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One-Pot Assembly and Synthetic Applications of Geminal Acyl/Alkoxy Tetrasubstituted Allenes

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Abstract

Polysubstituted allenes are useful synthetic intermediates in many applications, offering structural complexity, modularity, and their axial chirality in further transformations. While acyl and alkoxy substituted allenes are known, there are currently few examples of allenes containing both functionalities, and no reports of geminally substituted acyl/alkoxy allenes being isolated and characterized. Herein we report the synthesis of tetrasubstituted allenes featuring novel geminal acyl/alkoxy substitution. These unique “push-pull” allenes are bench-stable and exhibit interesting reactivity in several applications.

Keywords: dipolar cycloaddition ∗ spirocycles ∗ pyrazole ∗ sigmatropic rearrangement

Allenes are well established as useful chemical intermediates, demonstrating unique reactivity in heterocycle preparation, transition metal catalysis, and natural product synthesis.[1] While tetrasubstituted allenes are accessible by a number of methods, the makeup and pattern of their substituents can be limited, leaving their synthetic utility underexplored.[2] Reaction conditions to synthesize these scaffolds can have poor functional group tolerance and may result in products that are too reactive to isolate.[3] Electron-deficient acyl substituted allenes can be accessed by a variety of methods, such as palladium-catalyzed carbonylation of propargylic substrates and HWE/Wittig reactions of ketenes or their acyl chloride precursor (Figure 1). The resulting products are typically bench stable and can be employed as electrophiles in subsequent transformations. Electron-rich alkoxy-substituted allenes are primarily generated *in situ* through the isomerization of propargyl precursors with base and used immediately in subsequent

reactions. Alkoxy-substituted allenes have seen considerable attention from Reissig, Tius, and coworkers, where they are often employed as nucleophiles.[4–9]

Reports of electron withdrawing and electron donating substituents on the same allene structure are rare,[10–12] and geminal acyl/alkoxy allenes are unreported as isolable intermediates, with only one example being reported as a transient intermediate in Nazarov cyclizations by Tius and coworkers.[7–9] In their report, they also demonstrate examples of alkoxy/amide allenes, but these intermediates require a multi-step sequence.[13] Herein we report a simple one-pot method for the synthesis of geminal acyl/alkoxy tetrasubstituted allenes and demonstrate their synthetic utility in further transformations.

While investigating propargyl ether **1a** for the synthesis of benzophenone **3**, we discovered that upon treatment with *n*-butyllithium and a Weinreb amide electrophile, tetrasubstituted allene **9a** was observed as the major product (Figure 2). NMR studies suggested that the substitution pattern was geminal with respect to the acyl and alkoxy substituents, which was later confirmed by X-ray crystallography (**9a**, Figure 2). Based on prior work by Reissig and Tius, a mechanism was proposed to rationalize the formation of allene **9a** (Figure 2). Lithium-halogen exchange occurs first, due to its kinetic favorability,[14,15] and is followed by the deprotonation of the propargylic proton. The resulting lithiate **5** is in equilibrium with the allenyl lithiate **6** through a metallotropic shift. A trisubstituted allene is produced when **6** attacks the equivalent of *n*-butyl bromide generated *in situ*. Per Reissig, a second equivalent of *n*-butyllithium can form allenyl lithiate (**8**), which then acts as a nucleophile, attacking Weinreb amide **2** to form allene **9a**.

Evidence for the proposed mechanism is supported by the isolation of several byproducts of the one-pot allene synthesis. Careful purification and analysis of the reaction revealed byproducts, **11** and **12**, resulting from an *ortho*-[2,3] Wittig rearrangement (Figure 2).[16] These products provide support for the existence of a propargyl lithiate intermediate and highlight a competing pathway for allene formation. Another byproduct was isolated and was identified as the *ortho* double-acylation product **13** (Figure 3A). This compound indicates that after lithium-halogen exchange, the deprotonation and lithiation of the propargylic position is not necessarily intramolecular, but potentially also the result of an intermolecular process with another equivalent of lithiated substrate or *n*-butyllithium. To test this hypothesis, a *para*-bromobenzyl propargyl ether **14** was synthesized, which we reasoned would be geometrically incapable of an intramolecular deprotonation. Upon subjection to *n*-butyllithium and Weinreb amide, both mono-acylated allene **9a** and the *para* double acylation product **15** were observed (Figure 3B). Given these results, we concluded the allene formation step may proceed through an intermolecular deprotonation generating a dilithiated intermediate **16**, which has been

