Tandem Nucleophilic Addition/Fragmentation of Vinylogous Acyl Nonaflates for the Synthesis of Functionalized Alkynes, with New Mechanistic Insight

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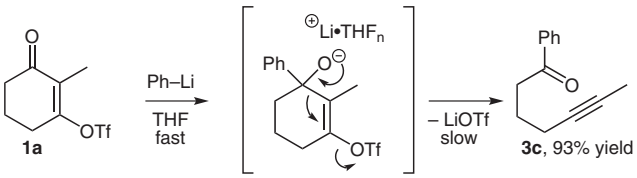
Abstract: Vinylogous acyl nonaflates, like the corresponding triflates, are subject to nucleophile-triggered fragmentation as part of a tandem process for generating functionalized alkynes. Advantages to the use of nonaflates in lieu of triflates include cost and stability. Computational analysis supports a postulated fragmentation mechanism involving a closed (cyclic) transition state with concerted extrusion of lithium sulfonate.

Key words: alkynes, fragmentation, nucleophilic addition, solvent effects, tandem reaction

Tandem processes[1] involve the coordinated execution of two or more distinct reactions in one experimental protocol. Under the umbrella of tandem processes are cascade/domino reactions,[2] in which all reactions take place without altering the experimental conditions, and consecutive/sequential processes that require additional input (energy and/or reagents) to complete the process.[3] Tandem reactions are typically associated with reduced time, effort, cost, and waste, especially as they pertain to avoiding the need to isolate and purify intermediates. In addition, such processes expand the synthetic utility of reactive intermediates for which isolation and purification may not be appropriate.

We have been developing a tandem process based on vinylogous acyl triflates in which C–C bond-forming addition of organometallic nucleophiles sets up a C–C bond-cleaving fragmentation event, with release of metal triflate salt, to generate functionalized alkynes (Scheme 1).[4] The first stage of this tandem process – addition to a vinylogous ester – is reminiscent of the Woods enone synthesis,[5] which is perhaps best known for its role in the Stork–Danheiser alkylation strategy.[6] The second stage intersects with the classic Eschenmoser–Tanabe fragmentation reaction.[7]

Alkynogenic (alkyne-generating) fragmentations like this one are rare compared to those that produce alkenes.[8] For generating alkynes, better nucleofuges[9] and/or higher temperatures are needed. Release of molecular nitrogen (and a sulfinic acid) drives the Eschenmoser–Tanabe fragmentation; more recently, Brewer and co-workers have exploited this most powerful nucleofuge in a variety of novel alkynogenic fragmentation pathways.[10] Selenones are also competent nucleofuges.[11] In contrast, Coke showed that chlorides participate in ring-opening fragmentations only upon rather intense heating.[12] Prior to our work, Fleming reported that simultaneous release of carbon dioxide and metal triflate salts can drive the alkynogenic fragmentation of β-keto ester derivatives.[13] Fleming's decarboxylative elimination to alkynes was in turn foreshadowed by Brummond's LDA-mediated elimination of vinyl triflates.[14]



Scheme 1 Nucleophilic addition/C–C bond-cleaving fragmentation of a vinylogous acyl triflate, with initial mechanistic hypothesis

An advantage of our tandem addition/fragmentation process is versatility (Scheme 2). By varying the nature of the nucleophile, one can generate alkynes optionally tethered to aryl and alkylketones, β-keto esters and phosphonates,[15] alcohols,[16] and amides.[4] Ring-expansion to cycloalkynes is also possible.[17] Likewise, varying the triflate substrate leads to alternative fragmentation products. Heterocyclic triflates provide access to homopropargyl alcohol[18] and amine[19] derivatives, and Williams[20] and Cramer[21]independently exploited deconjugated cyclohexenone triflates for the production of chiral allenes. On the other hand, the use of triflate building blocks can be cost-prohibitive, and some vinylogous acyl triflates are unstable to prolonged storage, as discussed herein.

In this report, we focus on vinylogous acyl nonaflates as an alternative to triflates (Figure 1). Nonaflates can provide certain specific advantages over triflates.[22] Nonaflyl fluoride (NfF) is produced industrially for surfactant applications, and as such it is inexpensive by pharmaceutical standards. Enol nonaflates are regarded as being more stable to storage than analogous triflates, while providing similar (if not greater) levels of reactivity.[24] We had previously examined nucleofuges including bromide, mesylate, and benzenesulfonate in place of triflate,[23]but none of these enabled the desired fragmentation process at temperatures up to refluxing toluene. Our studies on the synthesis, stability, and tandem addition/fragmentation reactivity of vinylogous acyl nonaflates are disclosed here.

