J|A|C|S COMMUNICATIONS

Published on Web 08/25/2009

Allene Synthesis via C−C Fragmentation: Method and Mechanistic Insight

Robert V. Kolakowski, Madhuri Manpadi, Yue Zhang, Thomas J. Emge, and Lawrence J. Williams*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854

Received July 23, 2009; E-mail: lawjw@rci.rutgers.edu

The rich structural and reactive properties of allenes complement the chemistry of alkenes and alkynes and render them uniquely versatile synthetic intermediates.[1−4] Allenes are also present in many natural products[5] and are relevant to certain biosynthetic pathways.[6] The importance of allenes in synthesis is attenuated by the lack of methods for their preparation and strategies for their application. The most generally useful stereoselective methods for allene synthesis are the S_N2' displacement of propargylic esters by organocuprates and rearrangement of propargyl diazenes.[1,7] In the course of our studies,[8] we identified instances where available approaches are not expedient and, consequently, developed a new entry to allenes via C−C fragmentation, as described below.

Olefin-forming C−C fragmentation (**1**→**2**, Figure 1) was recognized in natural product degradation studies, for example by Prelog,[9] and significantly developed by Grob.[10] Recently, Dudley reported that β-triflyl-α,β-unsaturated ketones also undergo efficient C−C fragmentation to give alkynes (**3**→**4**).[11] This fragmentation strategy has not been applied to allene synthesis. Allenes have been accessed by a variety of anion-initiated and thermolytic fragmentation reactions of suitably functionalized alkenes.[7b,12−15] We wondered whether vinyl triflates would fragment to give the corresponding allenes via a framework that complements the Grob and Dudley reactions (**5**→**6**) and whether this transformation could be used to prepare allenes stereospecifically.

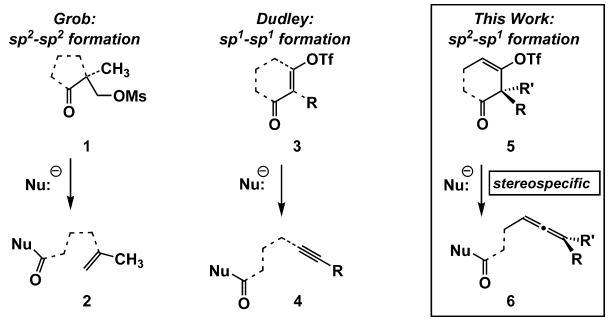
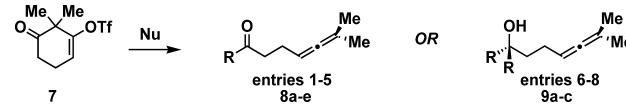


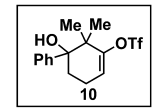
Figure 1. Fragmentation to alkenes, alkynes, and allenes.

Addition of carbon nucleophiles to the carbonyl of **7** generated a transient alkoxide that induced fragmentation/allene formation (Table 1). Use of approximately stoichiometric quantities of nucleophile gave allenic ketones **8a**−**e**. Use of excess reagent gave allenic alcohols **9a**−**c**. Organolithium and Grignard reagents, including alkyl, aryl, and alkynyl nucleophiles, smoothly added and induced fragmentation. Ketone and ester enolates also added as did dithiane anions. Use of cerium chloride was necessary to suppress competitive enolate formation of this substrate in instances where hard carbon nucleophiles were used.[16] Addition of alkoxides or lithiated amines as nucleophiles for carbonyl addition, which in principle would give ester or amide products, gave recovered **7** or complex mixtures (not shown). As suggested by the selective preparation of compounds **8** and **9**, fragmentation appears rate limiting for at least some substrates. For example, when a reaction mixture of **7** with $CeCl_3$ (2.5 equiv) and PhLi (2.5 equiv) at −78 °C was quenched after 10 min, the nonfragmented tertiary alcohol **10** was isolated in 20% yield (Table 1, see inset). These data demonstrate that allenes form rapidly from carbon nucleophile addition/vinyl triflate fragmentation for suitable substrates.

Table 1[a]



entry	R-	product	yield (%)	entry	R-	product	yield (%)
1	Ph	8a	76[a]	6	Ph	9a	86[f]
2	Ph	8b	78[b]	7	Bun	9b	81[g]
3	EtO	8c	89[c]	8		9c	74[h]
4		8d	87[d]				
5	TMS	8e	75[e]				



[a] 1.0 equiv of PhLi, 45 min, THF −78 °C - rt, 1 h. [b] 1.3 equiv of NaHMDS, 1.3 equiv of $PhCOCH_3$, THF, −78 °C, 15 min. [c] 1.4 equiv of LiHMDS, 1.3 equiv of EtOAc, THF, −78 °C, 15 min. [d] 1.1 equiv of *n*BuLi, 1.2 equiv of dithiane, THF, −78 °C−rt, 1 h. [e] 1.1 equiv of *n*BuLi, 1.2 equiv of TMSCCH, THF, −78 °C−rt, 1 h. [f] 3.0 equiv of $CeCl_3$, 3.0 equiv of PhMgBr, THF, −78 °C−rt, 1 h. [g] 3.0 equiv of $CeCl_3$, 3.0 equiv of *n*BuLi, THF, −78 °C−rt. [h] 3.0 equiv of *n*BuLi, 3.0 equiv of dithiane, THF, −78 °C−rt.

