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Direct Synthesis of Disubstituted Trifluoromethylthiolated Alkenes

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Abstract: In the field of organofluorine chemistry, the quest for emergent fluorinated groups is in high demand. In particular, the scientific community has shown special interest in the SCF₃ residue thanks to its unique properties. Indeed, over the last decade, the SCF₃ group has become a pivotal fluorinated moiety as demonstrated by several SCF₃-containing compounds of interest and related to that, the steadily increasing synthetic methods to access such molecules. In this Short Review, the main advances made for the synthesis of trifluoromethylthiolated disubstituted alkenes will be discussed and highlighted.

- 1 Introduction
- 2 Trifluoromethylthiolation of pre-functionalized alkenes
- 3 Direct C-H Trifluoromethylthiolation of alkenes
- 4 Trifluoromethylthiolation of miscellaneous derivatives
- 5 Conclusion

Keywords

Trifluoromethylthiolation – Synthetic Methodologies – Organofluorine Chemistry– Disubstituted Olefins – Homogeneous Catalysis – Transition Metal-free Reactions

Introduction

Since the 50's, fluorinated compounds have emerged as pivotal molecules for medicinal chemistry, material sciences, agrochemical and pharmaceutical industries¹ thanks to the unique properties of the fluorine atom and fluorinated groups.^{2,3} Therefore the field of organofluorine chemistry has been steadily evolving over the years, by means of the development of original and efficient synthetic methods to access fluorinated molecules.⁴ Among the wide diversity of fluorinated residues, the SCF₃ group has already shown attractive and unique properties. Indeed, it has been established that this group displays a strong electron-withdrawing effect, comparable to the one of the CF₃ moiety. It is also known to impact the lipophilicity of the molecules in which it is incorporated with a high Hansch parameter ($\pi = 1.44$), in comparison with those of other fluorinated groups like the CF₃ ($\pi = 0.88$) and the OCF₃ ($\pi = 1.04$) residues.⁵ Over the last years, this emergent fluorinated group has aroused the interest of the scientific community and a large panel of straightforward synthetic methodologies to access SCF₃-containing compounds has been developed.^{6,7} Generally, their synthesis relied on two main approaches: a) the construction of the SCF₃ moiety⁸ including the fluorination of trichloromethylthioether compounds⁹ and the trifluoromethylation of thiol derivatives,¹⁰ and b) the direct introduction of a SCF₃ moiety on various classes of molecules. In the latter case, albeit the trifluoromethylthiolation of (hetero)arenes¹¹ and to some extent of aliphatic derivatives¹² was well studied, the number of reports dealing with the synthesis of 1,1- and 1,2-disubstituted olefins remains rather limited. Nevertheless,

disubstituted alkenes are common scaffolds found in several compounds of interest in medicinal chemistry and agrochemicals (Figure 1, **A**).¹³ Among these alkenes, two trifluoromethylthiolated compounds demonstrated interesting properties as weed killer¹⁴ and insecticide¹⁵ (Figure 1, **B**). Herein, this Short Review will provide an overview of the different approaches for the synthesis of disubstituted trifluoromethylthiolated alkenes by direct trifluoromethylthiolation reaction and the main advances will be discussed and highlighted.¹⁶

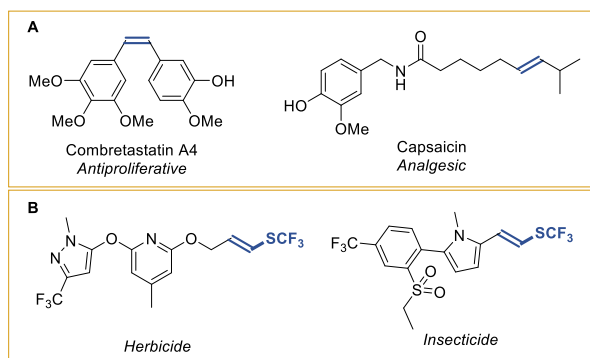
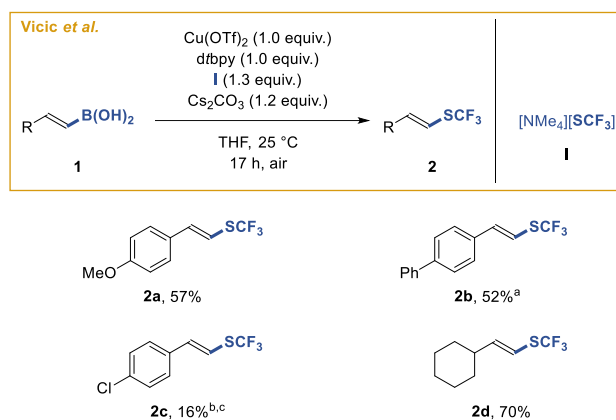


Figure 1 A: Selected examples of bioactive derivatives possessing a 1,2-disubstituted alkene pattern. B: Key compounds containing a 1,2-disubstituted trifluoromethylthiolated alkene.

