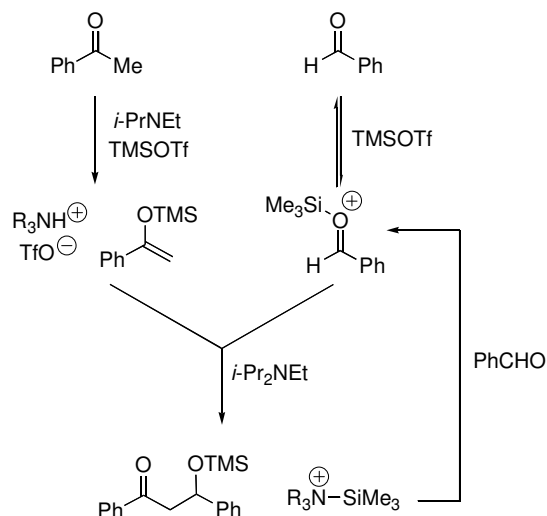
entry	Nucleophile	conversion (%) <sup>b</sup>
1	<i>i</i> -Pr <sub>2</sub> NEt	90
2	2,6-lutidine	71
3	Et <sub>3</sub> N	6
4	imidazole	<5
5	Ph <sub>3</sub> P	<5
6	TBAI	52
7	TBABr	6
8		0

<sup>a</sup>Reaction conditions: acetophenone enol silane (1 equiv), aldehyde (1.4 equiv), TMSOTf (0.1 equiv), nucleophile (0.2 equiv), CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), 0 °C to rt, 24 h.

<sup>b</sup>Conversion calculated by <sup>1</sup>H NMR spectroscopic analysis. No further reaction was observed after 24 h.

As expected, the two amine bases that mediate the tandem enol silane formation-Mukaiyama aldol reaction also are active catalysts for the TMSOTf-catalyzed Mukaiyama aldol (Table 1, entries 1 and 2). In contrast, strongly nucleophilic amines such as triethylamine and imidazole provided low conversion to the Mukaiyama aldol adduct (entries 3 and 4). We speculate that these amines react irreversibly with TMSOTf to form a nucleophile-TMS salt, removing the silicon catalyst from the reaction mixture. The same trend was observed when non-nitrogen nucleophiles were tested (entries 5-8); only the very weakly nucleophilic tetrabutylammonium iodide (TBAI) provided a conversion comparable to Hunig's base and 2,6-lutidine.<sup>xiii,xiv</sup> Upon examination of these data, it appears that only very weak nucleophiles are appropriate co-catalysts with TMSOTf, which may be attributable either to reversible complexation of the nucleophile to the silicon center or to the formation of a pentavalent silicon species.

A general mechanistic scheme consistent with these data is presented in Scheme 1. Treatment of acetophenone with TMSOTf and Hunig's base produces the enol silane nucleophile. Unreacted TMSOTf then activates the aldehyde, and addition occurs in the presence of Hunig's base. Silyl transfer from the aldol adduct to another molecule of aldehyde completes the catalytic cycle.



**Scheme 1.**

As our mechanistic studies progressed, we began to investigate the synthetic applications of the tandem enol silane formation-Mukaiyama aldol reaction. A brief optimization survey determined standard reaction conditions to be ketone (1 equiv), aldehyde (1.4 equiv), TMSOTf (1.2 equiv),<sup>xv</sup> *i*-Pr<sub>2</sub>NEt (1.5 equiv),<sup>xvi</sup> and CH<sub>2</sub>Cl<sub>2</sub> (0.2 M) at room temperature. Under these conditions, the addition of acetophenone to a range of non-enolizable aldehydes was observed (Table 2). Benzaldehyde and its derivatives were uniformly excellent substrates, providing the  $\beta$ -hydroxy aldol adducts after desilylation in >90% yield (entries 1-4). Both electron-rich and electron-poor aromatic aldehydes are reactive substrates under these conditions. Heterocyclic aldehydes were also effective reaction partners (entries 5-6), as were sterically demanding naphthyl derivatives (entries 7-8). A slight decrease in yield was observed with  $\alpha,\beta$ -unsaturated aldehydes (entries 9-10), but the synthetic utility of these products makes them particularly attractive, since ozonolysis provides access to an  $\alpha$ -alkoxy aldehyde. Attempted addition of acetophenone to enolizable aldehydes and to acrolein provided no desired products, presumably due to competing polymerization pathways.

**Table 2.** Aldehyde Scope<sup>a</sup>

		product	yield (%) <sup>b</sup>
entry	R		
1	X=H	<b>1</b>	96
2	X=Me	<b>2</b>	93
3	X=OMe	<b>3</b>	92
4	X=NO <sub>2</sub>	<b>4</b>	92
5		<b>5</b>	93
6		<b>6</b>	93
7		<b>7</b>	85
8		<b>8</b>	95
9		<b>9</b>	75
10		<b>10</b>	88

<sup>a</sup>Reaction conditions: 1. acetophenone (1 equiv), aldehyde (1.4 equiv), TMSOTf (1.2 equiv), *i*-Pr<sub>2</sub>NEt (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), 0 °C to rt, 24 h. 2. 1.0 N HCl (3 equiv), THF (0.05 M), rt, 1 h.

