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Catalytic Radical Trifluoromethylalkynylation of Unactivated Alkenes

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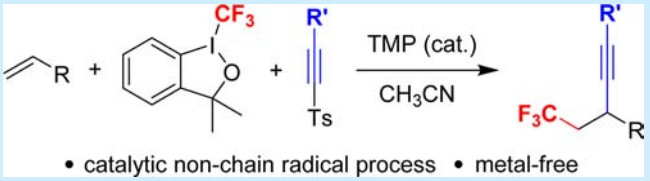
Supporting Information

ABSTRACT: The trifluoromethylalkynylation of unactivated alkenes with alkynyl sulfones and Togni's reagent was developed. The reaction was catalyzed by 2,4,6-trimethylpyridine, leading to various β-trifluoromethylated alkynes under metal-free conditions with a broad substrate scope and wide functional group compatibility. A mechanism involving catalytic nonchain radical processes is proposed.



The prominent roles of trifluoromethylated compounds in pharmaceuticals and agrochemicals have spurred a considerable interest in the development of new methods for the introduction of trifluoromethyl groups into organic molecules.[1] Trifluoromethyl radical-mediated difunctionalization of alkenes serves as a versatile tool for this purpose and has become a hot topic in recent years.[1c−h] To this end, carbotrifluoromethylation of alkenes is extremely valuable in that it allows the fast assembly of CF_3 and a second functionality into an alkene via two new C(sp^3)−C bond formations.[2−5] In particular, the intermolecular introduction of the second functional group is highly desired and synthetically more useful. Unfortunately, only a few examples were reported in this aspect,[3−5] while in most literature works the second functionality was incorporated intramolecularly via cyclization, rearrangement, or aryl migration.[2] Herein we report the amine-catalyzed intermolecular trifluoromethylalkynylation of unactivated alkenes via three-component condensation, leading to various β-trifluoromethylated alkynes under mild conditions.

The only example of trifluoromethylalkynylation was reported by Fuchs et al. two decades ago via ultraviolet (254 nm)-induced or AIBN-initiated reaction of an alkene with phenylethynyl triflone.[5] It is a radical chain reaction in that (1) trifluoromethyl radical adds to an alkene to give the adduct radical, (2) the adduct radical adds to the C≡C bond in phenylethynyl triflone to produce the final product and trifluoromethanesulfonyl radical, and (3) the SO_2 extrusion of trifluoromethanesulfonyl radical regenerates trifluoromethyl radical (Figure 1a).[6] Despite its excellent atom-economy and innate radical chain, this method suffers from the insufficient initiation and is vulnerable to side reactions and impurities as possible radical chain inhibitors. Indeed, the reaction had to be carried out in excess alkene as solvent and allylic C−H alkynylation byproducts were also produced.[5] To avoid these disadvantages, we designed a nonchain radical reaction (vide infra) with Togni's reagent[7] as trifluoromethyl source and alkynyl *p*-tolyl sulfones as alkynylating agent, thus allowing the easy tuning of reaction processes. Furthermore, the use of

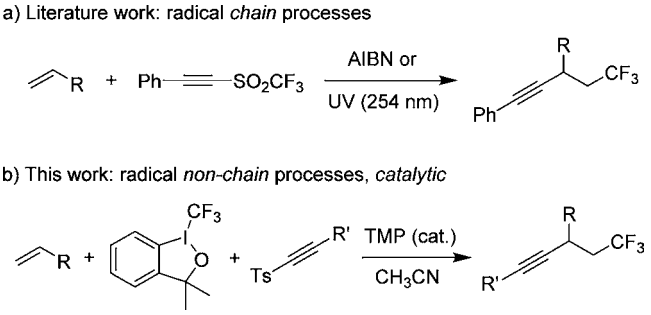


Figure 1. Trifluoromethylalkynylation of alkenes.

