Communication

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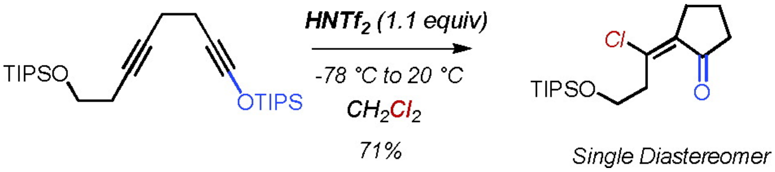

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Brønsted Acid-Promoted Cyclizations of 1-Siloxy-1,5-diynes

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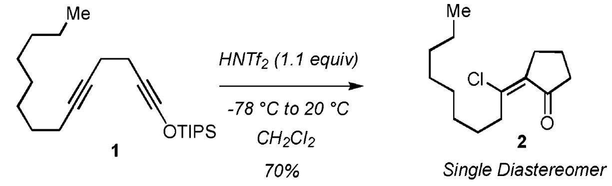
Siloxy alkynes represent a versatile synthetic platform for the development of new C−C bond forming reactions.[1−3] We previously established that soft and hard electrophiles (AuCl and $HNTf_2$) were capable of efficient activation of siloxy alkynes toward subsequent intramolecular additions of arenes and alkenes via the intermediacy of highly reactive ketenium ions.[3d,e] In this communication, we further expand this broadly useful reactivity concept and describe the discovery of the first Brønsted acid-promoted 5-*endo-dig* cyclizations of 1-siloxy-1,5-diynes, which proceed with concomitant formation of C−Hal bonds as a result of halide abstraction from a halocarbon by the intermediate alkenyl cation. This process is enabled by chemoselective activation of an electron-rich siloxy alkyne moiety of the diyne cyclization precursor. Excellent diastereoselectivity of the present method combined with the ability to access a range of β-halo enones compares this approach favorably to the known methods for preparation of this class of compounds.[4]

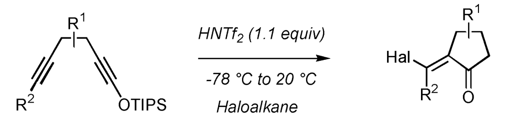
In the course of our continuing investigation aimed at the development of new C−C bond forming reactions involving electron-rich alkynes, we found that treatment of 1-siloxy-1,5-diyne **1** with $HNTf_2$ resulted in efficient formation of enone **2** containing the β-chloride that originated from CH_2Cl_2 (Scheme 1).[5] Structural assignment of **2** was based on COSY, NOESY, HMBC, MS, and preparation by an independent method.[4]

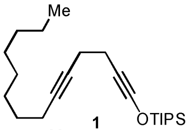
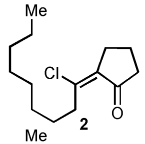
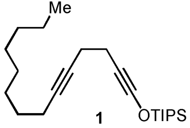
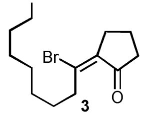
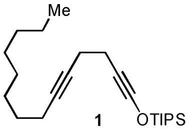
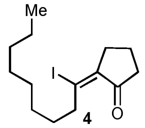
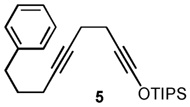
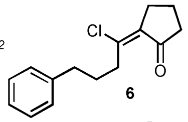
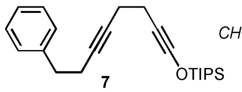
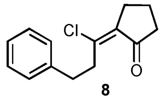
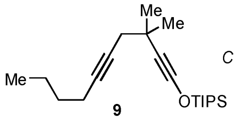
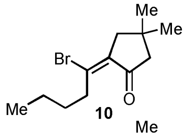
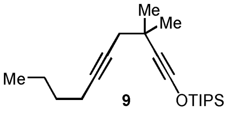
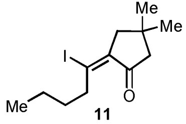
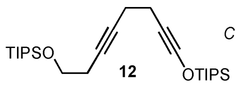
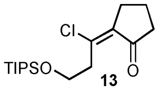
Scheme 1



