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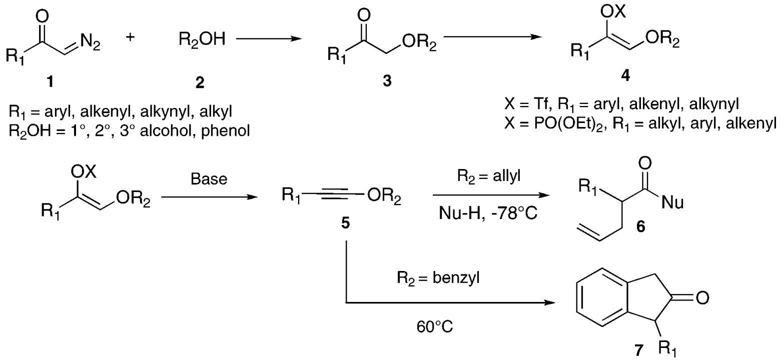

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Synthesis of Alkynyl Ethers and Low-Temperature Sigmatropic Rearrangement of Allyl and Benzyl Alkynyl Ethers

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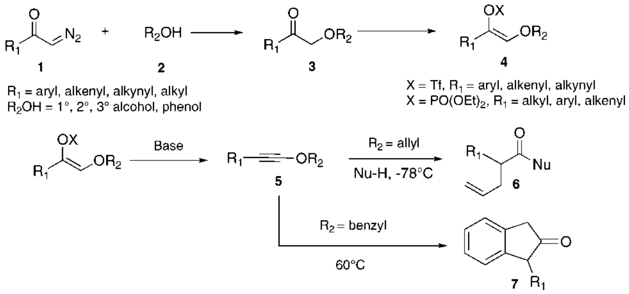
ABSTRACT



α-Alkoxy ketones 3 can be transformed into 1-alkynyl ethers 5 by a two-step procedure involving formation of the enol triflate or phosphate and base-induced elimination. Performing the same reaction sequence with allylic alcohols (R_2OH, R_2 = allyl) furnishes instead γ,δ-unsaturated carboxylic acid derivatives 6, derived from [3,3]-sigmatropic rearrangement of the intermediate allyl alkynyl ethers at −78 °C and trapping of the subsequently formed ketene with nucleophiles (Nu-H). Benzyl alkynyl ether 5 (R_2 = benzyl) rearranges to indanone 7 upon heating to 60 °C.

Electron-rich alkynes, such as ynamines and ynol ethers, are functional groups that possess significant potential in organic chemistry for the formation of carbon−carbon bonds.[1] The synthetic utility of ynamides has been considerably expanded recently, along with the development of new methods for their facile preparation from simple building blocks.[2] 1-Alkynyl ethers, while possessing many of the reactivity features of ynamides, have been far less investigated due to the relatively few methods currently available for their synthesis.[3] In this paper, we present a mild and efficient method for the synthesis of diverse 1-alkynyl ethers and demonstrate that a facile sigmatropic rearrangement of allyl and benzyl alkynyl ethers furnishes products containing new carbon−carbon bonds.

We have previously shown that treatment of allyl 1,1-dichlorovinyl ethers with 2.2 equiv of *n*-butyllithium at −78 °C, followed by quenching of the reaction mixture with excess alcohol, leads to rearranged γ,δ-unsaturated esters in

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(1) (a) Shindo, M. *Tetrahedron* **2007**, *63*, 10. (b) Brandsma, L.; Bos, H. J.; Arens, J. F. In *The Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 751. Stang, P. J.; Zhdankin, V. V. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons: New York, 1994; Chapter 19.

(2) For reviews of the chemistry of ynamines and ynamides, see: (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L. L *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, *10*, 1379. (c) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455. (d) Tetrahedron Symposium-In-Print: Chemistry of Electron-Deficient Ynamines and Ynamides. *Tetrahedron* **2006**, *62*, Issue No. 16.

(3) (a) Bruckner, D. *Synlett* **2000**, *10*, 1402. (b) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919. (c) Pericas, M. A.; Serratosa, F.; Valenti, E. *Tetrahedron* **1987**, 2311. (d) Smithers, R. H. *Synthesis* **1985**, 556. (e) Himbert, G.; Loffler, A. *Synthesis* **1992**, 495.

