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Ring Opening of Cyclic Vinylogous Acyl Triflates Using Stabilized Carbanion Nucleophiles: Claisen Condensation Linked to Carbon−Carbon Bond Cleavage

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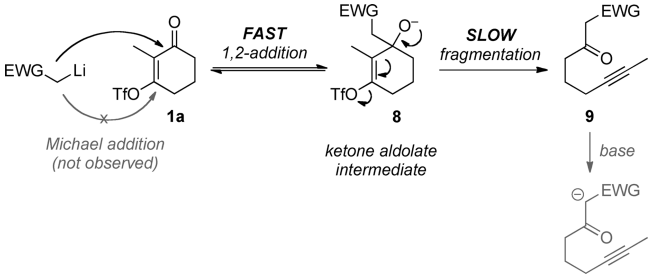
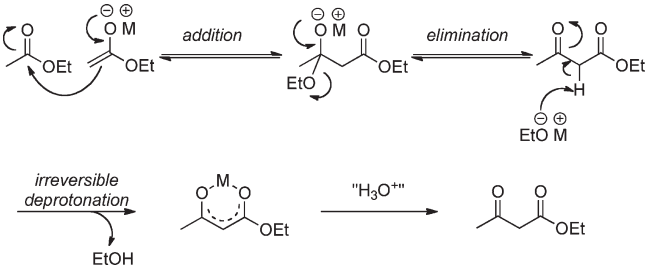


Addition of stabilized carbanionic nucleophiles to cyclic vinylogous acyl triflates (VATs) triggers a ring-opening fragmentation to give acyclic β-keto ester and related products, much like those observed traditionally in the Claisen condensation. Unlike in the classical Claisen condensation, however, the VAT-Claisen reaction described herein is rendered irreversible by C−C bond cleavage, not by deprotonation of the activated methylene product. Full details of this original reaction methodology are disclosed herein, including how subtle differences between the various nucleophiles impact the proper choice of reaction conditions for making 1,3-diketones, β-keto esters, and β-keto phosphonates.

Introduction

The Claisen condensation has been an important reaction in synthetic organic chemistry for over a century.[1] In the classic Claisen condensation, an ester enolate nucleophile reacts with a carboxylic ester electrophile in a reversible addition and elimination sequence. The resulting β-keto ester is then subject to irreversible deprotonation at the α-position, which shifts equilibrium in favor of the condensation product (Scheme 1).[2] Ketone enolates, phosphonyl- and sulfonyl-stabilized carbanions, and similar nucleophiles react with esters in an analogous fashion to provide β-keto derivatives.[1,2]

SCHEME 1. Mechanism of the Classical Claisen Condensation of Ethyl Acetate



This report is focused on the use of a Grob-type heterolytic fragmentation pathway to drive formation of Claisen condensation-type products: β-keto derivatives of ketones,

(1) For reviews on the Claisen condensation, see: (a) Davis, B. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 795−863. (b) Hauser, C. R.; Hudson, D. E. *Org. React.* **1942**, *1*, 266. (c) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59. For a review on the Dieckman condensation, see: (d) Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1.

(2) (a) Hauser, C. R. *J. Am. Chem. Soc.* **1938**, *60*, 1957–1959. (b) McElvain, S. M. *J. Am. Chem. Soc.* **1929**, *51*, 3124–3130. (c) Roberts, D. C.; McElvain, S. M. *J. Am. Chem. Soc.* **1937**, *59*, 2007–2008. (d) Nishimura, T.; Sunagawa, M.; Okajima, T.; Fukasawa, Y. *Tetrahedron Lett.* **1997**, *38*, 7063–7066.

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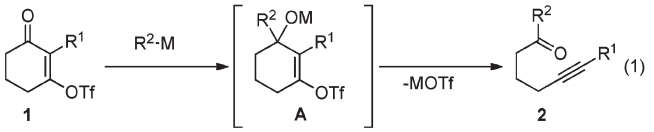
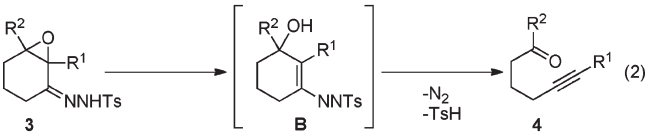
esters, phosphonates, phosphine oxides, and sulfones. The classic addition and elimination of *esters* (Claisen condensation) is replaced by the addition and fragmentation of *vinylogous esters*, specifically, cyclic vinylogous acyl triflates (VATs). Our lab has been exploring the synthetic utility of triggering Grob fragmentation reactions by nucleophilic addition to VATs.[3] A broad range of nucleophiles react with cyclic VATs in an addition/bond cleavage process to provide acyclic alkynyl ketones (eq 1). This reaction has been applied and extended to the synthesis of a moth pheromone, homopropargyl alcohols, and indane building blocks.[4]

Tandem Addition/ Fragmentation of Vinylogous Acyl Triflates



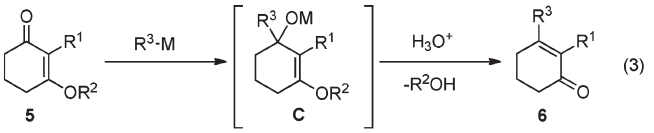
(1)

Eschenmoser-Tanabe Fragmentation

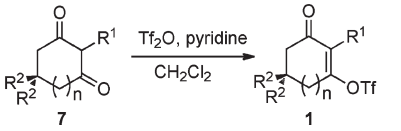


(2)

Enone Formation from Vinylogous Acid Esters



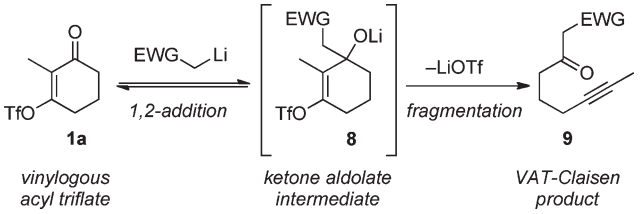
(3)



(4)