Further studies demonstrated that $HNTf_2$ is a highly effective Brønsted acid promoter.[6] Broad evaluation of other Brønsted acids revealed that only HBF_4 or HOTf was capable of promoting siloxy diyne cyclizations. However, the reactions proceeded with significantly lower efficiency (32 and 22% yield, respectively). These intriguing results could be explained by the increased Brønsted acidity of $HNTf_2$ in a polar aprotic solvent combined with a low nucleophilicity of the trifluoromethane sulfonimide anion.[7] Interestingly, the use of either CSA or anhydrous HCl resulted in formation of alternative reaction products.[8]

Table 1. $HNTf_2$-Promoted Cyclizations of 1-Siloxy-1,5-diynes



Entry	*Siloxy Alkyne*	*Haloalkane*	*Product*[a]	*Yield, %*[b]
1	 **1**	$CHCl_3$	 **2**	60
2	 **1**	CH_2Br_2	 **3**	71
3	 **1**	MeI	 **4**	74
4	 **5**	CH_2Cl_2	 **6**	50
5	 **7**	CH_2Cl_2	 **8**	70
6	 **9**	CH_2Br_2	 **10**	81
7	 **9**	MeI	 **11**	69
8	 **12**	CH_2Cl_2	 **13**	71

[a] General reaction protocol for CH_2Cl_2: Trifluoromethanesulfonimide (0.28 mmol) was dissolved in CH_2Cl_2 (10 mL), cooled to −78 °C, and treated with siloxy diyne (0.25 mmol) dissolved in CH_2Cl_2 (5 mL). The resulting solution was stirred at −78 °C for 10 min, allowed to reach room temperature, diluted with CH_2Cl_2 (30 mL), and subjected to a standard aqueous work up. The crude product was purified by flash chromatography on silica gel. [b] Refers to isolated yields of spectroscopically pure products that were fully characterized by NMR, IR, and MS.

The use of other halogen sources, such as $CHCl_3$, CH_2Br_2, or MeI, resulted in efficient incorporation of chloride, bromide, and iodide into the reaction products **2**, **3**, and **4**, respectively (Table 1, entries 1, 2, and 3). Subjection of phenyl-substituted enynes **5** and **7** to the general reaction protocol efficiently afforded the expected enones **6** and **8**, respectively (entries 4 and 5). These results indicate that aryl substitution at the 8- and 9-position of the diyne was well tolerated despite the possible intra- or intermolecular arylation of the intermediate alkenyl cation (vide infra). Subjection of 3,3-dimethyl diyne **9** to $HNTf_2$ in either CH_2Br_2 or MeI afforded the expected enones **10** and **11** (entries 6 and 7), indicating that increased steric congestion at the siloxy alkyne terminus was well tolerated. Finally, TIPS-protected primary alcohol **12** was retained under our standard cyclization protocol (entry 8), illustrating

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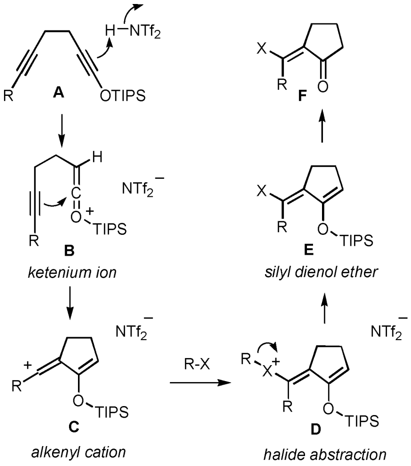
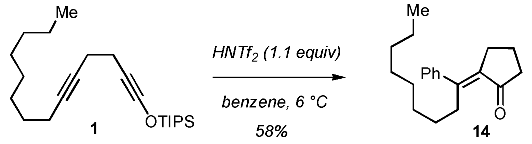
Scheme 2



functional group compatibility of the present method to the use of silyl protecting groups. While a range of 1,5-diynes efficiently participated in the cyclization process, subjection of the corresponding 1-siloxy-1,6-diynes to HNTf$_2$ afforded a complex product mixture under the current conditions.

