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Silver-Mediated *anti*-Markovnikov and Markovnikov-Selective Hydrotrifluoromethylthiolation of Terminal Alkynes

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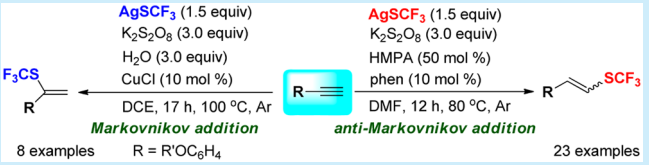
Supporting Information

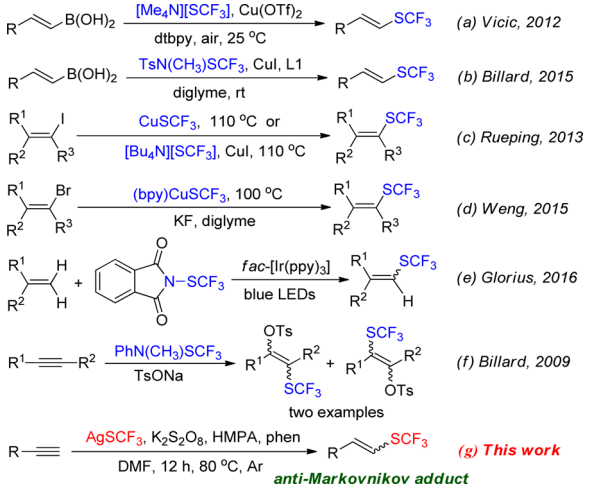
ABSTRACT: The first example of direct hydrotrifluoromethylthiolation of terminal alkynes in the presence of $AgSCF_3$ and $K_2S_2O_8$ was established for the synthesis of a variety of vinyl trifluoromethyl thioethers. The *anti*-Markovnikov and Markovnikov adducts were obtained in moderate to good yields via two different reaction systems. Studies to probe the mechanism of the *anti*-Markovnikov addition reactions including the radical trapping experiments, kinetic isotope effect experiments, and deuterated experiments for determination of H-sources were conducted.



The incorporation of trifluoromethylthio group (CF_3S-) into a small molecule often profoundly alters the physical, chemical, and biological properties of the parent compound because of the strong electron-withdrawing nature, higher Hansch lipophilicity parameter, and the better metabolic stability of the trifluoromethylthio group.[1] Therefore, the CF_3S-containing compounds have attracted continuous interest in the fields of pharmaceuticals, agrochemicals, and materials.[2] To date, numerous methods have been developed for the synthesis of trifluoromethylthiolated organic compounds.[3] However, most of the research has been focused on the construction of the aryl–SCF_3 bond, alkyl–SCF_3 bond, and alkynyl–SCF_3 bond;[4] the creation of alkenyl–SCF_3 bond still remains to be exploited.

The classical method for the synthesis of vinyl–SCF_3 compounds involves the use of excess amounts of toxic and corrosive gaseous trifluoromethylsulfenyl chloride (CF_3SCl).[5] The transition-metal-mediated or catalyzed trifluoromethylthiolation of vinyl boronic acids and vinyl halides with different electro- or nucleophilic trifluoromethylthiolating reagents have provided other options for the synthesis of vinyl trifluoromethylthioethers.[6] However, these strategies mentioned above require prefunctionalized starting materials prior to the trifluoromethylthiolation reactions (Scheme 1a–d).[7] Alternatively, the direct C–H trifluoromethylthiolation alkene represents an attractive protocol due to its atom and step economy. More recently, Hopkinson and Glorius reported a new method for the trifluoromethylthiolation of styrenes by using *N*-(trifluoromethylthio)phthalimide as the CF_3S source with assistance of photocatalyst *fac*-[Ir(ppy)$_3$] and blue LEDs (Scheme 1e).[8] Unfortunately, to date, examples regarding the transformation of alkynes into vinyl trifluoromethyl thioethers are very scarce.[9] For example, Billard reported the addition reaction of $CF_3SNMePh$ and TsONa to an internal alkyne under the activation of $BF_3\cdot Et_2O$ to furnish a regioisomeric mixture of CF_3S-enols (Scheme 1f).[10] Herein, we report a new approach for the preparation of vinyl trifluoromethyl thioethers via hydrotrifluoromethylthiolation of terminal alkynes in the presence of $AgSCF_3$ and $K_2S_2O_8$ (Scheme 1g).