(4) Christopher, A.; Brandes, D.; Kelly, S.; Minehan, T. G. *Org. Lett.* **2006**, *8*, 451.

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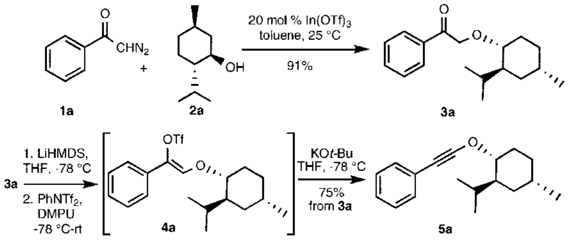
high yield.[4] The reaction possesses many of the characteristics of a sigmatropic process, both in terms of its stereospecificity and geometrical requirements. We have proposed that an initially generated allyl alkynyl ether intermediate undergoes a [3,3]-sigmatropic rearrangement either as a neutral or as a negatively charged species.

Due to its reactivity toward a range of functional groups, the use of the nucleophilic base *n*-BuLi to generate the key intermediate in this reaction may be viewed as a potential limitation. Furthermore, the preparation of the allyl 1,1-dichlorovinyl ether substrate via methylenation of an allylic formate ester requires the use of toxic carbon tetrachloride in combination with triphenylphosphine. Since terminal and internal alkynes have been previously prepared from ketones by treatment of the corresponding enol phosphates or triflates with a non-nucleophilic base,[5] we sought to investigate the preparation of 1-alkynyl ethers from α-alkoxy ketones via E2 elimination of the derived enol triflates or phosphates.

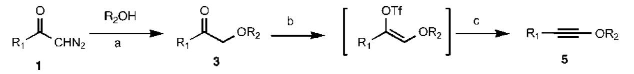
Following the procedure of Muthusamy et al.,[6] treatment of a toluene solution of diazoacetophenone **1a** and menthol with a catalytic amount (10 mol %) of indium triflate at room temperature furnished α-alkoxy ketone **3a** in 91% yield (Scheme 1). Formation of the enol triflate was achieved by stirring **3a** with LiHMDS at −78 °C for 1 h, followed by quenching with $PhNTf_2$ in DMPU/THF (1:2) and warming to room temperature. The enol triflate obtained (**4a**) was sufficiently stable to be purified by silica gel chromatography; ^1H NMR spectroscopy of the purified material revealed that the triflate was formed as a single *Z* geometric isomer (the configuration of the double bond was confirmed by NOESY experiments; see the Supporting Information for details). Subsequent treatment with 2 equiv of potassium *tert*-butoxide at −78 °C in THF smoothly furnished the corresponding alkynyl ether **5a** in 75% overall yield from **3a**. Alternatively, and more expediently, the crude enol triflate can be directly transformed into **5a** in similar overall yield by addition to an excess (3 equiv) of potassium *tert*-butoxide in THF at −78 °C. The presence of the alkynyl ether moiety in **5a** was verified by the chemical shifts of the alkyne carbons in the ^{13}C NMR spectrum (41.8 and 98.5 ppm, respectively) and also by the sharp spike at 2254 cm^{-1} in the IR spectrum.

Scheme 1. Preparation of Phenylethynyl Menthyl Ether



To extend this protocol to the preparation of a diverse range of substituted alkynyl ethers, we required access to a variety of α-diazoketones. The procedure of Danheiser et al.[7] allowed the preparation of aryl (**1a**), alkenyl (Table 1, **1e** and **1f**), and alkyl (**1h**, **1i**) diazoketones from the corresponding ketones in high yields. However, the preparation of alkynyl diazoketone **1g** was problematic due to self-condensation/cycloaddition side reactions.[8]