implicated under similar reaction conditions (Figure 3C).[17–21] If the aryl lithiate of **16** (or other subsequent aryl lithiates) does not deprotonate any other species in the reaction mixture, double acylation product **13** (or **15**) is formed when the Weinreb amide is introduced. Alternatively, if **16**, **17**, or **18** undergoes aryl proto-delithiation, then the reaction proceeds to form mono acylation product **9a** *via* **5**, **7**, and **8**, respectively. To test this hypothesis, a non-brominated propargyl benzyl ether substrate was subjected to reaction conditions (not shown, see SI), where the only isolated products were **11** and **12**, suggesting the importance of the dilithiated intermediates **16**-**18** for allene formation. More specifically, when intermediates **17** and **18** form **7** and **8**, the competing *ortho*-[2,3] Wittig pathway is avoided. In this way, we propose that the reaction mechanism most likely requires the persistence of dilithiated intermediates to form allene and circumvent rearrangement products.

Following the initial discovery, reaction conditions were optimized to produce a general method (Table 1). In the original reaction, a slight excess of *n*-butyllithium was used so as to ensure complete lithium halogen exchange (entry 1). Per the proposed mechanism, two equivalents of *n*-butyllithium were employed and an increase in the yield of allene was observed (entry 2). Next, several solvents were screened to assess the effect of solvation/aggregation of lithiated intermediates.[22–26] Interestingly, in diethyl ether, hexanes, and toluene no allene was observed (entries 3-5). Several temperatures were then explored to determine any kinetic control over the sequence of deprotonations and the stability of the lithiates. At –100 ºC, the yield of product was suppressed, at –40 ºC only trace product was observed, while at –20 ºC, no product was detected by NMR (entries 6-8). Therefore, a fine control of temperature (–78 ºC) was necessary for achieving good allene formation. Common additives for lithiate mediated reactions, LiCl and tetramethylethylenediamine (TMEDA), were then investigated; LiCl was observed to give a significantly cleaner and more easily purified reaction mixture, albeit in reduced yield (entry 9). TMEDA was observed to produce allene **9a** with no pronounced effect, other than to suppress yield (entry 10).

With suitable reaction conditions in place, a substrate scope including the geminal acyl/alkoxy motif was produced (Figure 4). Modifications of the Weinreb amide component were accessed in a straightforward manner. Both electron withdrawing and electron donating substituents on the aryl Weinreb amides were tolerated, affording **9a**, **9b**, and **9c** in comparatively low yields. Fluoro-arene **9d** was also generated in good yield. Heterocycles were amenable to the procedure, affording nicotinyl, furyl, and thiophenyl substituted acyl allenes (**9e**-**9g**). Sterically demanding alkyl Weinreb amides and even a dimethyl-Weinreb urea also furnished allene products (**9j**-**9l**). Modifications to the alkyne terminus of the allene precursor were investigated as well. Interestingly, electron donating groups still led to a productive reaction (**9h**), while electron withdrawing groups led to only trace allene formation (**9i**). Other attempts to modulate the electronic

effects of the alkyne terminus were unsuccessful; for example, *para*-dimethylamino, *para*- morpholino phenyl alkynes, and alkynes substituted directly with amides (i.e. *N*-alkynyl oxazolidinone, *N*-alkynyl camphorsultam) were not productive in the reaction (not shown). In general, yields were low for substrates **9a-l**; we found varying degrees of double-acylation products and *ortho*-[2,3] Wittig rearrangement products but with no discernible trend per substrate.

