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Copper-mediated Trifluoromethylthiolation of Alkenyl Iodides with $AgSCF_3$

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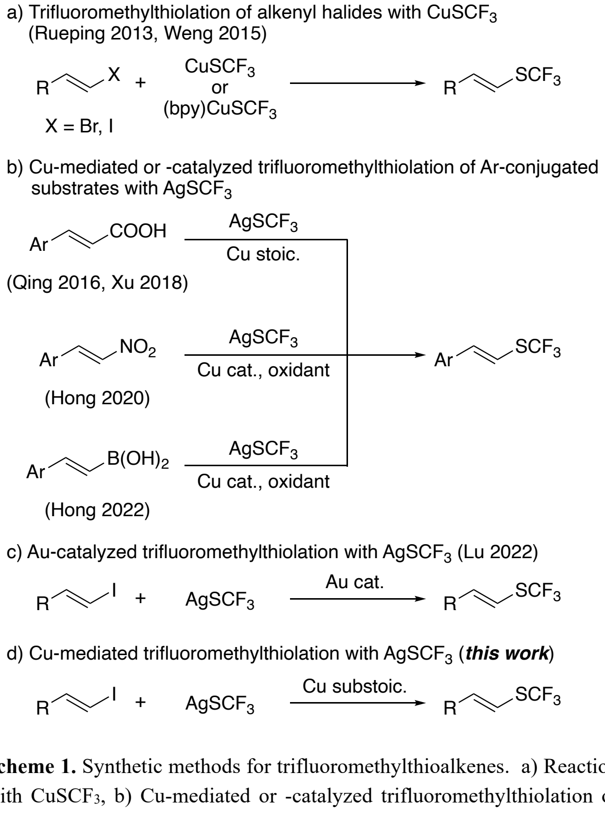
A copper-mediated trifluoromethylthiolation of alkenyl iodides with $AgSCF_3$ has been developed. $CuSCF_3$ species generated in-situ from a copper salt and $AgSCF_3$ can be coupled with alkenyl iodides to produce the corresponding trifluoromethylthioalkenes efficiently. The reaction conditions are compatible with various functional groups. Moreover, its scale-up synthesis is also possible to provide the desired trifluoromethylthiolated product even on a gram-scale.

Keywords: Copper, Fluorine, Trifluoromethylthio group

Organofluorine derivatives are an important class of compounds in the current medicinal chemistry, and the introduction of fluorine-containing functional groups is aggressively considered in the design of pharmaceuticals and agrochemicals.[1] In particular, trifluoromethylthio (SCF_3) group is one of the most attractive fluorinated substituents because of its strong electron-withdrawing nature and high lipophilicity. The electron-withdrawing property of SCF_3 group (Hammett substituent constant $\sigma_p = 0.50$) is compatible to that of a trifluoromethyl (CF_3) group ($\sigma_p = 0.54$).[2] Meanwhile, the lipophilicity of SCF_3 group (Hansch parameter $\pi_R = 1.44$) is much greater than that of the CF_3 group ($\pi_R = 0.88$).[3] Therefore, numerous synthetic methods for SCF_3-containing molecules have been explored in the past decades.[4] Among them, the SCF_3-substituted alkene is an important target structure because of its prevalence in bioactive molecules.[5] For its preparation, the vinylic $sp^2C–SCF_3$ coupling reaction with some trifluoromethylthiolation reagents was often conducted.[6] In particular, $CuSCF_3$ is the most frequently employed owing to its high reactivity. For example, Rueping reported the synthesis of SCF_3-substituted alkenes using alkenyl iodides and $CuSCF_3$ (Scheme 1a).[6c] Weng also developed the trifluoromethylthiolation of alkenyl bromides using modified $(bpy)CuSCF_3$.[6d] These reactions can prepare the SCF_3-alkenes from readily available alkenyl halides in a single step. However, $CuSCF_3$ is unstable and difficult to handle.[7] The stability of $(bpy)CuSCF_3$ is greatly improved by the bpy ancillary ligand, but it should be pre-synthesized from $TMSCF_3$, CuF_2, and S_8, and carefully purified before use.[8] Accordingly, the further development of synthetic method for SCF_3-substituted alkenes, particularly using readily available and stable trifluoromethylthiolation reagents is still strongly desired. In this context, $AgSCF_3$ is promising,[9] and several transformations with $AgSCF_3$ have been reported. For instance, copper-mediated or -catalyzed reaction systems have been developed to form trifluoromethylthioalkenes from *α,β*-unsaturated carboxylic acids,[10] nitroalkenes,[11] and alkenyl boronic acids[12] (Scheme 1b). However, since these reactions proceed through radical pathways, the applicable substrates are limited to alkenes conjugated with aromatic rings. On the other hand, Lu achieved the synthesis of SCF_3-alkenes by the Au-catalyzed trifluoromethylthiolation of a variety of alkenyl iodides with $AgSCF_3$ (Scheme 1c).[13] This approach has a great advantage in the substrate scope, but there is room for improvement of cost associated with the expensive Au catalyst.

