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Radical Alkynyltrifluoromethylation of Alkenes Initiated by an Electron Donor–Acceptor Complex

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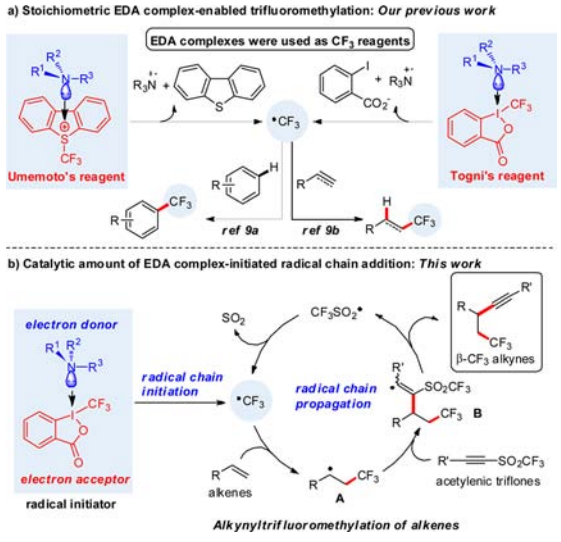
Supporting Information

ABSTRACT: Radical alkynyltrifluoromethylation of alkenes with acetylenic triflones has been achieved. This radical chain reaction is initiated by a catalytic amount of an electron-donor–acceptor complex composed of Togni's reagent and *N*-methylmorpholine. This transformation proceeds under exceptionally mild and operationally simple conditions. A variety of alkenes are compatible in this protocol including aliphatic alkenes, vinyl ethers, enecarbamates, styrenes, and even acrylates, providing diverse β-trifluoromethyl alkynes in good to excellent yields.

Radical addition reactions serve as an efficient and practical strategy to achieve difunctionalization of alkenes and alkynes through a radical-chain pathway. These reactions have been extensively studied through the development of diverse initiation conditions (ultraviolet irradiation, azo compounds, organotin reagents, or trialkylboranes).[1] Recent progress focuses on the exploitation of highly efficient and environmentally benign visible-light photosensitizers to initiate the radical-chain addition reactions.[2] However, the scope of these visible-light-promoted transformations is mainly restricted to the addition of an alkyl halide[3] or trifluoromethylsulfonyl chloride (CF_3SO_2Cl)[4] to an alkene to simultaneously generate a new C–C and C–X (X = halide or sulfur) bond. Therefore, the discovery of efficient and easily accessible initiators to achieve diverse radical-chain addition reactions,[5] especially the difunctionalization of alkenes by simultaneously assembling two new C–C bonds across the C=C bond under mild conditions, is still challenging, but highly valuable in the radical chemistry community.[6]

Electron-donor–acceptor (EDA) complexes are a type of molecular aggregate generated from noncovalent interaction between an electron donor and an electron acceptor, which were disclosed by Mulliken decades ago.[7] The EDA complex involved organic transformations related to single-electron-transferred radical pathways have gathered increasing attention with promising advances in recent years.[8] Recently, our group defined a type of EDA complex composed of a tertiary amine with an electrophilic trifluoromethylating reagent (Togni's or Umemoto's reagent), which can be thermally activated to an excited state and subsequently dissociated into trifluoromethyl radical ($^{\bullet}CF_3$) and nitrogen-based radical cations. These EDA complexes had also been successfully applied to the trifluoromethylation of arenes and hydrotrifluoromethylation of alkenes and alkynes (Scheme 1a).[9] Motivated by these achievements, we envisaged that the use of a catalytic amount of an EDA complex consisting of an electrophilic trifluoromethylating reagent and a tertiary amine would be capable of initiating a radical-chain addition of acetylenic triflones to alkenes, leading to β-CF_3 alkynes in a single operation.[10]

