Communication

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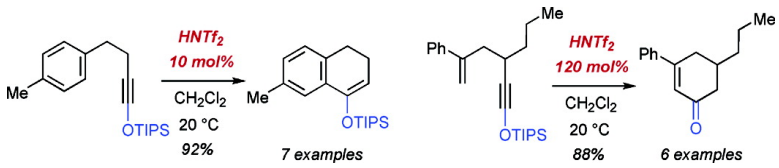

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Brønsted Acid-Promoted Cyclizations of Siloxyalkynes with Arenes and Alkenes

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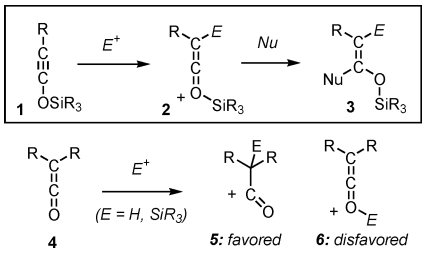
Catalysis of carbocyclizations of alkynes with arenes and alkenes has emerged as an important strategy for the assembly of carbocyclic and heterocyclic compounds.[1,2] In this communication, we report the first Brønsted acid-mediated cyclizations of siloxyalkynes[3,4] with simple arenes and alkenes to afford substituted tetralone and cyclohexenone derivatives. Our approach is based on generation of highly electrophilic ketenium ion **2** from siloxyalkyne **1**, followed by intramolecular trapping of this reactive intermediate by an appropriately positioned nucleophile (Scheme 1). While ketenes have been widely exploited in organic synthesis, ketenium ions have been rarely implicated as reactive intermediates.[5] Indeed, electrophilic attack on ketenes occurs preferentially at the β-carbon leading to the acyl cation **5**.[6] Siloxyalkynes, on the other hand, represent a unique platform for generation of ketenium ions via addition of an appropriate electrophile at the β-carbon. The resulting highly reactive ketenium ion **2** is poised for subsequent interception with a range of nucleophiles. To our knowledge, this important and broadly useful aspect of reactivity of siloxyalkynes has not been exploited.[7]

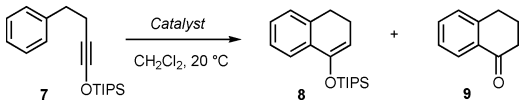
Scheme 1



In search for an effective catalyst for carbocyclization of siloxyalkyne **7**,[8] we examined various Lewis-acidic additives depicted in Table 1. Unfortunately, a range of metal salts known to promote alkyne carbocyclizations,[1] including $GaCl_3$, $HfCl_4$, and $Hg(OTf)_2$, failed to catalyze the reaction. Prompted by our recent success in the development of [2 + 2] cycloadditions of siloxyalkynes,[3b] we examined several silver-based catalysts and discovered that $AgNTf_2$ (20 mol %) resulted in formation of silyl enol ether **8** with good efficiency (entry 5). Our subsequent studies revealed that the active catalyst of this process was the conjugate acid produced during the rearomatization step. Indeed, subjection of alkyne **7** to 10 mol % $HNTf_2$ afforded enol ether **8** in 86% isolated yield (entry 6).[9] Importantly, the efficiency of the reaction was diminished significantly using other silver salts and Brønsted acids, highlighting the importance of the trifluoromethanesulfonimide anion.[10]

Investigation of the scope of $HNTf_2$-catalyzed siloxyalkyne arene cyclization revealed that a range of unactivated aromatic precursors can efficiently participate in this process (Table 2), distinguishing this reaction uniquely from the metal-mediated carbocyclizations of alkynes that generally require electron-rich arenes and alkenes.[1] To probe the reaction mechanism, we prepared alkyne **13** in highly enantiomerically enriched form (entry 4, Table 2).[11] Subjection of **13** to the cyclization conditions afforded enol ether **19** without any detectable loss of enantiomeric purity. This result supports an

Table 1. Effect of Lewis and Brønsted Acids on the Carbocyclization of Siloxyalkyne **7**

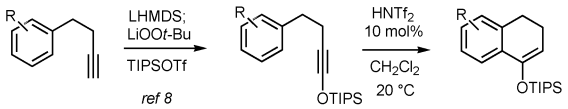


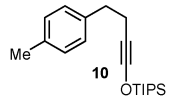
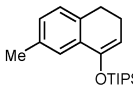
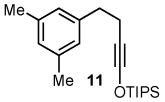
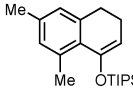
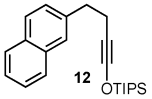
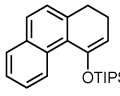
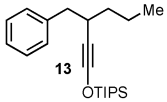
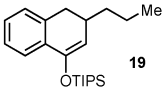
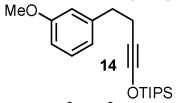
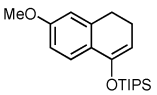
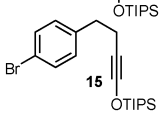
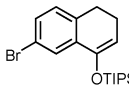
7 **8** **9**

entry	catalyst (mol %)	reaction time	product	yield (%)
1	$Hg(OTf)_2(TMU)_2$ (10)	24 h		<2[a]
2	$HfCl_4$ (10)	10 min		<2[a]
3	$GaCl_3$ (10)	10 min		<2[b]
4	$AuCl_3$ (10)	10 min		<2[b]
5	$AgNTf_2$ (20)	10 min	8	65[c]
6	**Tf_2NH (10)**	**10 min**	**8**	**86**[c]
7	AgOTf (20)	24 h	9	15[d]
8	TfOH (20)	24 h	9	25[d]

[a] No reaction was observed under these conditions. [b] Complex product mixture was produced. [c] Isolated yield of spectroscopically pure product. [d] Yield estimated from by ^{1}H NMR of the reaction mixture.

