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Generation of Medium-Ring Cycloalkynes by Ring Expansion of Vinylogous Acyl Triflates

Jumreang Tummatorn and Gregory B. Dudley*

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390, United States

gdudley@chem.fsu.edu

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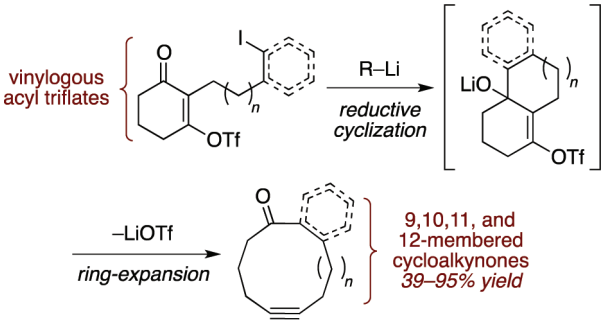

Reductive cyclization of aryl and vinyl iodides tethered to vinylogous acyl triflates (VATs) induces a ring-expanding fragmentation to provide cyclic alkynyl ketones, including strained nine-membered cycloalkynes, in fair to excellent yield. The tandem cyclization/C−C bond-cleavage is initiated under carefully optimized conditions by halogen−metal exchange in the presence of carbonyl and vinyl triflate functionality. A modified protocol for alkylation of 1,3-cyclohexanedione is described for preparing the relevant VAT substrates.

As the utility of alkyne chemistry expands,[1] so too does the demand for functionalized alkynes. Strained and medium-ring cycloalkynes are especially difficult to prepare.[2] Macrocyclic alkynes can be made by cyclization of linear acetylenes,[3] but such tactics are not suitable for producing smaller cycloalkynes because of entropic constraints. We now report new ring expanding fragmentation reactions that generate medium-ring cycloalkynes from nonacetylenic precursors.

Fragmentation reactions have been under development for nearly 60 years, led by the pioneering work of Eschenmoser,[4] Grob,[5] Wharton,[6] and others.[7] Aside from the Eschenmoser−Tanabe alkyne synthesis,[8] the vast majority of fragmentations used in organic synthesis have involved formation of *alkene* (not alkyne) π-systems.[9,10] The relative dearth of what we call "alkynogenic" (alkyne-generating)

(1) (a) Polyynes, Arynes, Enynes, and Alkynes. In *Science of Synthesis: Houben−Weyl Methods of Molecular Transformation*; Thomas, E. J., Hopf, H., Eds.; Thieme: Stuttgart, 2008; Vol. 43. (b) *Acetylene Chemistry: Chemistry, Biology, and Materials Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005. (c) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988.

(2) (a) Hopf, H.; Grunenberg, J. Angle-Strained Cycloalkynes. In *Strained Hydrocarbons*; Dodziuk, H., Ed.; Wiley-VCH: Weinheim, 2009; pp 375−397. (b) Meier, H. *Synthesis* **1972**, 235–253.

(3) (a) Gleiter, R.; Werz, D. B. Product Class 9: Cycloalkynes. In *Science of Synthesis: Houben−Weyl Methods of Molecular Transformation*; Thomas, E. J., Hopf, H., Eds.; Thieme: Stuttgart, 2008; Vol. 43, Chapter 9, pp 631−668. (b) Gleiter, R.; Merger, R. Cyclic Alkynes: Preparation and Properties. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995; pp 285−319.

(4) Eschenmoser, A.; Frey, A. *Helv. Chim. Acta* **1952**, *35*, 1660–1666.

(5) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1–15.

(6) Wharton, P. S. *J. Org. Chem.* **1961**, *26*, 4781–4782.

(7) 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.

(8) Kürti, L.; Czakó, B. Eschenmoser−Tanabe Fragmentation. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: New York, 2003; pp 158−159 and references cited.

(9) Prantz, K.; Mulzer, J. *Chem. Rev.* **2010**, *110*, 3741–3766.

(10) The review cited in ref 9 focuses on synthetic applications of Grob fragmentations; almost all examples involve alkene-generating fragmentations, with only a few in which alkynes are produced: (a) Fleming, I.; Harley-Mason, J. *J. Chem. Soc.* **1963**, 4771–4778. (b) Grob, C. A.; Csapilla, J.; Cseh, G. *Helv. Chim. Acta* **1964**, *47*, 1590–1602. (c) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028–5029. (d) Kamijo, S.; Dudley, G. B. *Tetrahedron Lett.* **2006**, *47*, 5629–5632.