Togni's reagent enables the generation of trifluoromethyl radicals in a catalytic and more efficient manner (Figure 1b).[6]

Thus, *N*-(pent-4-en-1-yl)phthalimide (**1a**) was chosen as the model substrate for the optimization of reaction conditions (Table 1). In a preliminary test, the mixture of **1a**, Togni's reagent **2a** (1.5 equiv), phenylethynyl *p*-tolyl sulfone **3a** (2.0 equiv), and CuCl (20 mol %) in acetonitrile was stirred at 80 °C for 15 h. The trifluoromethylalkynylation product **4a** was obtained in 60% yield. Switching the CF_3 source to Togni's reagent II (**2b**) resulted in a lower yield of **4a**, while no expected product could be detected using Umemoto's reagent[8] **2c** (entries 1−3, Table 1). The catalytic role of CuCl can be inferred from the first two experiments. It is well documented[2] that Togni's reagent **2a** can be reduced by Cu(I) to give trifluoromethyl radicals. However, the regeneration of Cu(I) is not easy to understand under the above reaction conditions. This urged us to test other catalysts. We next chose **2a** as the CF_3 source and screened a number of amines as catalysts as they were reported[9] to catalyze the generation of CF_3 radicals from **2b** and **2c**. Gratifyingly, with 2,4,6-trimethylpyridine (TMP) as the catalyst, alkyne **4a** was achieved in 74% yield

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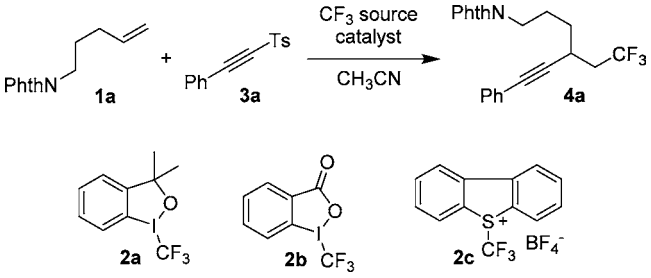
Table 1. Optimization of Reaction Conditions



entry[a]	CF_3 source (equiv)	catalyst (mol %)	temp (°C)	yield (%)[b]
1	2a	CuCl (20)	80	60
2	2b	CuCl (20)	80	48
3	2c	CuCl (20)	80	0
4	2a	TMP (30)	80	74
5	2a	DMP (30)	80	52
6	2a	DMAP (30)	80	33
7	2a	DIPEA (30)	80	49
8	2a	DBN (30)	80	14
9	**2a**	**TMP (30)**	**60**	**81**
10	2a	TMP (30)	40	38
11	2a	TMP (20)	60	58
12	2a	none	60	5

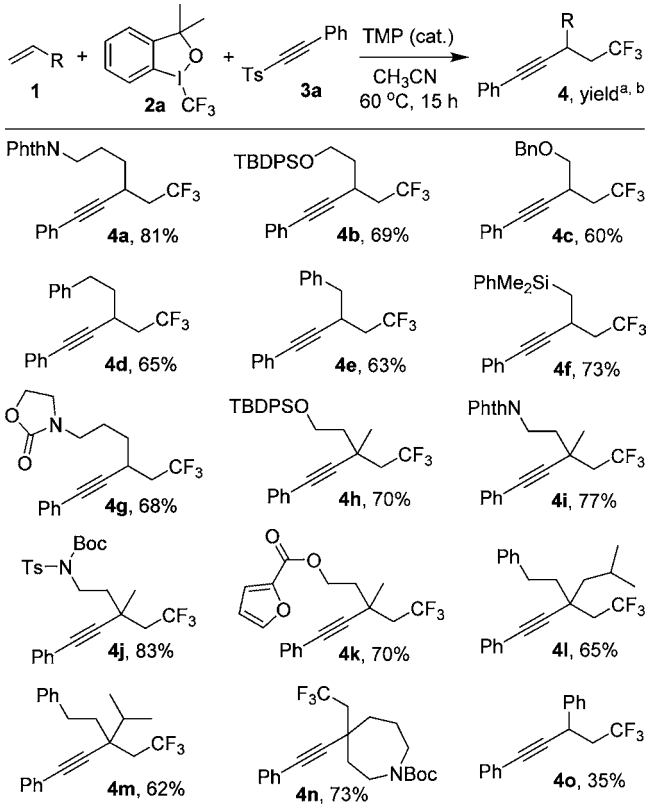
[a]Reaction conditions: **1a** (0.2 mmol), CF_3 source (0.3 mmol), **3a** (0.4 mmol) and catalyst, CH_3CN (2 mL), 15 h. [b]Isolated yield based on **1a**.