Figure 2 shows the conversion of other vinyl triflates to allenes and that stereogenic allenes form stereospecifically. Exposure of carvone-derived silyl ether **11** to fluoride led to rapid and clean formation of allenic aldehyde. For convenience, the reaction mixture was then treated with reducing agent, which gave the corresponding acyclic alcohol **12**. Excess phenyl magnesium bromide smoothly added to cyclopentenone **13** to give allenic alcohol **14**. Ten-membered cyclic allene **16** was prepared by fluoride-induced fragmentation from bicyclic silyl ether[17,18] and was obtained as a single isomer. The reaction efficiency for these more complex substrates is primarily a reflection of triflate hydrolysis as a competing side reaction. Thus, the precursor used to prepare **15** was also isolated from the reaction mixture (see **21**). The yield of **16**, based on recovered **21**, was 85%.

The fragmentations are stereospecific. Highly enantioenriched acyclic vinyl triflates **17** and **19** fragmented upon treatment with fluoride to give the corresponding enantioenriched allenes. Mosher ester analysis showed that in this fragmentation allene **20** was not formed from **17**→**18** and allene **18** was not formed from **19**→**20**.[18]

10.1021/ja906189h CCC: $40.75

We close with observations regarding the mechanism of fragmentation (Figure 3). In principle, anionic *O*-triflyl piperidone **22** could give an allene of type **23** or an alkyne of type **24** (*cf.* Dudley fragmentation). The corresponding trifluoroacetate salt was treated with excess PhMgBr in diethyl ether at −20 °C.[18,19] Only **23** was observed after 5 min (>20:1, **23**:**24**, 5% yield, 5% conversion). As the reaction proceeded, **24** became evident and the ratio of **23:24** gradually decreased. After 1 h the ratio of **23:24** was 3:1 (82% yield, 82% conversion). The increase in alkyne is readily understood in terms of the known propensity of terminal allenes to isomerize to terminal alkynylides under strongly basic conditions.[1] These data demonstrate that fragmentation of this system favors allene over alkyne formation.

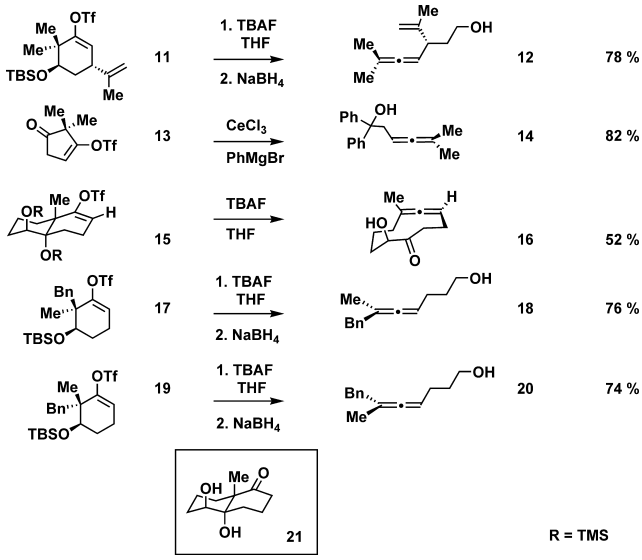


Figure 2. Vinyl triflate-to-allene fragmentation.

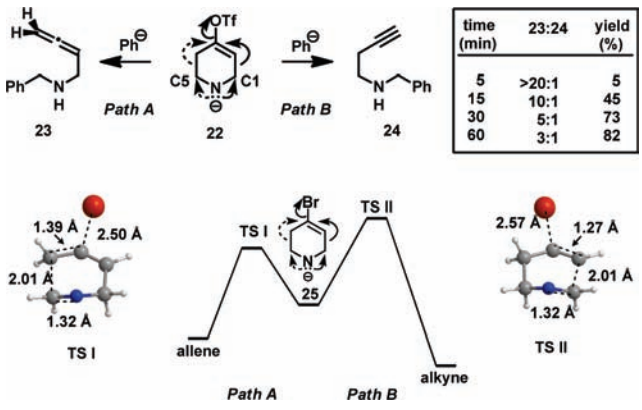


Figure 3. Fragmentation and mechanistic insight of vinyl triflate **22**.

Why does the allene form faster than the alkyne? Computed transition states were found for allene and alkyne formation using B3LYP/6-31G+(2d,2p).[20] The $\delta\Delta H^{\ddagger}_{calc}$ for the computed transition structures **TSI** and **TSII** was 2.39 kcal/mol, favoring allene formation.[21,22] Moreover, the optimized ground state energy of **25** indicates, by NBO analysis, a greater positive charge on C5 than on C1.[20a,23] Hence the calculated transition structures are consistent with a rationale wherein the triflate polarizes the carbon framework. Despite proper stereoelectronics for both pathways, the sp^3 network, being more polarized than the sp^2 network, interacts more strongly with the anionic nitrogen and, as a result, allene formation becomes the kinetically more facile pathway.