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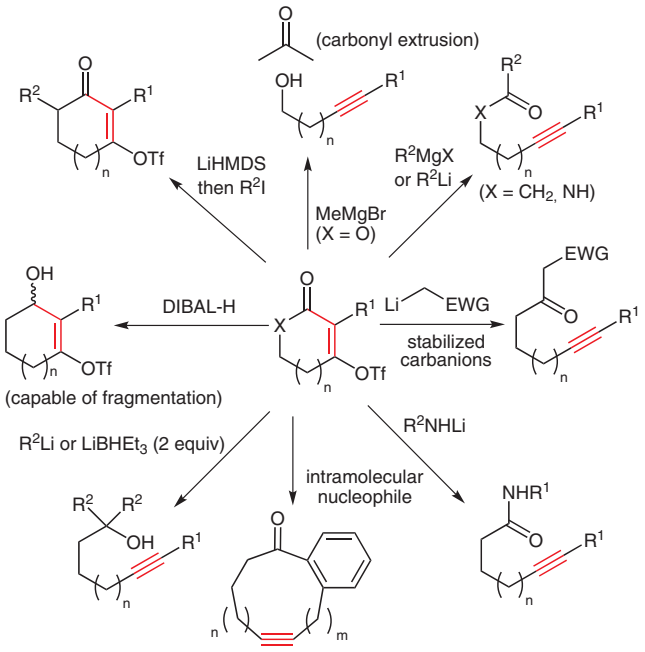


Scheme 2 Versatility of the tandem addition/fragmentation process for producing diverse alkyne building blocks

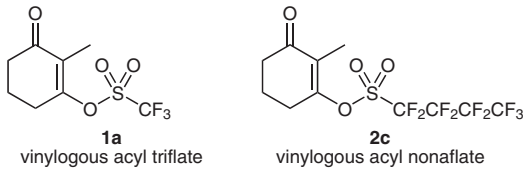


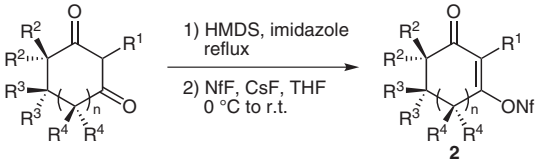
Figure 1 Vinylogous acyl triflate **1a** and nonaflate **2c**

Synthesis of Vinylogous Acyl Nonaflates

Synthesis of the vinylogous acyl nonaflate (VAN) substrates for tandem addition/fragmentation was carried out from commercially available 1,3-diones by analogy to literature reports (Table 1).[24] Direct dione sulfonylation was impractical, but the two-step process of silylation followed by TMS → Nf exchange provided general access to the desired VANs. Entries 5 and 6 are actually the result of a single experiment, in which a nonsymmetrical dione was converted into regioisomeric nonaflates **2e** (major) and **2f** (minor), which were then separated by chromatography.

There are advantages and disadvantages of this VAN synthesis compared with the corresponding triflates. Our preferred triflate synthesis involves cryogenic conditions, chlorinated solvent, and highly reactive (i.e., hazardous) and expensive triflic anhydride.[25] On the other hand, it provides triflate **1a** (Figure 1) in one step and 98% yield (vs. 73% for nonaflate **2c**, Table 1, entry 3). The VAN synthesis is potentially more amenable to large-scale production,[24] with nonaflyl fluoride being cheaper and easier to handle than triflic anhydride. Nonaflates also tend to be more robust, as discussed herein.

Table 1 Synthesis of Vinylogous Acyl Nonaflates (VANs) **2a–f**



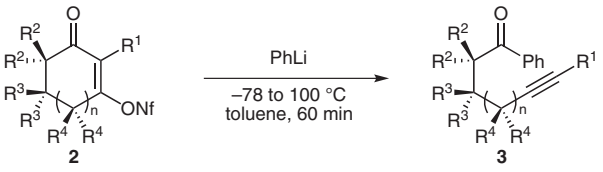
Entry	n	R^1, R^2, R^3, R^4	Nonaflate	Yield (%)[a]
1	0	Me, H, H, –	**2a**	85
2	1	H, H, H, H	**2b**	67
3	1	Me, H, H, H	**2c**	73
4	1	H, H, Me, H	**2d**	80
5	1	H, Me, H, H	**2e**	54[b]
6	1	H, H, H, Me	**2f**	20[b]

[a] Isolated yield.
[b] Nonaflates **2e** and **2f** (entries 5 and 6) were prepared from 6,6-dimethylcyclohexane-1,3-dione as a mixture of regioisomers, which were then separated by chromatography.

