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Silver-Mediated Trifluoromethylthiolation–Iodination of Arynes

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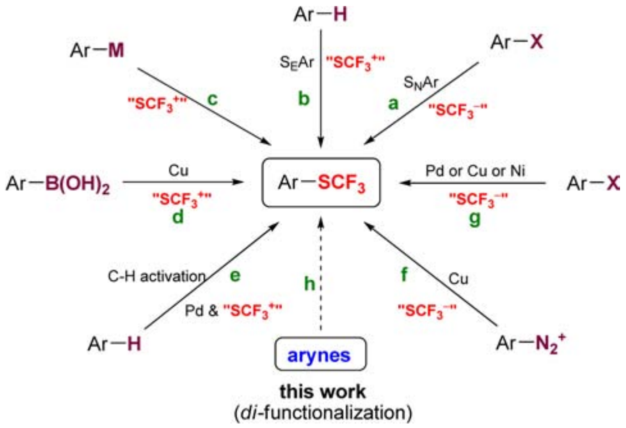
S *Supporting Information*

ABSTRACT: A one-pot trifluoromethylthiolation–iodination of arynes with trifluoromethylthiosilver ($AgSCF_3$) and 1-iodophenylacetylene is described. This protocol allows rapid construction of *o*-trifluoromethylthiolated arene building blocks in moderate yields. These products were found to be excellent precursors for Yagupolskii–Umemoto-type electrophilic trifluoromethylation reagents.

The incorporation of fluorine-containing functional groups into organic molecules often leads to an improvement of their physical and biochemical properties.[1] Among fluorinated molecules, aryl trifluoromethylthioethers ($ArSCF_3$) have attracted considerable attention in life sciences owing to the intrinsic properties of the SCF_3 group,[2,3] including strong electronegativity (Hammett constant: $\sigma_m = 0.40$ and $\sigma_p = 0.50$; larger than F and similar to CF_3) and high lipophilicity (Hansch constant $\pi_R = 1.44$; much higher than F and CF_3). Thus, the development of straightforward and efficient approaches for the introduction of the SCF_3 group onto aromatic rings is highly desirable.

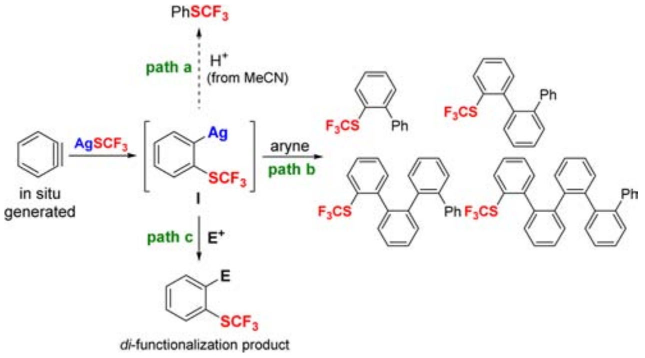
Although numerous methods are now available for synthesizing $ArSCF_3$ (Scheme 1),[4] prominent limitations still remain. For example, while traditional nucleophilic/electrophilic trifluoromethylthiolation reactions (Scheme 1, a–c) are less efficient and limited to specific substrates,[5] recent transition-metal-mediated cross-coupling reactions (Scheme 1, d–g) usually require the use of toxic and/or expensive trifluoromethylthiolating reagent under rather harsh conditions.[6] Moreover, existing protocols feature monofunctionalization. Herein, we report a vicinal difunctionalization protocol for aryne trifluoromethylthiolation under mild conditions (Scheme 1, h), which offers another functional group (iodine) for further transformation.[7]

Scheme 1. Strategies for the Introduction of Trifluoromethylthio Group(s) onto Aromatic Rings



In our previous studies on perfluoroalkylation of arynes,[8] we demonstrated that silver is a promising metal for aryne insertion reactions. In this scenario, we initially screened the stable and readily prepared $AgSCF_3$ as a nucleophilic SCF_3 source.[9] We reasoned that the in situ generated aryne could undergo Ag–S bond insertion to provide an *o*-SCF_3 arylsilver intermediate **I**, which may further undergo protonation to afford a trifluoromethylthiolated product (Scheme 2, path a). However, this reaction turned out to be messy, and only a trace

Scheme 2. Trifluoromethylthiolation of Aryne



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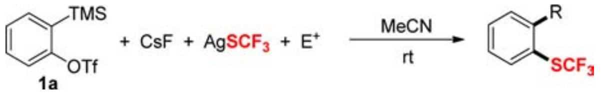
amount of $PhSCF_3$ was observed (Table 1, entry 1). We then analyzed the reaction mixture and found a large quantity of aryne multiple-insertion compounds as major byproducts (Scheme 2, path b). These byproducts indicate that, unlike the unstable arylsilver intermediate[10] and moderately stable *o*-trifluoromethyl-substituted arylsilver intermediate,[8a] intermediate **I** is a much more stable species that possesses a much longer lifetime and can undergo uncontrollable insertion with the short-lived aryne to afford a series of congeners.[11] Although not conclusive, we believe that these differences in stability and activity may stem from the intramolecular coordination between the silver center and *ortho* heteroatoms (Scheme 3).