Trifluoromethylthiolation of pre-functionalized alkenes

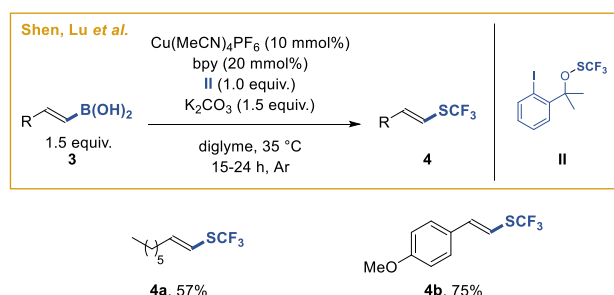
Starting from boronic acids

In 2012, Vicic and co-workers reported a copper-mediated synthesis of trifluoromethylthiolated derivatives (Scheme 1).¹⁷ During their investigations on the trifluoromethylthiolation of (hetero)aromatic boronic acids as a potent alternative to the use of aryl chlorides, the functionalization of vinyl boronic acids was studied. Indeed, under mild conditions (room temperature, air as oxidant), the synthesis of four trifluoromethylthioethers was achieved using this copper-mediated transformation in the presence of NMe_4SCF_3 . Note that the transformation was completely selective towards the formation of the *E*-isomer. Both styrenes substituted with electron-donating groups and halogens (**1a-c**) were smoothly trifluoromethylthiolated. The (cyclohexylvinyl)boronic acid was more reactive, as **2d** was prepared in 70% yield.



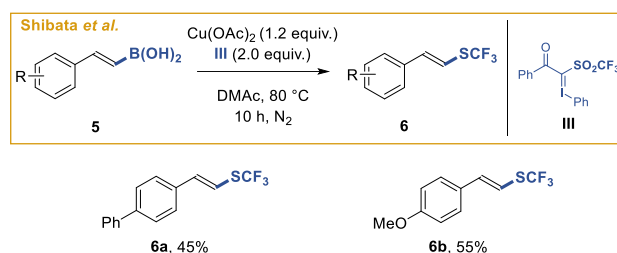
Scheme 1 Copper-mediated trifluoromethylthiolation using $[\text{NMe}_4][\text{SCF}_3]$. Yields were determined by ^{19}F NMR using PhCF_3 as the internal standard. dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine. ^a **2b** was obtained in 74% yield using O_2 as oxidant. ^b A pinacolboronate was used instead of the corresponding boronic acid. ^c **2c** was obtained in 33% yield when the reaction was carried out at 50 °C.

In 2013, Shen, Lu and co-workers developed an alternative approach for the trifluoromethylthiolation of aryl, vinyl boronic acids and alkynes (Scheme 2).¹⁸ Using the electrophilic reagent **II**¹⁹ as an electrophilic source, the copper-catalyzed trifluoromethylthiolation reaction went smoothly, although restricted to the selective synthesis of the compounds **4a** and **4b** as *E*-isomers.



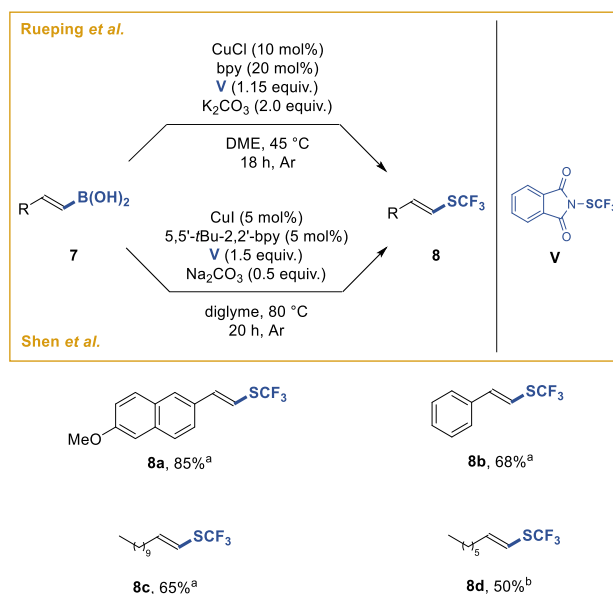
Scheme 2 Trifluoromethylthiolation reaction using the electrophilic reagent **II**. bpy = 2,2'-bipyridine.

In 2015, the group of Shibata used their in-home reagent, the trifluoromethanesulfonyl hypervalent iodonium ylide **III**, for the functionalization of various substrates (Scheme 3).²⁰ In this study, both allyl alcohols and boronic acids were trifluoromethylthiolated including two examples of vinyl boronic acids, which were trifluoromethylthiolated in moderate yields (**6a** and **6b**, 45% yield and 55% yield, respectively).



