Copper-Catalyzed Trifluoromethylselenolation of Aryl and Alkyl Halides: The Silver Effect in Transmetalation

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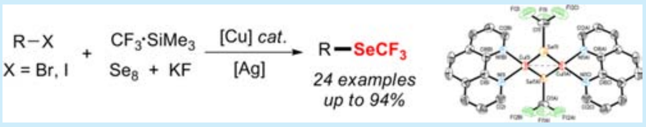
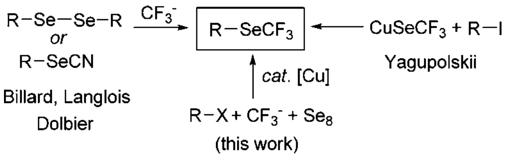
Ⓢ *Supporting Information*

ABSTRACT: A catalytic trifluoromethylselenolation of aryl and alkyl halides by a Cu(I) catalyst has been developed. A key intermediate, $[(\text{phen})Cu(SeCF_3)]_2$ (**5**) was successfully isolated and characterized by X-ray diffraction. The important role of silver in the transmetalation process during the catalytic cycle was elucidated. A wide range of trifluoromethylselanes have been prepared from readily available starting materials from a method that tolerates various important functional groups.



The trifluoromethylthiolato group ($-SCF_3$),[1] an important class of heteroatom-containing fluorinated molecules, has attracted increasing interest in recent years due to their strong electron-withdrawing effect[2] and high lipophilicity.[3] The trifluoromethylseleno group ($-SeCF_3$),[4] containing a larger selenium atom, has beneficial effects similar to those of the trifluoromethylthio group.[5] Much recent attention has been devoted to the development of new methods for the construction of $C-SCF_3$ bonds.[6−8] In contrast, trifluoromethylselenolation is much less developed (Scheme 1), presumably because selenium substances are normally extremely toxic, instable against air and/or moisture,[9] and exhibit a penetrating odor.[10] In view of their potential applications as intermediates of fluorine-containing compounds[11] in the pharmaceutical, agricultural, and advanced materials industries, the development of a convenient synthetic pathway is highly desirable.

Scheme 1. Methods for Preparation of Trifluoromethylselenolate Compounds



For instance, Langlois, Billard, and co-workers reported the nucleophilic trifluoromethylation of selenocyanates or diselenides with trifluoromethyl trimethylsilane,[12] trifluoroacetaldehyde,[13] or trifluoromethane[14] to form phenyl trifluoromethyl selenide; Dolbier and co-workers published an atom-economic procedure for the preparation of trifluoromethyl selenoethers by the reaction of tetrakis(dimethylamino)ethylene (TDAE) and CF_3I with diphenyl diselenide;[15] Yagupolskii and co-workers described the synthesis of trifluoromethylselenocopper from the reaction of copper power with bis(trifluoromethyl) diselenide and the trifluoromethylselenolation with iodoarenes (Scheme 1).[16] However, these existing methods suffer from disadvantages of limited substrate scope by the use of selenocyanates or diselenides and the use of specific reagents such as $CuSeCF_3$.[12b]

As part of our ongoing program in copper-catalyzed and -mediated trifluoromethylation[17] and trifluoromethylthiolation chemistry[18] and platinum-mediated synthesis of macrocyclic diselenoethers,[19] we recently reported a copper(I) trifluoromethylthiolate reagent $(bpy)Cu(SCF_3)$ prepared from the reactions of $Cu(II)F_2$ with Ruppert's reagent (Me_3SiCF_3), sulfur, and bipyridine ligand.[20] This reagent reacted with a variety of aryl and heteroaryl halides to produce aryl trifluoromethyl thioethers in good yields.

Encouraged by these results, we next sought to extend our research to develop a catalytic version of synthetic routes to the preparation of their selenium analogs with a broad substrate scope. In this contribution, we report a new Cu(I)-catalyzed trifluoromethylselenolation of aryl and alkyl halides with readily available starting materials.