To investigate the effect of the geminal acyl/alkoxy substitution pattern on general reactivity, we exposed the parent allene **9a** to a variety of reaction conditions (Figure 5). Given the density and potential lability of the functional groups on **9a**, we initially screened reactions that were noted in the literature for similar tetrasubstituted acyl allenes. Gevorgyan and coworkers report the metal catalyzed cyclization and 1,2-phenyl migration of tetrasubstituted acyl allenes to form polysubstituted furans.[27] To explore the potential for these acyl/alkoxy allenes to undergo metal-catalyzed cyclizations, we exposed **9a** to several catalysts used in their work, (i.e. $[Au(PPh_3)]OTf$, AgOTf, and $SnOTf_2$) and found $SnOTf_2$ to give the best conversion to a cyclization product. However, upon purification and analysis of spectra, we discovered that furan was not formed and instead a new debenzylated product **19** was generated as a single diastereomer. In the report by Gevorgyan and coworkers, the metal catalyst coordinates to the more electron rich π-bond that is distal to the acyl substituent and subsequently generates the furan **23**. Our observed formation of the *alpha*-hydroxy unsaturated ketone **19** diverges from reported reactivity: we hypothesize the coordination of the metal to the more electron rich π-bond proximal to the benzyloxy substituent (**24**), subsequently affording **19** in >95:5 dr (Figure 5). The relative configuration of the major diastereomer was investigated using B3LYP computational methods to find the lowest energy conformer of each diastereomer.[28,29] Using Gaussian16, geometry optimizations in the gas phase and NMR GIAO calculations under implicit solvent were conducted on the functional using the 6-31+G(d,p) basis set.[30] DFT calculations ultimately demonstrated that diastereomer **19** was most likely the major diastereomer (see SI). These products are also similar to those reported by Liu and coworkers, where they observe a single diastereomer when their *geminal* vinyloxy unsaturated ketone substrates are subjected to catalytic base and acetone.[31] Simple condensations with hydrazine and *N*-tosyl hydrazine afforded heterocycles, but with differing regioselectivity in the subsequent cyclization. Hydrazine, after condensation to the hydrazone, proceeded to form the pyrazole 1,5-cyclization product **20**, isolated as a mixture of **20** *sans* benzyloxy fragment and *with* the benzyloxy intact at the 4-position (85:15 ratio). On the other hand, the analogous *N*-tosyl hydrazone underwent 1,6-cyclization to form the corresponding 1,5-dihydropyridazine **21** with the benzyloxy group intact; this type of 5-substituted heterocycle is uncommon in the literature.[32–35] Finally, Johnson-Corey-Chaykovsky conditions were used to achieve the epoxidation product **22**.[36,37]

In conclusion, we report the simple, one-pot assembly of tetrasubstituted acyl/alkoxy allenes from *ortho*-bromo benzyl propargylic ethers. We propose a mechanism involving lithium halogen exchange followed by intermolecular deprotonation events to form a propargylic lithiate, evidenced by *ortho*-[2,3] Wittig rearrangement products. The propargylic lithiate can then become alkylated *in situ* by transposition to form a trisubstituted allene. Similar to reports by Reissig and Tius, this alkoxy allene is then deprotonated to form an allenyl lithiate nucleophile for addition to a Weinreb amide. After exploring different reaction conditions, we produced a substrate scope with varied substitution derived from the Weinreb amide and the terminus of the alkyne starting material. To investigate the reactivity of these largely unreported acyl/alkoxy allenes, we applied the scaffold in several different applications. We found that this structure is amenable to several cyclization pathways by either transition metal catalysis or condensation/intramolecular cyclization, affording novel structures. Furthermore, we used Johnson-Corey-Chaykovsky sulfur ylide epoxidation conditions to afford an allenyl oxirane. With this method in place, we expect further development in the synthesis and application of these bench-stable acyl/alkoxy allenes.

Experimental Section

Experimental procedures and compound characterization can be found in the Supporting Information (PDF). ^{1}H and ^{13}C NMR spectra for all new compounds (PDF). X-ray data for compound 9a (CIF), 9j (CIF), 9k (CIF), and 13 (CIF).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

[1] A. Hoffmann-Röder, N. Krause, *Angew. Chemie Int. Ed.* **2004**, *43*, 1196–1216.

[2] W. D. Chu, Y. Zhang, J. Wang, *Catal. Sci. Technol.* **2017**, *7*, 4570–4579.

[3] S. Yu, S. Ma, *Chem. Commun.* **2011**, *47*, 5384–5418.

[4] M. A. Chowdhury, H. U. Reissig, *Synlett* **2006**, *12*, 2383–2386.

[5] H. U. Reissig, R. Zimmer, *Synth.* **2017**, *49*, 3291–3302.

[6] H. U. Reissig, R. Zimmer, in *Multicomponent React. Org. Synth.* (Eds.: J. Zhu, Q. Wang, M.-X. Wang), Wiley-VCH Verlag GmbH & Co. KGaA, **2015**, pp. 301–332.

[7] M. A. Tius, J. Busch-Petersen, M. Yamashita, *Tetrahedron Lett.* **1998**, *39*, 4219–4222.

[8] B. K. Tokeshi, M. A. Tius, *Synthesis (Stuttg).* **2004**, 786–790.

[9] M. A. Tius, *Chem. Soc. Rev.* **2014**, *43*, 2979–3002.