Table 1. Scope of Alkynyl Ether Sythesis via Elimination of Enol Triflates[a]



entry	R1	R2	**3** (% yield)	**5**	**5** (% yield)
1	Ph	menthyl	91	**a**	75
2	Ph	$CH_2CH(CH_2)_3$	89	**b**	82
3	Ph	*t*-Bu	67	**c**	68
4	Ph	Ph	78	**d**	70
5	1-cyclohexenyl	menthyl	84	**e**	90
6	$(CH_3)_2CCH$	$CH_2CH(CH_2)_3$	81	**f**	68
7	PhCC	menthyl	69[b]	**g**	64
8	*t*-Bu	$CH_2CH(CH_2)_3$	87	**h**	–[c]
9	C_6H_{13}	menthyl	90	**i**	–[c]

[a] Reaction conditions: (a) R_2OH (1.5 equiv), $In(OTf)_3$ (10 mol %), toluene, rt; (b) LiHMDS, THF, −78 °C, then $PhNTf_2$, DMPU, −78 °C to rt; (c) KO-*t*-Bu, THF, −78 °C. [b] Yield of **3g** prepared in three steps from menthol via an alternative route described in the text. [c] No alkynyl ethers were detected in the reaction mixture; see the text for details.

The three-step protocol for alkynyl ether synthesis (diazoketone−alcohol coupling, enol triflate formation, and elimination) was carried out starting with a number of different diazoketones and alcohols (Table 1). Primary, secondary, and tertiary alcohols and phenols all work equally well, furnishing the expected alkynyl ethers (entries 1−4) in good yields. Aromatic (R_1 = Ph, entries 1−4), α,*β*-unsaturated (R_1 = 1-cyclohexenyl, $(CH_3)_2CCH$, entries 5 and 6), and alkynyl (R = CCPh, entry 7) ketones **3** were all effective precursors of alkynyl ethers. Due to the problems encountered in preparing alkynyl diazoketones (vide supra), an alternative protocol for the synthesis of α-alkoxy ketone **3g** was developed, involving reaction of the sodium alkoxide of menthol with chloroacetic acid,[9] formation of the Weinreb amide,[10] and addition to phenylethynyllithium (2 equiv) at −78 °C. Enol triflate formation then proceeded uneventfully, furnishing a ∼1:1 mixture of *E* and Z geometrical isomers. Subsequent treatment with KO-*t*-Bu under standard conditions then allowed the preparation of compound **5g**, a 1,3-diynyl menthyl ether.

Unlike results for aromatic, alkenyl, and alkynyl ketone substrates, aliphatic α-alkoxy ketones failed to generate the corresponding enol triflates upon treatment with LiHMDS/

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(5) (a) Brummond, K. M.; Gesenberg, K. D.; Kent, J. L.; Kerekes, A. D. *Tetrahedron Lett.* **1998**, *39*, 8613. (b) Negishi, E.; King, A. O.; Tour, J. M. *Org. Synth.* **1990**, *7*, 63.

(6) Muthusamy, S.; Babu, S. A.; Gunanathan, C. *Tetrahedron Lett.* **2002**, *43*, 3133.

(7) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.

(8) This problem has been previously noted: Boyer, J. H.; Selvarajan, R. *J. Org. Chem.* **1971**, *36*, 1679.

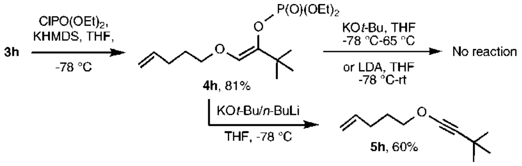
(9) Gibson, H. W.; Berg, M. A.; Clifton Dickson, J.; Lecavalier, P. R.; Wang, H.; Merola, J. S. *J. Org. Chem.* **2007**, *72*, 5759.

(10) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

$PhNTf_2$ (Table 1, entries 8 and 9). A survey of different reaction conditions and triflating agents (Tf_2O, Comins' triflimide) yielded no improvement, with high R_f decomposition products obtained in all cases. We suspect that the enol triflates derived from aliphatic ketones are unstable, perhaps decomposing to allenic compounds that undergo side reactions.