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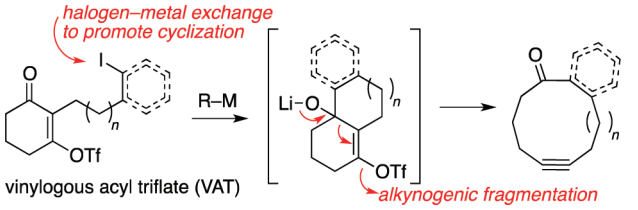
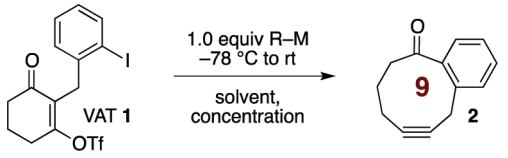
fragmentations likely reflects a higher enthalpic barrier to forming the alkyne π-bond as compared to alkenes or even allenes.[11] Alkynogenic fragmentations require either an exceedingly high temperature[12] or an exceptionally strong nucleofuge,[13] namely molecular nitrogen[14] or triflate.[15,16]

Scheme 1. Ring Expansion Strategy for the Synthesis of Medium-Ring Cycloalkynones



The central hypothesis of the present study is that reductive cyclization of vinylogous acyl triflates (VATs) will trigger ring-expanding fragmentation to produce medium-sized cycloalkynes (Scheme 1) and that this process can be initiatied by halogen−metal exchange in the presence of VAT functionality. We have used VAT fragmentation to produce acyclic alkynyl ketones, but our methodology had been limited to aryl nucleophiles[10c] and stabilized carbanions.[17] More reactive alkyllithium and Grignard reagents, such as could be employed for halogen−metal exchange with aryl iodides, induced decomposition of the VAT substrates. As the study evolved, however, we came to realize that nucleophilic 1,2-addition is easier to control—or rather, that VAT decomposition is suppressed—using toluene as the solvent.[18] This observation facilitated expansion of the methodology to heterocyclic VATs, providing access to homopropargyl alcohols and amines.[19] It also improved the prospects of generating active carbanion nucleophiles tethered to the VAT substrate (Scheme 1), so as to enable cyclization and ring-expansion pathways.[20]

Table 1. Optimization of the Reductive VAT Ring Expansion



entry	R−M	solvent[a]	concn (M)	yield[b] (%)
1	*n*-BuLi	THF	0.07	0
2	*t*-BuMgCl[c]	THF	0.06	0
3	*n*-BuLi	Toluene	0.07	0
4	*n*-BuLi	THF/HMPA	0.1	22
5	*n*-BuLi	Et_2O/HMPA	0.1	25
6	*n*-BuLi	toluene/HMPA	0.1	36[d]
7	*t*-BuLi[c]	toluene/HMPA	0.1	0
8	*n*-BuLi	toluene/HMPA	0.03	44
9	*n*-BuLi	toluene/HMPA	0.025	51
10	*n*-BuLi	toluene/HMPA	0.01	62
11	*n*-BuLi	toluene/HMPA	0.005	83

[a] 3.0 equiv of HMPA in entries 4−11. [b] Isolated yield of pure material; see Supporting Information for details. [c] 2.0 equiv. [d] Changing the initial temperature to either −40 or −100 °C led to inferior results.

Experiments designed to provide evidence in support of our central hypothesis are recounted in Table 1. We chose benzocyclononyne **2** as the initial target and 2-iodobenzyl-VAT **1** as the prototype substrate for method development. As expected, treatment of **1** with either *n*-BuLi or *t*-BuMgCl in THF resulted in decomposition of the substrate with no evidence of cycloalkyne formation (entries 1 and 2). However, switching the solvent to toluene provided no measurable improvement (entry 3). The first promising results were obtained when HMPA (3.0 equiv) was added.[21] Entries 4−6 reveal that toluene is indeed preferable to ethereal solvents, although *t*-BuLi continued to induce general decomposition

(11) Using an elegant combination of theory and experiment, Williams recently described fragmentation reactions that preferentially generate allenes over alkynes. For more information and applications in synthesis, see: (a) Kolakowski, R. V.; Manpadi, M.; Zhang, Y.; Emge, T. J.; Williams, L. J. *J. Am. Chem. Soc.* **2009**, *131*, 12910–12911. (b) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 8962–8965.

(12) Coke, J. L.; Williams, H. J.; Natarajan, S. *J. Org. Chem.* **1977**, *42*, 2380–2382.

