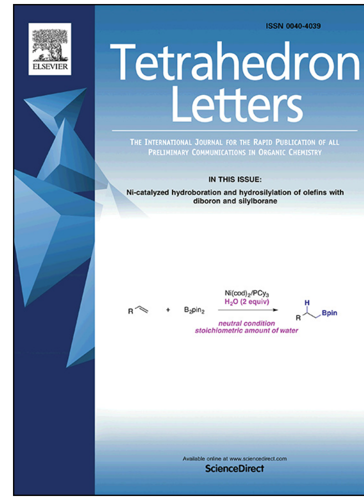

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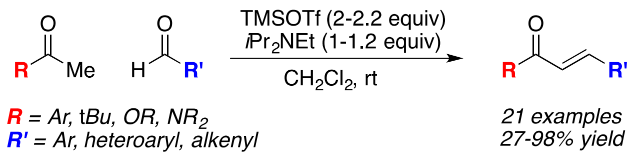

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Chalcone and Cinnamate Synthesis via One-Pot Enol Silane Formation-Mukaiyama Aldol Reactions of Ketones and Acetate Esters

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ABSTRACT

Aryl alkyl ketones, acetate esters, and acetamides undergo facile one-pot enol silane formation, Mukaiyama aldol addition, and dehydrosilyloxylation in the presence of an amine base and excess trimethylsilyl trifluoromethanesulfonate. The chalcone and cinnamate products are generally recovered in high yield. The relative stoichiometry of the trimethylsilyl trifluoromethanesulfonate and amine base reagents determines whether the reaction yields the β-silyloxy carbonyl product or the α,β-unsaturated carbonyl.

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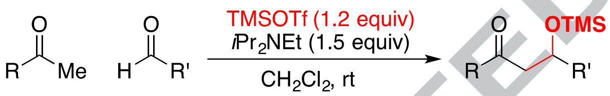
The construction of chalcones and cinnamates via aldol condensation of ketones or esters with aromatic aldehydes is a staple of synthetic organic chemistry.[1] These syntheses are typically performed through the mediation of relatively strong bases like hydroxides and alkoxides. Construction of these valuable building blocks through a mild, Lewis acid-promoted Mukaiyama aldol pathway is relatively rare, however, and requires the preformation of an enol silane or related nucleophile.[2] In the course of our study of one-pot enol silane formation-Mukaiyama aldol and Mannich addition reactions promoted by trimethylsilyl trifluoromethanesulfonate (TMSOTf),[3] we recently discovered that either the β-silyloxycarbonyl or the α,β-unsaturated carbonyl aldol products can be produced in high yield, dependent upon the stoichiometry of the reagents. We report here that the use of a tertiary amine base and 2.0 equiv TMSOTf promotes the condensation of ketones, esters, or amides with aromatic aldehydes to yield α,β-unsaturated carbonyl products. This discovery emphasizes the versatility of the R_3N/TMSOTf system for the synthesis of various aldol products.

We previously reported that a one-pot enol silane formation-Mukaiyama aldol reaction occurs when a ketone and an aromatic aldehyde are subjected to a mixture of 1.5 equiv *i*-Pr_2NEt and 1.2 equiv TMSOTf, yielding the β-silyloxycarbonyl product (eq 1).[3a,4] Optimization attempts at that time were directed solely toward maximization of the yield for the β-silyloxycarbonyl, but later results in our laboratory suggested that a change in the stoichiometry of the TMSOTf could significantly alter the product distribution to favor the α,β-unsaturated carbonyl. A brief optimization study showed that when the TMSOTf loading was increased to 2.0 equiv, rapid and efficient transformation of acetophenone and benzaldehyde to chalcone was effected in >95% conversion (eq 2).