The pivotal fragmentation process is related to the Eschenmoser–Tanabe reaction[5,6] (**3** → **4**, eq 2), but it is approached by nucleophilic addition to cyclic vinylogous esters by analogy to a related reaction that is known to provide cyclic enones (**5** → **6**, eq 3).[7] Consequently, ring opening of VATs provides products that are not accessible using the Eschenmoser–Tanabe fragmentation, such as amides and homopropargyl alcohols, as detailed in previous reports.[3c,4b] VATs are readily available in high yield from symmetrical diones (eq 4). The two-step conversion of cyclic diones to tethered alkynyl ketones has been shown to be general, affording a wide variety of differentially functionalized substrates.[3c]

SCHEME 2. VAT-Claisen Reaction



Recent contributions from other laboratories complement our ongoing methodology and add to the growing arsenal of C–C bond cleavage reactions for production of valuable synthetic building blocks. The Williams lab recently expanded the utility of VATs to the synthesis of allenes, showing through elegant competition experiments and calculations that loss of triflate and formation of the strong carbonyl bond can drive rapid formation of the higher energy cumulated allene π-system.[8] Brewer and co-workers employed an analogous yet distinct addition and C–C bond cleavage process to prepare tethered alkynyl aldehydes;[9] note that aldehydes are difficult to access using our method of hydride-triggered ring opening of VATs.[10]

VAT-Claisen Reaction

Enolate nucleophiles trigger fragmentation of VATs in a process we call the VAT-Claisen reaction (Scheme 2).[3b] The VAT-Claisen reaction provides 1,3-dicarbonyl-type compounds through an addition and C–C bond cleavage process, as opposed to the traditional Claisen condensation, which delivers 1,3-dicarbonyl-type compounds through addition and alkoxide elimination reaction of simple esters.

The success of the VAT-Claisen reaction is noteworthy for several reasons. Enolate addition to ketones (cf. **1a** → **8**) is reversible, and in many cases the equilibrium lies on the side of reactants. Moreover, α,β-unsaturated ketones react with enolates typically via Michael 1,4-addition, not 1,2-addition. Nonetheless, we observed products derived from 1,2-addition of enolates to VAT **1**, followed upon warming by fragmentation to generate 1,3-dicarbonyl compounds. Preliminary observations were reported previously, and a more detailed study is the subject of this report.

Results and Discussion

The VAT-Claisen reaction is a key part of a two-step strategy for converting symmetric cyclic 1,3-diones (e.g., **7**,[11] eq 4) into value-added acyclic building blocks comprising

(3) (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028–5029. (b) Kamijo, S.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 175–177. (c) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499–6507.

(4) (a) Jones, D. M.; Kamijo, S.; Dudley, G. B. *Synlett* **2005**, 936–938. (b) Tummatorn, J.; Dudley, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 5050–5051. (c) Jones, D. M.; Dudley, G. B. *Tetrahedron* **2010**, in press; DOI: 10.1016/j.tet.2010.03.014.

(5) (a) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708–713. (b) Felix, D.; Shreiber, J.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 2896–2912. (c) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, *40*, 3943–3946. (d) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, *38*, 3739–3743.

(6) (a) Weyerstahl, P.; Marschall, H. Fragmentation Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 6, pp 1041–1070. (b) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1–15. (c) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535–546.

(7) (a) Woods, G. F.; Tucker, I. W. *J. Am. Chem. Soc.* **1948**, *70*, 2174–2177. (b) Zimmerman, H. E.; Nesterov, E. E. *J. Am. Chem. Soc.* **2003**, *125*, 5422–5430.

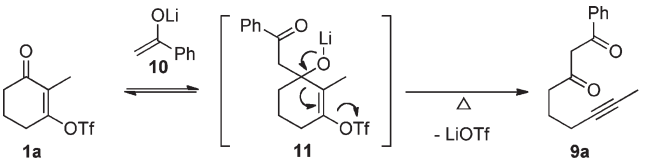
(8) Kolakowski, R. V.; Manpadi, M.; Zhang, Y.; Emge, T. J.; Williams, L. J. *J. Am. Chem. Soc.* **2009**, *131*, 12910–12911.

(9) (a) Draghici, C.; Brewer, M. *J. Am. Chem. Soc.* **2008**, *130*, 3766–3767. (b) Bayir, A.; Draghici, C.; Brewer, M. *J. Org. Chem.* **2010**, *75*, 296–302.

(10) Kamijo, S.; Dudley, G. B. *Tetrahedron Lett.* **2006**, *47*, 5629–5632.

(11) Preparation of triflate **1a** is essentially a quantitative process (yields typically >95%) when freshly recrystallized 2-methyl-1,3-cyclohexanedione (cf. **7**) is employed. However, 2-methyl-1,3-cyclohexanedione is unstable to prolonged storage. Routinely, we elect to make use of the crude dione as received from commercial sources, then purify and store the more stable VAT **1a**. For example, a ca. 80% pure sample of 2-methyl-1,3-cyclohexanedione can be converted in ca. 80% yield to VAT **1a**, which can then be stored in the freezer for several months without noticeable decomposition.