Table 2. Arene-Siloxyalkyne Carbocyclizations Catalyzed by $HNTf_2$

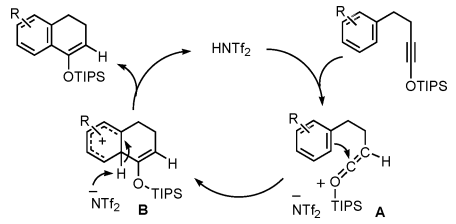


Entry	Siloxy Alkyne	Yield, %[a]	Silyl Enol Ether	Yield, %[a]
1	 **10**	92	 **16**	92
2	 **11**	93	 **17**	88
3	 **12**	96	 **18**	74
4	 **13**	99	 **19**	92
5	 **14**	94	 major **20**	84[b]
6	 **15**	91	 **21**	40

[a] Refers to isolated yields of products that were fully characterized by NMR, IR, and MS. [b] Reaction afforded a 75:25 ratio of para-/ortho-substituted products.

10.1021/ja046586x CCC: $27.50

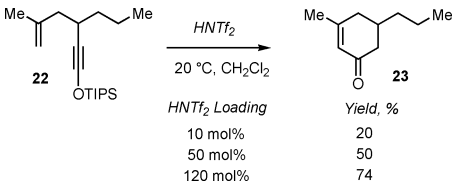
Scheme 2



electrophilic aromatic substitution mechanism (Scheme 2). An alternative mechanism involving a [3,3]-sigmatropic rearrangement of intermediate **A**, followed by 6π-electrocyclic ring closure, would result in formation of racemic **19**. The key feature of the reaction is generation of a highly reactive ketenium ion **A** upon protonation of siloxyalkyne. We believe that the low nucleophilicity of the NTf_2^- anion is crucial for enabling the formation and effective interception of **A** to give a σ-complex **B**, which affords the final product with concomitant regeneration of the acid catalyst.

Encouraged by the ability of $HNTf_2$ to promote efficient arene-siloxyalkyne carbocyclizations, we next examined the corresponding enyne cyclizations. Indeed, subjection of siloxy enyne **22** to $HNTf_2$ afforded enone **23** (Scheme 3). Our systematic studies revealed that

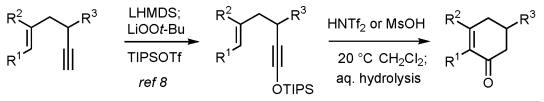
Scheme 3

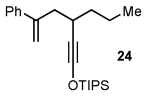
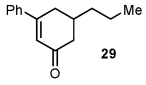
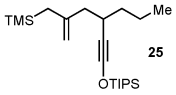
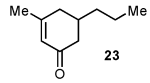
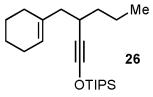
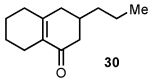
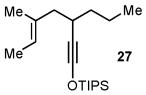
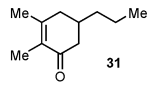
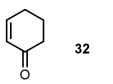


a stoichiometric amount of acid is required for efficient carbocyclization of **22**. Under optimized conditions, cyclohexenone **23** was obtained in 74% yield using 120 mol % $HNTf_2$.

Our investigation of the scope of enyne carbocyclizations is summarized in Table 3. Subjection of disubstituted alkenes **24** and **25** to $HNTf_2$ gave the expected cyclohexenones **29** and **23** in good yields (entries 1 and 2). Cyclizations of trisubstituted and monosubstituted alkenes were promoted more efficiently using MsOH (entries 3−5). We are continuing our search for a catalytic protocol to promote the siloxy enyne cyclizations.

Table 3. Alkene-Siloxyalkyne Carbocyclizations



Entry	Siloxy Alkyne	Yield, %	Silyl Enol Ether	Method	Yield, %
1	 **24**	98	 **29**	*Method A*	80[a]
2	 **25**	99	 **23**	*Method A*	88[a]
3	 **26**	93	 **30**	*Method A*	78[b]
4	 **27**	93	 **31**	*Method B*	91[b]
5	 **28**	84	 **32**	*Method B*	76[b,c]

[a] Method A: $HNTf_2$ (120 mol %), CH_2Cl_2, 20 °C, 2 h. [b] Method B: MsOH (4 equiv), CH_2Cl_2, 20 °C, 2 h. [c] Yield was determined by ^1H NMR using 1,2-dibromobenzene as an internal standard.

In closing, we have developed efficient acid-promoted carbocyclizations of siloxyalkynes to give a range of substituted tetralones and cyclohexenones. The most notable aspect of this process is the ability to efficiently generate highly reactive ketenium ions that are readily intercepted by nucleophiles that are not restricted to those containing electron-rich arenes and allyl silanes.

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

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(11) For complete details, see Supporting Information.

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