ChemPubSoc Europe

DOI: 10.1002/chem.201601338

CHEMISTRY
A European Journal
Full Paper

Synthetic Methods

Copper-Catalyzed Perfluoroalkylthiolation of Alkynes with Perfluoroalkanesulfenamides

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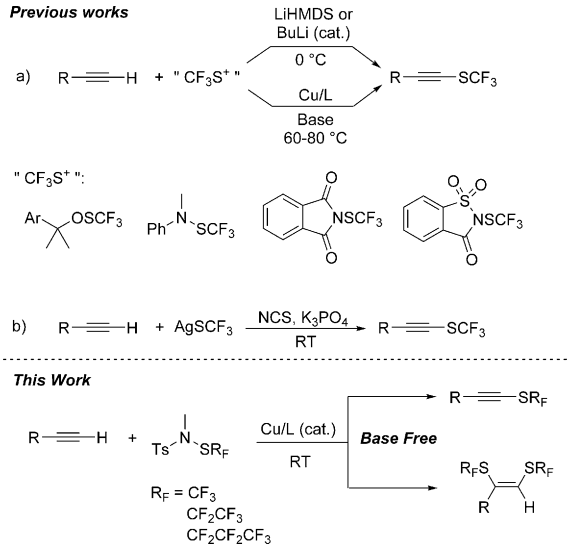
Abstract: Copper-catalyzed direct perfluoroalkylthiolation of alkynes by using the corresponding perfluoroalkanesulfenamide reagent is reported. The selective mono- and bis-perfluoroalkylthiolation of alkynes can be conducted under very mild conditions (no base, room temperature) in very good to excellent yields. This approach, which uses a low toxicity, inexpensive copper catalyst that incorporates a commercially available ligand, is applied in the absence of any additional base. Preliminary mechanistic investigations shed some light on the nature of the unprecedented reactivity observed.

Introduction

In the past few years, direct incorporation of an SCF_3 moiety has been extensively studied due to the intrinsic properties it imparts to a compound, especially high lipophilicity.[1] In this context, a plethora of methods have emerged, many of which already show high potential and constitute a powerful tool for organic synthesis.[2] The key to advances in trifluoromethylthiolation reactions is the design and development of new reactants, which can be categorized into two types. On the one hand, nucleophilic SCF_3 donors that mainly consist of σ-bonded metal SCF_3 derivatives[2g] ($AgSCF_3$[3] and $CuSCF_3$[4]) are most commonly used. It should be noted that ammonium derivatives are also attractive sources of SCF_3,[4l,5] though their usefulness in trifluoromethylthiolation reactions is less explored. On the other hand, discrete electrophilic reagents have been designed to overcome the shortcomings encountered in reactions for which an electrophilic SCF_3 reagent is required. More specifically, these efforts aim to circumvent the necessity to operate under inconvenient conditions and/or with highly toxic reagents[6] such as CF_3SCl or CF_3SSCF_3.

Both types of reagent have proven their efficiency in numerous syntheses, and several elegant procedures have been published recently.[2g,h,7] Among the studied reactions, the direct formation of a C(sp)–SCF_3 bond by using well-defined trifluoromethylthiolating reagents gave rise to renewed interest. In this context different approaches have been evaluated, including generation of the SCF_3 moiety in situ.[8] We reported a direct approach to trifluoromethylthiolation by using either shelf-stable trifluoromethanesulfenamide reagents in the presence of Grignard derivatives or lithium alkynides generated in situ with a catalytic amount of base.[9] The groups of Shen[7c,10] and Rueping[11] developed different strategies by employing catalytic or stoichiometric amounts of a copper–ligand complex in the presence of a base and a shelf-stable trifluoromethylthiolating reagent (Scheme 1 a). Thermal activation was necessary; the reactions were performed at temperatures up to 80 °C. Moreover, Qing and co-workers[12] demonstrated that an electrophilic reagent could be obtained in situ by mixing $AgSCF_3$ with N-chlorosuccinimide (NCS); alkynes underwent trifluoromethylthiolation at room temperature in the presence this reagent and a base (Scheme 1 b).