We have shown that suitably functionalized vinyl triflates serve as precursors to allenes by way of direct fragmentation or as part of an addition/cascade reaction. Mechanistic studies provide a framework for understanding this reaction in relation to other known modes of fragmentation, and as such, these findings complement methods of alkene and alkyne synthesis that rely upon C−C fragmentation. This work is complementary to allene synthesis methods that use alkyne precursors, provides access to highly enantioenriched allenes, including cyclic allenes, and is stereospecific.

Acknowledgment. Financial support from Merck & Co. is gratefully acknowledged.

Supporting Information Available: Complete ref 20a, synthetic methods, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hashmi, A. S. K. In *Modern Allene Chemistry*, Vol. 1; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH Verlag: Weinhelm, 2004; pp 3−36.
(2) Ma, S. In *Modern Allene Chemistry*, Vol. 2; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH Verlag: Weinhelm, 2004; pp 595−684.
(3) Wei, L.-L.; Xiong, H.; Hsung, R. P *Acc. Chem. Res.* **2003**, *36*, 773.
(4) (a) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, *6*, 795. (b) Kim, H.; Williams, L. J. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 870.
(5) (a) Krause, N.; Hoffmann-Roder, A. In *Modern Allene Chemistry*, Vol. 2; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH Verlag: Weinhelm, 2004; pp 997−1017. (b) Hu, G.; Liu, K.; Williams, L. J. *Org. Lett.* **2008**, *10*, 5493.
(6) (a) Corey, E. J.; D'Alarco, M.; Matsuda, S. P.; Lansbury, P. T., Jr.; Yamada, Y. *J. Am. Chem. Soc.* **1987**, *109*, 289. (b) Song, W.-C.; Brash, A. R. *Science* **1991**, *253*, 781.
(7) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492 See also. (b) Ready, J. M.; Pu, X. *J. Am. Chem. Soc.* **2008**, *130*, 10874. (c) Furstner, A.; Mendez, M. *Angew. Chem, Int. Ed.* **2003**, *115*, 5513. (d) Burton, B. S.; von Pechmann, H. *Ber. Dtsch. Chem. Ges* **1887**, *20*, 145.
(8) (a) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093. (b) Kolakowski, R. V.; Williams, L. J. *Tetrahedron Lett.* **2007**, *48*, 4761. (c) Wang, Z.; Shangguan, N.; Cusick, J. R.; Williams, L. J. *Synlett* **2008**, *2*, 213.
(9) (a) Prelog, V.; Zalan, E. *Helv. Chim. Acta* **1944**, *27*, 535. (b) Prelog, V.; Haflinger, O. *Helv. Chim. Acta* **1950**, *33*, 2021.
(10) Grob, C. A. *Angew. Chem., Int. Ed.* **1969**, *8*, 535.
(11) (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028. (b) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499. (c) Eschenmoser, A.; Frey, A. *Helv. Chim. Acta* **1952**, *35*, 1660.
(12) Foster, A. M.; Agosta, W. C. *J. Org. Chem.* **1972**, *37*, 61.
(13) (a) Maity, P.; Lepore, S. D. *J. Org. Chem.* **2009**, *74*, 158. (b) Brummond, K. M.; Dingess, E. A.; Kent, J. L. *J. Org. Chem.* **1996**, *61*, 6096. (c) Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535. (d) Negishi, E. -I.; King, A. O.; Klima, W. L. *J. Org. Chem.* **1980**, *45*, 2526. (e) Negishi, E. -I.; King, A. O.; Tour, J. M. *Org. Synth.* **1985**, *64*, 44.
(14) Torres, E.; Larson, G. L.; McGarvey, G. J. *Tetrahedron Lett.* **1988**, 1355.
(15) Sugai, M.; Tanino, K.; Kuwajima, I. *Synthesis* **1997**, 461.
(16) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(17) Triflate **15** was derived from enantioenriched Wieland−Miecher Ketone.
(18) See Supporting Information for details.
(19) The immediate fragmentation products (not observed) are imines. Use of THF accelerated the isomerization process (1 h: 23:24 = 1:1, 85% yield, 85% conversion).
(20) (a) Frisch, M. J.; *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004. Exchange potentials: (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. Correlation functional: (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(21) Caution must be exercised in light of the known difficulties in calculating allene and alkyne ground states. (See: Wodrich, M. D.; Corminboeuf, C.; Schleyer, P. V. R. *Org. Lett.* **2006**, *8*, 3631.). The good correlation between $\Delta H^{\ddagger}_{calc}$ and experiment is likely due in part to the degree of separation that exists between the transition states and the product ground states.
(22) Transition states for chlorine and fluorine substituted piperidines were calculated and compared with the bromine substituted TS I (see Supporting Information). The enthalpy of the reaction for the series was−F 13.5 kcal/mol,−Cl 9.2 kcal/mol, and−Br 8.3 kcal/mol, consistent with leaving group ability.
(23) Weinhold, F. Landis, C. *Valency and Bonding*; Cambridge University Press: Cambridge, U.K., 2005.

JA906189H