Table 1. Reactions of Aryne, Trifluoromethylthiosilver, and Electrophiles

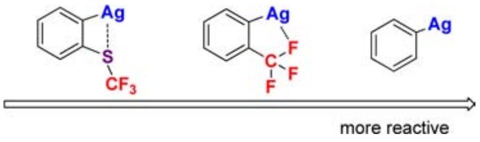


1a

entry[a]	electrophile	R	yield (%)
1	none	H	1
2	2-naphthaldehyde	CH(OH)Nap	0
3	phenyloxirane	$CH_2CH(OH)Ph$	0
4	$TEMPO^+ BF_4^-$	TEMPO	0
5	$NO_2^+ BF_4^-$	NO_2	0
6	$NO^+ BF_4^-$	NO	0
7	$Col_2Br^+ PF_6^-$	Br	0
8	$Py_2I^+ BF_4^-$	I	0
9	NIS	I	0
10	iC_3F_7I	I	53
11	nC_4F_9I	I	28
12	PhC≡C–I	I	61
13[b]	PhC≡C–I	I	69

[a] Reaction condition: **1a** (0.1 mmol, 1 equiv), CsF (4 equiv), $AgSCF_3$ (1.5 equiv) and electrophile (2 equiv) in MeCN (4 mL). Yields were determined by ^{19}F NMR. [b] $AgSCF_3$ (3 equiv).

Scheme 3. Comparison of Different Arylsilvers

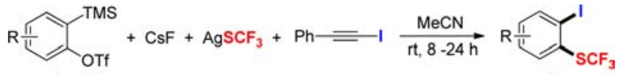


To diminish these undesired aryne multiple-insertion reactions and achieve the desired vicinal difunctionalization product, we envisioned that introducing a quenching step[12] to terminate this reaction after the initial trifluoromethylthiolation step may solve this problem (Scheme 2, path c). Here, an interesting dichotomy exists in choosing a suitable trapping reagent, which is that the incoming reagent should not only be stable (compatible with excess fluoride anions and the highly active aryne intermediate)[13] but also possess a sufficient reactivity to capture the stable arylsilver intermediate **I**. In this context, we screened a series of electrophiles with either good stability (Table 1, entries 2 and 3) or high reactivity (Table 1, entries 4–9). However, these reagents could not meet the aforementioned requirements simultaneously.

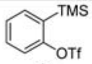
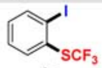
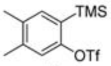
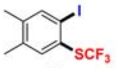
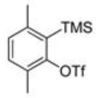
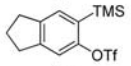
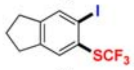
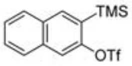
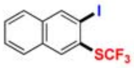
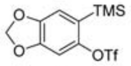
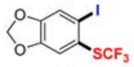
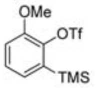
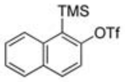
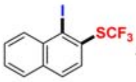
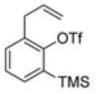
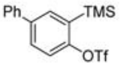
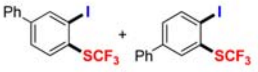
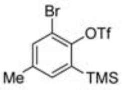
We then continued trying some electrophilic iodination reagents with moderate reactivity (Table 1, entries 10–12). These reactions afford the corresponding trifluorothiolation–iodination product. These results are in line with our previous work,[8,12] in which iodination reagents are found to be superb in trapping arylsilver intermediates. Among those I^+ reagents, 1-iodophenylacetylene provides the best result (Table 1, entry 12). The effect of ligand was also investigated.[14] However, no higher yields were obtained, probably due to the interference of intramolecular coordination of the S atom. Finally, after further tuning of the reaction parameters, the reaction yield increased to 69% (Table 1, entry 13).