Although these previous strategies are valuable, basic conditions and/or heating can constitute a drawback for some sensi-



Scheme 1. Trifluoromethylthiolation of alkynes. LiHMDS = lithium bis(trimethylsilyl)azide, Ts = *p*-toluenesulfonyl.

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Supporting information for this article is available on the WWW under: http://dx.doi.org/10.1002/chem.201601338.

tive compounds. Even with our previous base-catalyzed method,[9b] highly base-sensitive substrates cannot be efficiently trifluoromethylthiolated. In this context copper-catalyzed, base-free transformations could constitute efficient alternatives. Furthermore, extrapolations to higher fluorinated homologues have never been performed.

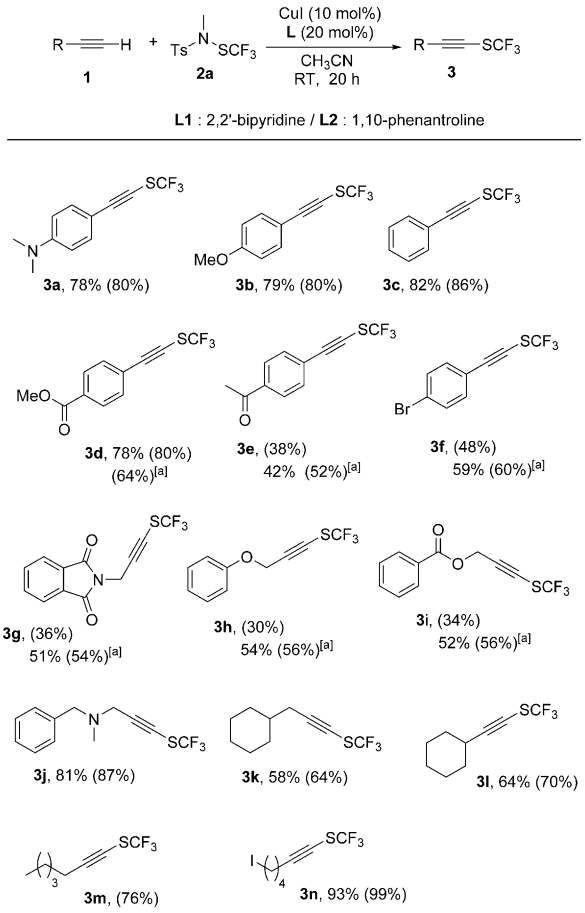
Results and Discussion

We recently demonstrated direct access to a wide range of perfluoroalkylthiolated compounds from perfluoroalkanesulfenamides.[7d,9a,b,13] We decided to investigate the copper-catalyzed perfluoroalkylthiolation of alkynes, but first we studied the copper-catalyzed trifluoromethylthiolation reaction.

A short series of optimization experiments revealed the best reaction conditions to be copper iodide (10 mol%), 2,2′-bipyridine **L1** (20 mol%), alkyne (1 equiv), and trifluoromethanesulfenamide **2a** (1.2 equiv). The reactions were performed at room temperature for 20 h under an ambient atmosphere.

To demonstrate the applicability of the described trifluoromethylthiolation of alkynes, we focused on the scope and limitations of the catalytic system. Therefore, a variety of different alkynes (aliphatic and aromatic) were applied under the standard reaction conditions. As shown in Scheme 2, aryl acetylenes bearing electron-donating groups were trifluoromethylthiolated in very good to excellent yields (**3a**–**b**). Aliphatic alkynes were also well tolerated in our protocol: very good yields of **3k**–**m** were obtained. More-challenging substrate **2n**, with an iodide group on a C(sp^3) carbon atom, underwent the transformation smoothly and **3n** was obtained in excellent yield.