Tandem Nucleophilic Addition/Fragmentation Reactions of Vinylogous Acyl Nonaflates

The central question of this study – *Will VAN substrates undergo the tandem addition/fragmentation process by analogy to vinylogous acyl triflates?* – is addressed in Table 2. The best result was obtained in the reaction of

Table 2 Reaction of PhLi with Nonaflates **2a–f**



Entry	Concn	PhLi (equiv)	n	R^1, R^2, R^3, R^4	Alkyne	Yield (%)[a]
1[b]	0.28 M	0.9	1	Me, H, H, H	**3c**	72[c]
2[b]	55 mM	0.9	1	Me, H, H, H	**3c**	96[c]
3	28 mM	1.0	1	H, H, H, H	**3b**	63
4	28 mM	1.5	1	H, H, H, H	**3b**	76
5	28 mM	1.5	1	H, H, Me, H	**3d**	72
6	28 mM	1.5	1	H, Me, H, H	**3e**	68
7	28 mM	1.5	1	H, H, H, Me	**3f**	68
8	55 mM	1.0	0	Me, H, H, –	**3a**	56
9	55 mM	1.5	0	Me, H, H, –	**3a**	66
10	28 mM	1.5	0	Me, H, H, –	**3a**	76

[a] Isolated yield.
[b] Temp: –78 to 0 °C over 75 min.
[c] Based on PhLi.

phenyllithium with nonaflate **2c** (→ **3c**, Table 2, entry 2, 96%) under dilute conditions in toluene. The analogous transformation of triflate **1a** → **3c** (93% yield) was achieved at a higher concentration in THF.[4]

The reactions of phenyllithium with nonaflates **2a**–**f** are highlighted in Table 2. Yields of alkynyl ketones **3** correlate well with yields from our previous studies[4] involving vinylogous acyl triflates. Most yields here are slightly higher – the biggest improvement was in alkyne **3a** (entry 10, 76% vs. 61%[4]) – whereas the yield of **3d** is dramatically lower (entry 5, 72% vs. 96%[4]). Alkynes **3e** and **3f** (entries 6 and 7) had not been reported previously.

Optimal conditions here involved toluene as solvent (instead of THF) under more dilute conditions. Toluene emerged as the optimal solvent in previous studies involving alkyl nucleophiles,[15,20,21] which we rationalized based on aggregation effects with the organometallic partner, and the impact of these effects on the initial carbonyl addition step. However, in this case we are unable to reconcile the experimental observation with our working mechanistic hypothesis for the rate-determining fragmentation (Scheme 1). Consequently, we have revised our mechanistic model to account for the new observations (vide infra).

A brief scan of the scope of suitable nucleophiles for the tandem addition/fragmentation of vinylogous acyl nonaflates mostly parallels the previously studied triflates (Table 3). Both aryl and alkyl carbanions are appropriate, with lithium reagents outperforming Grignards (Table 3, entries 1–5). Phosphonate[17] anions are effective triggers for fragmentation (entries 6–8), but enolate addition to VAN **2b** produced alkyne **3m** much less efficiently than previously reported.[16]

Comparing Vinylogous Acyl Triflates and Nonaflates

We noted previously the cost advantages to nonaflates over triflates.[24] In addition, nonaflates generally provide enhanced stability over the corresponding triflates. Most of our methodology has focused on reactions of triflate **1a** (Figure 1), which is indefinitely stable. In fact, triflate **1a** is easier to purify, store, and handle than the dione from which it is derived. However, the same cannot be said for triflate **1b** (Figure 2), which must be freshly prepared for best results. In this case, the enhanced stability of VAN **2b** provides an advantage.

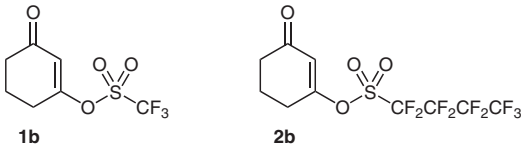
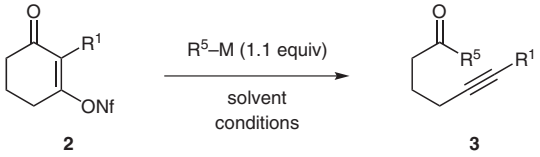


Figure 2 Vinylogous acyl triflate **1b** and nonaflate **2b**

We prepared fresh samples of **1b** and **2b** and left them overnight in the freezer (–25 °C). ^{1}H NMR analysis of the samples after 18 hours revealed that triflate **1b** had de-

Table 3 Reaction of Nonaflates with Diverse Nucleophiles[a]