Having established optimized reaction conditions, we then explored the scope of this silver-mediated trifluoromethylthiolation–iodination reaction (Table 2). For electron-neutral and electron-rich arynes (entries 1–10), moderate yields were

Table 2. Scope of Silver-Mediated Trifluoromethylthiolation–Iodination of Arynes



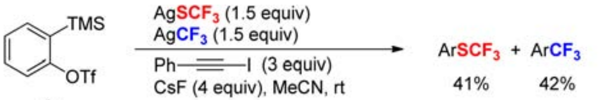
1 **2**

entry[a]	aryne precursors	products	yield (%)[b]
1	 **1a**	 **2a**	65
2[c]	 **1b**	 **2b**	58
3[c]	 **1c**	 **2c**	64
4[c]	 **1d**	 **2d**	46
5	 **1e**	 **2e**	48
6	 **1f**	 **2f**	66
7	 **1g**	 **2g**	70
8	 **1h**	 **2ha** +  **2hb**	**2ha**: 46 **2hb**: 28
9	 **1i**	 **2i** (3.2:1)	63
10	 **1j**	 **2j** (1.3:1)	74
11	 **1k**	 **2k**	32

[a] Reaction conditions: aryne precursor (0.5 mmol, 1 equiv), CsF (4 equiv), $AgSCF_3$ (3 equiv), 1-iodophenylacetylene (2 equiv), MeCN (20 mL). [b] Isolated yields. [c] CsF (6 equiv).

obtained (46–74%), while an aryne with an electron-withdrawing group (entry 11) gives a reduced yield (32%), probably owing to more preferred, unproductive pathways. Functional groups such as acetal, allyl, and bromide are compatible in this transformation (entries 6, 9, and 11). Additionally, sterically hindered 3,6-dimethylbenzyne (entry 3) is also amenable to this reaction (64%). However, for dialkyl-substituted substrates (**1b**–**d**), more CsF (6 equiv) and longer reaction times (24 h) are needed to achieve full conversions. Although good regioselectivities were observed in 3-substituted benzynes (**1g**, **1i**, and **1l**), the regioselectivity of 4-substituted benzyne **1j** is distinctly low (1.3:1).

To gain more insights into the trifluoromethylthiolation process, we carried out a competing experiment in which the same amount of $AgCF_3$ and $AgSCF_3$ was employed as different perfluoroalkyl sources (eq 1). After the reaction reached completion, we found that the yield of trifluoromethylthiolated products ($ArSCF_3$, 41%) is close to that of trifluoromethylated products ($ArCF_3$, 42%), indicating that the rate of benzyne thioargentation is comparable with that of benzyne carboargentation. This result further demonstrates that the different outcome of trifluoromethylthiolation of benzyne (Table 1, entry 1) (compared to the trifluoromethylation of benzyne as previously reported in ref 8a) comes not from the silver-mediated insertion (the first step), but from the exceptional stability of the arylsilver intermediate **I** (affecting the second step) (Scheme 2).

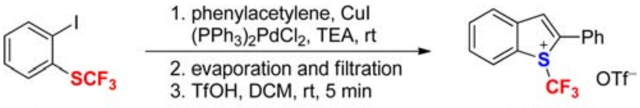


1a

(1)

To illustrate further the synthetic value of these *o*-trifluoromethylthiolated aryl iodides, we performed the Sonogashira coupling reaction between compound **2a** and the phenylacetylene. After simple evaporation and filtration, the coupling product could readily undergo triflic acid mediated intramolecular cyclization reaction to afford a Yagupolskii–Umemoto-type reagent **3** in high yield (Scheme 4).[15] It is worth noting that during the whole transformation the nucleophilic trifluoromethylthiolation reagent ($AgSCF_3$) was converted into an electrophilic trifluoromethylation reagent (R_2S^+–CF_3),[16] which serves as an interesting example of interconversion of different perfluoroalkylated functional groups in organofluorine chemistry. Moreover, compared to the original work,[15] our method may bring this type of reagent with more structural diversity and tunable reactivity.

Scheme 4. Synthesize of Yagupolskii–Umemoto-Type Electrophilic Trifluoromethylation Reagent



2a

3a, 82%

In summary, we have developed a new method for vicinal trifluoromethylthiolation–iodination of arynes. In this reaction, the iodination step not only diminishes the undesired aryne insertion of ArAg species but also provides a new handle (C–I bond) for further elaborations. We also demonstrated that these *o*-trifluoromethylthiolated iodoarene products can be used as key precursors for synthesizing Yagupolskii–Umemoto-type electrophilic trifluoromethylation reagent.[15]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00142.

Experimental procedures and characterization data for products (PDF)

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Notes

The authors declare no competing financial interest.

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(11) In ref 7b, the reaction temperature is 90 °C; thus, even the stable arylsilver intermediate can quickly undergo protonation to give the monofunctionalization product.

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