To address this important limitation, we investigated the preparation of putatively more stable enol phosphates from α-alkoxy ketones.[11] Indium triflate catalyzed coupling of *tert*-butyl diazoacetate with 4-penten-1-ol provided ketone **3h** in 89% yield. Addition of a toluene solution of KHMDS to a mixture of **3h** and diethylphosphoryl chloride in THF at −78 °C furnished enol phosphate **4h** (again as a single *Z* geometric isomer; see the NOESY data in the Supporting Information) in 81% yield (Scheme 2). Disappointingly, no reaction was observed upon treatment of the enol phosphate with KO-*t*-Bu in THF at −78 °C; even after the reaction mixture was warmed to room temperature and then to reflux, only starting material was isolated. Use of the stronger bases LDA or LiTMP also led to no reaction. Finally, it was found that addition of 2−3 equiv of Schlosser's base (*n*-BuLi−KO-*t*-Bu) to the enol phosphate at −78 °C led to the rapid formation of the alkynyl ether in 60% yield.

Scheme 2. Preparation of Alkyl-Substituted Alkynyl Ethers

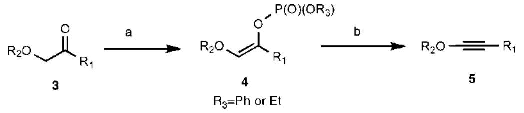


A variety of alkyl-substituted alkynyl ethers may be prepared efficiently from the corresponding enol phosphates (Table 2, entries 1−3). Either the diphenyl phosphate or the diethylphosphate derivative may be employed for the elimination step, and the order of addition of base and substrate appears to have no effect on the reaction yield (addition of *n*-BuLi to a mixture of enol phosphate and KO-*t*-Bu vs addition of the enol phosphate to preformed BuK). Performing the two-step sequence on hexyl and isopropyl ketones **3i** and **3j** furnished enol phosphates **4i** and **4j** and alkynyl ethers **5i** and **5j**, respectively, in good yields. This method is also an effective means of synthesizing aryl- and alkenyl-substituted alkynyl ethers (Table 2, entries 4 and 5).

Interestingly, when methyl ketone **3m** (Scheme 3) was treated with KHMDS and $ClPO(OEt)_2$, a 3:1 mixture of enol phosphates **4n** and **4m** was obtained in 65% yield. Subjection of this mixture to *n*-BuLi/KO-*t*-Bu at −78 °C cleanly gave rise to allenyl ether **8** in 85% yield.

Finally, we wished to examine the special case of alkynyl ethers derived from allylic and benzylic alcohols.

Table 2. Scope of Alkynyl Ether Synthesis via Elimination of Enol Phosphates[a]

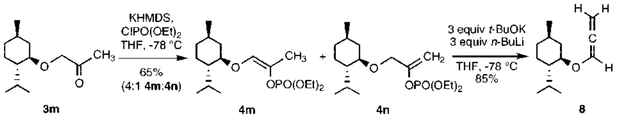


entry	R_1	R_2	**4**	% yield of **4**	**5**	% yield of **5**
1	*t*-Bu	$CH_2CH(CH_2)_3$	**h**[b]	81	**h**	60
2	C_6H_{13}	menthyl	**i**[c]	89	**i**	72
3	*i*-Pr	menthyl	**j**[b]	78	**j**	85
4	1-cyclohexenyl	*t*-Bu	**k**[b]	72	**k**	70
5	Ph	*t*-Bu	**l**[b]	82	**c**	56

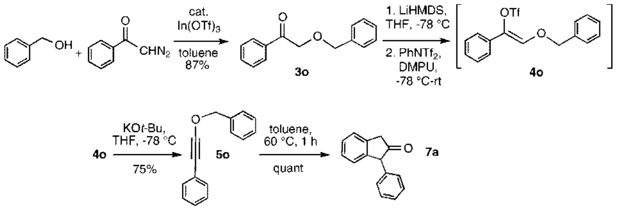
[a] Reaction conditions: (a) KHMDS, $ClPO(OR_3)_2$, THF, 78 °C; (b) *n*-BuLi, KO-*t*-Bu, THF, −78 °C. [b] The diethyl phosphate derivative was synthesized. [c] The diphenyl phosphate derivative was synthesized.