Entry	Nonaflate **2**	R^1	R^5–M	Conditions	Alkyne	Yield (%)[b]
1	**2c**	Me	*n*-BuLi[c]	–78 → 0 °C	**3g**	98
2	**2c**	Me	PhLi[c]	–78 → 0 °C	**3c**	96
3	**2c**	Me	*n*-BuMgCl[c]	0 → 60 °C	**3g**	69
4	**2c**	Me	PhMgCl[c]	0 → 60 °C	**3c**	77
5	**2c**	Me	$PhCH_2MgCl$[c]	0 → 60 °C	**3h**	75
6	**2c**	Me	$(MeO)_2(O)PCH_2Li$	–78 → 60 °C	**3i**	89
7	**2b**	H	$(MeO)_2(O)PCH_2Li$	–78 → 60 °C	**3j**	53[d]
8	**2b**	H	$(MeO)_2(O)PCH(Me)Li$	–78 → 60 °C	**3k**	85[d]
9	**2b**	H	$PhC(OLi)=CH_2$[e]	–78 → 60 °C	**3m**	41

[a] Typical procedure: a solution of nonaflate **2** and R^5–M nucleophile (55 mM in toluene for entries 1–5, in THF for entries 6–9) stirred at low temperature for the initial addition, followed by warming to induce fragmentation; see 'Conditions' for specific temperatures.
[b] Isolated yield based on limiting reagent.
[c] Amount used = 0.9 equiv.
[d] Estimated yield based on ^{1}H NMR analysis.
[e] Amount of enolate = 2.2 equiv.

composed beyond recognition, whereas VAN **2b** remained essentially unchanged. Typically, **2b** is stored in a lab freezer for up to a week before repurification is warranted. The recommendation here is therefore to consider the nonaflate analogue in cases where triflate stability is a problem.

On the other hand, fragmentation of the nonaflate substrates optimally involves toluene as solvent under higher dilution than fragmentation of the triflates. Why are these changes in protocol beneficial for the fragmentation of nonaflates? Our initial mechanistic model (lithium ion solvation aids fragmentation, Scheme 1) is inconsistent with the positive effect of increasing the amount of toluene as the solvent for fragmentation. Therefore, we reconsider our initial hypothesis and now postulate a revised mechanism.

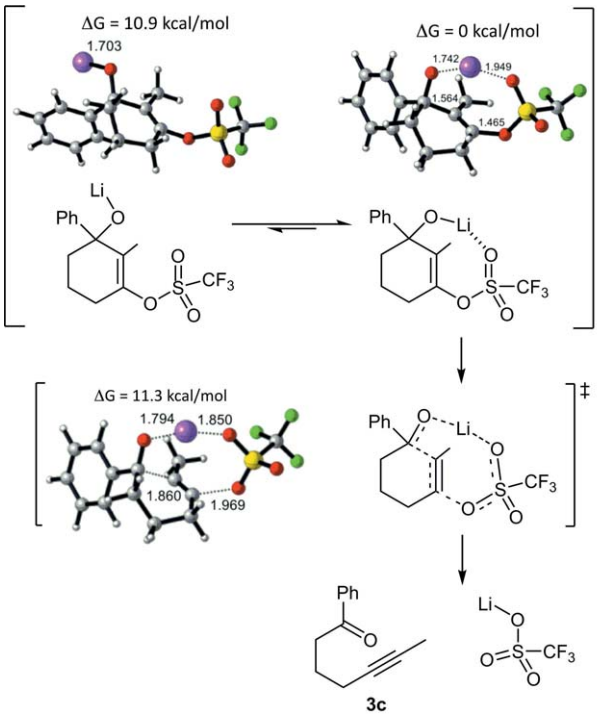
Revised Mechanistic Hypothesis

Why is toluene an effective fragmentation solvent? According to gas-phase free-energy calculations at the B3LYP/6-31(d) level of theory, the lithium alkoxide intermediate adopts a bridged conformation in which the lithium ion establishes points of contact with both the alkoxide and one of the sulfonate oxygens (Scheme 3). Such a chelate is likely strongest in nonpolar solvents and at low concentration, with fewer external Lewis basic sites available to compete with the sulfonate for coordination to lithium. In the gas phase, this cyclic eight-atom chelate is predicted to be 10.9 kcal/more more stable than the nonchelated structure.

The chelate structure offers the significant and specific advantage of releasing lithium triflate directly as a contact ion pair, through what we are calling a 'closed' transition state. The calculated energy barrier ($\Delta G^{\ddagger}$ =11.3 kcal/mol) is consistent with fragmentation occurring below room temperature as observed[4] (cf. Table 2, entry 2).[26] Note that these values were calculated for the triflate, which is simpler and easier to calculate than the nonaflate. Likewise in solution, the additional rotational degrees of freedom (and steric profile) of the nonaflate may disfavor the more ordered chelate structure, increasing the importance of a nonpolar solvent and high dilution conditions.