SCHEME 3. VAT-Claisen Reaction of 1a and 10, the Lithium Enolate of Acetophenone



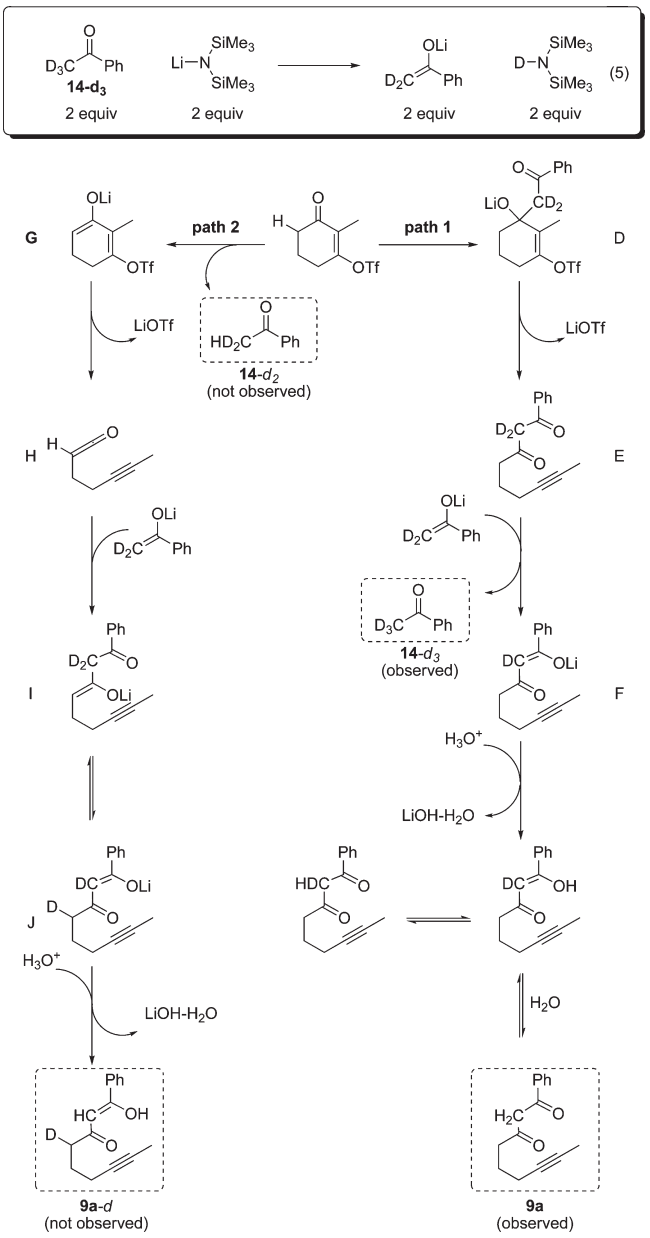
Stoichiometry: need two equivalents of base		
Amount of **10**	excess LiHMDS	Yield of **9a**
1.2 equiv	0	56%
2.2 equiv	0	85%
1.2 equiv	1.0 equiv	78%

alkyne and carbonyl-activated methylene functionality (e.g., **9**, Scheme 2). Such building blocks are valuable for a range of synthetic applications, as the alkyne and activated methylene can be processed in parallel by taking advantage of their complementary reactivity.[12] These compounds are also valuable tools for synthetic methodology, especially for the development of intramolecular reactions for the synthesis of five-membered rings.[13]

Preliminary Identification and Analysis of the VAT-Claisen Reaction. In our examination of the Claisen-type condensation reactions of VATs, we first studied the reaction of the lithium enolate of acetophenone.[3b] The stoichiometry of this reaction played a pivotal role in the ability of the reaction to proceed to completion. In analogy to the traditional Claisen condensation, which requires excess base, at least 2 equiv of enolate nucleophile is necessary to drive the VAT-Claisen fragmentation of **1** to completion (Scheme 3). The initial addition is conducted cold, with subsequent warming of the reaction mixture to promote fragmentation. Reaction of 2.2 equiv of the lithium enolate of acetophenone with VAT **1a** gave rise to 1,3-diketone **9a** in 85% yield, whereas with only 1.2 equiv of enolate the yield of **9a** dropped to 56% and unreacted **1a** was recovered. If the enolate (1.2 equiv) is supplemented with additional base (1.0 equiv of LiHMDS), then complete consumption of VAT **1a** is observed and β-diketone **9a** is isolated in 78% yield.

Two mechanistic alternatives were initially considered to account for the need for 2 equiv of enolate and/or base. Deuterium labeling helped differentiate between the two (Scheme 4). The first (path 1, cf. Scheme 3), which we ultimately came to favor, parallels the addition and fragmentation pathway for the Grignard-triggered ring opening of VATs: direct 1,2-addition of the ketone enolate to VAT **1a** provides tetrahedral intermediate aldolate **D**, which undergoes fragmentation upon warming to diketone **E**. The acidic methylene of diketone **E** is metalated as it forms in an acid/base reaction with excess enolate, which explains the need for 2 equiv of enolate.

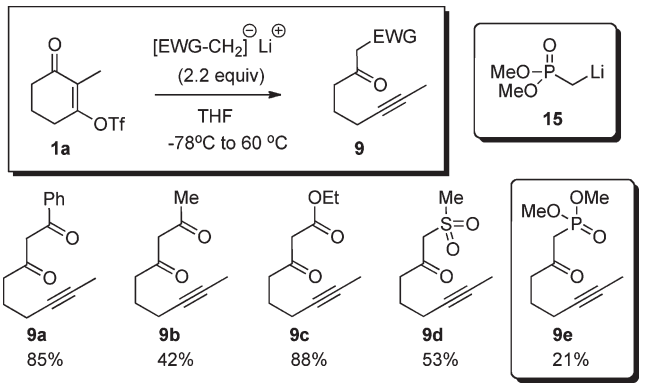
SCHEME 4. Possible Mechanistic Pathways and Deuterium-Labeling Experiment



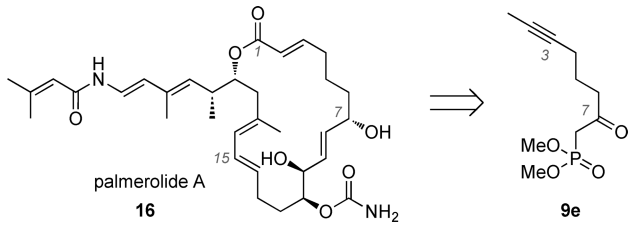
Specific concerns regarding the feasibility of this pathway prompted us to consider, evaluate, and ultimately discard an alternative mechanism (path 2). The first concern with path 1 was that ketone enolates typically add to α,β-unsaturated ketones in a Michael 1,4 fashion, whereas the mechanism proposed in path 1 involves a direct 1,2-addition. Moreover, ketone aldolates typically undergo retro-aldol cleavage upon warming, and (unproductive) proton transfer between the enolate and ketone often out-competes ketone aldol addition processes. In other words, we were initially skeptical as to the feasibility of path 1. Although general reactivity trends do not necessarily translate to this specific system, we considered an alternative mechanism initiated by *productive* proton transfer between the enolate and VAT **1a** (path 2).