When methyl 4-ethynylbenzoate (**1d**) was evaluated, a very good yield of 80% was observed by ^{19}F NMR spectroscopy. Additionally, two new singlets were observed at $\delta_F = -39$ and -41 ppm. Remarkably, during purification of the product **3d** this byproduct was isolated and confirmed as alkene **4d** (see Scheme 3 below), which was formed by bis-trifluoromethylthiolation of the corresponding alkyne. Furthermore, the presence of acetyl- or bromo-substituents on the arylacetylene moiety decreased the efficiency of the coupling process: **3e** and **3f** were formed in only 38 and 48% yield, respectively, under the standard conditions. Moreover, the formation of bis-trifluoromethythiolated byproducts was also observed in more-considerable quantities (up to 20%). This lack of selectivity could be resolved by changing the ligand to 1,10-phenanthroline (**L2**). Consequently, less than 1% of the bis-trifluoromethylthiolation products were observed and products **3e** and **3f** were formed selectively in higher yields (Scheme 2). Next, more-challenging non-aromatic acetylene substrates were studied. Propargylic substrates with a chelating oxygen atom demonstrate that an even higher ratio of bis-/mono-trifluoromethylthiolated product was obtained under the standard conditions. Once again, using **L2** allowed for highly selective formation of the terminal mono-trifluoromethylthiol products in moderate yields (**3g**–**i**, Scheme 2). The presence of a coordinating oxygen atom in the starting alkyne appears essential for the double insertion of SCF_3 because **3j** was formed exclusively without any trace of the bis-trifluoromethylthiolated product.

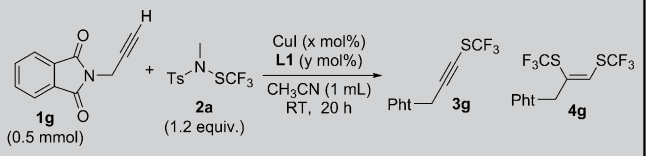


Scheme 2. Copper-catalyzed trifluoromethylthiolation of alkynes with **2a**. Reaction conditions: alkyne **1** (0.5 mmol), **2a** (0.6 mmol), CuI (10 mol%), **L1** (20 mol%), CH_3CN (1 mL), RT, 20 h. The yield of the isolated product is reported (the yield determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard is given in parentheses). [a] **L2** (20 mol%) was used instead of **L1**.

After observing partial bis-trifluoromethylthiolation of aromatic and propargylic alkynes we attempted to develop a selective bis-trifluoromethylthiolation procedure. We decided to double the catalyst loading: CuI (20 mol%)/ligand (40 mol%). In consideration of previous observations, **L1** was applied as the ligand to enable higher selectivity for the bis-trifluoromethylation. Indeed, a higher ratio of bis-/mono-trifluoromethylthiolation product was confirmed (Table 1, entry 2). Further increasing the catalyst loading (CuI (30 mol%)/**L1** (60 mol%) eventually enabled full conversion and excellent selectivity for the desired bis-trifluoromethylthiolated product **4g** (Table 1, entry 3). Nevertheless, the use of **2a** (2.4 equiv) to overcome the expected maximum yield of 60% based on **1g** appeared to be deleterious for the reaction.

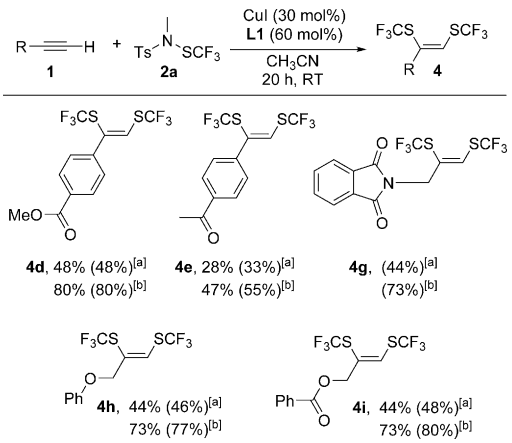
These conditions were found to be generally applicable, and the desired products were obtained with full selectivity towards the *Z* isomer (Scheme 3). Under these conditions only the bis-trifluoromethylthiolated products **4** were obtained; some trace amounts of **3** (<1%) were observed in few cases.