In conclusion, the tandem nucleophilic addition/fragmentation reactions of vinylogous acyl nonaflates provide access to alkyne-tethered ketones and β-keto phosphonates. This chemistry follows logically from previous work involving vinylogous acyl triflates, but with several distinctions. In general, nonaflates are cheaper to prepare, more stable to storage and handling, and at least equal in nucleofugality compared to their triflate counterparts. These advantages are expected to provide a positive impact for large-scale applications and in cases of poor triflate stability (e.g., **1b**).

Preliminary computational analysis of the postulated fragmentation pathway revealed an alternative 'closed' transition state, in which precomplexation within the intermediate lithium alkoxide leads to release of lithium sulfonate as a contact ion pair. More work is needed to probe this new mechanistic hypothesis experimentally, but it is consistent with recent observations. Importantly, the closed transition state model has predictive value for expanding the scope of the tandem addition/fragmentation process. Such studies are now underway.



Scheme 3 A revised mechanistic hypothesis for the tandem addition/fragmentation process, supported by gas-phase calculations at the B3LYP/6-31(d) level of theory (bond lengths given in Ångstroms). The lithium alkoxide intermediate preferentially adopts a bridging eight-atom ring chelate structure, which then undergoes extrusion of lithium triflate via a 'closed' transition state. Compared to the alternative release of lithium triflate as a solvent-separated ion pair (cf. Scheme 1), this pathway enables favorable interactions between lithium and the triflate in the fragmentation transition state, which provides an additional driving force for fragmentation.

^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer using $CDCl_3$ as the deuterated solvent. The chemical shifts (δ) are reported in parts per million (ppm) relative to the residual $CHCl_3$ peak (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR) and α,α,α-trifluorotoluene (–63.72 ppm for ^{19}F NMR spectra peak). The coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a FT-IR spectrometer with diamond ATR accessory as thin film. Mass spectra were recorded using electrospray ionization (ESI) or electron impact (EI). Yields refer to isolated material judged to be ≥95% pure by ^{1}H NMR spectroscopy following silica gel chromatography, unless otherwise noted. All chemicals were used as received unless otherwise stated. Nonafluorobutanesulfonyl fluoride (purity 98%) was obtained from Aldrich. All solvents, solutions and liquid reagents were added via syringe. THF was purified by distillation over Na and benzophenone. CH_2Cl_2 was distilled from CaH_2. Toluene was dried over a column of molecular sieves under N_2. The *n*-BuLi solutions were titrated against a known amount menthol dissolved in THF using 1,10-phenanthroline as the indicator. All reactions were carried out under an inert N_2 atmosphere unless otherwise stated. The purifications were performed by flash chromatography using silica gel F-254 (230–499 mesh particle size). Cartesian Coordinates: all stationary points have been

shown to be either minima (zero imaginary frequencies) or first-order saddle points (one imaginary frequency).

Nonaflates 2; 3-Oxocyclohex-1-enyl Nonafluorobutanesulfonate (2b); Typical Procedure

To a suspension of cyclohexane-1,3-dione (1.00 g, 8.92 mmol) in HMDS (7.0 mL, 31.21 mmol) was added imidazole (36.4 mg, 0.54 mmol) at r.t. The resulting mixture was stirred at 130 °C for 3 h and then cooled to r.t. The excess HMDS was distilled off under reduced pressure to obtain a crude oil (TMS-enol ether), which was used further without purification. To a solution of the TMS-enol ether in THF (18 mL) was added CsF (271 mg, 1.78 mmol) at 0 °C. After stirring for 10 min, perfluoro-1-butanesulfonyl fluoride (1.76 mL, 9.81 mmol) was added dropwise. The resulting mixture was slowly warmed to r.t. and stirred for 18 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (2 × 15mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL). The solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an oil. Purification by column chromatography on silica gel (gradient elution from 10% to 15% EtOAc–hexanes) gave 2.36 g (67%) of **2b** as a colorless oil (See Table 1 for experimental modifications and yields for each entry).

IR (neat): 1693, 1646, 1428, 1353, 1224, 1197, 1141, 1069, 1033, 910 cm^{-1}.

^1H NMR (400 MHz): δ = 2.10 (quint, *J* = 6.5 Hz, 2 H), 2.43 (t, *J* = 6.7 Hz, 2 H), 2.66 (t, *J* = 6.2 Hz, 2 H), 6.05 (d, *J* = 1.2 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 20.7, 28.4, 36.3, 119.1, 167.6, 197.4.

^{19}F NMR (376 MHz): δ = –81.8 (t, *J* = 9.7 Hz, 3 F), –110.25 to –110.30 (m, 2 F), –121.08 to –121.16 (m, 2 F), –127.1 to –127.1 (m, 2 F).

