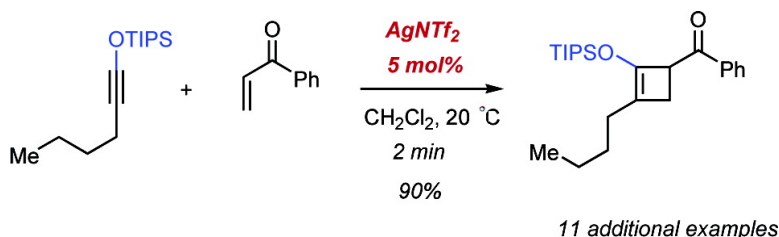


Silver-Catalyzed [2 + 2] Cycloadditions of Siloxy Alkynes

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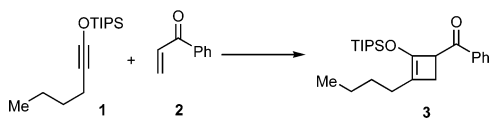
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Silver-based catalysis is emerging as a novel paradigm in organic synthesis leading to the development of an arsenal of mild and efficient carbon-carbon bond-forming reactions¹ and group-transfer processes.² In continuation of our systematic investigation of reactivity of siloxy alkynes,^{3,4} we describe herein the discovery of the first silver-catalyzed [2 + 2] cycloadditions of siloxy alkynes with simple unsaturated ketones, esters, and nitriles. Efficiently promoted by a catalytic amount of silver trifluoromethanesulfonimide, this transformation represents a new mode of reactivity of siloxy alkynes⁵ and provides an efficient method for the assembly of highly functionalized siloxy cyclobutenes. Our work is distinguished uniquely from the previously described thermal [2 + 2] cycloadditions of ynamines,⁶ enantioselective Ti-promoted cycloadditions of alkynyl sulfides,⁷ and metal-catalyzed cycloadditions of alkenes.⁸ Indeed, mild silver(I) catalysis is essential for its compatibility with labile siloxy alkynes. Furthermore, we believe that the reaction mechanism entails a silver-based activation of siloxy alkyne toward subsequent 1,4-addition.

Our investigation began with an examination of reaction between 1-siloxy-1-hexyne **1** and enone **2** (Table 1). While no reaction was observed under thermal conditions,⁹ the use of strong Lewis acids, i.e., BF₃ or TiCl₄, resulted in formation of cyclobutene **3** with only low efficiency (entries 2, 3), despite the previous successful studies by Narasaka on [2 + 2] cycloadditions of alkynyl sulfides.⁷ Furthermore, only moderate improvement was achieved using TIPSOTf and Sc(OTf)₃ (entries 4, 5). Unexpectedly, our attempt to generate TIPSNTf₂ in situ (entry 6) resulted in the discovery of AgNTf₂¹⁰ as an exceptional and unique promoter of [2 + 2] cycloaddition between **1** and **2** (entry 8). The reaction proceeded within minutes at 20 °C in CH₂Cl₂ in the presence of 5 mol % of catalyst to furnish siloxy cyclobutene **3** in 90% isolated yield. The efficiency was diminished employing other silver salts, i.e., AgOTf, and AgSbF₆ (entries 9, 10).

Table 1. Initial Catalyst Evaluation



entry	catalyst (mol %)	solvent	temperature, °C	yield, % ^a
1	none	CH ₃ CN	80	<5
2	BF ₃ OEt ₂ (10)	CH ₂ Cl ₂	-78	17
3	TiCl ₄ (10)	CH ₂ Cl ₂	0	28
4	Sc(OTf) ₃ (5)	CH ₃ NO ₂	20	58
5	TIPSOTf (10)	CH ₂ Cl ₂	20	62
6	TIPSCl/AgNTf ₂ (5)	CH ₂ Cl ₂	20	80
7	TIPSCl (10)	CH ₂ Cl ₂	20	<5
8	AgNTf ₂ (5)	CH ₂ Cl ₂	20	90
9	AgSbF ₆ (7)	CH ₂ Cl ₂	20	56
10	AgOTf (10)	CH ₂ Cl ₂	20	41

^a Refers to isolated yields after chromatographic purification of the silyl enol ether **3**.

Table 2. [2 + 2] Cycloadditions Catalyzed by AgNTf₂ (5 mol %)

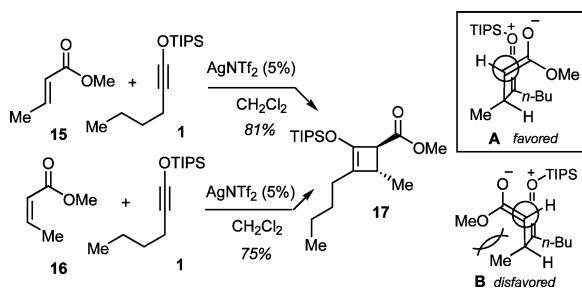
Entry	Siloxy Alkyne	Alkene	Product	Yield, % ^a
1				77
2				69
3				78
4				73
5				83
6				70
7				68
8				75
9				76

^a Refers to isolated yields of the silyl enol ethers that were fully characterized by NMR, IR, and MS.