(13) Lepore, S. D.; Mondal, D. *Tetrahedron* **2007**, *63*, 5103–5122.

(14) (a) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708–713. (b) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943–3946. (c) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, 3739–3743. (d) Felix, D.; Shreiber, J.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 2896–2912. (e) Draghici, C.; Brewer, M. *J. Am. Chem. Soc.* **2008**, *130*, 3766–3767. (f) Draghici, C.; Huang, Q.; Brewer, M. *J. Org. Chem.* **2009**, *74*, 8410–8413. (g) Bayir, A.; Draghici, C.; Brewer, M. *J. Org. Chem.* **2010**, *75*, 296–302. (h) Dias-Jurberg, I.; Gagosz, F.; Zard, S. Z. *Org. Lett.* **2010**, *12*, 416–419.

(15) See ref 10c and (a) Fleming, I.; Ramarao, C. *Org. Biomol. Chem.* **2004**, *2*, 1504–1510. (b) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499–6507. (c) Murphy, J. A.; Mahesh, M.; McPheators, G.; Anand, R. V.; McGuire, T. M.; Carling, R.; Kennedy, A. R. *Org. Lett.* **2007**, *9*, 3233–3236. For related examples involving a selenium-derived nucleofuge, see:(d) Shimizu, M.; Ando, R.; Kuwajima, I. *J. Org. Chem.* **1981**, *46*, 5246–5248. (e) Shimizu, M.; Ando, R.; Kuwajima, I. *J. Org. Chem.* **1984**, *49*, 1230–1238.

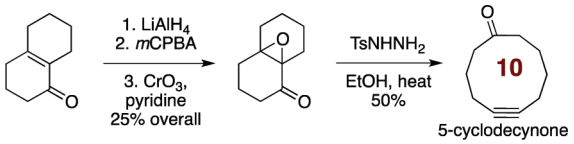
(16) Use of carbon dioxide as an electrofuge has also been used to drive alkyne formation; see refs 10a, 10b, 14h, and 15a.

(17) (a) Kamijo, S.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 175–177. (b) Jones, D. M.; Lisboa, M. P.; Kamijo, S.; Dudley, G. B. *J. Org. Chem.* **2010**, *75*, 3260–3267.

(18) Jones, D. M.; Kamijo, S.; Dudley, G. B. *Synlett* **2006**, 936–938.

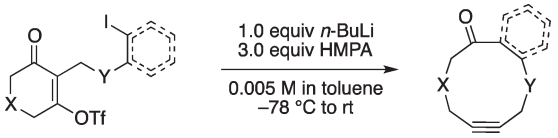
(19) (a) Tummatorn, J.; Dudley, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 5050–5051. (b) Tummatorn, J.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 158–160.

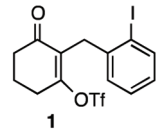
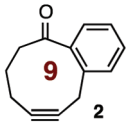
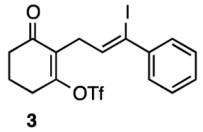
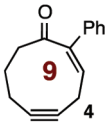
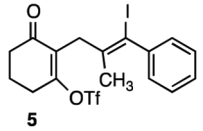
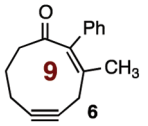
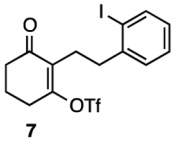
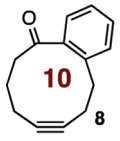
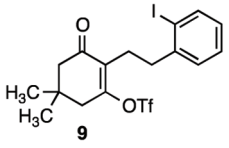
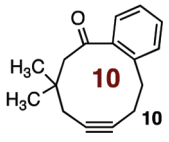
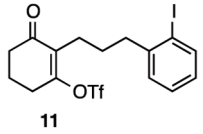
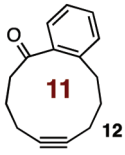
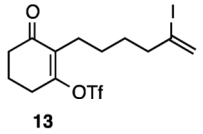
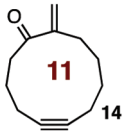
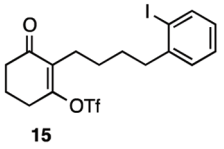
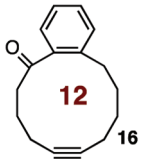
(20) Note that Tanabe generated 5-cyclodecynone, albeit in modest overall yield, using what we now call the Eschenmoser−Tanabe strategy; this result was both encouraging and motivating with respect to developing new reductive ring expansions of iodoaryl- and iodovinyl-tethered VATs. See ref 14b for details, and for a related example, see: Gordon, D. M.; Danishefsky, S. J.; Schulte, G. K. *J. Org. Chem.* **1992**, *57*, 7052–7055.