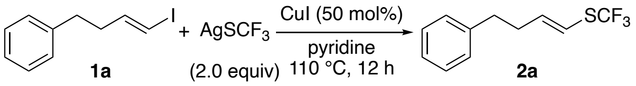
Herein, we report the synthesis of SCF_3-containing alkenes by a copper-mediated trifluoromethylthiolation of alkenyl iodides with $AgSCF_3$ (Scheme 1d). This protocol can directly use $CuSCF_3$ generated in-situ from commercially available CuI and $AgSCF_3$, which is convenient and salient synthetic advantageous. The reaction conditions are compatible with various functionalized alkenyl iodides and accommodate both aromatic and aliphatic substrates. In addition, its scale-up synthesis is also possible, and the SCF_3-alkene is obtained on a gram-scale.



Scheme 1. Synthetic methods for trifluoromethylthioalkenes. a) Reaction with $CuSCF_3$, b) Cu-mediated or -catalyzed trifluoromethylthiolation of Ar-conjugated substrates with $AgSCF_3$, c) Au-catalyzed trifluoromethylthiolation with $AgSCF_3$, and d) Cu-mediated trifluoromethylthiolation with $AgSCF_3$.

Inspired by Rueping's report,[6c] we initially examined optimal conditions with alkyl-substituted alkenyl iodide **1a** as a model substrate (Table 1). In the presence of CuI (50 mol%), treatment of **1a** (0.30 mmol) with $AgSCF_3$ (2.0 equiv) in pyridine solvent at 110 °C produced the corresponding trifluoromethylthioalkene **2a** in 92% ^1H NMR yield (entry 1). The stereochemistry of the starting material was retained after the reaction; (*E*)-**2a** was obtained with high purity. Reducing the amount of CuI to 10 mol% resulted in a drop of the yield (entry 2). Using a stoichiometric amount of CuI, the reaction also proceeded with a similar efficiency (entry 3). In contrast, no reaction occurred in the absence of CuI (entry 4). The change of reaction solvent from pyridine to DMF largely decreased the reaction efficiency (entry 5). Decreasing the amount of $AgSCF_3$ (1.5 or 1.2 equiv) gave the target product in comparable yields (entries 6 and 7). However, a small but significant amount of unreacted **1a** remained when using 1.2 equiv of $AgSCF_3$, and separation of **1a** and **2a** was thus problematic. Therefore, conditions in entry 6 were decided to be optimal to completely convert **1a** for ease of purification.

Table 1. Optimization studies for trifluoromethylthiolation of alkenyl iodide **1a** with $AgSCF_3$.[a]

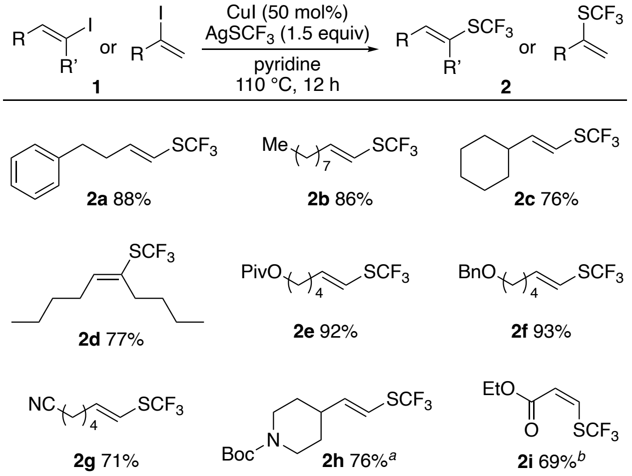


entry	Deviation	Yield[b]/%
1	—	92
2	CuI (10 mol%)	62
3	CuI (100 mol%)	86
4	without CuI	0
5	DMF instead of pyridine	59
6	$AgSCF_3$ (1.5 equiv)	90
7	$AgSCF_3$ (1.2 equiv)	89