HRMS (EI$^+$): *m*/*z* calcd for $C_{10}H_7F_9O_4S$ $(M)^+$: 393.9921; found: 393.9935.

2a

Yield: 2.99 g (85%); colorless oil.

IR (neat): 1724, 1680, 1429, 1225, 1142, 1083, 1052, 1033, 901 cm^{-1}.

^1H NMR (400 MHz): δ = 1.78 (app t, *J* = 2.2 Hz, 1 H), 2.64–2.66 (m, 2 H), 2.91–2.93 (m, 2 H).

^{13}C NMR (100 MHz): δ = 6.7, 26.9, 129.7, 172.4, 203.2.

^{19}F NMR (376 MHz): δ = –81.6 (t, *J* = 9.5 Hz, 3 F), –110.2 to –110.3 (m, 2 F), –121.78 to –121.82 (m, 2 F), –126.7 to –126.8 (m, 2 F).

HRMS (EI$^+$): *m*/*z* calcd for $C_{10}H_7F_9O_4S$ $(M)^+$: 393.9921; found: 393.9008.

2c

Yield: 2.36 g (73%); colorless oil.

IR (neat): 1690, 1669, 1420, 1344, 1223, 1195, 1142, 1026, 914 cm^{-1}.

^1H NMR (400 MHz): δ = 1.88 (t, *J* = 1.2 Hz, 3 H), 2.08 (quint, *J* = 6.5 Hz, 2 H), 2.49 (t, *J* = 6.8 Hz, 2 H), 2.72–2.76 (m, 2 H).

^{13}C NMR (100 MHz): δ = 9.3, 20.6, 28.7, 36.6, 128.2, 162.2, 197.7.

^{19}F NMR (376 MHz): δ = –81.6 (t, *J* = 9.6 Hz, 3 F), –110.75 to –110.85 (m, 2 F), –121.7 to –121.8 (m, 2 F), –126.8 to –126.9 (m, 2 F).

HRMS (EI$^+$): *m*/*z* calcd for $C_{11}H_9F_9O_4S$ $(M)^+$: 408.0078; found: 408.0079.

2d

Yield: 2.41 g (80%); colorless oil.

IR (neat): 1689, 1648, 1429, 1350, 1224, 1199, 1142, 1051, 951 cm^{-1}.

^1H NMR (400 MHz): δ = 1.13 (s, 6 H), 2.31 (s, 2 H), 2.540 (s, 2 H), 2.543 (s, 2 H), 6.08 (s, 1 H).

^{13}C NMR (100 MHz): δ = 27.9, 33.3, 42.3, 50.5, 118.2, 166.2, 197.5.

^{19}F NMR (376 MHz): δ = –81.8 (t, *J* = 9.5 Hz, 3 F), –110.25 to –110.33 (m, 2 F), –122.1 to –122.2 (m, 2 F), –127.0 to –127.1 (m, 2 F).

HRMS (EI$^+$): *m*/*z* calcd for $C_{12}H_{11}F_9O_4S$ $(M)^+$: 422.0234; found: 422.0233.

2e

Yield: 1.64 g (54%); colorless oil.

IR (neat): 1690, 1653, 1428, 1353, 1226, 1198, 1142, 1055, 1030, 920 cm^{-1}.

^1H NMR (400 MHz): δ = 1.13 (s, 6 H), 1.92 (t, *J* = 6.2 Hz, 2 H), 2.70 (td, *J* = 6.2, 1.3 Hz, 2 H), 5.98 (s, 1 H).

^{13}C NMR (100 MHz): δ = 23.5, 26.2, 34.3, 40.8, 117.6, 165.6, 202.1.

^{19}F NMR (376 MHz): δ = –81.6 (t, *J* = 9.6 Hz, 3 F), –110.0 to –110.1 (m, 2 F), –121.8 to –121.9 (m, 2 F), –126.8 to –126.9 (m, 2 F).

HRMS (EI$^+$): *m*/*z* calcd for $C_{12}H_{11}F_9O_4S$ $(M)^+$: 422.0234; found: 422.0215.

2f

Yield: 0.59 g (20%); colorless oil.

IR (neat): 1694, 1632, 1420, 1228, 1197, 1142, 1019, 1884 cm^{-1}.

^1H NMR (400 MHz): δ = 1.30 (s, 6 H), 1.96 (dd, *J* = 6.9, 5.8 Hz, 2 H), 2.50 (dd, *J* = 7.4, 6.2 Hz, 2 H), 6.02 (s, 1 H).

^{13}C NMR (100 MHz): δ = 24.9, 33.9, 35.8, 36.2, 116.1, 172.9, 197.4.