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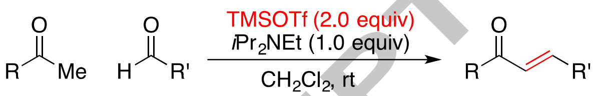
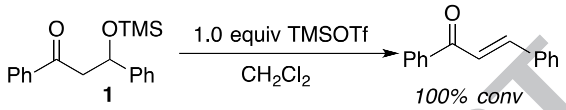


(2)

Presumably, formation of the chalcone product occurs through dehydrosilyloxylation of the initially formed β-silyloxycarbonyl product.[5] To provide evidence for this hypothesis, silyl ether **1** was first generated under our previously reported reaction conditions (1.5 equiv *i*-Pr_2NEt and 1.2 equiv TMSOTf).[3a] The reaction mixture was then passed through a plug of silica with ether and concentrated in vacuo to yield a 91% by mass mixture of the desired product, where the remaining mass consisted of unreacted acetophenone and benzaldehyde. This mixture was redissolved in CH_2Cl_2 and treated with 1.0 equiv TMSOTf, which resulted in 100% conversion to chalcone (eq 3). In order to gauge the effect that residual trialkylamine base might play in the reaction, and to better duplicate reaction conditions that might occur at partial conversion, the experiment was repeated with 0.2 equiv *i*-Pr_2NEt and 1.2 equiv TMSOTf; identical results were observed (eq 4). When β-silyloxycarbonyl **1** was treated with 1.0 equiv Et_3N•HCl, however, no elimination occurred, which suggests that trialkylammonium salts are not sufficiently acidic to activate the β position (eq 5). These data corroborate the likely intermediacy of β-silyloxycarbonyl **1** in the reaction mechanism, and further suggest that coordination of TMSOTf to the silyl ether oxygen, rather than protonation by an ammonium salt, promotes the elimination reaction. Finally, it is noteworthy that the deprotected β-hydroxy analog of silyl ether **1** also undergoes elimination to form chalcone in the presence of TMSOTf, but for this deprotected substrate, retroaldol to regenerate acetophenone and benzaldehyde competes with elimination (58% retroaldol, 42% elimination). Based on these results, β-silyloxycarbonyl **1** appears to be the more likely intermediate in the reaction described in this manuscript.



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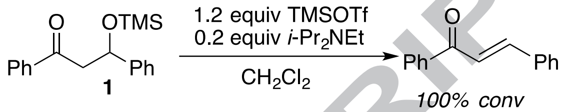

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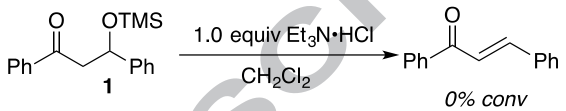
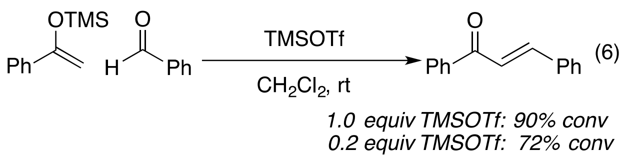


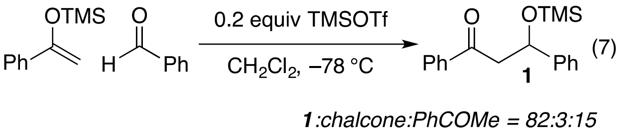
(5)

Although the ability of β-silyloxycarbonyl **1** to be converted to chalcone under the reaction conditions was now well established, generation of the final product via the intermediacy of an enol silane remained conjectural. Accordingly, the commercially available enol silane derived from acetophenone was subjected to benzaldehyde and 1.0 equiv TMSOTf in CH_2Cl_2. After 1 h, ^1H NMR spectroscopy of the reaction mixture showed 90% conversion to chalcone[3f] but no evidence of β-silyloxycarbonyl **1** (eq 6).[6] This experimental result is consistent with an enol silane intermediate in the reaction pathway. When the amount of TMSOTf in the reaction was decreased to 0.2 equiv, 72% conversion to chalcone was observed, but again no β-silyloxycarbonyl compound appeared in the ^1H NMR spectrum (eq 6). These experiments highlight two important characteristics of this reaction. First, once formation of the enol silane is complete, only a catalytic amount of TMSOTf is necessary for both the addition and elimination steps to reach high conversion.[7] Second, because the β-silyloxycarbonyl product is not observed under these conditions, it must undergo elimination rapidly after formation.