[10] A. W. Sromek, A. V. Kel'in, V. Gevorgyan, *Angew. Chemie - Int. Ed.* **2004**, *43*, 2280–2282.

[11] K. R. Shiroodi, M. Sugawara, M. Ratushnyy, D. C. Yarbrough, D. J. Wink, V. Gevorgyan, *Org. Lett.* **2015**, *17*, 4062–4065.

[12] R. Kazem Shiroodi, V. Gevorgyan, *Chem. Soc. Rev.* **2013**, *42*, 4991–5001.

[13] H. Hu, D. Smith, R. E. Cramer, M. A. Tius, *J Am Chem Soc* **1999**, *121*, 9895–9896.

[14] W. F. Bailey, J. J. Patricia, T. T. Nurmi, W. Wang, *Tetrahedron Lett.* **1986**, *27*, 1861–1864.

[15] M. Lamrani, R. Hamasaki, Y. Yamamoto, *Tetrahedron Lett.* **2000**, *41*, 2499–2501.

[16] K. Tomooka, M. Harada, T. Hanji, T. Nakai, *Chem. Lett.* **2000**, 1394–1395.

[17] Y. Leroux, R. Mantione, *Tetrahedron Lett.* **1971**, *12*, 591–592.

[18] J. J. Eisch, M. Behrooz, J. E. Galle, *Tetrahedron Lett.* **1984**, *25*, 4851–4854.

[19] Y. Pang, S. A. Petrich, V. G. Young, M. S. Gordon, T. J. Barton, *J Am Chem Soc* **1993**, *115*, 2534–2536.

[20] D. Seyferth, P. Langer, M. Döring, *Organometallics* **1995**, *14*, 4457–4459.

[21] P. Langer, M. Döring, D. Seyferth, H. Görls, *Chem. - A Eur. J.* **2001**, *7*, 573–584.

[22] J. F. Mcgarrity, C. A. Ogle, *J Am Chem Soc* **1985**, *107*, 1805–1810.

[23] J. M. Gruver, L. R. Liou, A. J. McNeil, A. Ramirez, D. B. Collum, *J. Org. Chem.* **2008**, *73*, 7743–7747.

[24] V. H. Gessner, C. Däschlein, C. Strohmann, *Chem. - A Eur. J.* **2009**, *15*, 3320–3334.

[25] T. Stey, D. Stalke, *Lead Structures in Lithium Organic Chemistry*, John Wiley & Sons, Ltd., Hoboken, New Jersey, **2009**.

[26] H. J. Reich, *Chem. Rev.* **2013**, *113*, 7130–7178.

[27] A. S. Dudnik, V. Gevorgyan, *Angew. Chemie - Int. Ed.* **2007**, *46*, 5195–5197.

[28] P. R. Rablen, S. A. Pearlman, J. Finkbiner, *J. Phys. Chem. A* **1999**, *103*, 7357–7363.

[29] M. W. Lodewyk, M. R. Siebert, D. J. Tantillo, *Chem. Rev.* **2012**, *112*, 1839–1862.

[30] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.

[31] N. Sun, M. Chen, Y. Liu, *J. Org. Chem.* **2014**, *79*, 4055–4067.

[32] P. de Mayo, M. C. Usselman, *Can. J. Chem.* **1973**, *51*, 1724–1728.

[33] W. A. Butte, F. H. Case, *J. Org. Chem.* **1961**, *26*, 4690–4692.

[34] M. Hartnagel, K. Grimm, H. Mayr, *Liebigs Ann.* **1997**, 71–80.

[35] I. Crossland, E. Kelstrup, *Acta Chem. Scand.* **1968**, *22*, 1669–1676.

[36] A. W. Johnson, R. B. LaCount, *J Am Chem Soc* **1961**, *83*, 417–423.

[37] E. J. Corey, M. Chaykovsky, *J Am Chem Soc* **1965**, *87*, 1353–1364.