We began with scouting experiments employing 4-iodotoluene (**1a**) as a substrate to optimize the reaction conditions. Treatment of **1a** with $CF_3{\cdot}SiMe_3$ and elemental selenium in the presence of 20 mol % of CuI, 20 mol % of 1,10-phenanthroline (phen), and KF (3 equiv) in 1.5 mL of dimethylformamide (DMF) at 80 °C for 16 h led to *p*-tolyl(trifluoromethyl)selane (**2a**) in 50% yield determined by ^{19}F NMR (entry 1). In the absence of CuI and phen, no product formation was observed (entry 2), thus showing that the copper is necessary for the reaction to occur.

These preliminary results encouraged us to further explore the precise reaction conditions. We then started to examine the use of a number of additives for their ability to promote this

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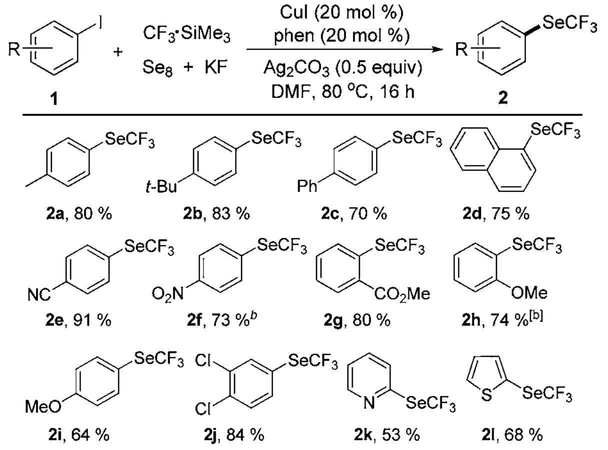
transformation. Silver reagents have recently proven to behave as efficient promoters for trifluoromethylation,[17a,21] trifluoromethylthiolation,[7a] and trifluoromethoxylation.[22] Formation of **2a** increased substantially to 87% when 0.5 equiv of Ag_2CO_3 was added as additive (entry 3). The significantly increased yield of product in the presence of Ag_2CO_3 clearly shows the importance of the silver effect in this reaction. No reaction occurred in the presence of Ag_2CO_3 alone (entry 4), suggesting that both the Cu catalyst and silver additive are required for the reaction.

Changing the copper salts also influenced the result. CuSCN and $Cu(OTf)_2$ provided slightly lower yields of the products (entry 6 and 7), whereas the use of CuBr instead of CuI dramatically slowed the reaction (entry 5). After screening a variety of bidentate or monodentate nitrogen ligands, we found that using Me_2phen, TMEDA, or 2,6-lutidine unfortunately gave unsatisfactory results (entries 8−11). Surprisingly, bpy, which is a useful ligand for copper-mediated trifluoromethylthiolation,[20] is not effective for catalytic trifluoromethylselenolation of aryl iodides (entry 9). Variation of the silver salts showed that Ag_2CO_3 is superior to other silver reagents. Use of $AgNO_3$, AgF, and AgOTf resulted in a sluggish reaction with poor yields of products because of several side reactions (e.g., trifluoromethylation) (entries 12−14). The choice of solvent has a significant impact on the efficiency of the reactions; employing DMSO, NMP, CH_3CN, CH_2Cl_2, diglyme, THF, or toluene leads to marked diminished yields (entries 15−22). Lowering or increasing the reaction temperature or reducing the reaction time to 8 h significantly decreased the product yields (entries 23−25).

Having established an efficient Cu-based catalytic system, the scope of iodoarenes and heteroarenes was examined (Scheme 2). Various electronically and structurally diverse iodoarenes **1** were applied to this reaction.

p-Alkyl or aryl-substituted aryl iodides were treated with $CF_3\cdot SiMe_3$ and elemental selenium to give the corresponding trifluoromethylselenolated products **2a**−**c** in 70−83% yields. 1-Iodonaphthalene furnished **2d** in 75% yield. The reaction proceeded smoothly with aryl iodides bearing both electron-withdrawing and electron-donating groups, affording the corresponding products **2e**−**i** in 64−91% yields. Intriguingly, Cl-containing substrate underwent trifluoromethylselenolation to produce **2j** in 84% yield, leaving the C−Cl bond intact, which is attractive for further transformation. The substrates containing important heterocyclic groups such as pyridine and thiophene were also successful, affording the products **2k** and **2l** in 53% and 68% yields, respectively.