(entry 4, Table 1). Switching TMP to other amines such as 2,6-dimethylpyridine (DMP), 4-(dimethylamino)pyridine (DMAP), diisopropylethylamine (DIPEA), or 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) decreased the product yield (entries 5−8, Table 1). Lowering the temperature to 60 °C further increased the product yield to 81% (entry 9, Table 1). Nevertheless, the yield of **4a** was decreased when the reaction was performed at 40 °C or with the use of 20 mol % TMP (entries 10 and 11, Table 1). The catalytic effect of TMP was evidenced by the control experiment in which only a trace amount of **4a** was observed in the absence of TMP (entry 12, Table 1). It is worth mentioning that in all cases no allylic C−H alkynylation byproduct could be observed.

With the optimized conditions in hand (entry 9, Table 1), we set out to explore the generality of this method. As shown in Scheme 1, the reactions of various monosubstituted alkenes proceeded smoothly, furnishing the corresponding products **4a**−**4g** in satisfactory yields. Electron-rich disubstituted alkenes also underwent trifluoromethylalkynylation nicely, as exemplified by the synthesis of *β*-trifluoromethylated alkynes **4h**−**4k** in high yields. Styrene could also be utilized as the substrate to produce alkyne **4o**, albeit in a low efficiency, presumably due to the easy oligomerization of styrene under the reaction conditions. A wide range of functional groups were well tolerated, including ether, ester, amide, sulfonamide, carbamate, benzyl, silyl, and furan.

The above method is also applicable to other alkynylating agents such as triisopropylethynyl *p*-tolyl sulfone **3b**, and the results are summarized in Scheme 2. Again, a wide substrate scope and broad functional group compatibility were observed. Also note that in the reactions of cyclohexene and cycloheptene, only trans-configured products **5n** and **5o** were achieved, respectively. This excellent stereoselectivity might be attributed to the steric effect caused by the bulkiness of triisopropylsilyl (TIPS) group in **3b**.[10] The use of **3b** as the

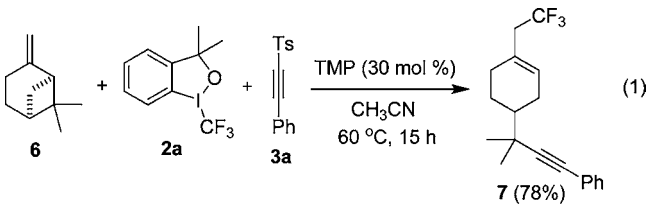
Scheme 1. Trifluoromethylalkynylation of Unactivated Alkenes with 3a

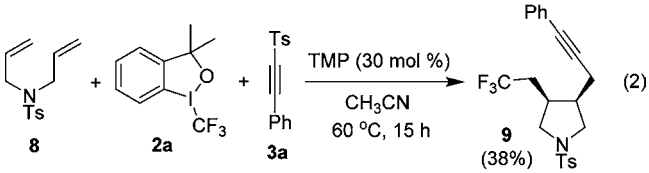


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.4 mmol), TMP (0.06 mmol), CH_3CN (2 mL), 60 °C, 15 h. [b]Isolated yields based on **1**.

alkynylating agent further increases the potential of application of this methodology because synthetically more useful terminal alkynes can be readily accessed by simple desilylation of products **5**.

The above results also implied that the trifluoromethylalkynylation proceeds via a free radical mechanism. To provide more evidence, the following two experiments were designed. The reaction of *β*-pinene (**6**) afforded exclusively the ring-opening product **7** in 78% yield (eq 1). *N*,*N*-Diallyltoluene-





sulfonamide (**8**) underwent addition−cyclization−alkynylation sequence to provide pyrrolidine **9** as a mixture of two stereoisomers (*cis*/*trans* = 8:1 determined by ^{19}F NMR) (eq 2).