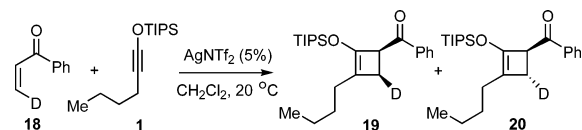
Our investigation of the scope of the present method is summarized in Table 2. α,β -Unsaturated ketones, esters, and nitriles reacted with siloxy hexyne **1** to give the corresponding siloxy cyclobutenes **6–8** in 69–78% yield (entries 1–3). The use of cyclohexenone afforded the corresponding [4.2.0]bicyclic silyl enol ether **9** (entry 4). Additional studies revealed that aryl substitutions in siloxy alkynes **4** and **5** were compatible with the general reaction protocol (entries 5–9). Furthermore, the structure of siloxy cyclobutene **14** was confirmed by X-ray crystallography.

Subjection of *E*- and *Z*-crotonates **15** and **16** to siloxy alkyne **1** resulted in the formation of the same *trans*-substituted siloxy cyclobutene **17** (Scheme 1). This outcome suggested for the first time that the reaction proceeded via a stepwise mechanism. The observed diastereoselection could be rationalized by considering the minimization of the A_{1,3} strain in the two diastereomeric transition states **A** and **B**. To provide additional support for the stepwise mechanism of the [2 + 2] cycloaddition, and to rule out the possibility of isomerization of *Z*-crotonate prior to the reaction, we subjected a deuterated enone **18** (*Z*:*E* = 92:8) to alkyne **1**

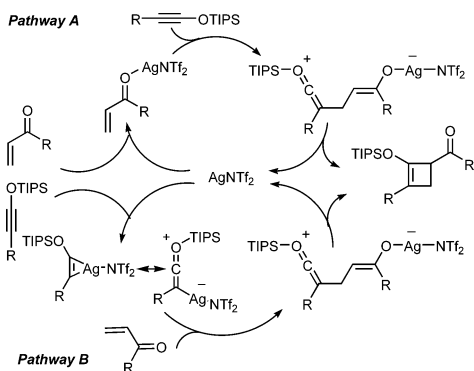
Scheme 1



Scheme 2



Scheme 3



(Scheme 2). This experiment revealed a complete scrambling of the deuterium label, which is fully consistent with the stepwise reaction mechanism.¹¹

Scheme 3 depicts two plausible mechanistic pathways, including a classical LUMO-lowering Lewis acid activation of the enone (path A), and silver-based activation of siloxy alkyne, followed by 1,4-addition and trapping of the ketenium ion (path B). While the catalytic mechanism has not been fully elucidated, we currently favor path B. We observed that treatment of a suspension of AgNTf_2 in CH_2Cl_2 with siloxy alkyne resulted in formation of a homogeneous solution. Subsequent low-temperature NMR studies revealed facile complexation of siloxy alkyne **1** with AgNTf_2 even at -73°C , as indicated by profound changes in ^1H and ^{13}C chemical shifts of the alkyne (Figure 1).¹² Addition of the enone **2** to this Ag-alkyne complex resulted in rapid formation of product **3** within 1 min at -43°C . Interestingly, a similar effect was not observed using AgOTf , highlighting the importance of the counterion. In contrast, addition of a stoichiometric amount of AgNTf_2 to the enone **2** at 20°C results in only moderate changes in the NMR spectrum. Furthermore, AgNTf_2 did not efficiently catalyze [2 + 2] cycloadditions of enones with silyl enol ethers.¹³ These results indicate that the catalytic role of AgNTf_2 is most likely due to complexation and activation of the siloxy alkyne toward subsequent stepwise cycloaddition (path B).¹⁴

In summary, we have described the first silver-catalyzed [2 + 2] cycloadditions of silyl ynoles with a range of unsaturated carbonyl compounds. The discovery of a unique AgNTf_2 catalyst, which promotes this transformation presumably via nucleophile-

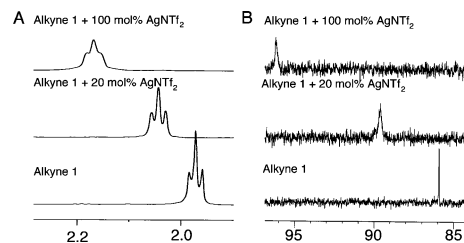


Figure 1. 500 MHz ^1H NMR (A) and 125 MHz ^{13}C NMR (B) complexation experiments between siloxy alkyne **1** (0.1 M in CD_2Cl_2) and AgNTf_2 at 200 K.

based activation, distinguishes our findings from [2 + 2] cycloadditions of other heteroatom-functionalized alkynes and sets an important precedent for broad investigation of reactivity of this silver(I) catalyst.

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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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