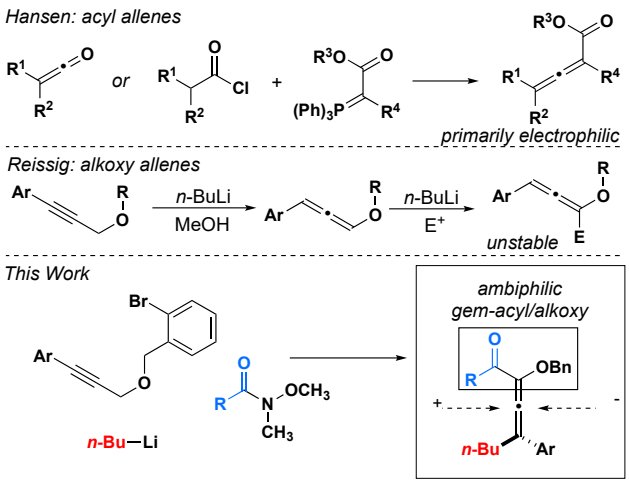


Figure 1. Strategies for synthesizing acyl, alkoxy, and geminal acyl/alkoxy allenes

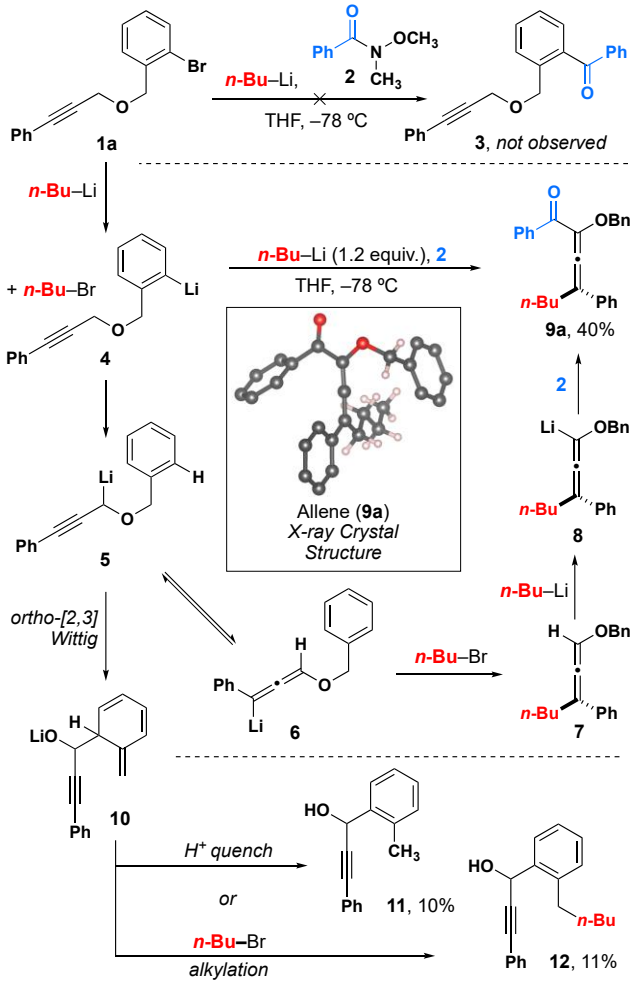


Figure 2. Proposed mechanism and byproducts for allene formation

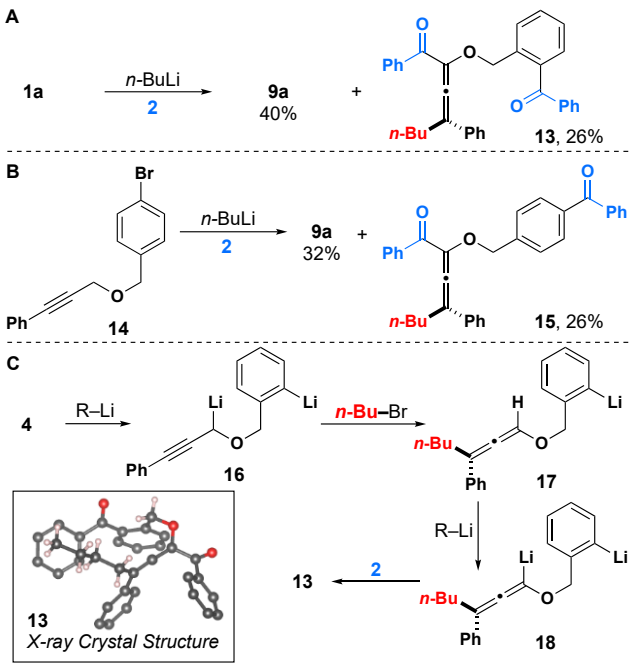
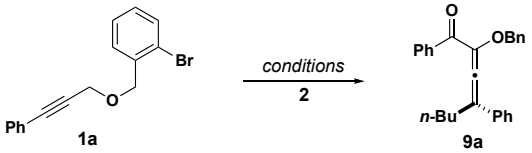