(21) The ^{1}H NMR spectrum of **2** displays unusually broad resonance signals suggestive of a complex mixture of conformational isomers (see p S27 of the Supporting Information for a copy of the spectrum).

Table 2. Preliminary Scope and Limitations



entry	VAT substrate	cycloalkyne product	yield[a]
1	 **1**	 **2**	83%
2	 **3**	 **4**	44%
3	 **5**	 **6**	66%
4	 **7**	 **8**	95%
5	 **9**	 **10**	91%
6[b]	 **11**	 **12**	95%
7[c]	 **13**	 **14**	39%
8[c]	 **15**	 **16**	46%

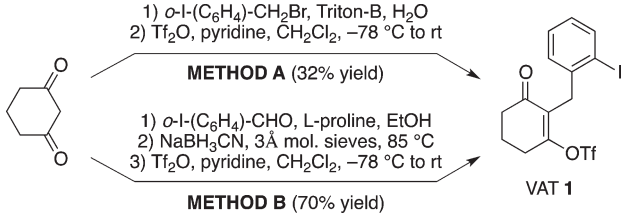
[a] Isolated yield of pure material; see Supporting Information for details. [b] Temperature = −42 °C to rt. [c] Concentration = 0.01 M.

(entry 7). Increasing the amount of toluene (decreasing the substrate concentration) resulted in progressively higher yields of **2** (entries 6 and 8−11). At a substrate concentration of 0.005 M (entry 11), cyclononyne **2** was isolated in 83% yield.[22]

(22) This concentration corresponds to slightly more than 2 mg of substrate per mL of solvent. In our hands, the reaction becomes impractical below this concentration.

Building on this initial example, a variety of medium-sized cycloalkynes was prepared (Table 2). Vinyl iodide **3** underwent reductive ring expansion to cyclononyne **4** in modest yield (entry 2); dehydroiodination of **3** competes with halogen−metal exchange, reducing the yield of the desired cycloalkyne (see also entry 7). When this elimination pathway is blocked, the yield rebounds to a more satisfactory level (entry 3). Extending the tether by one methylene unit provides cyclodecyne **8** in excellent yield (entry 4, cf. entry 1). Indeed, high yields were obtained for all benzo-fused ten- and eleven-membered cycloalkynes (entries 4−6). The reductive cyclizations in these experiments, which form transient six- and seven-membered rings, evidently proceed more efficiently than the analogous five- and eight-membered cyclizations involved in the ring expansions of VATs **1** and **15**.[23]

Scheme 2. Methods for Preparation of VAT Substrates[a]



[a] See Suporting Information for details.

The VAT substrates were prepared by either of two methods (**A** or **B**), as outlined in Scheme 2; both methods conclude with enol triflation of the requisite 2-alkyl-dione using our standard procedure.[24] Alkylation of cyclic 1,3-diones (Method **A**) is notoriously difficult,[25] but we were able to achieve modest yields in cases where the alkylating agent was either allylic or benzylic (VATs **1**, **3**, and **5**).[26] In general, however, it was more convenient (and effective in terms of overall yield) to condense the appropriate aldehyde with excess 1,3-cyclohexanedione using proline catalysis, followed by conjugate reduction of the intermediate 2-alkylidene-dione (Method **B**, Scheme 2).[27,28]

Cyclononyne **2** displays unusual spectroscopic behavior[21] consistent with restricted conformational movement,

(23) We speculate that these cyclization pathways are compromised by angle strain and transannular interactions, respectively, and that decomposition through competing pathways involving the vinyl triflate may be occurring. Our initial attempts to generate cyclooctynes by this method were unsuccessful, and further efforts are in progress.

(24) Lisboa, M. P.; Hoang, T. T.; Dudley, G. B. *Org. Synth.* (submitted).

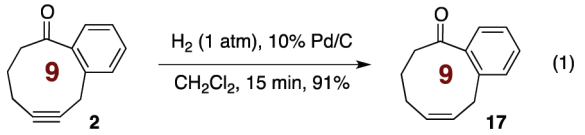
(25) Piers, E.; Grierson, J. R. *J. Org. Chem.* **1977**, *42*, 3755–3757.