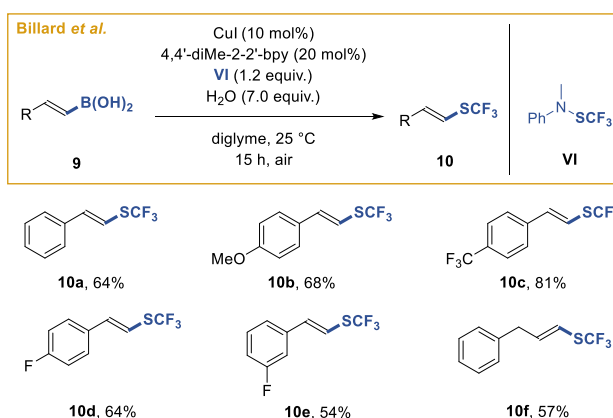
Scheme 3 Copper-mediated trifluoromethylthiolation reaction using the reagent of Shibata.

A complementary approach to get trifluoromethylthiolated 1,2-disubstituted alkenes relied on the use of the Munavalli reagent **V**.²² In 2014, Rueping²³ and Shen²⁴ independently reported the trifluoromethylthiolation of boronic acid derivatives (Scheme 4). The copper-catalyzed methodology described by Rueping was effective for the trifluoromethylthiolation of various vinyl boronic acids substituted with a naphthyl, a phenyl and an alkyl moiety (**7a-7c**) and the corresponding products were isolated in good to excellent yields (**8a-8c**, up to 85% yield). In case of Shen, a single example was depicted and the compound **8d** was obtained in 50% yield.



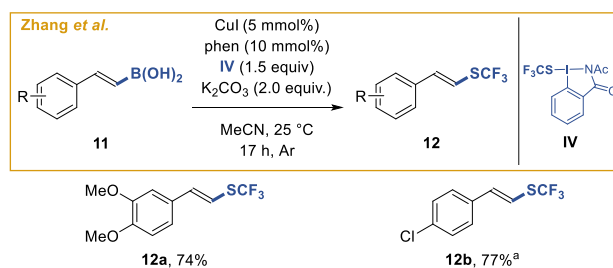
Scheme 4 Trifluoromethylthiolation using the Munavalli reagent **V**. bpy = 2,2'-bipyridine. ^a Using Rueping's conditions. ^b Using Shen's conditions.

The copper-catalyzed cross-coupling reaction of boronic acids with the Billard reagent **VI** was also reported (Scheme 5).²⁵ Under these reaction conditions, both aromatic and benzylic vinyl boronic acids were functionalized at room temperature under air. In this transformation, the presence of water (7 equivalents) was crucial, although its role was not clear.



Scheme 5 Trifluoromethylthiolation of boronic derivatives using the Billard reagent. 4,4'-diMe-2-2'-bpy = 4,4'-dimethyl-2,2'-bipyridine.

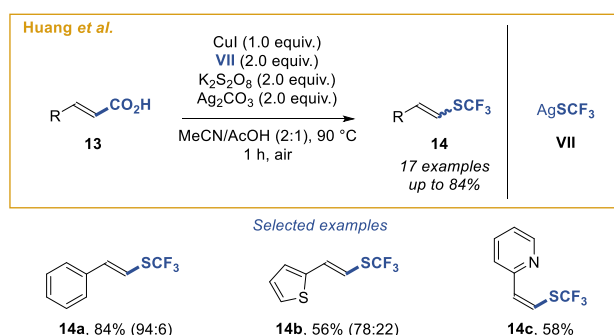
More recently, in 2020, Zhang and co-workers developed an electrophilic hypervalent trifluoromethylthio-iodine(III) reagent **IV** (Scheme 6).²¹ The synthetic utility of **IV** was demonstrated with the functionalization of several nucleophiles, including bio-relevant thio-containing compounds and vinyl boronic acids. Hence, the trifluoromethylthiolated styrenes **12a** and **12b** were synthesized in high yields using CuI as a catalyst.



Scheme 6 Copper-catalyzed trifluoromethylthiolation using the reagent **IV**. ^a Reaction was carried out at 0 °C. phen = 1,10-phenanthroline.

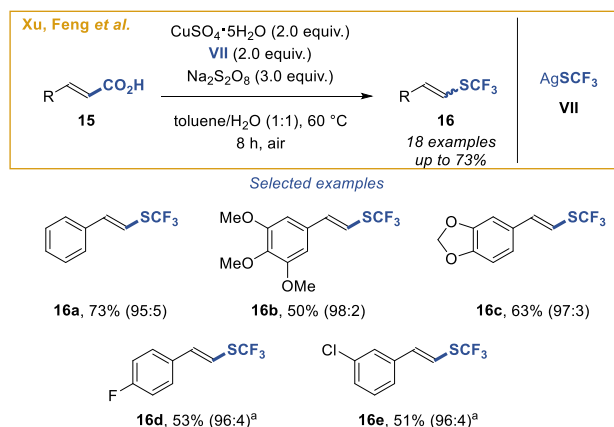
Starting from α,β -unsaturated carboxylic acids