Scheme 1. Recent Methods for the Synthesis of Vinyl Trifluoromethyl Thioethers



We first chose the reaction between 4-methoxyphenylacetylene **1a** and $AgSCF_3$ as a model reaction to optimize the reaction conditions, and the results are summarized in Table 1. Initially, the effect of solvent on the reaction was examined. Among the various solvents examined, DMF (*N*,*N*′-dimethylformamide) was the most suitable for the reaction (entry 9). When CH_3CN, DMSO (dimethyl sulfoxide), or NMP (*N*-methyl-2-pyrrolidinone) was used as solvent, only a trace amount of **2a** was observed (entries 1–3). Replacement of DMF with DMAC (dimethylacetamide) or mixed solvents led to decreased

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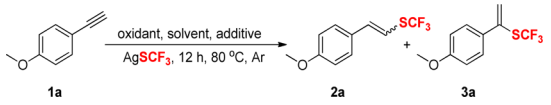
Table 1. Optimization of Hydrotrifluoromethylthiolation of 4-Methoxyphenylacetylene 1a[a]



1a 2a 3a

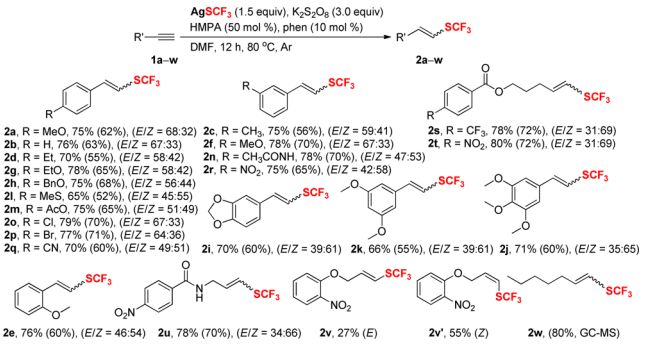
entry	oxidant (equiv)	solvent	additive (equiv)	2a (%)[b]
1	$K_2S_2O_8$ (3.0)	CH_3CN	–	trace
2	$K_2S_2O_8$ (3.0)	DMSO	–	trace
3	$K_2S_2O_8$ (3.0)	NMP	–	trace
4	$K_2S_2O_8$ (3.0)	DMAC	–	45
5	$K_2S_2O_8$ (3.0)	DMF/CH_3CN (1:1)	–	20
6	$K_2S_2O_8$ (3.0)	DMF/DCE (1:1)[c]	–	40
7	$K_2S_2O_8$ (3.0)	DMF + H_2O (2.0 equiv)	–	50
8	$K_2S_2O_8$ (3.0)	DMF (anhydrous)	–	20
9	$K_2S_2O_8$ (3.0)	DMF	–	55
10	*m*-CPBA (3.0)[c]	DMF	–	0
11	$PhI(CF_3CO_2)_2$ (3.0)	DMF	–	0
12	DTBP (3.0)[c]	DMF	–	0
13	Oxone (3.0)	DMF	–	0
14	$(NH_4)_2S_2O_8$ (3.0)	DMF	–	46
15	$K_2S_2O_8$ (2.0)	DMF	–	40
16	$K_2S_2O_8$ (4.0)	DMF	–	45
17	$K_2S_2O_8$ (3.0)	DMF	phen (0.1)[c]	43
18	$K_2S_2O_8$ (3.0)	DMF	HMPA (0.5)[c]	45
19	$K_2S_2O_8$ (3.0)	DMF	HMPA (0.5) + phen (0.3)	45
20	$K_2S_2O_8$ (3.0)	DMF	HMPA (0.2) + phen (0.1)	60
21	$K_2S_2O_8$ (3.0)	DMF	HMPA (0.5) + phen (0.1)	77

[a]Reaction conditions: **1a** (0.1 mmol), $AgSCF_3$ (0.15 mmol), organic solvent (1 mL, obtained from commercial suppliers and used without further purification), Ar, 80 °C 12 h. [b]Yields obtained by GC analysis and based on **1a**. [c]DCE = dichloroethane; *m*-CPBA = *meta*-chloroperbenzoic acid; DTBP = di-*tert*-butyl peroxide; phen = 1,10-phenanthroline; HMPA = hexamethylphosphoramide.