(6)

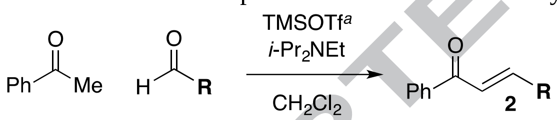
It still remained to verify that the β-silyloxycarbonyl intermediate does in fact form under these reaction conditions, which are slight modifications of the conditions in our original report. Accordingly, the temperature was lowered to –78 °C and the catalytic TMSOTf experiment was performed again (eq 7). After 1 h under these conditions, generation of the β-silyloxycarbonyl was confirmed.[8] Analysis of the reaction mixture by ^1H NMR spectroscopy showed 82% β-silyloxycarbonyl **1**, 15% unreacted acetophenone, and only 3% chalcone. With these results in place, a reasonable mechanistic pathway can be proposed that accounts for all of the data. Conversion of the acetophenone to the enol silane occurs easily in the presence of TMSOTf and base, and residual TMSOTf catalyzes Mukaiyama addition to the aldehyde followed by elimination to yield the chalcone.



Although the strongly Lewis acidic reaction conditions described in eqs 3, 4, and 6 suggest an E1 mechanism for the elimination step, an E2 mechanism through the action of a mild base such as TfO^- or trace H_2O cannot be ruled out, nor can a possible E1cb mechanism that proceeds via the enol silane. We further note that the elimination step of our proposed mechanism may yield HOTf or another hydronium analog as a byproduct, which may in turn catalyze further elimination reactions. As shown in eq 4, however, the β-silyloxycarbonyl intermediate undergoes elimination even when there is initially no possibility of an HOTf-like species; this result appears to verify that TMSOTf is capable of the *initiation* of the elimination reaction. When the standard reaction conditions were modified by an increase in the loading of amine base (up to 2.0 equiv)[9] in order to sequester adventitious acid, elimination was curtailed but not completely prevented. These results may be due to the neutralization of adventitious acid, but it should be noted that amine bases also interact reversibly with TMSOTf itself, which could also impact that rate of elimination.

An investigation of the scope of this aldol condensation reaction showed it to be general to a range of aryl alkyl ketones and aromatic aldehydes. As illustrated in Table 1, acetophenone condensed successfully with a range of benzaldehyde derivatives (entries 1-5). Similar reactions were attempted with both heteroaromatic and more sterically challenging aldehydes, most of which reacted in moderate to high yields (entries 5-7). Only the 2-furanaldehyde substrate proved incompatible with the reaction conditions: reactions with this substrate were capricious and reproducible yields could not be obtained.

Table 1. Reaction of Acetophenone with Various Aldehydes



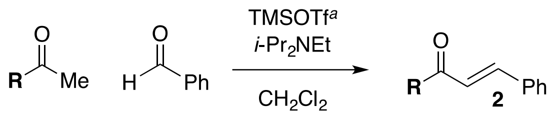
entry	R	product	yield (%)[b]
1	Ph	**2a**	90
2	4-(MeO)C_6H_4	**2b**	81
3	4-FC_6H_4	**2c**	96
4	4-BrC_6H_4	**2d**	91
5	4-(F_3C)C_6H_4	**2e**	72
6	2-naphthyl	**2f**	89
7	2-furyl	**2g**	0
8	2-thiophenyl	**2h**	82

a. Reaction conditions: acetophenone (1.0 mmol), aldehyde (1.2 mmol), *i*-Pr_2NEt (1.0 mmol), TMSOTf (2.0 mmol), CH_2Cl_2 (1.0 mL), rt, 1 h. See Supporting Information for details.

b. isolated yield after chromatography

In addition to acetophenone, several other aryl methyl ketones were reacted under similar reaction conditions. As illustrated in Table 2, both electron-rich and electron-poor acetophenones reacted in high yield, as did the sterically encumbered 2-acetonaphthone (entries 1-4). In addition, the highly sterically encumbered, wholly aliphatic pinacolone underwent aldol condensation with benzaldehyde in good yield, which shows that the reaction scope is not limited to aryl ketones (entry 5). Propiophenone did not reach complete conversion after overnight reaction, but did provide a yield of 50% (eq 8). Conversion did not appear to change significantly over 2-24 h time period, but the E:Z ratio increased from 3:1 at 2 h to 27:1 at 24 h.[10]