Scheme 1. EDA Complex-Enabled Trifluoromethylation



The rationale of this proposal originates from the generation of $^{\bullet}CF_3$ through single-electron transfer of an EDA complex composed of a tertiary amine and Togni's reagent (Scheme 1b).[9] Radical attack of $^{\bullet}CF_3$ onto an olefin produces the radical intermediate **A**, which can be trapped by an acetylenic triflone to give radical intermediate **B**. β-Elimination of **B** affords triflyl radical ($CF_3SO_2^{\bullet}$) and the desired alkynyltrifluoromethylation adduct of the alkene.[10] Afterward, radical chain propagation is launched by reproducing $^{\bullet}CF_3$ through the release of SO_2 from $CF_3SO_2^{\bullet}$. Although Fuchs and co-workers reported AIBN-

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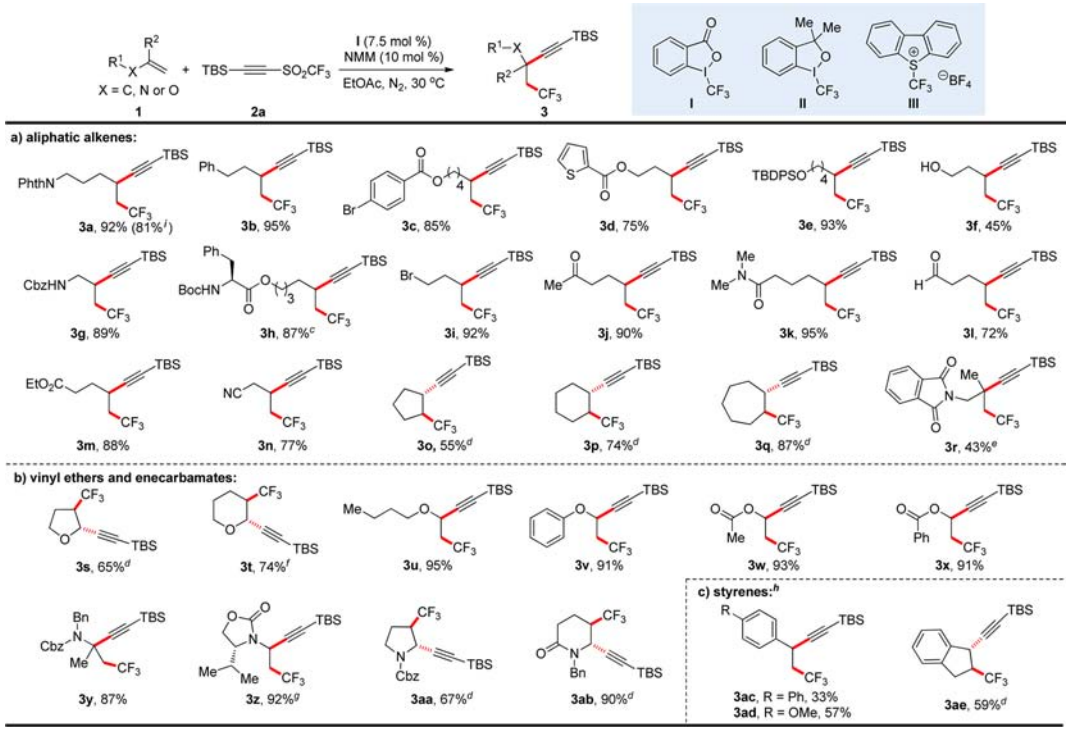
Scheme 2. Scope of the Alkynyltrifluoromethylation of Alkenes with Silyl Alkyne-Derived Triflone 2a[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), Togni's reagent **I** (7.5 mol %), and NMM (10 mol %) in dry EtOAc (0.5 mL) at 30 °C for 24 h. [b]Isolated yield. [c]dr = 1:1. [d]dr > 20:1. [e]Reaction time: 48 h. [f]dr = 12:1. [g]dr = 10:1. [h]Reactions were performed in 0.5 mL of 1,4-dioxane for 72 h. [i]2 mmol scale.

initiated alkynyltrifluoromethylation of alkenes with actylenic triflones two decades ago,[10a] the strategy presented here possesses several interesting features: (I) a catalytic amount of EDA complex is used as an initiator, which avoids the use of a hazardous initiator; (II) this process simultaneously introduces two new C−C bonds; (III) acetylenic triflones serve as both trifluoromethyl and alkynyl sources, which makes this process atom economical; and (IV) trifluoromethyl radical ($^{\bullet}CF_3$) generated from the initiator is involved in the radical-chain propagation directly, which obviates the formation of byproducts derived from initiators.