(12) Jones, D. M.; Dudley, G. B. *Synlett* **2010**, *02*, 223–226.
(13) Kitagawa, O.; Suzuki, T.; Inoue, T.; Watanabe, Y.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 9470–9475. Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2003**, *9*, 2627–2635. Hashimi, A. S. K.; Schwarz, L.; Choi, J. -H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285–2288. Itoh, Y.; Tsuji, H.; Yamagata, H. -I.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161–17167.

SCHEME 5. Reported Claisen-Type Condensation Reactions of VAT 1a



SCHEME 6. Prospective Application to Palmerolide A



The alternative mechanistic pathway starts with abstraction of the acidic α-proton of triflate **1a** to form enolate **G**. Heterolytic fragmentation then would generate ketene intermediate **H**, analogous to the allene formation reported by Williams.[8] Addition of another molecule of the lithium enolate of **14** and proton transfer would yield the most stable lithium enolate of the 1,3-diketone **J** through the intermediate **I**. Aqueous workup and keto−enol equilibrium in the presence of proton source would furnish the final product **9a**.

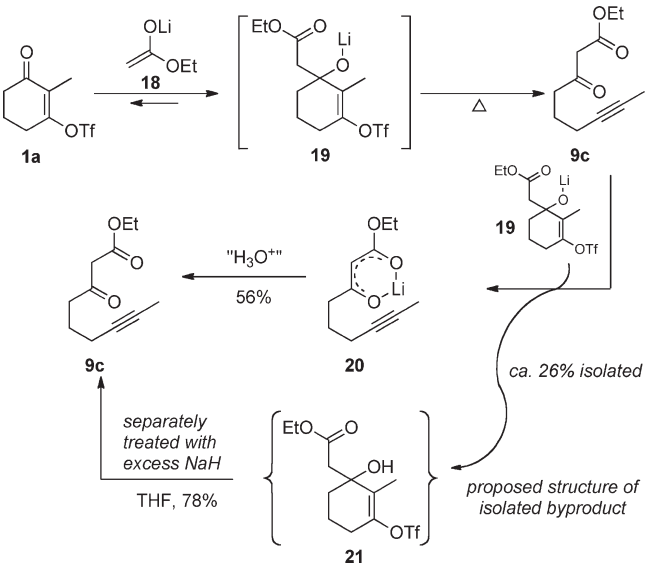
A deuterium-labeling experiment (eq 5, Scheme 4) provided insight into the mechanistic pathway for the present Claisen-type condensation. We conducted the reaction using VAT **1a** and acetophenone-methyl-d_3 (**14**-d_3). The resultant products were the corresponding 1,3-diketone **9a** without noticeable deuteration and recovery of **14**-d_3. These products are consistent with expectations based on path 1, and they are inconsistent with material that would be formed via path 2. Accordingly, we favored the mechanism outlined in path 1.

Preliminary Scope. With this mechanistic model in mind, we carried out the remainder of our initial experiments under the same protocol. Many of the nucleophiles examined gave satisfactory results (Scheme 5),[3b] but not the anion of dimethyl methylphosphonate (**15**); Horner−Wadsworth−Emmons reagent **9e** was isolated in only 21% yield. This limitation was not inconsequential, as **9e** promised to be an ideal starting material for a total synthesis of palmerolide A (Scheme 6).[14]

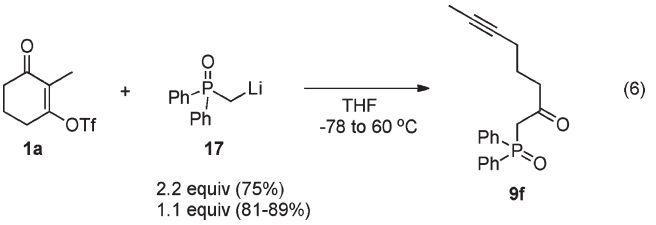
We became interested in the synthesis of palmerolide A, in part because **9e** maps conveniently onto the "northeast" (as drawn) region of the target molecule. However, the

(14) Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *J. Am. Chem. Soc.* **2006**, *128*, 5630–5631.

SCHEME 7. Proposed Fragmentation Reaction Pathway Between 1a and 18



Claisen-type condensation reaction had to be reoptimized for the synthesis of olefinating reagents similar to **9e**. Changing the nucleophile from the lithium anion of dimethyl methylphosphonate (**15**) to the lithium anion of methyldiphenylphosphine oxide (**17**) afforded Horner−Wittig reagent **9f** in the 70% yield range. Upon further optimization, we found that only 1.1 equiv of the phosphine oxide nucleophile was necessary to convert VAT **1a** effectively to the corresponding product **9f** (eq 6). This optimization culminated in the synthesis of the C1−C15 fragment of palmerolide A.[12]



(6)

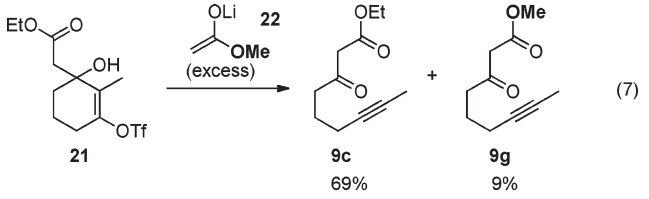
Refined Mechanistic Analysis. We reopened our investigation into the VAT-Claisen mechanism in order to gain a better understanding of the subtle balance of factors involved in determining optimal conditions. To reiterate our previous observations, the VAT-Claisen reaction of **1a** with the lithium enolate of acetophenone requires 2 equiv of enolate (Scheme 3), whereas the similar reaction involving the lithium anion of methyldiphenylphosphine oxide is best accomplished with 1 equiv of the stabilized nucleophile (eq 6).