yields (entries 4–6). The addition of a small amount of water as a cosolvent had no obvious effect on the reaction (entry 7). However, when anhydrous DMF was used as solvent, the yield of **2a** decreased to 20% (entry 8). These results indicated that DMF or its counterpart DMAC is crucial for the success of this transformation. Further screening of different oxidants revealed that only $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ could afford the desired product **2a** in reasonable yields (entries 9 and 14), whereas the use of other oxidants resulted in no reaction (entries 10–13). Under identical conditions, upon increasing or lowering the amount of $K_2S_2O_8$, the yield of **2a** decreased (entries 15 and 16). To further increase the reactivity of $AgSCF_3$ and the yield of **2a**, extra additive was added to the reaction system (entries 17–21). It was found that the combination of 0.5 equiv of HMPA and 0.1 equiv of phen could promote the efficiency of the transformation and the yield of **2a** increased to 77% (entry 21). It should be noted that no Markovnikov adduct **3a** was observed under the above experimental conditions.

With the optimized reaction conditions in hand (Table 1, entry 21), the scope and limitation of the *anti*-Markovnikov-selective hydrotrifluoromethylthiolation of terminal alkynes with $AgSCF_3$ and $K_2S_2O_8$ were studied, and the results are summarized in Scheme 2. All the terminal alkynes showed excellent *anti*-Markovnikov selectivity, and no Markovnikov

Scheme 2. *anti*-Markovnikov-Selective Hydrotrifluoromethylthiolation of Terminal Alkynes[a,b]



[a]Reaction conditions: **1a–w** (0.2 mmol), $AgSCF_3$ (0.3 mmol), $K_2S_2O_8$ (0.6 mmol), HMPA (0.1 mmol), phen (0.02 mmol), DMF (2 mL, obtained from commercial suppliers and used without further purification), Ar, 80 °C, 12 h. [b]Yields were determined by GC-MS analysis, and yields of isolated products are given in parentheses. The *E*/*Z* ratio in parentheses was determined by ^1H NMR and ^{19}F NMR spectroscopy. The configuration of the *E*- or *Z*-isomer was determined by its $^3J_{H-H}$ coupling constant in the ^1H NMR spectra (ca. 10.0 Hz for *E*-isomers and 15.0 Hz for *Z*-isomers).

products were detected. This reaction exhibited good functional group compatibility, and various functional groups such as methoxy, methylthio, acetoxy, acetamido, nitro, cyano, and trifluoromethyl were well tolerated. Both electron-deficient and -rich terminal alkynes could be converted into their corresponding vinyl trifluoromethyl thioethers in moderate to good yields. It seemed that the presence of strong electron-donating or -withdrawing substituents on the aromatic ring of alkynes makes no difference to the reaction yields (for example, **2a** versus **2r**). To our delight, substrates bearing acidic protons (**1n** and **1u**) could also afford the SCF_3 products in good yields. Moreover, the chlorine and bromine substituents within substrates **1o** and **1p** are left untouched, which offers the opportunity for further modifications. Long chain alkyl substituted alkynes were also successfully converted to the corresponding vinyl trifluoromethyl thioether in good yields. Although the regioselectivity of the hydrotrifluoromethylthiolation was excellent, the stereoselectivity of this reaction is not satisfactory and an inseparable mixture of *E*- and *Z*-olefin isomers was obtained (except for **2v**). Finally, no reaction took place when the internal alkyne was employed.

During the course of screening the reaction conditions for the *anti*-Markovnikov-selective hydrotrifluoromethylthiolation of alkynes, we were pleasantly surprised to find that when this reaction was performed in DCE in the absence of an additive, an observable amount of Markovnikov adduct **3a** was detected. Encouraged by this initial promising result, we further optimized the reaction conditions by tuning the reaction parameters including catalyst, solvent, temperature, and reaction time, with the aim of increasing the yield of Markovnikov adduct **3a**. Gratifyingly, further optimizations revealed that the reaction of 4-methoxyphenylacetylene **1a** with $AgSCF_3$ in the presence of $K_2S_2O_8$, CuCl, and H_2O in DCE at 100 °C for 17 h could proceed smoothly to give Markovnikov adduct **3a** in 72% yield (GC) (Scheme 3) and no trace amount of *anti*-Markovnikov adduct **2a** was detected.