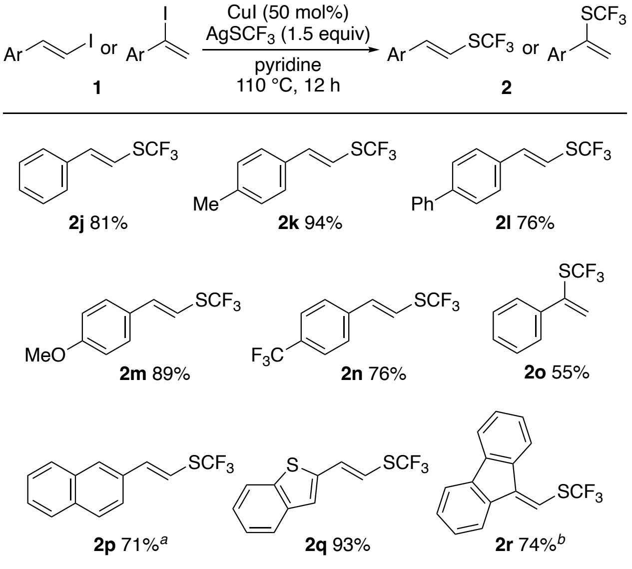
[a] Conditions: CuI (0.15 mmol), **1a** (0.30 mmol), $AgSCF_3$ (0.60 mmol), pyridine (0.3 mL), 110 °C, 12 h, N_2. [b] Estimated by ^1H NMR with dibenzyl ether as the internal standard.

With optimal reaction conditions in hand, we next investigated the substrate scope of reaction (Scheme 2). In general, the reaction was performed on a 3.0 mmol scale to demonstrate the practicality and reliability of procedure. The phenethyl-substituted trifluoromethylthioalkene **2a** was isolated in 88% yield even on a 3.0 mmol scale. The primary and secondary alkyl-substituted alkenyl iodides could be converted to the corresponding trifluoromethylthioalkenes **2b** and **2c** in 86% and 76% yields, respectively. Notably, the internal alkenyl iodide **1d** also underwent the stereoselective trifluoromethylthiolation to yield the SCF_3-substituted internal alkene **2d** in 77% yield. The reaction conditions were also compatible with several functional groups, including pivalic ester (**2e**), benzyl ether (**2f**), nitrile (**2g**), and Boc-protected amine (**2h**). Moreover, the (*Z*)-ethyl 3-iodoacrylate **1i** (*E/Z* = 1:99) successfully reacted with $AgSCF_3$ to form the corresponding trifluoromethylthioalkene **2i** in a *Z*-enriched form (*E/Z* = 5:95). Thus, the present reaction is basically stereospecific.

Furthermore, the reaction of aryl-conjugated substrate also proceeded well (Scheme 3). Under the identical conditions, phenyl-substituted SCF_3-alkene **2j** was obtained in 81% yield on a 3.0 mmol scale. The alkenyl halides with either electron-withdrawing or electron-donating groups on the phenyl ring afforded the corresponding trifluoromethylthiolated alkenes in high yields (**2k**-**2n**). *α*-SCF_3-substituted styrene **2o** was also isolated in an acceptable yield. In addition, other styrenyl-type substrates containing naphthalene and benzothiophene moieties could also be employed (**2p** and **2q**). Even when using trisubstituted alkene substrate **1r**, the corresponding product **2r** was isolated in a good yield. On the other hand, unfortunately, the silyl ether and allylic ester functionalities were not tolerated under the reaction conditions (see the Supporting Information for details).



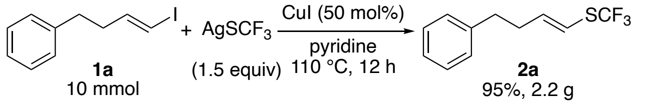
Scheme 2. Aliphatic trifluoromethylthioalkenes **2** by copper-mediated trifluoromethylthiolation of alkenyl iodides **1** with $AgSCF_3$. Conditions: CuI (1.5 mmol), **1** (3.0 mmol), $AgSCF_3$ (4.5 mmol), pyridine (3.0 mL), 110 °C, 12 h, N_2. Isolated yields are shown. [a] On a 1.5 mmol scale. [b] Obtained with *E/Z* = 5:95 from (*Z*)-**1i** with *E/Z* = 1:99.