The next logical experiment was reaction of VAT **1a** with 1.1 equiv of **18**, the lithium enolate of ethyl acetate (Scheme 7). Ethyl acetate was one of the best prenucleophiles in our earlier study (**1a** → **9c**, 88% yield, Scheme 5),[3b] and esters are intermediate in acidity between ketones and phosphine oxides.[15]

(15) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

The enolate of ethyl acetate provided valuable data. When 1.1 equiv of **18** was added to VAT **1a**, the desired fragmentation product (**9c**) was obtained in 56% yield (Scheme 7). This result was in line with our previous observation using 1.2 equiv of the acetophenone enolate (**10**) (56% yield, Scheme 3).[3b] In this case, however, a previously unobserved byproduct was isolated, which we have tentatively identified as alcohol **21** (ca. 26% yield) on the basis of its ^{1}H NMR spectrum. This byproduct proved to be unstable to storage, but when immediately dissolved in THF, treated with excess NaH (approximately 3 equiv), and heated to 60 °C for 30 min, this byproduct gave rise to the fragmentation product **9c** in 78% yield, which provides support for our proposed structure (**21**).

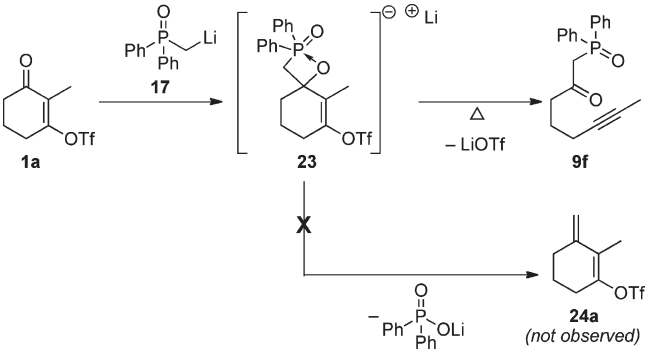
A revised mechanistic hypothesis is needed to account for the formation of β-hydroxy ester **21**. On the basis of identification of aldol **21** after aqueous workup, we now consider aldolate **19** to be a persistent intermediate. In other words, ester enolate addition to **1a** is not freely reversible. Aldolate **19** begins to undergo fragmentation upon warming, providing β-ketoester **9c**. When only 1 equiv of enolate **18** is employed, the enolate is essentially consumed following addition to **1a** and prior to fragmentation. Subsequent deprotonation of the β-ketoester by the alkoxide, not the enolate, occurs. Aldol **21** does not undergo fragmentation, so full conversion to β-keto ester **9c** is not realized. Thus, 2 equiv of base is still required for compete conversion of VAT **1a** to **9c**. Although the isolation of byproduct **21** provides evidence for the proposed reaction pathway, a competing deprotonation of the β-ketoester by the enolate resulting from a retro-addition cannot be ruled out.



A crossover experiment confirms that ester enolate addition is reversible to only a limited degree (eq 7). We generated what we presume to be a 1:1.8 mixture of aldolate **19** and the lithium enolate of methyl acetate (**22**) by treating aldol **21** with 2.8 equiv of **22**. The isolated fragmentation product mixture comprised ethyl and methyl esters **9c** and **9g** in an 88:12 ratio (as estimated by ^{1}H NMR, 78% combined yield), indicating that retro-aldol reaction is occurring only to a minor extent. If the aldol addition were rapidly reversible, then we would expect to see a 35:65 ratio[16] of **9c** and **9g**. If no retro-aldol reaction were occurring, then only ethyl ester **9c** would be observed. Because both esters are detected with the ethyl ester as the major product, we conclude that enolate addition is reversible to a limited extent in this system.

This more detailed understanding of the reaction pathway enabled us to reconsider the reaction between 1.0 equiv of phosphine oxide nucleophile **17** and VAT **1a** (eq 6). Specifically, we must discard the assumption of an initial reversible addition of the phosphorus-stabilized anion to VAT **1a**, but

SCHEME 8. Proposed Mechanism of the Reaction between VAT 1a and 17



we must then rationalize why deprotonation of the product β-ketophosphine oxide does not occur (only 1 equiv of base is needed). That full conversion was realized with only 1 equiv of nucleophile suggests that either the β-ketophosphine oxide product (**9f**) is not acidic or the presumed[17] intermediate oxy-anion (**23**) is not basic (Scheme 8). We favor the latter alternative; the organolithium nucleophile adds irreversibly at cold temperatures, and the resulting oxy-anion coordinates to the phosphine oxide to provide intermediate **23**. This intermediate is envisioned to resemble an oxaphosphetane intermediate, much like that formed during a Wittig olefination reaction.[18] Such an intermediate would reduce the oxy-anion's ability to deprotonate the β-ketophosphine oxide product, *and* it would reduce the possibility of a retro-addition, thus allowing for the use of 1 equiv of nucleophile to consume the starting material. When the reaction mixture is subsequently warmed, the postulated oxaphosphetane-like intermediate collapses and provides the fragmentation product **9f**, instead of undergoing the classical retro-[2 + 2] pyrolysis reaction to provide dienyl triflate **24a** (not observed[19]).

The results of the condensation reactions of VAT **1a** with the various stabilized anions (cf. **10**, **17**, and **18**) provided a better understanding of the intricacies of the VAT-Claisen reaction pathway. It is not solely the reactivity of the nucleophile that determines stoichiometry requirements, and the chemical properties of the aldolate-type intermediate (cf. **11**, **19**, and **23**) must be considered. Armed with new mechanistic insights, we expanded our methodology to the synthesis of various β-ketophosphonates. β-Ketophosphonates provide reactivity similar to that of β-ketophosphine oxides (both are olefinating reagents), but the phosphonates provide some distinct advantages: they are cheaper, more widely available, and easier to work with than their phosphine oxide analogues. The next section addresses the conversion of VATs to novel phosphonate-based olefinating reagents.