This EDA complex initiated alkynyltrifluoromethylation of alkenes was initially examined through the reaction of phthalyl-protected 1-penten-5-amine (**1a**) with silyl alkyne-derived triflone **2a** (Scheme 2). A combination of 7.5 mol % of Togni's reagent **I** with 10 mol % of NMM in EtOAc was capable of initiating this transformation smoothly at 30 °C to give the desired product **3a** in 92% yield. Togni's reagent **II** was ineffective in this transformation. Although the EDA complex of Umemoto's reagent **III** with NMM can be successfully used in C−H trifluoromethylation of arenes and hydrotrifluoromethylation of alkenes/alkynes,[9b] it failed to initiate this reaction. Other electron donors including secondary and tertiary amines dramatically decreased the yield. Both of Togni's reagent **I** and NMM are indispensable; otherwise, the transformation could not be initiated with full recovery of starting materials (for full condition screening, see the Supporting Information).

Afterward, a variety of aliphatic alkenes were examined in this reaction (Scheme 2). Different kinds of functional groups were well tolerated under the optimal reaction conditions, including aromatic rings, heterocycles, silyloxy esters, free alcohols, carbamates, alkyl bromides, ketones, amides, aldehydes, esters, and nitriles (**3a−n**). Cyclic alkenes (**3o−q**) and a sterically hindered alkene (**3r**) were also compatible in this reaction (Scheme 2a). It is noteworthy that vinyl ethers and enecarbamates proceeded smoothly in this reaction, providing the desired alkynyltrifluoromethylated adducts **3s−ab** in good to excellent yields (Scheme 2b). Electron-neutral and electron-rich styrenes were also effective reaction partners with **2a**, affording **3ac−ae** in moderate yields (Scheme 2c).

We next sought to examine the reactivity of alkenes with phenylacetylene-derived acetylenic triflone **2b** to prepare more structurally diverse β-CF_3 alkynes through this EDA complex-initiated radical reaction (Scheme 3). The combination of 5 mol % of Togni's reagent **I** and 10 mol % of NMM was capable of initiating this reaction efficiently to give the desired product **4a** in 89% yield. A variety of functional groups in alkenes were well tolerated, including silyloxy esters, carbamates, ketones, esters, alkyl bromides, and amides, providing the desired alkynyltrifluoromethylation products in good to excellent yields (**4b−g**). Cyclohexene (**4h**), cycloheptene (**4i**) and the sterically hindered alkene (**4j**) also worked quite well in this transformation (Scheme 3a). Furthermore, vinyl ethers and enecarbamates were also suitable coupling partners with **2b**, affording products **4k−p** in satisfactory yields. Remarkably, electron-deficient alkenes such as acrylates and vinyl phosphonates were also effective to afford the desired products **4q−s** in moderate to good yields (Scheme 3b). We also evaluated the reactivity of substituted styrenes with **2b** (Scheme 3c). A variety of electron-rich or electron-deficient styrenes were well tolerated in this reaction, affording alkynyltrifluoromethylation adducts **4t−ah** in moderate to satisfactory yields. Internal alkenes such as β-methylstyrene, α-methylstyrene, indene, and 1,2-dihydronaphthalene were also compatible to produce **4ai−al** in moderate to good yields. Some