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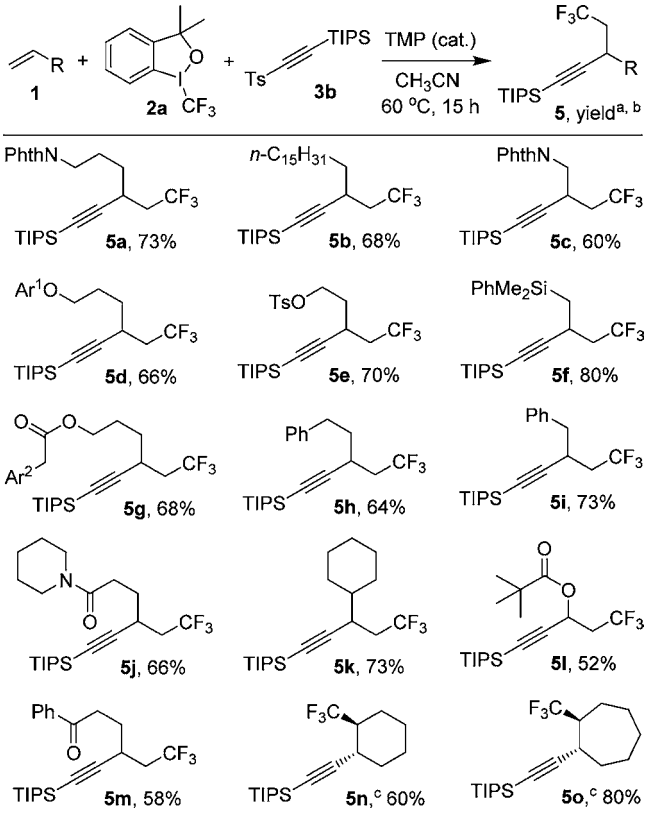
Scheme 2. Trifluoromethylalkynylation of Unactivated Alkenes with 3b



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), **3b** (0.4 mmol), TMP (0.06 mmol), CH_3CN (2 mL), 60 °C, 15 h. [b]Isolated yields based on **1** [c]*trans*/*cis* > 20:1 determined by ^1H NMR.

A plausible mechanism is then proposed based on the above results, as depicted in Figure 2. The interaction of TMP with **2a**

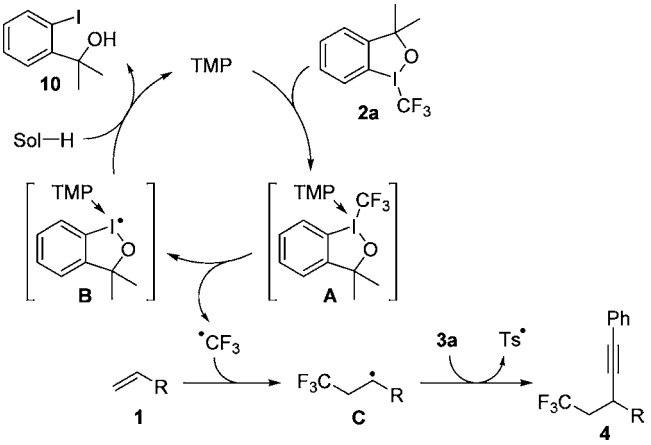


Figure 2. Proposed mechanism of trifluoromethylalkynylation.

leads to the formation of electron-donor−acceptor complex **A**,[9] which upon heating undergoes homolytic cleavage to produce trifluoromethyl radical and species **B**. The addition of trifluoromethyl radical to alkene **1** gives the radical adduct **C**, which in turn adds to alkynyl sulfones **3a** to afford the product **4**.[10,11] The intermediate radical **B** undergoes either H-abstraction (presumably from the solvent) or single electron reduction (presumably by tosyl radical) followed by proto-nation to regenerate TMP along with the formation of alcohol **10** (see the SI for details).

In conclusion, we have successfully developed the TMP-catalyzed trifluoromethylalkynylation of unactivated alkenes by condensation with Togni's reagent and alkynyl sulfones. These nonchain radical reactions proceeded under mild and metal-free conditions, offering a convenient entry to various β-CF_3 alkynes with wide functional group compatibility. In view of the rich chemistry of alkynes, this method should find important applications in the synthesis of trifluoromethylated compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03870.

Full experimental details, characterizations of new compounds, and copies of ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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