Table 1. Optimization of the bis-trifluoromethylthiolation of **1g**.

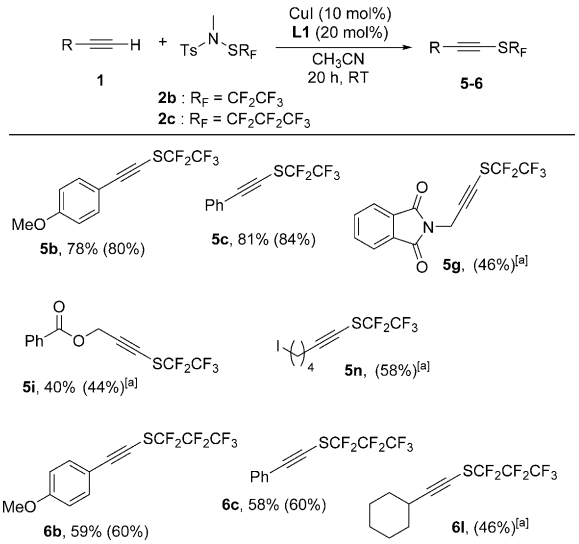


Entry	CuI [mol%]	**L1** [mol%]	**3g** [%][a]	**4g** [%][a]
1	10	20	36	20[b] (33)[c]
2	20	40	6	40[b] (67)[c]
3	30	60	< 1	44[b] (73)[c]

[a] The yield was determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard. [b] The yield relative to **1g**. [c] The yield relative to **2a**.



Scheme 3. Copper-catalyzed selective bis-trifluoromethylthiolation of alkynes with **2a**. Reaction conditions: alkyne **1** (0.5 mmol), **2a** (0.6 mmol), CuI (30 mol%), **L1** (60 mol%), CH_3CN (1 mL), RT, 20 h. The yield of the isolated product is reported (the yield determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard is given in parentheses). [a] Yield reported relative to **1**. [b] Yield reported relative to **2a**.



Scheme 4. Copper-catalyzed perfluoroalkylthiolation of alkynes with **2b**–**c**. Reaction conditions: alkyne **1** (0.5 mmol), **2** (0.6 mmol), CuI (10 mol%), **L1** (20 mol%), CH_3CN (1 mL), RT, 20 h. The yield of the isolated product is reported (the yield determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard is given in parentheses). [a] **L2** (20 mol%) was used instead of **L1**.

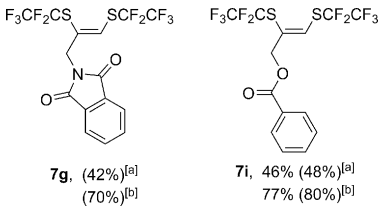


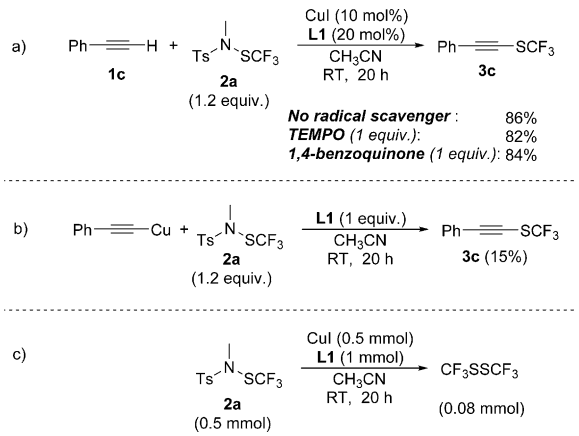
Figure 1. Bis-pentafluoroethylthiolation of alkynes with **2b**. The yield of the isolated product is reported (the yield determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard is given in parentheses). [a] Yield reported relative to **1**. [b] Yield reported relative to **2b**.