<sup>b</sup>Isolated yield after chromatography.

We were particularly interested in the scope of the enolate partner for this tandem enol silane formation-Mukaiyama aldol reaction, *because the reaction conditions obviate the need for preformation and purification of the enol silane* (Table 3). Aryl methyl ketones, including acetophenone and acetonaphthones, were superior substrates, providing high yields of aldol adducts. Gratifyingly, acetate esters also reacted well, providing  $\beta$ -hydroxy ester products in >80% yield. This yield is outstanding when compared to the standard Mukaiyama aldol procedures, which require a separate synthesis and purification of the ester-derived silyl ketene acetal nucleophile in 40-70% yield<sup>xvii</sup> before the addition step can be performed. Thus, our system provides a significant increase in yield over the standard Mukaiyama aldol procedure for ester-derived enol silanes.

At present, addition reactions of alkyl-alkyl ketones proceed in somewhat diminished conversion (50-75%),<sup>xviii</sup> but further optimization of these substrates is underway. Propionate nucleophiles such as propiophenone react more sluggishly, and with poor diastereoselectivity (70% conversion, 1.5:1 syn:anti).<sup>xix</sup>

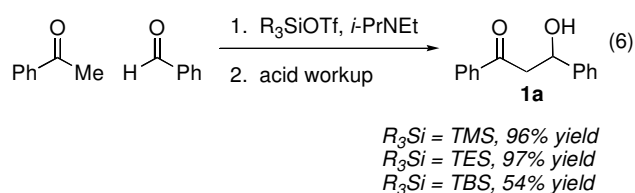
**Table 3.** Enolate Scope<sup>a</sup>

$\text{R}-\text{C}(=\text{O})\text{Me} + \text{H}-\text{C}(=\text{O})\text{Ph} \xrightarrow[2. \text{1.0 N HCl, THF}]{1. \text{TMSOTf, } i\text{-PrNEt}} \text{R}-\text{C}(=\text{O})\text{CH}_2\text{CH}(\text{OH})\text{Ph}$			
entry	RCOMe	product	yield (%) <sup>b</sup>
1		<b>1</b>	96
2		<b>11</b>	99
3		<b>12</b>	89
4		<b>13</b>	82
5		<b>14</b>	83

<sup>a</sup>Reaction conditions: 1. enolate precursor (1 equiv), benzaldehyde (1.4 equiv), TMSOTf (1.2 equiv), *i*-Pr<sub>2</sub>NEt (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), 0 °C to rt, 24 h. 2. 1.0 N HCl (3 equiv), THF (0.05 M)

<sup>b</sup>Isolated yield after chromatography.

Other silyl trifluoromethanesulfonates are also effective mediators of this aldol addition. When TMSOTf was replaced with TESOTf under otherwise identical reaction conditions, acetophenone and benzaldehyde reacted in 97% yield (eq 6). The reaction rate with TBSOTf suffered considerably, however, providing the aldol adduct in only 54% yield after 72 h.<sup>xviii</sup>



In conclusion, we have developed a new tandem enol silane formation-Mukaiyama aldol process that clarifies our understanding of the power of silyl trifluoromethanesulfonates to catalyze Mukaiyama aldol reactions. This new method proceeds without preformation and purification of the enol silane nucleophile. The presence of an amine base is crucial for high conversion to the aldol adducts. Mechanistic data suggests that both the amine and the silyl trifluoromethanesulfonate play dual roles in the reaction mechanism. Based on these results, synthetic chemists can more accurately predict when cationic silicon species may interfere with stereoselective

Mukaiyama aldol systems. Expansion of the reaction scope and the development of stereoselective variants of this transformation are underway.

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**Supplementary Data** Experimental procedures and spectral data.

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- (a) No further reaction was observed after 24 h. (b) NMR experiments suggest that Hunig's base and TMSOTf form an adduct under the reaction conditions.
- No product was observed when TBAI was mixed with acetophenone enol silane and benzaldehyde for 24 h, eliminating the possibility of a pure Lewis base-catalyzed reaction. Likewise, no aldol product was observed when Hunig's base was replaced with TBAI in the tandem enol silane formation-Mukaiyama aldol reaction.
- These results with TBAI are very similar to Bosnich's results with TBAOTf. See reference 5.
- No product was observed with TMSCl.
- Use of 2,6-lutidine resulted in a slight decrease in yield. Poor yield (<20%) was observed with Et<sub>3</sub>N.
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18. Reaction proceeded to completion as determined by <sup>1</sup>H NMR. In order to remove the TBS group, the initial adduct was treated with trifluoroacetic acid rather than HCl.