^{19}F NMR (376 MHz): δ = –81.8 (t, *J* = 9.6 Hz, 3 F), –110.4 to –110.5 (m, 2 F), –122.1 to –122.2 (m, 2 F), –127.0 to –127.1 (m, 2 F).

HRMS (EI$^+$): *m*/*z* calcd for $C_{12}H_{11}F_9O_4S$ $(M)^+$: 422.0234; found: 422.0221.

Reaction of VANs 2 with PhLi; 1-Phenylhex-5-yn-1-one (3b); Typical Procedure

PhLi (0.28 mL, 0.50 mmol; 1.8 M in Bu_2O) was added dropwise to nonaflate **2b** (0.27 g, 1.02 mmol) in toluene (25 mL) at –78 °C under N_2. The resulting mixture was stirred at –78 °C for 15 min, warmed to r.t., and then heated at 100 °C for 45 min. H_2O (15 mL) was added to quench the reaction and then the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an oil, which was purified by column chromatography on silica (gradient elution from 10% to 15% EtOAc–hexanes) to give 89.5 g (76%) of **3b** as a colorless oil (see Table 2 for experimental modifications and yields for each entry).

Characterization data for **3e** and **3f** are provided; data for **3a** (entry 10, 134 mg, 76%), **3b** (entry 4, 134 mg, 76%), **3c** (entry 2, 182 mg, 96%), and **3d** (entry 5, 157 mg, 72%) match our previous report.[4]

3e

Yield: 65 mg (68%); colorless oil.

IR (neat): 3297, 2969, 1671, 1598, 1472, 1390, 1261, 1200, 1180 cm^{-1}.

^1H NMR (400 MHz): δ = 1.25 (s, 6 H), 1.85 (app t, *J* = 2.6 Hz, 1 H), 1.95–2.00 (m, 2 H), 2.04–2.07 (m, 2 H), 7.30–7.34 (m, 2 H), 7.36–7.40 (m, 1 H), 7.58–7.60 (m, 2 H).

^{13}C NMR (100 MHz): δ = 14.3, 25.8, 39.5, 47.3, 68.5, 84.0, 127.6, 128.1, 131.0, 138.5, 208.0.

HRMS (EI$^+$): *m*/*z* calcd for $C_{14}H_{16}O$ $(M)^+$: 200.1201; found: 200.1197.

3f
Yield: 65 mg (68%); colorless oil.

IR (neat): 3297, 2971, 1683, 1598, 1449, 1364, 1289, 1215, 1003 cm^{-1}.

^1H NMR (400 MHz): δ = 1.25 (s, 6 H), 1.85 (app t, *J* = 2.6 Hz, 1 H), 1.95–2.00 (m, 2 H), 2.04–2.07 (m, 2 H), 7.30–7.34 (m, 2 H), 7.36–7.40 (m, 1 H), 7.58–7.60 (m, 2 H).

^{13}C NMR (100 MHz): δ = 29.0, 30.6, 35.0, 36.9, 68.7, 90.8, 128.0, 128.5, 132.9, 136.8, 200.0.

HRMS (EI$^+$): *m*/*z* calcd for $C_{14}H_{16}O$ $(M)^+$: 200.1201; found: 200.1209.

Reaction of VANs 2 with Organometallic Nucleophiles; Undec-9-yn-5-one (3g); Typical Procedure
n-BuLi (0.29 mL, 0.45 mmol; 1.5 M in hexane) was added dropwise to **2c** (0.20 g, 0.49 mmol) in toluene (9 mL) at –78 °C under N_2. The resulting mixture was stirred at –78 °C for 15 min, then at 0 °C for 60 min. H_2O (15 mL) was added to quench the reaction, and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an oil, which was purified by column chromatography on silica (gradient elution from 10% to 15% EtOAc–hexanes) to give 73 g (98%) of **3g** as a colorless oil (see Table 3 for modifications and yields for each entry).

Characterization data for **3c** (entry 2, 80 mg, 96% and entry 4, 64 mg, 77%), **3g** (entry 1, 73 mg, 98% and entry 3, 51 mg, 69%), and **3h** (entry 5, 67 mg, 75%) match our previous report.[4]

Claisen-Type Condensation of VANs 2 with Phosphonate Nucleophiles; Dimethyl 1-Methyl-2-oxohept-6-ynylphosphonate (3k); Typical Procedure
A THF solution (10 mL) of diethyl ethylphosphonate (0.10 mL, 0.61 mmol) was treated with *n*-BuLi (0.35 mL, 0.56 mmol; 1.6 M solution in hexanes,) at –78 °C. After 20 min, a solution of nonaflate **2b** (0.20 g, 0.50 mmol) in THF was added dropwise. The resulting solution was stirred at –78 °C for 10 min, warmed to r.t., stirred for 40 min, and then heated at 60 °C for 30 min. The reaction mixture was diluted with sat. aq NH_4Cl (10 mL) and then extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated reduced pressure to give an oil, which was purified by column chromatography on silica (gradient elution from 80% to 100% EtOAc–hexanes) to afford 124 mg of a pale yellow oil. Based on ^1H NMR analysis, this mixture comprised 112 mg of **3k** (85% estimated yield) and 12 mg of diethyl ethylphosphonate (see Table 3 for experimental modifications and yields for each entry).