Synthesis of β-Ketophosphonates Using the VAT-Claisen Reaction. The use of phosphonates in organic chemistry

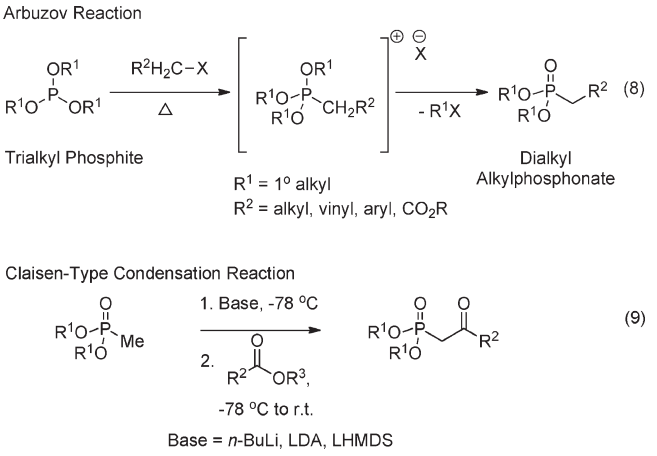
(16) The ratio of **9c** to **9g** would be as low at 25:75 if proton transfer between ethyl acetate, methyl acetate, and their respective enolates were also to occur.

(17) Unlike intermediate **21** from ethyl ester enolate addition, the aldol-type product derived from aqueous quench (protonation) of **23** has not been isolated.

(18) (a) Kelly, S. E. Alkene synthesis. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 729–818. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. (c) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1–157.

(19) Small amounts of such byproduct are observed in some cases, as discussed later in the manuscript.

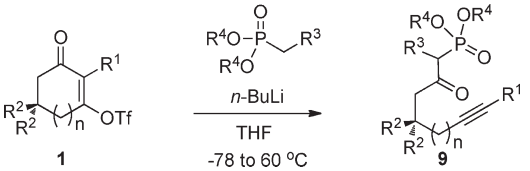
SCHEME 9. Common Methods for the Preparation of Phosphonates

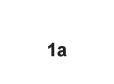
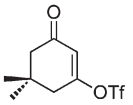
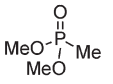
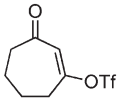
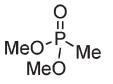
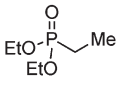
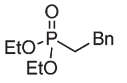
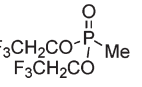


revolutionized the synthesis of alkenes.[20] The ability to generate *E*- and *Z*-alkenes selectively, the mild conditions required for reaction, and the ease of their synthesis are distinct advantages of phosphonates as olefination reagents over their phosphorane (Wittig reagents) or phosphine oxide (Horner−Wittig) counterparts. Two general strategies are available for the synthesis of phosphonates (Scheme 9): (1) the Arbuzov reaction,[21] which involves the alkylation of the corresponding trialkyl phosphite to prepare alkyl-, benzyl-, and allylphosphonates as well as ester-derived phosphonates (eq 8) or (2) a Claisen-type condensation between esters and a dialkyl methylphosphonates to prepare β-ketophosphonates (eq 9).[22] Synthesis of β-ketophosphonates using the Arbuzov reaction is also known, but one must recognize the potential for the competing Perkow reaction, which gives rise to enol phosphates.[21a]

The synthesis of β-ketophosphonates was of particular interest to us. Having obtained a poor yield (21%) of phosphonate product **9e** upon treating VAT **1a** with 2.2 equiv of dimethyl lithiomethylphosphonate (**15**) under our original conditions,[3b] we aimed to determine if the conditions optimized for the lithiomethyldiphenylphosphine oxide nucleophile (**17**) would provide increased yields of the β-ketophosphonates. The use of lithiomethyldiphenylphosphine oxide as the nucleophile trigger provided excellent yields (up to 89%, eq 6). However, the use of phosphonates for alkene synthesis is much more common.[18a,20e,h] Moreover, the use of dimethyl methylphosphonate has a distinct advantage for large-scale synthesis, in that it costs far less than methyldiphenylphosphine oxide (ca. 66 mmol/$1 vs 1 mmol/$1, respectively).[23]

TABLE 1. Reactions of Vinylogous Acyl Triflates with 1.1 equiv of Phosphonates[a]



entry	VAT	phosphonate	product	yield, %[b]
1	**1a**		**9e**	97
2	 **1b**		**9h**	41[c]
3	 **1c**		**9i**	78
4	**1a**		**9j**	94
5	**1a**		**9k**	70[d]
6	**1a**		**9l**	–[e,f]

[a]Triflate **1a** (0.50 mmol) reacted with nucleophile (0.55 mmol, generated from 0.6 mmol of phosphonate and 0.55 mmol of *n*-BuLi). [b]Isolated yields. [c]Obtained byproduct **24b** (ca. 4% yield). [d]Obtained byproduct, proposed to be **24c** (ca. 8% yield). [e]Decomposition of VAT **1a**. [f]35% recovered VAT **1a**.

Table 1 summarizes the data resulting from the VAT-Claisen reactions of various VATs with 1.1 equiv of phosphonate-derived organolithium reagents. The reaction between VAT **1a** and 1.1 equiv of **15** (dimethyl lithiomethylphosphonate) proceeded in excellent yield (97%, entry 1). This result marks nearly a 5-fold increase in the yield of **9e** compared to our previous report, in which 2.2 equiv of nucleophile was used.[3b] The vinylogous acyl triflates derived from dimedone and 1,3-cycloheptanedione (**1b** and **1c**,

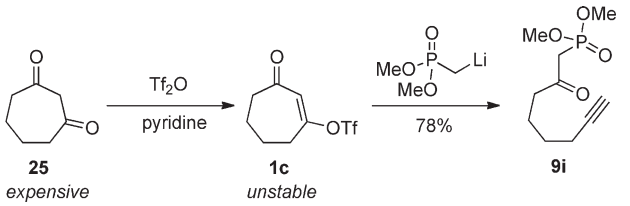
(20) (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99. (b) Heron, B. M. *Heterocycles* **1995**, *41*, 2357–2386. (c) Ernst, H.; Muenster, P. *Carotenoids* **1996**, *2*, 307–310. (d) Lawrence, N. J. The Wittig reaction and related methods. In *Preparation of Alkenes*; Oxford University Press: New York, 1996; pp 19−58. (e) Nicolaou, K. C.; Harter, M. W.; Gunzer, J. L.; Nadin, A. *Liebigs Ann. Rec.* **1997**, 1283–1301. (f) Motoyoshiya, J. *Trends Org. Chem.* **1998**, *7*, 63–73. (g) Minami, T.; Okauchi, T.; Kouni, R. *Synthesis* **2001**, 349–357. (h) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *2*, 2826–2830. (i) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408. (j) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186. (k) Iorga, B.; Eymery, F.; Mouries, V.; Savignac, P. *Tetrahedron* **1998**, *54*, 14637–14677.