Our mechanistic analysis is presented in Scheme 2. The reaction begins by protonation of the more electron-rich siloxy alkyne terminus of diyne **A**. Attack of the other alkyne moiety onto the resulting ketenium ion **B** leads to the 5-*endo-dig* cyclization, furnishing alkenyl cation **C**.[9] Subsequent reaction of alkenyl cation with the halocarbon results in the cleavage of the R−X bond,[10] presumably via the intermediacy of halonium ion **D**.[5c] We believe that low nucleophilicity of NTf$_2^-$ is uniquely responsible for efficient generation and interception of highly reactive cationic intermediates **B** and **C**. Subsequent protodesilylation of silyl dienol ether **E** affords the observed halo enone **F**. While protodesilylation of **E** proceeds competitively with the initial protonation of siloxy alkyne **A**, silyl dienol ether **E** can be detected or isolated as an exclusive reaction product by conducting the reaction with 20−30 mol % of HNTf$_2$, or by subjecting a diyne to 110 mol % of HNTf$_2$, followed by treatment with Et$_3$N.[11]

Interestingly, subjection of diyne **1** to HNTf$_2$ in benzene afforded tetrasubstituted enone **14** (eq 1) as a single alkene isomer (dr > 97:3). The outcome of this experiment can be rationalized by the interception of alkenyl cation **C** by benzene, demonstrating that this newly developed concept can be applied to a range of nucleophiles.



(1)

In closing, we have developed the first HNTf$_2$-promoted 5-*endo-dig* cyclizations of 1-siloxy-1,5-diynes featuring chemoselective activation of the electron-rich siloxy alkyne moiety and an unusual halide abstraction by the intermediate alkenyl cation. In addition to enabling rapid and diastereoselective assembly of a range of substituted β-halo enones, this process provides another demonstration of efficient generation of highly reactive ketenium ions that are poised for interception by the proximate alkyne to provide a simple concept for generating new C−C and C−Hal bonds.

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Supporting Information Available: Full characterization of new compounds and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Popov, S. A.; Tkachev, A. V. *Synth. Commun.* **2001**, *31*, 233.
(5) To our knowledge, there are two examples of halide abstraction from halocarbons by alkenyl cations: (a) Johnson, W. S.; Ward, C. E.; Boots, S. G.; Gravestock, M. B.; Markezich, R. L.; McCarry, B. E.; Okorie, D. A.; Parry, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 88. (b) Balog, A.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345. For other examples of halide abstraction from hydrocarbons by carbocations, see: (c) White, E. H.; Tiwari, H. P.; Todd, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 4734.
(6) The acidity of HNTf$_2$ was found to be higher than that of HOTf in gas phase (ref 6a), while the trend in H$_2$O or AcOH is reversed (ref 6b). The acidity of the two acids in ionic liquid is comparable (ref 6c). (a) Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu S.; Hu, L.; Sung, K.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, Y. L.; Ignat'ev, N. V.; Kondratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maria, P. *J. Am. Chem. Soc.* **1994**, *116*, 3047. (b) Foropoulus, J.; DesMarteau, D. D. *Inorg. Chem.* **1984**, *23*, 3720. (c) Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. *J. Am. Chem. Soc.* **2003**, *125*, 5264.
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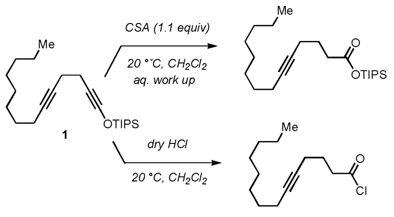
(8) Reactions of diyne **1** with CSA and HCl afforded siloxy ester and acid chloride respectively as shown below.



(9) For comprehensive monographs on the reactivity of alkenyl cations, see: (a) Stang, P. J.; Rappoport, Z. *Dicoordinated Carbocations*; Academic Press: New York, 1997. (b) Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. B. *Vinyl Cations*; Academic Press: New York, 1979.
(10) We were able to observe BrCH$_2$OMe by GC/MS by conducting the reaction in the presence of MeOH, which is evident of the generation of CH$_2$X cations in the reaction mixture.
(11) The second proton required for complete protodesilylation of **E** may originate from traces of water that are present in the reaction mixture. Indeed, the use of 2 equiv of HNTf$_2$ does not alter the efficiency of the reaction.

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