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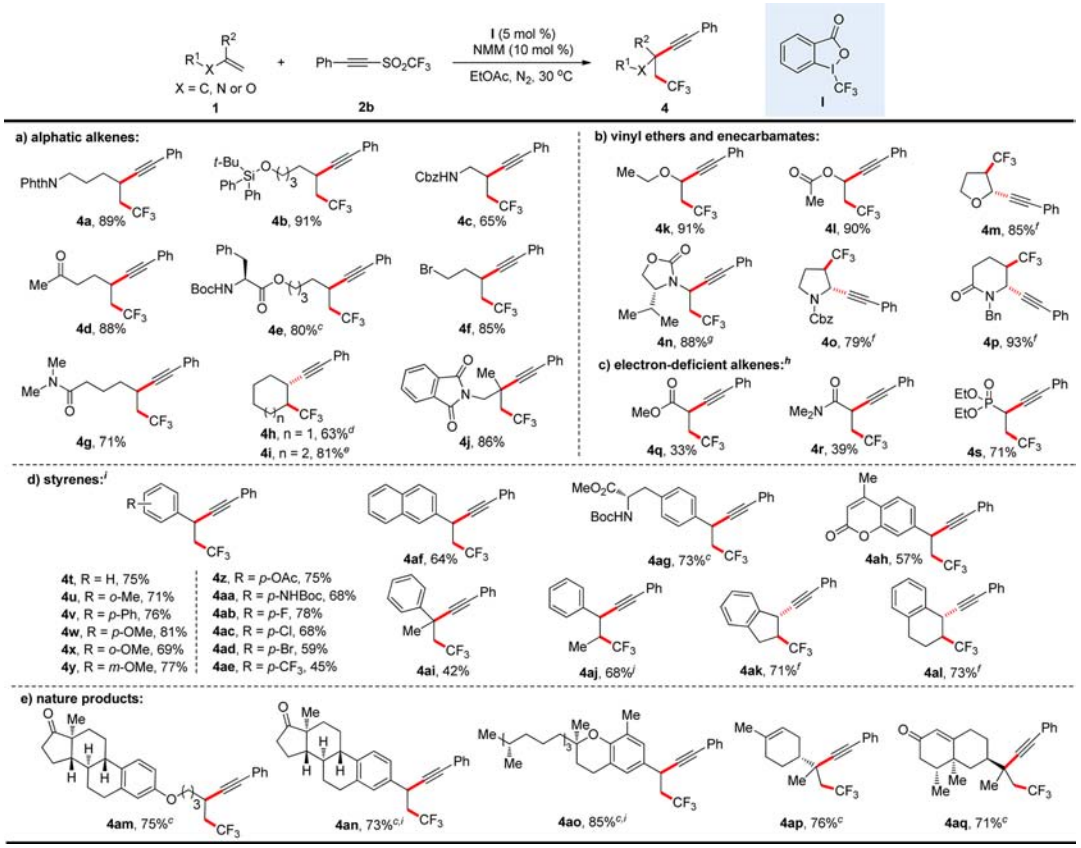
Scheme 3. Scope of the Alkynyltrifluoromethylation of Alkenes with Phenylacetylene-Derived Triflone 2b[a,b]



[a]Reaction conditions: **1** (0.24 mmol), **2b** (0.2 mmol), Togni's reagent **I** (5 mol %), and NMM (10 mol %) in dry EtOAc (0.5 mL) at 30 °C for 24 h. [b]Isolated yield. [c]dr = 1:1. [d]dr = 6:1. [e]dr = 9:1. [f]dr > 20:1. [g]dr = 10:1. [h]10 mol % of Togni's reagent **I** was used, 48 h. [i]10 mol % of Togni's reagent **I** was used in dry 1,4-dioxane (0.5 mL), 48 h. [j]dr = 4:1.

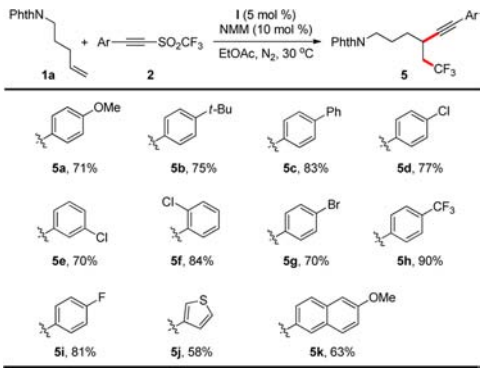
biologically important molecule-derived alkenes, such as estrone, δ-tocotrienol, (*R*)-limonene, and nootkatone, could also go through this ATRA reaction to give the corresponding alkynyltrifluoromethylation products **4am**−**aq** in 71−85% yields (Scheme 3d).