Scheme 3. Aryl-conjugated trifluoromethylthioalkenes **2** by copper-mediated trifluoromethylthiolation of alkenyl iodides **1**. Conditions: CuI (1.5 mmol), **1** (3.0 mmol), $AgSCF_3$ (4.5 mmol), pyridine (3.0 mL), 110 °C,

12 h, N_2. Isolated yields are shown. [a] On a 1.5 mmol scale. [b] With the corresponding bromide **1r**.

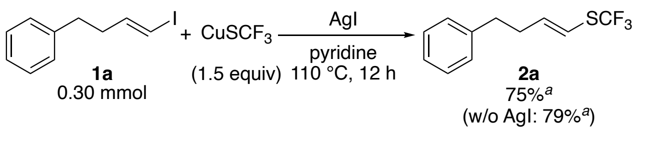
The trifluoromethylthiolation of **1a** could be further scaled up to a 10 mmol scale to provide the targeted product **2a** in 95% yield (2.2 g; Scheme 4). This result proves high productivity of the present methodology.



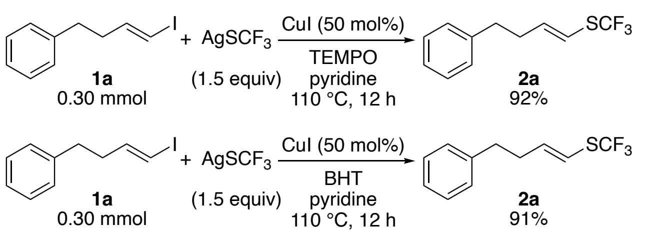
Scheme 4. Gram scale synthesis of trifluoromethylthioalkene **2a**.

Finally, several mechanistic studies of the copper-mediated trifluoromethylthiolation reaction were performed. As reported by Rueping,[6c] the desired product could also be obtained efficiently when using $CuSCF_3$ reagent instead of $CuI/AgSCF_3$ (Scheme 5a). The reason why the yield was slightly decreased compared to the combination of CuI and $AgSCF_3$ is not clear, but the addition of AgI gave only the negligible effect on the reaction efficiency. The trifluoromethylthiolation reaction also proceeded in the presence of radical scavengers such as TEMPO and BHT (Scheme 5b), thus suggesting that a radical pathway is unlikely. The plausible reaction mechanism is shown in Scheme 5c. First, CuI undergoes a salt metathesis with $AgSCF_3$ to form active $CuSCF_3$ species. It then reacts with the alkenyl halide to furnish the alkenyl copper intermediate. The desired trifluoromethylthiolated product and copper halide are then generated by reductive elimination. Finally, CuX reacts with $AgSCF_3$ to regenerate $CuSCF_3$ species.

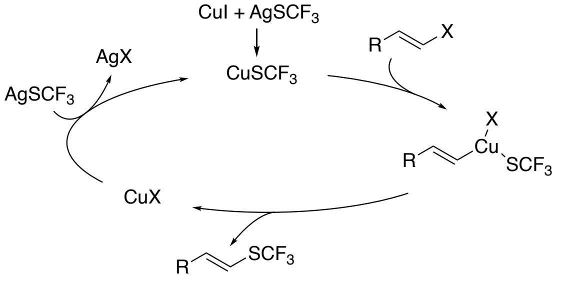
a) Reaction with $CuSCF_3$



b) Radical inhibition experiments



c) Plausible mechanism



Scheme 5. Mechanistic investigations. a) Reaction with $CuSCF_3$, b) radical inhibition experiments, and c) plausible mechanism. [a]Estimated by ^1H NMR with dibenzyl ether as the internal standard.

In conclusion, we have achieved the synthesis of SCF_3-substituted alkenes by a copper-mediated trifluoromethylthiolation of alkenyl halides. The feature of this protocol is successful combined use of CuI and $AgSCF_3$ as the trifluoromethylthiolation reagent, which can conveniently replace the previously used but unstable $CuSCF_3$ reagent. The $CuI/AgSCF_3$ reaction system can be applicable to both aliphatic and aromatic alkenyl iodides. Moreover, its high scalability will find wide applications in the synthesis of various SCF_3-containing molecules.

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Supporting Information is available on http://dx.doi.org/xxxx.

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Graphical Abstract

Textual Information

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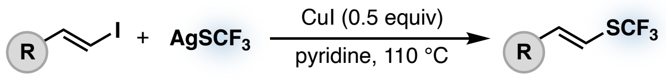
Graphical Information



- Readily available SCF_3 source
- R = alkyl and aryl
- High Scalability (up to 10 mmol scale)