Characterization data for **3j** and **3k** are provided; data for **3i** (101 mg, 89%) match our previous report.[4]

3k
IR (neat): 3945, 2987, 1715, 1456, 1355, 1237, 1136, 1053, 967 cm^{-1}.

^1H NMR (400 MHz): δ = 1.32 (t, *J* = 7.6 Hz, 6 H), 1.38 (app dd, *J* = 19.9, 7.1 Hz, 3 H), 1.81 (quint, *J* = 7.2 Hz, 2 H), 1.95 (t, *J* = 2.6 Hz, 1 H), 2.22 (app tq, *J* = 6.9, 1.4 Hz, 2 H), 2.66 (app dt, *J* = 18.4, 7.1 Hz, 1 H), 2.96 (dt, *J* = 18.3, 7.2 Hz, 1 H), 3.22 (dq, *J* = 13.1, 7.1 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 11.0 (d, $^2J_{C,P}$ = 6.2 Hz), 16.4 (d, $^3J_{C,P}$ = 6.2 Hz), 17.7, 22.2, 41.6, 46.1, 47.4, 62.58 (d, $^2J_{C,P}$ = 7.3 Hz), 62.70 (d, $^2J_{C,P}$ = 6.6 Hz), 69.0, 83.7, 205.5 (d, $^2J_{C,P}$ = 4.2 Hz).

HRMS (ESI$^+$) calcd for $C_{12}H_{21}O_4P$ + Na $(M + Na)^+$: 283.1075; found: 283.1082.

3j
Yield: 64 mg of a pale yellow oil, which based on ^1H NMR analysis comprised 58 mg of **3j** (85% estimated yield) and 5 mg of dimethyl methylphosphonate.

IR (neat): 2960, 1671, 1423, 1353, 1237, 1203, 1145, 1037, 914 cm^{-1}.

^1H NMR (400 MHz): δ = 1.81 (quint, *J* = 7.0 Hz, 2 H), 1.96 (t, *J* = 2.7 Hz, 2 H), 2.24 (td, *J* = 6.9, 2.6 Hz, 2 H), 2.77 (t, *J* = 7.1 Hz, 2 H), 3.11 (d, $^2J_{H,P}$ = 22.7 Hz, 2 H), 3.79 (d, $^3J_{H,P}$ = 11.2 Hz, 6 H).

^{13}C NMR (100 MHz): δ = 17.5, 22.0, 42.5, 42.0, 40.7, 53.1 (d, $^2J_{C,P}$ = 6.4 Hz), 69.1, 83.3, 201.3 (d, $^2J_{C,P}$ = 6.5 Hz).

HRMS (ESI$^+$): *m*/*z* calcd for $C_9H_{15}O_4P$ + Na $(M + Na)^+$: 241.0606; found: 241.0604.

Spectroscopic data match the data reported previously for **3j**.[27]

Claisen-Type Condensation of VAN 2b with the Lithium Enolate of Acetophenone; 1-Phenyl-oct-7-yne-1,3-dione (3m); Typical Procedure (Table 3, entry 9)
To a stirred solution of LDA [prepared by treating a solution of *i*-Pr_2NH (0.15 mL, 1.07 mmol) in THF (8 mL) with *n*-BuLi (0.70 mL, 1.07 mmol; 1.5 M in hexane) at 0 °C] was added dropwise acetophenone (0.13 mL, 1.07 mmol) at –78 °C. After 30 min, a solution of nonaflate **2b** (0.19 g, 0.49 mmol) in THF (2 mL) was added. The resulting solution was stirred at –78 °C for 20 min, at r.t. for 40 min, and at 60 °C for 30 min. The solution was diluted with sat. aq NH_4Cl (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated to an oil, which was purified by column chromatography on silica gel (gradient elution from 15% to 20% EtOAc–hexanes) to afford 43.1 mg (41%) of **3m**. Characterization data for **3m** match our previous report.[16]

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are copies of ^1H, ^{13}C, and ^{19}F NMR spectra and Cartesian coordinates and energies for calculations.

Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synthesis and can be cited using the following DOI: 10.4125/pd0027th.

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