Subsequently, we extended the methodology to the incorporation of perfluoroalkylthiol groups into alkynes. For the first time we demonstrate the copper-catalyzed coupling of pentafluoroethyl- (**2b**) and heptafluoropropylsulfenamides (**2c**) with aromatic and aliphatic alkynes, and products **5** and **6** were isolated in good-to-excellent yields (Scheme 4).

Notably, the corresponding bis-pentafluoroethylthiolation could also be performed by using the previous conditions (Table 1, entry 3); products **7g** and **7i** were obtained, again with *Z* selectivity (Figure 1).

After observing the general activity of the reaction, we turned our attention to the reaction mechanism. When the reaction was carried out in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) or 1,4-benzoquinone (1 equiv) almost no changes in the reaction outcome were observed (Scheme 5 a).

Alternatively, a common pathway in the chemistry of alkynes with copper is the formation of copper acetylide species, which are known to react with an electrophile or a nucleophile through an oxidative mechanism.[14] In this context, we investigated the reactivity of (phenylethynyl)copper[15] (1.0 equiv) in the presence of **2a**. The formation of the desired product **3c** was observed in only about 15% yield compared with the initial result of 86%. These results seem to contradict a mechanism that involves the initial formation of an acetylene–cop-

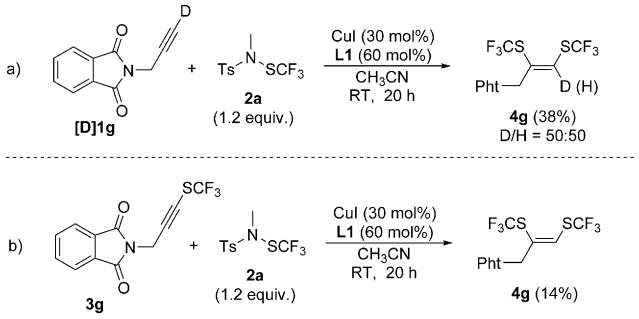


Scheme 5. Mechanistic investigations for the formation of **3c**. Yields were determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard.

per(I) complex, especially when the presence of base is required to obtain this complex in situ (Scheme 5b).

Moreover, we used a deuterium-labeled alkyne ([D]**1g**) to experimentally determine whether the bis-trifluoromethylthiolation reaction occurs exclusively via a two-step pathway, and a hydrogen–deuterium exchange (around 50% hydrogen atom incorporation) was detected in the final product (Scheme 6a). Hence, two pathways appear plausible: the second trifluoromethylthiolation could occur from the mono-trifluoromethylthiolated product (**3g**) or from a copper–vinyl intermediate.

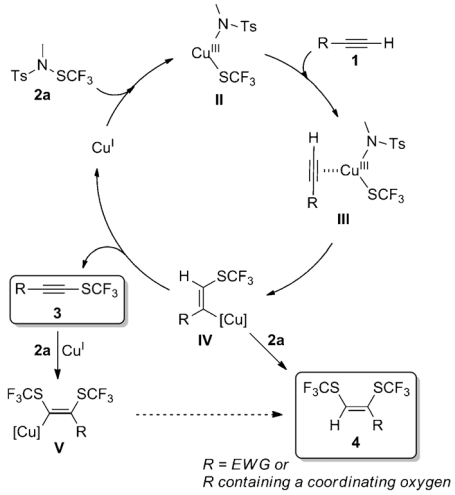
Further investigations focused on the nature of the bis-trifluoromethylthiolation of alkynes. Exemplarily, the reaction was performed with the SCF_3-substituted alkyne **3g** as the starting material under the standard conditions. The second trifluoromethylthiolation occurred, but with a lower yield of 14% (Scheme 6b).



Scheme 6. Mechanistic investigations for the formation of **4g**. Yields were determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard.