Among the other classes of precursors for the synthesis of trifluoromethylthiolated difunctionalized alkenes, the group of Huang was the first to develop, in 2016, a copper-mediated decarboxylative trifluoromethylthiolation of α,β -unsaturated carboxylic acids using AgSCF_3 (**VII**, Scheme 7).²⁶ Cinnamic acids with various substituents **13** were functionalized and the expected vinyl trifluoromethyl thioethers **14** were obtained in moderate to good yields with a good *E:Z* selectivity in favour of the *E*-isomer. Note however, that in case of the pyridyl α,β -unsaturated carboxylic acid **13c**, a complete selectivity for the *Z*-isomer was noticed. Although efficient, the method suffered from some limitations as the reaction was completely inefficient with cinnamic acids bearing a strong electron-withdrawing group or aliphatic substituted ones.



Scheme 7 Copper-mediated decarboxylative trifluoromethylthiolation of α,β -unsaturated carboxylic acids. *E:Z* ratios are given in parenthesis and were determined by ^{19}F NMR. Only the major isomer was depicted.

Using similar reaction conditions (no need of silver salt), Xu, Feng and co-workers reported in 2018 the preparation of a panel of disubstituted trifluoromethylthiolated alkenes **16**, with yields up to 73% starting from cinnamic acids **15** (Scheme 8).²⁷ Worth to mention that the *E:Z* ratios were in favour to the *E*-isomer.

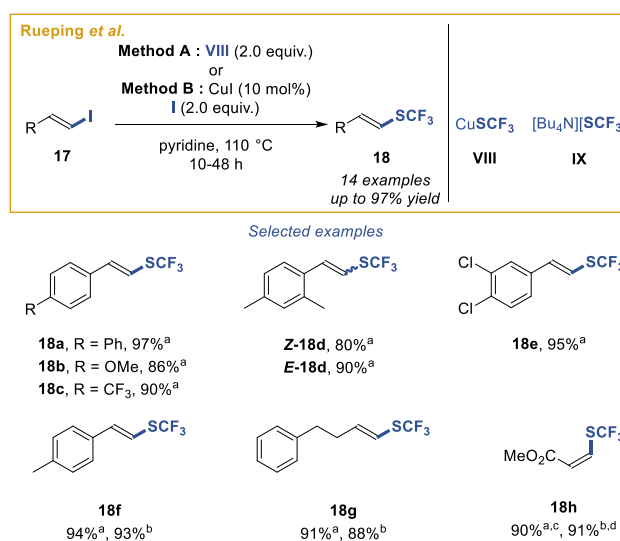


Scheme 8 Copper-mediated decarboxylative trifluoromethylthiolation of cinnamic acid derivatives. *E:Z* ratios are given in parenthesis and were determined by ^{19}F NMR. ^a Reaction was carried out at 80 °C. Only the major isomer was depicted.

Starting from halogenated alkenes

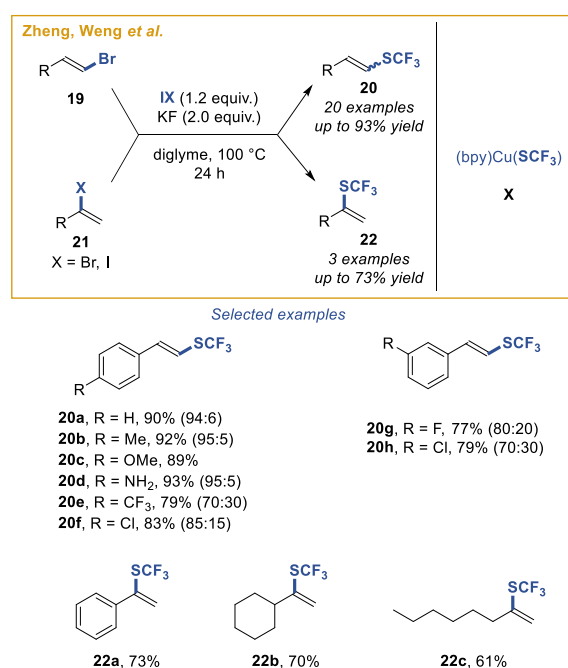
The trifluoromethylthiolation reaction has also been developed starting from halogenated alkenes. The group of Rueping, inspired by the nucleophilic *S*-addition of thiols on vinyl iodides and bromides,²⁸ was the first to propose the synthesis of trifluoromethylthioethers starting from a halogenated vinyl compound (Scheme 9).²⁹ In that purpose, two methods have been reported for the trifluoromethylthiolation of vinyl iodides. The first one, using two equivalents of CuSCF_3 , allowed the functionalization of aryl- and alkyl-substituted vinyl iodides (**17a-17h**) and the expected products (**18a-**

18h) were isolated in high yields (up to 97% yield). Note that compounds **18f**, **18g** and **18h** were also obtained using $[\text{Bu}_4\text{N}][\text{SCF}_3]$ as the SCF_3 source *via* a copper catalyzed reaction.