The scope of arylacetylene-derived acetylenic triflones was also investigated (Scheme 4). Functional groups with various electronic properties, including OMe, *t*-Bu, Ph, Cl, Br, CF_3, and F, were well tolerated to furnish the desired products **5a**−**i** in satisfactory yields (70−90%). Thiophene- and naphthalene-derived acetylenic triflones were also competent reaction partners with **2b**, affording **5j** and **5k** in 58% and 63% yields, respectively.

The resultant alkynyltrifluoromethylation products were easily modified (Scheme 5). For example, the silyl group of silylalkyne **3a** could be removed by treatment of **3a** with TBAF to give terminal alkyne **6**, which facilitates further transformations. The triple bond of alkyne **4a** could be easily reduced to compound **7** by Pd/C-catalyzed hydrogenation or converted to ketone **8** by acid-catalyzed hydrolysis.[11] All of these transformations proceeded smoothly to give CF_3-containing synthetic building blocks in excellent yields, which could be potentially used in pharmaceutical chemistry for modern drug discovery.[12]

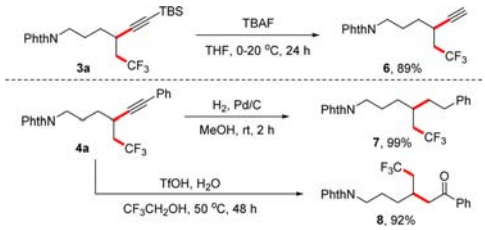
To support the mechanism of the radical-chain-addition reaction we proposed in Scheme 1b, a series of control experiments were conducted (Scheme 6). The model reaction

Scheme 4. Scope of Arylacetylene-Derived Triflones[a,b]



[a]Reaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol), Togni's reagent **I** (5 mol %), and NMM (10 mol %) in dry EtOAc (0.5 mL) at 30 °C for 24 h. [b]Isolated yield.

Scheme 5. Synthetic Applications



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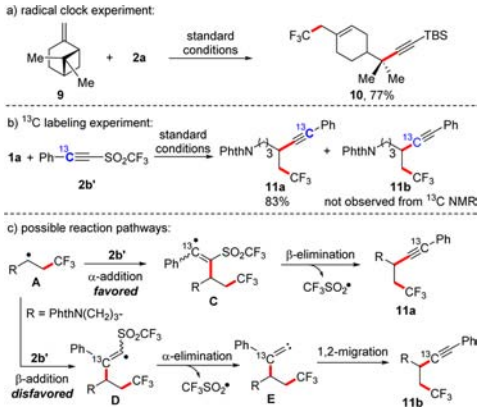
Scheme 6. Mechanistic Studies



could be totally terminated by introducing TEMPO into the reaction mixture. When (−)-β-pinene was employed under standard conditions, the ring-opening product **10** was obtained in 77% yield (Scheme 6a). These results suggest that the radical intermediates are involved in this transformation. Afterward, the ^{13}C-labeled acetylenic triflone **2b′** was used in this reaction (Scheme 6b). As a result, the ^{13}C-labeled product **11a** was isolated exclusively in 83% yield without detection of any ^{13}C-migration product **11b**. This result supports the notion that α-addition of radical intermediate **A** to acetylenic triflone **2b′** occurs predominantly to afford vinyl radical **C**. β-Elimination of **C** produces **11a** and $CF_3SO_2^{\bullet}$. Therefore, the alternative pathway of β-addition and subsequent α-elimination to form the vinylidene carbene **E** followed by 1,2-migration to give **11b** can be excluded in this radical-chain-addition reaction (Scheme 6c).[13]

In summary, we have described an electron donor−acceptor complex initiated radical-chain addition of acetylenic triflones to alkenes. The alkynyltrifluoromethylation of alkenes can be achieved under exceptionally mild and operationally simple conditions. The catalytic amount of EDA complex of Togni's reagent and NMM is capable of initiating this transformation efficiently. The reactivity of silylalkyne- and phenylacetylene-derived acetylenic triflones with a variety of alkenes, including aliphatic alkenes, vinyl ethers, enecarbamates, styrenes, and even acrylates, was extensively discussed. A variety of structurally diverse β-CF_3 alkynes can be easily prepared in a single operation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00337.

Full experimental details, characterization of new compounds, and ^{1}H and ^{13}C NMR (PDF)

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Notes

The authors declare no competing financial interest.

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