(21) (a) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307–353. (b) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430.

(22) (a) Somu, R. V.; Boshoff, J.; Quao, C.; Bennet, E. M.; Barry, C. E.; Aldrich, C. C. *J. Med. Chem.* **2006**, *49*, 31–34. (b) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2006**, *71*, 6141–6148. (c) Wetermann, J.; Schneider, M.; Platzek, J.; Petrov, O. *Org. Process Res. Dev.* **2007**, *11*, 200–205. (d) Maloney, K. M.; Chung, J. Y. *J. Org. Chem.* **2009**, *74*, 7574–7576. (e) Milburn, R. R.; McRae, K.; Chan, J.; Tedrow, J.; Larsen, R.; Faul, M. *Tetrahedron Lett.* **2009**, *50*, 870–872.

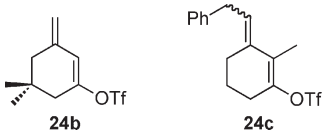
(23) Prices made available from Sigma-Aldrich: http://www.sigmaaldrich.com/united-states.html.

SCHEME 10. Synthesis of Phosphonate 9i



respectively) both provided their respective phosphonate products, **9h** and **9i**, in acceptable yields. Interestingly, in the case of **1b**, an unstable byproduct was isolated (ca. 4%), whose ^{1}H NMR spectrum is consistent with diene **24b**. Such a byproduct would support our proposed oxaphosphetane-like intermediate (cf. structure **23**, Scheme 8).

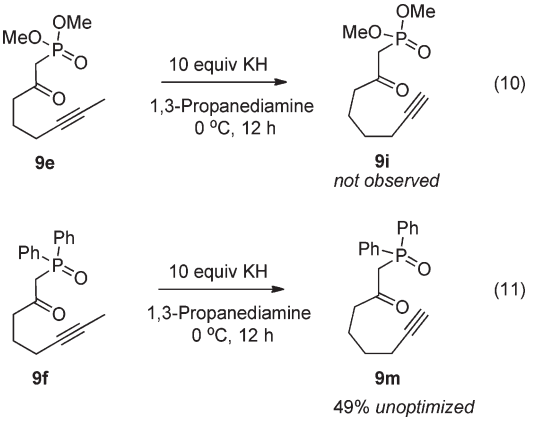
The reaction between VAT **1a** and the anion of diethyl ethylphosphonate proceeded cleanly in 94% yield (entry 4). This result is remarkable. In our previous studies of the Claisen-type condensation reactions, substituents at the α-position of the nucleophile were linked to decomposition of the starting VAT. In the case of the nucleophile derived from diethyl 2-phenylethylphosphorane (entry 5), the phosphonate product **9k** was obtained in 70% yield. This reaction provided an unstable byproduct consistent with an *E*/*Z* mixture of dienes **24c**, in a roughly 1:1 ratio (ca. 8% yield). Again, alkene byproducts are consistent with a postulated oxaphosphetane-like intermediate (Scheme 8). The anion of bis(trifluoroethyl)-methylphosphonate (entry 6), which would give rise to a Still−Gennari-type[20i] olefination reagent, is prone to homocondensation,[22d] thus hampering its viability in Claisen-type condensation reactions.



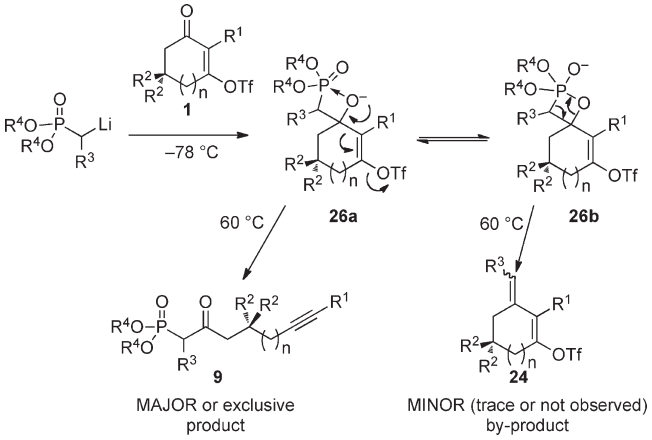
The stability of various VATs **1a**−**c** deserves comment. Vinylogous acyl triflates **1b** and **1c**, which lack the α-methyl substituent, are relatively unstable when compared to their analogue, VAT **1a**. Vinylogous acyl triflate **1a** can be stored under an inert atmosphere for several months at −10 °C without any observable decomposition by ^{1}H NMR spectroscopy, whereas VAT **1b** begins to discolor after 1−2 days. VAT **1c** is even less stable; it began to decompose upon removal of solvent and had to be used immediately. In addition, 1,3-cycloheptanedione, the precursor to VAT **1c**, is quite expensive (1 g/$264.50, approximately 30 μmol/$1).[23] For these reasons, the two-step conversion from 1,3-cycloheptanedione (**25**) to β-ketophosphonate **9i** (Scheme 10) is less than ideal.

We devised an alternative strategy for accessing olefination reagents linked to alkynes by homologated tethers (> 3 carbons, cf. **9i**) using the KAPA (potassium 3-aminopropylamide) acetylene zipper reaction.[24] The KAPA acetylene zipper reaction rearranges internal alkynes to terminal alkynes. Rearrangement of phosphonate **9e** was not effective (eq 10, Scheme 11), likely because of competing amidation of the phosphonate with 1,3-propanediamine. This technical problem was easily overcome by switching back to the corresponding phosphine oxide (**9f**). Fragmentation of VAT **1a** with lithiomethyldiphenylphosphine oxide provides **9f** (eq 6), and carrying out a subsequent KAPA zipper (alkyne isomerization) reaction provides Horner−Wittig reagent **9m** (eq 11, Scheme 11), an analogue of phosphonate **9i**.