Scheme 9 Trifluoromethylthiolation using CuSCF_3 or $[\text{Bu}_4\text{N}][\text{SCF}_3]$ as nucleophilic SCF_3 -sources. ^a Using method A. ^b Using method B. ^c Reaction was carried out at 25 °C for 3 h. ^d Reaction was carried out at 25 °C for 24 h.

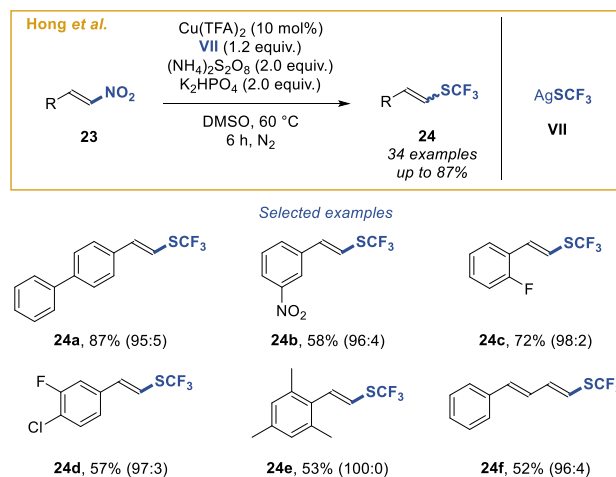
Few years later, Zheng and Weng developed the copper-mediated trifluoromethylthiolation of vinyl halides (Scheme 10).³⁰ In the presence of the $(\text{bpy})\text{Cu}(\text{SCF}_3)$ complex, the functionalization of aromatic vinyl bromides bearing electron-donating (**19b-19d**) or electron-withdrawing groups (**19e**) as well as a halogen (**19f-19h**) led to the 1,2-disubstituted alkenes in excellent yields (up to 93% yield). The synthesis of 1,1-trifluoromethylthiolated alkenes was also successively achieved starting from the \square -bromostyrene (**21a**), the (1-iodovinyl)cyclohexane (**21b**) and 2-iodooct-1-ene (**21c**) and afforded the corresponding products **22a-22c**. Note that the stereochemistry of the substrate (*E:Z* ratios) was retained in the course of the reaction.



Scheme 10 Trifluoromethylthiolation using $(\text{bpy})\text{Cu}(\text{SCF}_3)$ *via* a transition metal-free process. *E:Z* ratios are given in parenthesis and were determined by ¹⁹F NMR. Only the major isomer was depicted. bpy = 2,2'-bipyridine.

Starting from nitroalkenes

The denitrative trifluoromethylthiolation reaction is also an interesting way to prepare trifluoromethylthiolated alkenes. The group of Hong reported in 2020 the efficient preparation of several SCF₃-containing difunctionalized alkenes (Scheme 11).³¹ The copper-promoted denitrative trifluoromethylthiolation of monosubstituted β -nitrostyrenes (**23a-23c**) was achieved in good yields (up to 87% yield) using the reagent **VII** as the SCF₃ source. Interestingly, in case of **23b**, the reaction proceeded selectively leaving the nitro group on the aromatic part intact and the expected product **24b** was obtained in 58% yield in a 96:4 *E:Z* ratio. Di- and tri-substituted β -nitrostyrenes were also suitable substrates (**23d** and **23e**) but afforded the desired compounds with slightly lower yields than their monosubstituted analogues. The diene **23f** was also smoothly functionalized in this transformation.



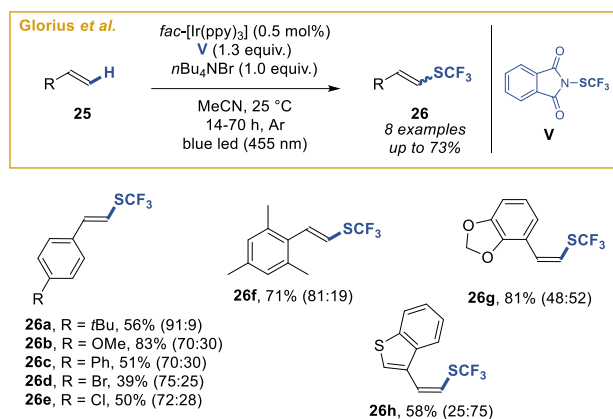
Scheme 11 Copper-catalyzed denitrative trifluoromethylthiolation of nitroalkenes. *E:Z* ratios are given in parenthesis and were determined by ¹⁹F NMR. Only the major isomer was depicted.

Direct C-H Trifluoromethylthiolation of alkenes

Recently an alternative to the above depicted approaches relied on the synthesis of disubstituted trifluoromethylthiolated olefins by direct C-H trifluoromethylthiolation. Such approach offered efficient and original retrosynthetic disconnections towards these fluorinated molecules. The recent breakthroughs for the synthesis of both 1,2- and 1,1-disubstituted trifluoromethylthiolated olefins will be summarized in that part.