These preliminary studies concerning the reaction mechanism suggest that an unprecedented reaction pathway takes place (Scheme 7). We hypothesize that the formation of a polarized Cu–SCF_3 species is crucial for the transformation. An oxidative addition of copper(I) takes place and forms a new copper(III) complex **II**.[14,16] When reagent **2a** was mixed with a stoichiometric amount of CuI in the absence of any alkyne, no intermediate of type **II** was detected by NMR or mass spectroscopy due to its high reactivity, however the volatile species CF_3SSCF_3 was formed (Scheme 5c). This is in accordance with the formation of **II**, which could react with **2a** to form CF_3SSCF_3.

Species **II** undergoes π complexation to the alkyne to form intermediate **III**.[17] Intermediate **III** could yield a copper–vinyl SCF_3 intermediate **IV**. The mono-trifluoromethylthiolated product **3** could then be obtained by β-hydride elimination in the copper–vinyl intermediate **IV**.[18] If the intermediate is stabilized by an electronic effect (the presence of an electron-withdrawing group or a coordinating oxygen atom) a second trifluoromethylthiolation step provides a competing pathway. If this second pathway is competitive, the *cis* copper–vinyl complex **IV** can react with a second molecule of **2a**. This, in turn, generates the desired bis-trifluoromethylthiolated product **4** with *Z* selectivity. Also, after the formation of the alkyne **3**, we reasoned that formation of a nucleophilic metal–vinyl intermediate **V** is plausible, but less reactive, and could yield the bis-functionalized product.



Scheme 7. Proposed mechanism for the formation of **3** and **4**.

Conclusion

We have disclosed an original strategy for the trifluoromethylthiolation of alkynes by the association of trifluoromethanesulfenamide and a commercially available copper reagent to form a catalyst in situ. This new mode of reactivity has been exploited for mono- and bis-trifluoromethylthiolation, as well as perfluoroalkylthiolation, of alkynes. Preliminary mechanistic studies suggest an unprecedented reaction pathway.

Experimental Section

Typical procedure

CuI (0.05 mmol, 10 mol% or 0.15 mmol, 30 mol%), ligand **L** (0.10 mmol, 20 mol% or 0.30 mmol, 60 mol%), alkyne **1** (0.5 mmol, 1.0 equiv), perfluoroalkanesulfenamide **2** (0.60 mmol, 1.2 equiv), and MeCN (1 mL) were added to a flask equipped with a magnetic stirrer bar. The reaction mixture was stirred for 20 h at RT. The conversion of the starting material was monitored by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard. The reaction was partitioned between pentane and water. The aqueous layer was extracted with pentane and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under a moderate vacuum (800 mbar) at 40 °C. The crude residue was purified by flash column chromatography to afford the desired product.

Acknowledgements

The authors are grateful to the CNRS and the French Ministry of Research for financial support. The French Fluorine Network is also acknowledged for its support.

Keywords: copper · cross-coupling · fluorine · trifluoromethanesulfenamide · trifluoromethylthiolation

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Received: March 21, 2016
Revised: April 10, 2016
Published online on ■■ ■■, 0000

FULL PAPER

Synthetic Methods

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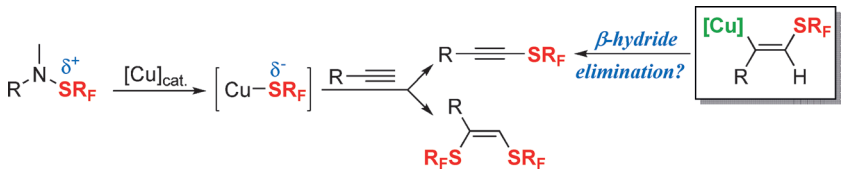
Copper-Catalyzed Perfluoroalkylthiolation of Alkynes with Perfluoroalkanesulfenamides



One or two? Selective mono- and bis-perfluoroalkylthiolation of alkynes could be performed with perfluoroalkanesulfenamides under copper-catalyzed base-free conditions (see scheme). This original approach seems to occur through an unprecedented pathway.