Figure 3. Byproducts from allene formation: A) double acylation byproduct; B) para-bromobenzyl propargyl ether experiment; C) proposed mono- and dilithiated intermediates

Table 1. Optimization of reaction conditions



Entry	*n*-BuLi equiv	Solv	Temp (°C)	Additive equiv	Yield (%)
1	1.3	THF	–78	-	40
2	2.0	THF	–78	-	68
3	2.0	Et_2O	–78	-	ND
4	2.0	hexane	–78	-	ND
5	2.0	$PhCH_3$	–78	-	ND
6	2.0	THF	–100	-	22
7	2.0	THF	–40	-	*trace*
8	2.0	THF	–20	-	ND
9	2.0	THF	–78	LiCl (6)	54
10	2.0	THF	–78	TMEDA (2)	39

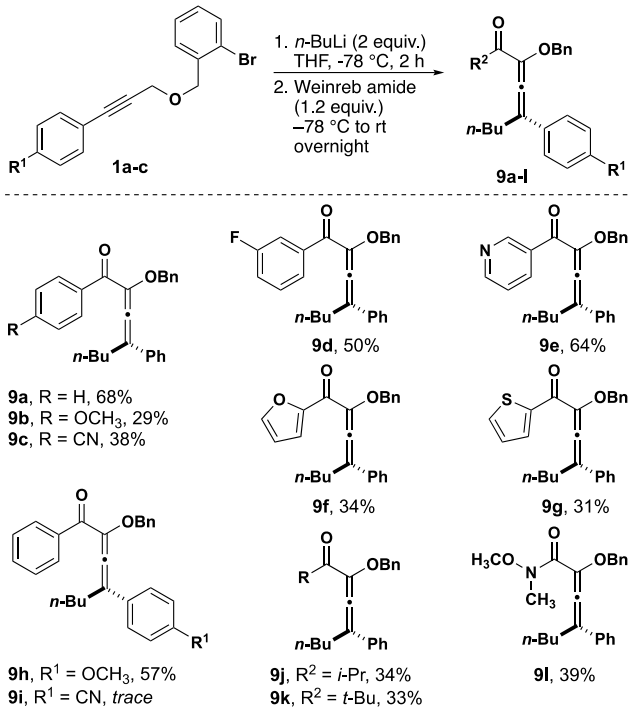


Figure 4. Substrate scope for tetrasubstituted acyl/alkoxy allenes

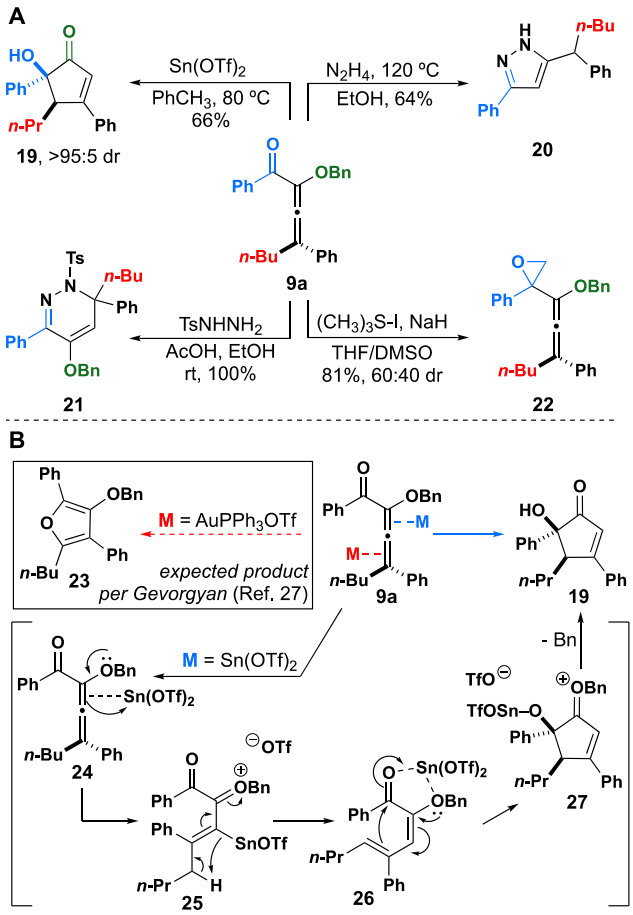


Figure 5. A) Reactivity of geminal acyl/alkoxy allenes; B) the proposed mechanism for divergent cyclization product **19**