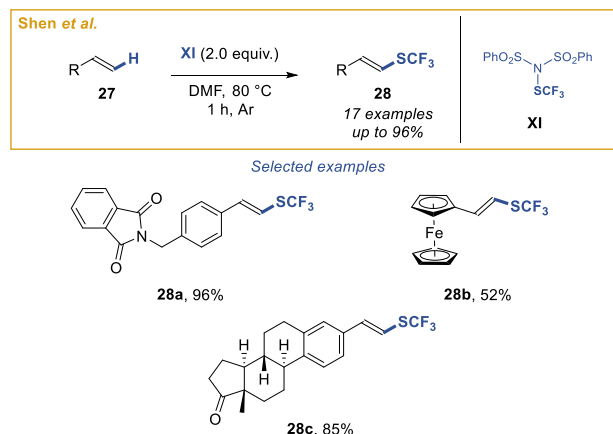
Preparation of 1,2-disubstituted trifluoromethylthiolated olefins

In 2016, Glorius group reported a visible-light photoredox catalyzed process for the trifluoromethylthiolation of (hetero)aromatic substituted alkenes using the electrophilic Munavalli reagent **V** (Scheme 12) and the *fac*-[Ir(ppy)₃] as photocatalyst.³² With this dual photoredox/halide catalysis, the preparation of various di- and tri-substituted alkenes was possible. Among them, the synthesis of eight disubstituted compounds was described. The stereoselectivity of this transformation was in favor of the *E*-isomer (**26a-26f**). However, a *Z*-favored transformation was achieved in case of **26g** and the benzo[*b*]thiophene derivative **26h**.



Scheme 12 Trifluoromethylthiolation of styrene derivatives using a dual halide/ photoredox catalysis. *E:Z* ratios are given in parenthesis and were determined by ^{19}F NMR. Only the major isomer was depicted. ppy = 2-phenyl-pyridine.

The same year, the group of Shen depicted the synthesis of a new electrophilic SCF_3 source, $(\text{PhSO}_2)_2\text{NSCF}_3$ **XI** and showed that it allowed the preparation of various trifluoromethylthiolated derivatives (Scheme 13).³³ Among them, the direct trifluoromethylthiolation of styrene derivatives such as **27a** was efficiently achieved and the desired products were obtained as *E*-isomers (17 examples, up to 96% yield). To further demonstrate the synthetic utility of their methodology, the functionalization of the ferrocene derivative **27b** and the steroid **27c** was reported and the expected products (**28b** and **28c**) were isolated in 52% yield and 85% yield, respectively.



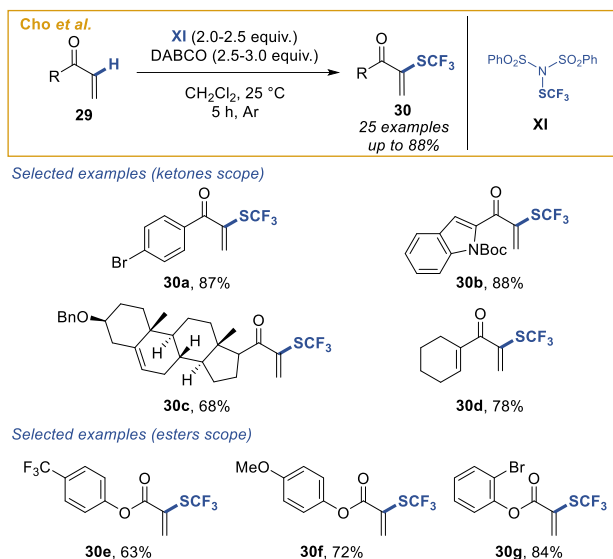
Scheme 13 Trifluoromethylthiolation reaction using the reagent **XI**.

Preparation of 1,1-disubstituted trifluoromethylthiolated olefins

In contrast with the synthesis of 1,2-disubstituted olefins by direct C-H trifluoromethylthiolation of alkenes, the access to 1,1-disubstituted trifluoromethylthiolated olefins starting from the non-prefunctionalized substrates is highly challenging. So far such transformation was restricted to activated olefins such as α,β -unsaturated carbonyl compounds, which can act as a Michael acceptor in Baylis-Hillman conditions.³⁴

Cho and co-workers described the synthesis of these 1,1-trifluoromethylthiolated difunctionalized alkenes by means of a DABCO-mediated electrophilic trifluoromethylthiolation reaction using the reagent **XI** (Scheme 14).³⁵ With this methodology, the trifluoromethylthiolation of α,β -unsaturated ketones (19 examples, up to 88% yield) and α,β -unsaturated esters (6 examples, up to 87% yield) was smoothly achieved. In the first case, the reaction was tolerant to (hetero)aromatic and aliphatic α,β -unsaturated ketones (**29a**, **29b** and **29c** respectively), but also regioselective in the case of the ketone **29d** in which the cyclohexene moiety remained intact. Even if the scope of the acrylates was substantially narrower, Cho and co-workers proved that substrates bearing a *para*-substituted electron-

poor and electron-rich arene (**29e** and **29f**) as well as an *ortho*-brominated arene (**29g**) were efficiently functionalized.