(26) Rajamannar, T.; Palani, N.; Balasubramanian, K. K. *Synth. Commun.* **1993**, *23*, 3095–3108.

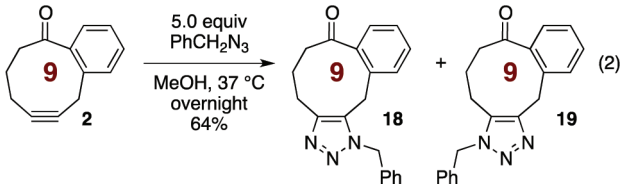
(27) (a) Ramachary, D. B.; Reddy, G. B. *Org. Biomol. Chem.* **2006**, *4*, 4463–4468. (b) Ramachary, D. B.; Kishor, M. *J. Org. Chem.* **2007**, *72*, 5056–5068.

(28) We modifed Ramachary's method for our purposes. Ramachary reported an ingenious one-pot proline-catalyzed reductive condensation, but his conditions require excess aldehyde (ref 27). Our two-step modification enables use of the aldehyde as the limiting reagent, which is ideal for more complex aldehydes. For application of $NaBH_3CN$ reduction in the synthesis of 2-alkyl-1,3-diones, see: Pashkovsky, F. S.; Lokot, I. P.; Lakhvich, F. A. *Synlett* **2001**, 1391–1394.

which is likely a consequence of alkyne angle strain.[2] Hydrogenation of **2** provided *cis*-cyclononene **17** (eq 1), for which a clear and well-resolved ^{1}H NMR spectrum was obtained.[29] The *cis*-alkene was significantly less reactive than the strained alkyne; no overreduction was observed, despite use of an active hydrogenation catalyst (10 wt % palladium on activated carbon).



Strained cycloalkynes are valuable tools in the design and execution of bioorthogonal[30] "click" reactions based on metal-free Huisgen cycloadditions.[31] The ideal reagent for these bioorthogonal couplings is stable, easy to make, and reactive under conditions that are compatible with native biochemical systems. Most current reagents are based on cyclooctyne,[32] but cyclononyne **2** provides hints of desirable "click" reactivity: the coupling of **2** with benzyl azide was slow at room temperature, but heating at 37 °C overnight gave rise to a mixture of triazoles **18** and **19** in 64% yield (eq 2, unoptimized). Thus, ring expansion of VATs may provide a convenient entry into the synthesis of cycloalkyne "click" reagents. As noted earlier,[23] efforts to prepare more reactive strained cycloalkynes (including cyclooctynes) are now underway.



In conclusion, ring expansion of vinylogous acyl triflates (VATs) to medium-ring cycloalkynones, including ones with sufficient strain energy as to display enhanced reactivity, has been accomplished in fair to excellent yield. Concomitant formation of the alkyne and the ring structure distinguishes this strategy from alternatives in which the two namesake features of medium-ring cycloalkynes are crafted separately. The key tactical innovation behind this methodology is the ability to induce halogen−metal exchange in the presence of the VAT functionality. A modified synthesis of 2-alkyl-1,3-cyclohexanediones was also developed as part of a convenient method for preparing the VAT substrates. The tandem reductive cyclization and ring expanding fragmentation pathway provides access to functionalized cycloalkynes that are otherwise difficult to prepare.

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Supporting Information Available. Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(29) See p S35 of the Supporting Information.

(30) (a) Lim, R. K. V.; Lin, Q. *Chem. Commun.* **2010**, *46*, 1589–1600. (b) Sletten, E. M.; Bertozzi, C. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6974–6998.

(31) (a) Jewett, J. C.; Bertozzi, C. R. *Chem. Soc. Rev.* **2010**, *39*, 1272–1279. (b) Ning, X.; Guo, J.; Wolfert, M. A.; Boons, G.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2253–2255. (c) Jewett, J. C.; Sletten, E. M.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 3688–3690. (d) See also: Sanders, B. C.; Friscourt, F.; Ledin, P. A.; Mbua, N. E.; Arumugam, S.; Guo, J.; Boltje, T. J.; Popik, V. V.; Boons, G.-J. *J. Am. Chem. Soc.* **2011**, *133*, 949–957.

(32) (a) Baskin, J. M.; Bertozzi, C. R. *Aldrichimica Acta* **2010**, *43*, 15–23. (b) For a related application of *trans*-cyclooctene, see: Blackman, M. L.; Royzen, M.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 13518–13519.