Table 2. Reaction of Benzaldehyde with Various Ketones

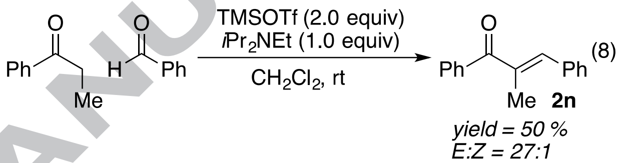


entry	R	product	yield (%)[b]
1	4-(MeO)C_6H_4	**2i**	83[c]
2	4-FC_6H_4	**2j**	92
3	4-BrC_6H_4	**2k**	95
4	2-naphthyl	**2l**	86
5	*t*-Bu	**2m**	79

a. Reaction conditions: ketone (1.0 mmol), benzaldehyde (1.2 mmol), *i*-Pr_2NEt (1.0 mmol), TMSOTf (2.0 mmol), CH_2Cl_2 (1.0 mL), rt, 1 h. See Supporting Information for details.

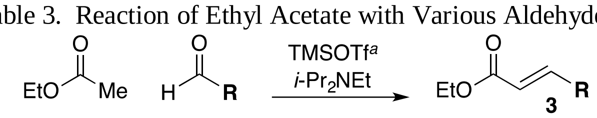
b. isolated yield after chromatography

c. yield corrected to account for ~4% impurities



The scope of this convenient aldol condensation reaction is not limited to ketones. Both acetate esters and acetamides are reactive under similar conditions, although reaction times are substantially longer than with ketones. Ethyl acetate is particularly convenient because it can be used as both an enolate precursor and the solvent in the reaction, producing cinnamate esters in high yield (Table 3). Benzaldehydes were again suitable reaction partners, although electron-rich aldehydes in general did not afford high yields under these conditions. Notably, cinnamaldehyde reacted in 65% yield, producing an α,β,γ,δ-unsaturated ester.

Table 3. Reaction of Ethyl Acetate with Various Aldehydes

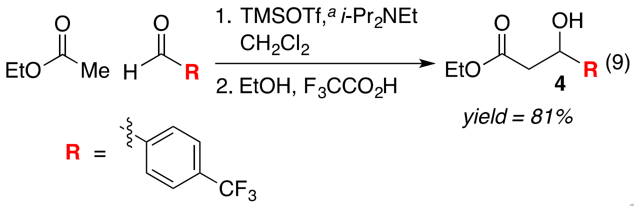


entry	R	product	yield (%)[b]
1	Ph	**3a**	89
2	4-MeC_6H_4	**3b**	98
3	4-(MeO)C_6H_4	**3c**	69
4	2-furyl	**3d**	33
5	2-thiophenyl	**3e**	53
6	cinnamyl	**3f**	65

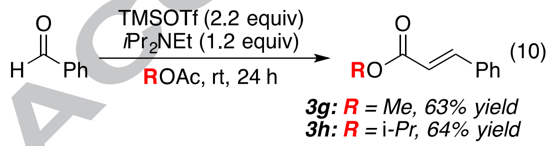
a. Reaction conditions: ethyl acetate (2.5 mL), benzaldehyde (1.0 mmol), *i*-Pr_2NEt (1.2 mmol), TMSOTf (2.2 mmol), rt, 16 h. See Supporting Information for details.