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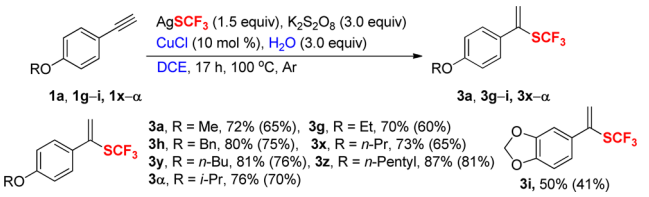
Scheme 3. Markovnikov-Selective Hydrotrifluoromethylthiolation of Alkoxy-Substituted Phenylacetylenes[a,b]

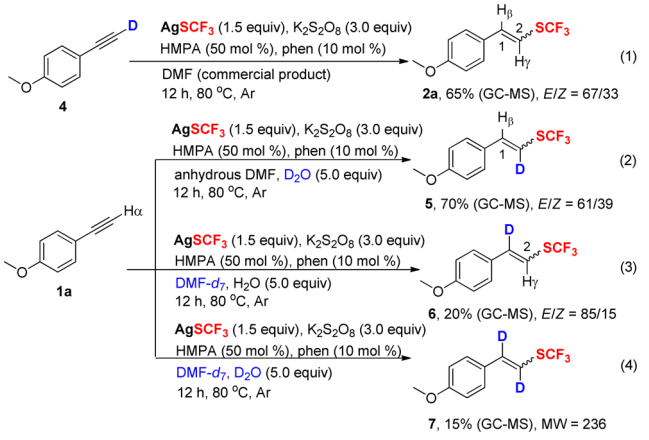


[a]Reaction conditions: **1a**, **1g–i**, **1x–α** (0.2 mmol), $AgSCF_3$ (0.3 mmol), $K_2S_2O_8$ (0.6 mmol), CuCl (0.02 mmol), H_2O (0.6 mmol), DCE (1.5 mL), Ar, 100 °C, 17 h. [b]Yields were determined by GC-MS analysis, and yields of isolated products are given in parentheses.

Subsequently, the reactions of a variety of terminal alkynes were explored. Unfortunately, most alkynes failed to afford the expected trifluoromethylthiolated products and gave a small amount of alkyl or arylketone byproducts along with the unreacted starting materials. Only *para*-alkoxy-substituted phenylacetylenes could proceed smoothly and furnish Markovnikov products in good yields (Scheme 3). The exact reason for the poor functional group tolerance of the reaction is still unclear and requires further investigated.

To elucidate the source of two hydrogens in the *anti*-Markovnikov products, a series of deuterium-labeling experiments were performed in different solvents (Scheme 4). First, a

Scheme 4. Deuterated Experiments for Determination of H-Sources

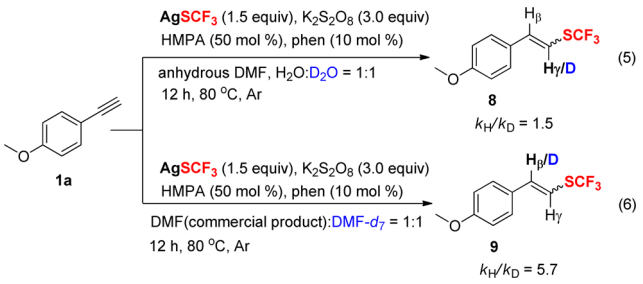


deuterium-labeled alkyne **4** was subjected to the reaction conditions; no deuterium was detected in the product, which indicated that two protons in the *anti*-Markovnikov products did not originate from the alkyne and C(sp)–H bond cleavage occurred during the reaction process (Scheme 4, eq 1). Subsequently, 4-methoxyphenylacetylene **1a** was allowed to react with $AgSCF_3$ in the presence of anhydrous DMF and 5.0 equiv of D_2O, and the deuterated product **5** was formed in 70% (GC-MS) yield (Scheme 4, eq 2). The structure of compound **5** was confirmed by ^1H NMR, HMQC spectroscopy, and HRMS. These results indicated that the proton Hγ in the product originated from water (see the SI).[11]

To understand the role of DMF in the reaction mechanism, a deuterium-labeling experiment was performed using deuterated DMF (DMF-d_7) instead of DMF (Scheme 4, eq 3). The ^1H NMR spectrum of **6** revealed that proton H_β was replaced by deuterium and the signal of proton H_β disappeared. The signal for the proton Hγ appeared at 6.56 ppm (*E*) and 6.25 ppm (*Z*), respectively. These results showed that the proton H_β in the product originated from DMF. Finally, when both DMF-d_7 and 5.0 equiv of D_2O were added to the reaction system, deuterated product **7** was formed (GC-MS) (Scheme 4, eq 4). Unfortunately, we could not isolate compound **7** because the yields dropped sharply when deuterated cosolvent was used. Based on a series of deuterium-labeling experiments, it was concluded that the two hydrogens, H_β and Hγ, introduced into the *anti*-Markovnikov product, originated from DMF and a trace amount of water in DMF, respectively.