Early investigations by Arens[12] and Schmid[13] revealed that substituted and unsubstituted benzyl alkynyl ethers undergo [3,3]-sigmatropic rearrangement followed by intramolecular ketene trapping to form indanones in high yield. Interestingly, these processes took place in refluxing CCl_4, at temperatures well below those typical for uncatalyzed aromatic Claisen rearrangements.[14] $In(OTf)_3$-catalyzed coupling of benzyl alcohol and diazoacetophenone **1a** furnished α-benzyloxy acetophenone **3o** in 87% yield (Scheme 4). Enol triflate formation proceeded smoothly to afford **4o**, which when treated with KO-*t*-Bu in THF at −78 °C gave rise to benzyl alkynyl ether **5o** in 75% yield. This compound proved to be

Scheme 3. Formation of Allenyl Ether **8** from Methyl Ketone **3m**



Scheme 4. Synthesis and Thermal Rearrangement of Phenylethynyl Benzyl Ether



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[11] 1-Ethynyl ethers have been previously prepared by base-induced elimination of enol phosphates derived from acetate esters: Cabezas, J. A.; Oehlschlager, A. C. *J. Org. Chem.* **1994**, *59*, 7523.

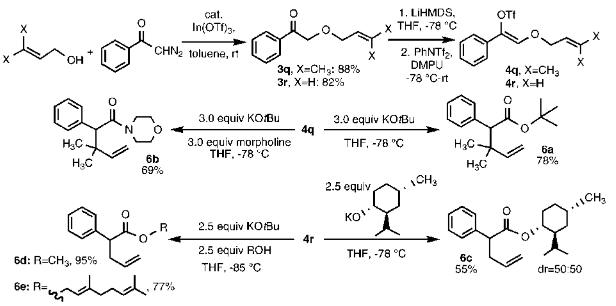
[12] Olsman, H.; Graveland, A.; Arens, J. F. *Rec. Trav. Chim. Pays-Bas* **1964**, *83*, 301.

[13] Wunderli, A.; Zsindely, J.; Hansen, H. J.; Schmid, H. *Chimia* **1972**, *26*, 643.

thermally labile, partially rearranging to indanone **7a** upon heating above room temperature for rotary evaporation; it also readily decomposed on silica gel chromatography. A solution of **5o** in toluene was thus heated to 60 °C for 60 min to effect conversion to indanone **7a** in quantitative yield.

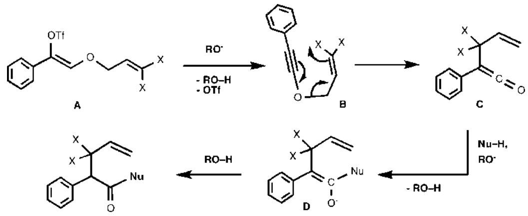
The previous studies of Katzenellenbogen,[15] as well as our own investigations,[4] have indicated that allyl-1-alkynyl ethers undergo rapid sigmatropic rearrangement at low temperatures (−33, −78 °C) once formed. Therefore, we wished to assess if sigmatropic rearrangement would also take place upon *t*-BuOK treatment of α-allyloxy ketone-derived vinyl trifates at −78 °C. Reaction of prenol or allyl alcohol with α-diazoacetophenone in the presence of indium triflate furnished α-alkoxyketones **3q** and **3r** in 88% and 82% yields, respectively (Scheme 5). Enol triflate **4q**, derived from **3q** (LHMDS, Tf_2NPh, DMPU, −78 °C−rt), was treated with 3 equiv of potassium *tert*-butoxide in THF at −78 °C; after the mixture was warmed to room temperature, *tert*-butyl ester **6a** was obtained in 78% yield. Performing the same reaction with 3 equiv each of potassium *tert*-butoxide and morpholine at −78 °C furnished amide **6b** in 69% yield. Enol triflate **4r**, derived from **3r** (LHMDS, Tf_2NPh, DMPU, −78 °C to rt), was similarly transformed into menthyl ester **6c** (54%, as a 1:1 mixture of diastereomers) by treatment with 2.5 equiv of the potassium alkoxide of menthol in THF at −78 °C. Surprisingly, however, attempts to prepare the simple methyl ester **6d** met with little initial success. Addition of **4r** to a solution of excess potassium methoxide in THF at −78 °C led to the exclusive production of **3r**, presumably arising from nucleophilic attack of methoxide at the triflate sulfur atom. Addition of KO-*t*-Bu to a solution of **4r** and methanol at −78 °C also gave rise to **3r** as major product, as well as minor amounts of rearranged methyl and *tert*-butyl ester products; inclusion of a tertiary amine catalyst (such as triethylamine)[16] led to no improvement in the yields of rearranged products obtained. Finally, it was found that rapid, sequential addition of 2.5 equiv of KO-*t*-Bu and 2.5 equiv of MeOH to a THF solution of **4r** at −85 °C led to the clean production of **6d** in 95% yield.[17] Repetition of this reaction with geraniol instead of methanol gave rise to *γ*,*δ*-unsaturated geranyl ester **6e** in 77% yield.