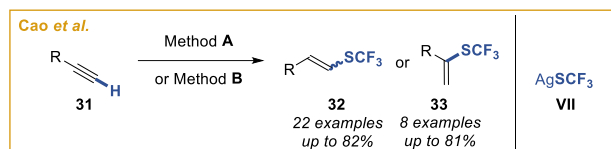


Scheme 14 Synthesis of trifluoromethylthiolated 1,1-disubstituted alkenes starting from α,β -unsaturated ketones and esters.

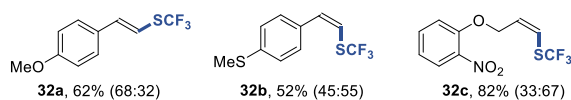
Trifluoromethylthiolation of miscellaneous derivatives

Over the years, several complementary approaches were developed to access 1,2-disubstituted alkenes starting from various classes of compounds. In this section, the main advances were summarized.

In 2016, the group of Cao described the hydrotrifluoromethylthiolation of terminal alkynes using AgSCF_3 **VII** and $\text{K}_2\text{S}_2\text{O}_8$ along with catalytic amounts of HMPA and phenanthroline (Scheme 15).³⁶ Under these conditions, the synthesis of the anti-Markovnikov selective trifluoromethylthiolated 1,2-alkenes was possible in good to high yields, with a wide functional tolerance (22 examples, up to 82% yield). Both aromatic (**31a** and **31b**) and alkyl (**31c**) substituted alkynes were suitable substrates. Note that the regioselectivity of the transformation was good although products were obtained as an inseparable *E:Z* mixture. Using slightly modified reaction conditions (H_2O and a catalytic amount of CuCl instead of HMPA and phenanthroline in DCE at 100°C), the Markovnikov-selective hydrotrifluoromethylthiolation occurred (8 examples, up to 81% yield). It is interesting to mention that this reaction was limited to *para*-alkoxy-substituted phenylacetylene derivatives affording the corresponding 1,1-trifluoromethylthiolated styrenes in very good yields (**33a** and **33b**, Scheme 15), while the benzo[*d*]oxolane derivative **33c** was prepared with a lower yield (41%).

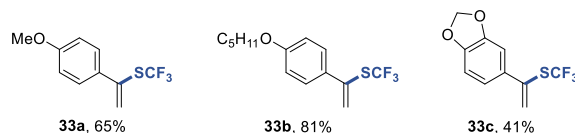


Selected examples of 1,2-disubstituted olefins



Method A: VII (1.5 equiv.), K₂S₂O₈ (3.0 equiv.), HMPA (50 mol%)
phen (10 mol%), DMF, 80 °C, 12 h, Ar

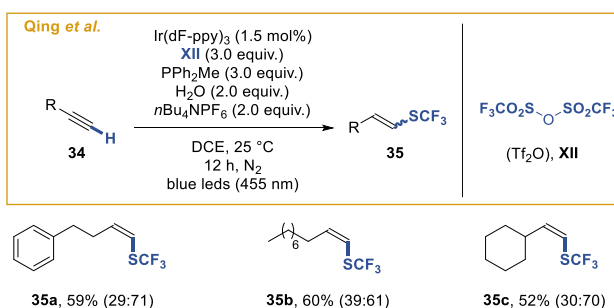
Selected examples of 1,1-disubstituted olefins



Method B: VII (1.5 equiv.), K₂S₂O₈ (3.0 equiv.), CuCl (10 mol%)
H₂O (3.0 equiv.), DCE, 100 °C, 17 h, Ar

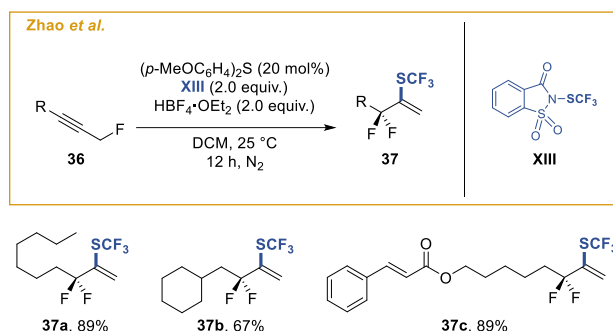
Scheme 15 Hydrotrifluoromethylthiolation of terminal alkynes using AgSCF₃. *E:Z* ratios are given in parenthesis and were determined by ¹⁹F NMR and ¹H NMR. Only the major isomer was depicted. phen = 1,10-phenanthroline.