To gain insight into the mechanism of *anti*-Markovnikov-selective hydrotrifluoromethylthiolation, the kinetic isotope effect (KIE) of 4-methoxyphenylacetylene **1a** was studied (Scheme 5). When the reaction of **1a** was carried out in

Scheme 5. Kinetic Isotope Experiments

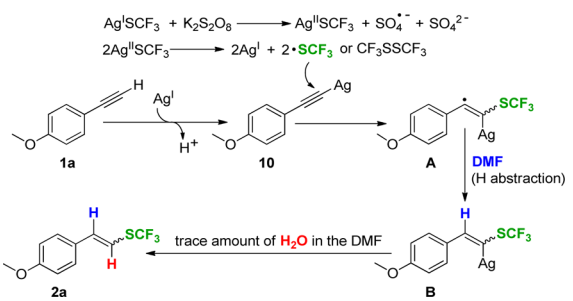


anhydrous DMF and a mixture of H_2O and D_2O (1:1), a small kinetic deuterium isotope effect of 1.5 was observed (Scheme 5, eq 5). When 4-methoxyphenylacetylene **1a** was reacted with a mixture of DMF (commercial product) and deuterated DMF (1:1) under the standard reaction conditions, a large kinetic isotope effect (k_H/k_D = 5.7) was observed (Scheme 5, eq 6), which suggested that cleavage of the C–H bond of DMF might be kinetically significant in this transformation (see the Supporting Information (SI)).[12]

Additionally, both *anti*-Markovnikov and Markovnikov-selective hydrotrifluoromethylthiolations were completely inhibited by radical inhibitors, such as 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) (3.0 equiv) and 2,6-di-*tert*-butyl-4-methylphenol (BHT, 2.0 equiv). These results suggest that the two reactions proceed via free-radical processes.

Moreover, only a trace amount of **2a** was formed by replacing $AgSCF_3$ with $CuSCF_3$ under the standard reaction conditions. Furthermore, by directly starting from ((4-methoxyphenyl)-ethynyl)silver **10** (Scheme 6), the desired product **2a** was also obtained in moderate yield. Such observations suggest that

Scheme 6. Proposed Reaction Mechanism



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silver(I) acetylide (R−C≡C−Ag) might be the key intermediate in hydrotrifluoromethylthiolation reactions (see the SI).[13]

Based on the above results and previous reports,[4b,9e,13b] we proposed a plausible mechanism for the *anti*-Markovnikov-selective hydrotrifluoromethylthiolation reaction (Scheme 6). Initially, $AgSCF_3$ is oxidized by $K_2S_2O_8$ to furnish the $\cdot SCF_3$ radical through single electron transfer.[3e,4c] Regioselective addition of $\cdot SCF_3$ to the C−C triple bond of silver acetylide **10**,[13] which is generated in situ from **1a** and Ag(I), affords relatively stable vinyl radical intermediate **A**. Subsequently, the hydrogen abstraction from DMF by vinyl radical **A** gives vinyl-silver intermediate **B**.[12c,14] Finally, the protonolysis of the alkenyl C−Ag bond of **B** with a trace amount of H_2O in the DMF produces the desired product **2a**.[15]

Unfortunately, the exact mechanism of the Markovnikov-selective hydrotrifluoromethylthiolation of alkoxy-substituted phenylacetylenes remains unclear, except that we can only postulate the reaction proceeds through a radical process.

In summary, we have developed a new and efficient method for the synthesis of vinyl trifluoromethyl thioethers through hydrotrifluoromethylthiolation of terminal alkynes in the presence of $AgSCF_3$ and $K_2S_2O_8$. The Markovnikov and *anti*-Markovnikov hydrotrifluoromethylthiolated products are obtained in moderate to good yields by changing the reaction conditions. Furthermore, the *anti*-Markovnikov-selective hydrotrifluoromethylthiolation displays a broad substrate scope and functional group compatibility. A set of deuterated experiments provide strong evidence that the two hydrogens in the *anti*-Markovnikov product originated from water and DMF, respectively. Preliminary mechanistic analyses suggest both Markovnikov and *anti*-Markovnikov reactions proceed via a radical process. We anticipate that this strategy may provide an alternative approach to prepare vinyl trifluoromethyl thioethers starting from readily available terminal alkynes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01286.

Experimental details and spectral data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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