b. isolated yield after chromatography

Interestingly, the electron-poor 4-(trifluoromethyl)benzaldehyde substrate was an outlier. When this aldehyde was reacted with ethyl acetate under the same reaction conditions described in Table 3, only the β-silyloxyester product was observed. Attempts to promote elimination of the β-silyloxyester to produce the cinnamate derivative failed. Neither resubmission of the silyl ether to the reaction conditions, heating the original reaction to reflux (77 °C), nor performing the experiment in CH_2Cl_2 produced any trace of the cinnamate. Nonetheless, deprotection of the observed silyl ether with ethanol and trifluoroacetic acid yielded β-hydroxyester **4** in 81% yield from ethyl acetate (eq 9). The failure of this very electron-poor substrate[11] to undergo elimination suggests that elimination may proceed via an E1 mechanism; the required carbocation derived from the trifluoromethylated product would be especially unstable and difficult to form. In addition, coordination of the silyl ether oxygen to TMSOTf (or another Lewis acid) may also be slowed by the nearby electron-poor aromatic ring, which would slow the elimination step regardless of the mechanism. The result illustrated in eq 10 does stand in some contrast with the reaction of acetophenone with 4-(trifluoromethyl)benzaldehyde (Table 1, entry 5), for which the chalcone product is observed. The difference between the 4-(trifluoromethyl)benzaldehyde results for ethyl acetate and acetophenone suggest that both stabilization of carbocationic character at the β position *and* the acidity of the α position influence the progress of the reaction. While these characteristics are consistent with an E1 reaction mechanism, they do not rule out an E2 pathway or an E1cb pathway that proceeds via an enol silane.

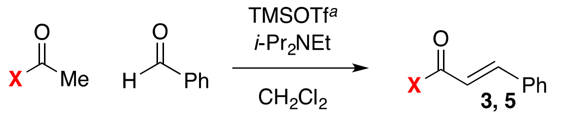


Given the success with ethyl acetate, the reaction of benzaldehyde in other convenient ester solvents was attempted. Both methyl acetate and isopropyl acetate were suitably reactive (eq 10), but neither approached the success of ethyl acetate. Indeed, simple replacement of ethyl acetate with either methyl acetate or isopropyl acetate under otherwise identical reaction conditions as those described in Table 3 resulted in low conversions. After some further experimentation, it was discovered that incubation of the ester with TMSOTf and *i*-Pr_2NEt for fifteen minutes prior to addition of the aldehyde provided significantly higher yields. Nonetheless, it appears that ethyl acetate is an optimal substrate: First, it lacks the steric encumbrance of isopropyl acetate. More subtly, the ammonium salt byproducts generated under the reaction conditions appear to be more soluble in methyl acetate than in ethyl acetate, which may help drive the ethyl acetate reaction to higher conversion.



When CH_2Cl_2 was employed as the reaction solvent, these were again suitably reactive as shown in Table 4 (entries 1 and 2).[13] When phenyl acetate was employed, poor conversion and multiple unidentified byproducts were observed. Morever, product **3i** proved unstable to chromatography, and only a small amount could be isolated (entry 3). On the other hand, employment of trimethylsilyl acetate as the enolate precursor[3c] was very successful, providing cinnamic acid as the product in excellent yield (entry 4). Finally, extension of this method to the convenient Weinreb amide proceeded very well, yielding the cinnamide with great efficiency (entry 5).

Table 4. Reaction of Esters and Amides with Benzaldehyde



entry	X	product	yield (%)[b]
1	MeO	**3g**	79
2	*i*-PrO	**3h**	85
3	PhO	**3i**	27
4	TMSO	**3j**	94[c]
5	Me(MeO)N	**5**	93

a. Reaction conditions: ester or amide (1.0 mmol), benzaldehyde (1.2 mmol), *i*-Pr_2NEt (1.2 mmol), TMSOTf (2.2 mmol), CH_2Cl_2 (2.5 mL), rt, 16 h. See Supporting Information for details.

b. isolated yield after chromatography

c. Isolated as the carboxylic acid, contaminated with <5% of an unidentified impurity.

In conclusion, the one-pot enol silane formation-Mukaiyama aldol reaction has been shown to provide different types of aldol products depending upon the stoichiometry of the TMSOTf. Past experiments have shown that when the amine base is in excess of the TMSOTf, the β-silyloxycarbonyl forms in high yield. The current work shows that an excess of TMSOTf with respect to amine base efficiently yields the α,β-unsaturated carbonyl. The reaction appears to be general to aryl alkyl ketones, acetate esters, and most unsaturated aldehydes.