SCHEME 11. Synthesis of Phosphonate 9l, an Analogue of Phosphonate 9h



SCHEME 12. Proposed Mechanism of the Reaction between VAT 1a and Phosphonates



The proposed mechanism of the VAT-Claisen reaction of phosphonate-derived nucleophiles is illustrated in Scheme 12. Addition of 1 equiv of lithioalkylphosphonate to VAT **1** generates β-alkoxyphosphonate **26a** and/or oxaphosphetane derivative **26b**, depending on the extent of interaction between oxygen and phosphorus. One equivalent of phosphonate nucleophile is necessary and sufficient for complete consumption of VAT **1**. Excess phosphonate nucleophile can react further with phosphonate intermediate **26a** and/or **26b** via the known phosphonate Claisen condensation.[22] Therefore, use of excess phosphonate nucleophile would be detrimental, as observed in our earlier report.[3b] The required stoichiometry stands in contrast to enolate nucleophiles (cf. Schemes 4 and 7). Upon warming, β-alkoxyphosphonate **26a** undergoes fragmentation to β-keto phosphonate **9**. Alternatively, pyrolysis of **26b** can occur to generate cyclic dienyl triflate **24** in small amounts, especially as steric congestion increases in the system (Scheme 12).

In summary, we have identified, explored, and refined the VAT-Claisen reaction for the synthesis of alkynes tethered to 1,3-dicarbonyl-type structures. This methodology further

(24) Yamashita, A.; Brown, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 891–892.

enables the convenient two-step strategy for the synthesis of differentially functionalized acyclic keto alkynes from symmetrical cyclic diones. The full details disclosed in this work provide valuable insight into the mechanism of the VAT-Claisen reaction. The observance of the suspected alcohol byproduct **21** in reactions of VAT **1a** with the lithium enolate of ethyl acetate allowed for a better understanding of the mechanism involving phosphine oxide derived nucleophiles. As is often the case, this is an example of natural products synthesis driving innovation in organic methodology: our interest in palmerolide encouraged us to reexamine a poor substrate and improve the scope of the earlier VAT-Claisen methodology. Ultimately, the results obtained from careful examination of various nucleophiles and VAT substrates provided a better understanding of these reactions and allowed for the expansion of the method to the synthesis of β-ketophosphonates.

We demonstrated throughout the course of our research into the tandem nucleophilic addition/C−C bond cleavage reactions of vinylogous acyl triflates that this class of compounds can give rise to interesting and synthetically useful compounds. Tethered alkynyl ketones, alkynyl β-ketoesters, alkynyl β-ketophosphine oxides, and now, through reoptimized conditions, alkynyl β-ketophosphonates are available from these easily prepared VAT substrates. The synthetic utility of the VAT-Claisen reaction has been demonstrated in the preparation of the C1−C15 fragment of palmerolide A and the synthesis of some new and useful β-ketophosphonates. Studies on the reactivity and synthetic utility of vinylogous acyl triflates continue in the Dudley laboratory.

Experimental Section

Standard Procedure for the Claisen-Type Condensation of the Triflate (1a) with Acetophenone. To a THF solution (2 mL) of acetophenone (0.14 mL, 1.2 mmol) was added LiHMDS (1.0 M solution in THF, 1.1 mL, 1.1 mmol) at −78 °C under Ar atmosphere. After 30 min of stirring at −78 °C, 2-methyl-3-(trifluoromethanesulfonyloxy)-2-cyclohexenone (**1a**) (93 μL, 0.50 mmol) was added to the resultant solution. The mixture was stirred at −78 °C for 10 min, at 0 °C for 10 min, at rt for 30 min, and then at 60 °C for 30 min. Saturated aqueous NH_4Cl solution was added to quench the reaction, and the mixture was extracted with ether. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes/ether = 100:1−20:1) to give 1-phenyl-1,3-dioxo-7-nonyne (**9a**, together with its enol tautomer) in 85% yield (96 mg).[3b]

Standard Procedure for the Claisen-Type Condensation of the Vinylogous Acyl Triflates with Phosphonate Nucleophiles. To a THF solution (2 mL) of dimethyl methylphosphonate (0.6 mmol) was added *n*-BuLi (2.5 M solution in hexanes, 0.22 mL, 0.55 mmol) at −78 °C. After 20 min of stirring at −78 °C, a solution of vinylogous acyl triflate **1a** (0.50 mmol) in THF was added dropwise to the resulting solution. The mixture stirred at −78 °C for 10 min, at 0 °C for 10 min, at rt for 30 min, and at 60 °C for 30 min; during the course of the reaction the solution changed from clear to yellow and then from yellow to a reddish solution. The solution was diluted with 3 mL of Et_2O. A half-saturated aqueous NH_4Cl solution was used to quench the reaction, and the mixture was extracted 3 times with 5 mL portions of EtOAc. The combined organic layers were washed with 5 mL of $NaHCO_{3(aq)}$ and 5 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated. The residual oil was purified by silica gel column chromatography (gradient elution from 10% to 40% EtOAc/hexanes) to afford 112 mg of β-ketophosphonate **9e**, together with its enol tautomer (97% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (d, J = 11 Hz, 6H), 3.10 (d, J = 22 Hz, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.16 (tq, J = 6.9, 2.5 Hz, 2H), 1.76 (t, J = 2.5 Hz, 3H), 1.75 (app. quintet, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 78.0, 76.3, 52.9 (d, J = 6.5), 42.8, 41.3 (d, J = 128 Hz), 22.6, 17.8, 3.3; IR (thin film) 1712, 1449, 1254, 1025, 810 cm^{-1}; HRMS (EI$^+$) Calcd for $C_{10}H_{17}O_4P^+$ [M$^+$] 232.0864, found 232.0860. Spectroscopic data consistent with previous report.[3b]

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Supporting Information Available: Characterization data and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.