Scheme 5. Synthesis of *γ*,*δ*-Unsaturated Esters and Amides



A logical mechanistic pathway (Scheme 6) for this process may involve hindered alkoxide-induced E2 elimination of triflate ion from **A** to produce the corresponding allyl alkynyl ether **B**, which undergoes [3,3]-sigmatropic rearrangement to furnish allyl ketene intermediate **C**. Nucleophilic trap of the ketene by the excess alkoxide base or other nucleophile present leads to enolate **D**, which is protonated by the conjugate acid of the base (*t*-BuOH, menthol, etc.) to furnish the *γ*,*δ*-unsaturated carboxylic acid derivative.

Scheme 6. Mechanistic Proposal for the Formation of *γ*,*δ*-Unsaturated Carboxylic Acid Derivatives



In summary, we have developed an efficient procedure for the synthesis of a diverse range of alkynyl ethers from α-diazoketones and alcohols. We have also shown that allyl and benzyl alkynyl ethers undergo sigmatropic rearrangement and nucleophilic trapping to produce α-substituted ketones, esters, and amides. Further studies on this useful low-temperature sigmatropic rearrangement are in progress and will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (SC2 GM081064-01), the ACS Petroleum Research Fund (No. PRF 45277-B1), and the Henry Dreyfus Teacher−Scholar Award for their generous support of our research program. We also thank Mr. Shayan Rab (USC), Mr. Nick Vidar (CSUN), and Ms. Yen-Nhi Do Nguyen (CSUN) for preparing **5b**, **5c**, and **7a**, respectively.

Supporting Information Available: Detailed experimental procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra for all compounds in Tables 1 and 2 and Schemes 3−5, as well as NOESY spectra for compounds **4a** and **4h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Typical reaction temperatures for sigmatropic rearrangement of allyl phenyl ether range from 170°C (neat) to 220 °C (in diphenyl ether). For mechanistic investigations of the thermal aromatic Claisen rearrangement, see: (a) Meyer, M. P.; DelMonte, A. J.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 10865. (b) Kupczyk-Subotkowska, L.; Subotkowski, W.; Saunders, W. H.; Shine, H. J. *J. Am. Chem. Soc.* **1992**, *114*, 3441. (c) Gozzo, F. C.; Fernandes, S. A.; Rodrigues, D. C.; Eberlin, M. N.; Marsaioli, A. J. *J. Org. Chem.* **2003**, *68*, 5493.

(15) Katzenellenbogen, J. A.; Utawanit, T. *Tetrahedron Lett.* **1975**, *16*, 3275.

(16) Tertiary amines have been used extensively to catalyze the addition of alcohols to ketenes; see: (a) Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1989**, *111*, 7650. (b) Cannizaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 10992. (c) Pracejus, H.; Kohl, G. *Justus Liebigs Ann. Chem.* **1969**, 722. (d) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637.

(17) At −85 °C, deprotonation of the enol triflate by KO-*t*-Bu is rapid, but nucleophilic addition of KO-*t*-Bu to the intermediate ketene is slow. Thus, when methanol is added rapidly after the addition of KO-*t*-Bu, the remaining alkoxide base (~1.5 equiv) rapidly deprotonates methanol to form potassium methoxide, which then adds to the ketene intermediate to form the corresponding methyl ester enolate; upon protonation, product **6d** results.