Acknowledgments

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References and notes

1. For recent reviews, see: (a) Bukhari SNA, Jasamai M, Jantan I, Ahmad W *Mini-Rev. Org. Chem.* 2013; 10; 73-83; (b) Liu S, You H *Eur. Chem. Bull.* 2013; 2; 76-77.
2. (a) Mukaiyama T, Banno K, Narasaka K *J. Am Chem. Soc.* 1974; 96; 7503-7509; For conversion of enol silanes to chalcones, see: (b) Boyer J, Corriu RJP, Perz R, Reye C *J. Organomet. Chem.* 1980; 184; 157-166; (c) Ishihara K, Kurihara H, Yamamoto H *Synlett* 1997; 597-599; (d) Mashraqui SH, Kellogg RM *J. Org. Chem.*1984; 49; 2513-2516; (e) Sutar RL, Joshi NN *Ind. J. Chem., Sect. B* 2014; 53B; 1553-1560; (f) Slough GA, Bergman RG, Heathcock CH *J. Am. Chem. Soc.* 1989; 111, 938-949. For a relevant review, see: (g) Palomo C, Oiarbide M, Garcia JM *Chem. Eur. J.* 2002; 8; 36-44.
3. (a) Downey CW, Johnson MW *Tetrahedron Lett.* 2007; 48; 3559-3562; (b) Downey CW, Johnson MW, Tracy KJ *J. Org. Chem.* 2008; 73; 3299-3302; (c) Downey CW, Johnson MW, Lawrence DH, Flesher AS, Tracy KJ *J. Org. Chem.* 2010; 75; 5351-5354; (d) Downey CW, Dombrowski CM, Maxwell EN, Safran CL, Akomah OA *Eur. J. Org. Chem.* 2013; 5716-5720; (e) Downey CW, Ingersoll JA, Glist HM, Dombrowski CM, Barnett AT *Eur. J. Org. Chem.* 2015; 7287-7291; (f) Downey CW, Johnson MW *Tetrahedron Lett.* 2018; 59; 1268.
4. For examples of intramolecular versions of this reaction that predate our own work, see: (a) Hoye TR, Dvornikovs V, Sizova E *Org. Lett.* 2006; 8; 5191-5194; (b) Rassu G, Auzzas L, Pinna L, Zombrano V, Battistini L, Zanardi F, Marzocchi L, Acquotti D, Casiraghi G *J. Org. Chem.* 2001; 66; 8070-8075.
5. The dehydration of β-hydroxycarbonyl compounds to yield chalcones in the presence of acids is well precedented, as highlighted in reference 2c.

6. We erroneously reported this reaction to yield no products in our original description of the one-pot enol silane formation-Mukaiyama aldol reaction (reference 3a). For corrected data from our laboratories, which confirm the lack of β-silyloxycarbonyl products but do describe the formation of chalcone, see reference 3f.
7. Although this observation suggests that less than 2.0 equiv TMSOTf should be adequate to achieve full conversion from the ketone to the chalcone, experiments showed that 2.0 equiv TMSOTf was necessary to achieve full conversion at shorter, more desirable reaction times.
8. This result was previously reported by Hanaoka et al. See: Mukai C, Hashizume S, Nagami K, Hanaoka M *Chem. Pharm. Bull.* 1990; 38; 1509-1512.
9. When the stoichiometry of the amine base exceeds the stoichiometry of the TMSOTf, β-silyloxycarbonyl products are observed exclusively. See references 3a and 3c.
10. For identification of the *E* isomer by NOE, see: Saito A, Umakoshi M, Yagyu N, Hanzawa Y *Org. Lett.* **2008**, *10*, 1783-1785.
11. Unoptimized results with the similarly electron-deficient 4-nitrobenzaldehyde showed similar reactivity.
12. The ability of methyl acetate to undergo aldol condensation with the trioxane-derived formaldehyde in CH_2Cl_2 is known: Wang G, Wang H, Li C, Zuo C, Li Z, Zhang S *J. Ind. Eng. Chem.* 2017, 55, 173-182.

• Unsaturated carbonyls are produced from reaction of ketones or esters with aldehydes

• Stoichiometry of trimethylsilyl trifluoromethanesulfonate determines reaction outcome

• Electron-poor aldehydes do not lead to elimination products