Three years after this initial report, Qing and co-workers developed a complementary approach for the hydrotrifluoromethylthiolation of unactivated alkenes and alkynes for the preparation of trifluoromethylthiolated alkanes and alkenes, respectively, under visible-light photoredox-catalysis (Scheme 16).³⁷ In this transformation, the trifluoromethanesulfonic anhydride (Tf₂O) is playing a key role as a radical trifluoromethylthiolating reagent. Both terminal aliphatic alkynes with linear and cyclic alkane as substituents (**34a-34c**) were suitable in this transformation leading to the products as a mixture of *E:Z* isomers, the *Z*-isomer being the major one.



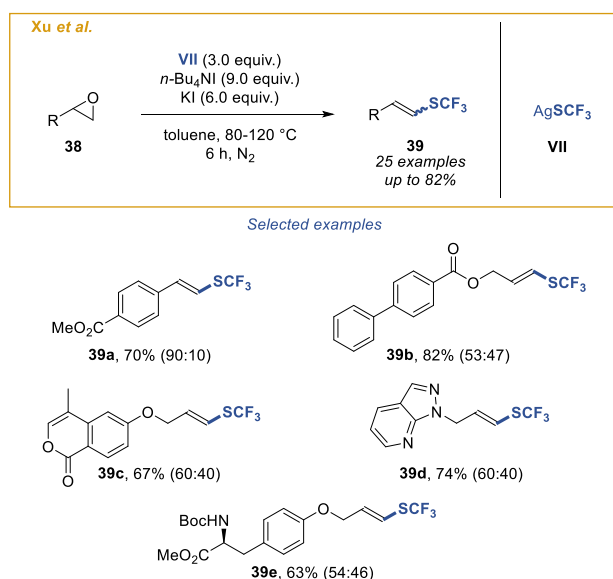
Scheme 16 Hydrotrifluoromethylthiolation of terminal alkynes under visible-light photoredox-catalysis. *E:Z* ratios are given in parenthesis and were determined by ¹⁹F NMR. Only the major isomer was depicted. dF-ppy = 2-(2,4-difluorophenyl)pyridine.

One year after, in the course of their study concerning the synthesis of functionalized allylic *gem*-difluorides, Zhao and co-workers proposed an elegant synthetic pathway to *gem*-trifluoromethylthiolated disubstituted alkenes *via* a catalytic fluorinative Meyer-Schuster-like rearrangement, using the saccharin derivative **XIII** as the trifluoromethylthiolating reagent (Scheme 17).³⁸ In the presence of **XIII**, HBF₄·OEt₂ and using a catalytic amount of a symmetric aryl sulfide, the functionalization of α -fluorinated alkynes afforded the corresponding 1,1-disubstituted SCF₃-containing alkenes **37a-37c** in good to high yields (3 examples, up to 89% yield).



Scheme 17 Diarylsulfide-catalyzed synthesis of trifluoromethylthiolated 1,1-disubstituted alkenes *via* a Meyer-Schuster-like rearrangement.

Finally, in 2020, the group of Xu reported the synthesis of the 1,2-disubstituted trifluoromethylthiolated compounds starting from epoxides and AgSCF_3 in the presence of $n\text{-Bu}_4\text{NI}$ and KI (Scheme 17).³⁹ The functionalization of a large panel of aliphatic and aromatic epoxides was smoothly achieved. Note that in the case of aromatic epoxides, a better selectivity towards the *E*-isomer was generally observed (**39a**), while an almost 1:1 mixture was obtained with aliphatic epoxides (**39b–39e**). Among the latter compounds, worth to mention that both *O*- and *N*-substituted alkyl epoxides were suitable substrates providing the corresponding products in 67% yield and 74% yield, respectively. These conditions also allowed the preparation of natural product derivatives such as the functionalized tyrosine **39e** in a good yield.



Scheme 17 Trifluoromethylthiolation of epoxides using AgSCF_3 . *E*:*Z* ratios are given in parenthesis and were determined by ^{19}F NMR. Only the major isomer was depicted.

Conclusion

In summary, this Short Review provides an overview of the major advances made to access 1,2- and 1,1-disubstituted trifluoromethylthiolated alkenes. Taking benefit from a myriad of SCF_3 -containing sources (both nucleophilic and electrophilic reagents), a panel of original methodologies was developed starting from diverse classes of compounds. Note that in contrast with 1,2-disubstituted SCF_3 -containing alkenes, the trifluoromethylthiolation of 1,1-disubstituted alkenes is still challenging, often restricted to the functionalization of acrylate or electron-rich styrene derivatives and the design of new approaches is of high demand. In addition, the quest for additional modern synthetic solutions towards the preparation of this class of compounds involving for instance, electrochemistry and photocatalyzed reactions will definitively be an asset. Appealing for the organofluorine chemistry research field, this ShortReview will have a strong impact on both academia and industry by providing an overview of original disconnections to access trifluoromethylthiolated disubstituted olefins. We do believe that this

Short Review will be inspiring for further developments in a near future regarding the synthesis of trifluoromethylthiolated alkenes, extending further the chemical space of these fluorinated molecules and potentially giving access to new lead compounds.

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Biosketches



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