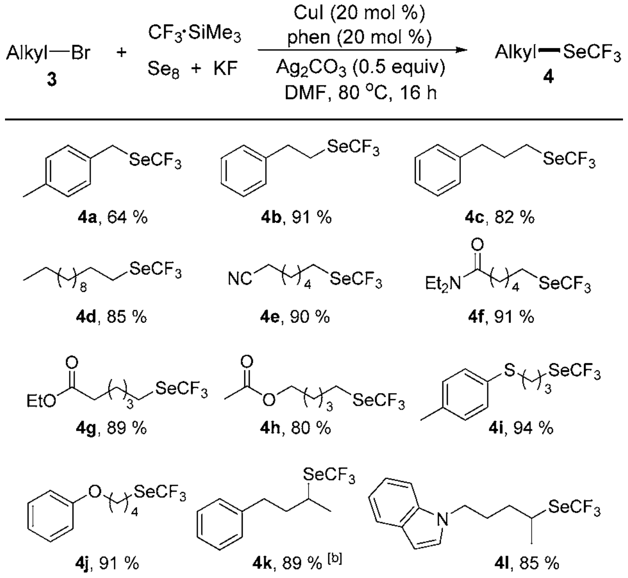
Scheme 2. Copper(I)-Catalyzed Trifluoromethylselenolation of Aryl and Heteroaryl Iodides[a]



[a]Reaction conditions: CuI (0.050 mmol), phen (0.050 mmol), aryl iodides (0.25 mmol), CF_3SiMe_3 (0.75 mmol), Se_8 (0.50 mmol), KF (0.75 mmol), Ag_2CO_3 (0.125 mmol), DMF (2.0 mL), 80 °C 16 h, N_2. Isolated yields. [b]With 30 mol % of CuI/phen.

Encouraged by the success in the catalytic trifluoromethylselenolation of aryl iodides, we next attempted to extend the substrate scope to alkyl halides. As shown in Scheme 3, a great variety of alkyl bromides can be converted into the corresponding trifluoromethylselanes. Moreover, a range of functional groups, such as nitrile (**4e**), amide (**4f**), ester (**4g**, **4h**), thioether (**4i**), and ether (**4j**), were tolerated in this reaction. Remarkably, secondary alkyl iodide and bromide could also be employed as facile substrates that provided the corresponding products (**4k** and **4l**, respectively) in good yields.

Scheme 3. Copper(I)-Catalyzed Trifluoromethylselenolation of Alkyl Bromides[a]



[a]Reaction conditions: CuI (0.050 mmol), phen (0.050 mmol), alkyl bromides (0.25 mmol), CF_3SiMe_3 (0.75 mmol), Se_8 (0.50 mmol), KF (0.75 mmol), Ag_2CO_3 (0.125 mmol), DMF (2.0 mL), 80 °C, 16 h, N_2. Isolated yields. [b]Alkyl iodide.

To gain an insight into the mechanism of this transformation, we have examined the reaction intermediates under stoichiometric conditions.

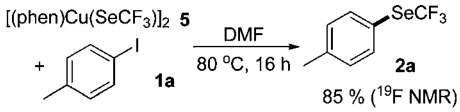
Treatment of Ag_2CO_3, Se_8, and KF with CF_3SiMe_3 (3 equiv) in DMF at 80 °C smoothly afforded the well-known silver(I) trifluoromethylselenate $AgSeCF_3$ (eq 1).[4a,10,23] Interestingly,

$$\begin{gathered} Ag_2CO_3 + Se_8 + CF_3SiMe_3 + KF \longrightarrow AgSeCF_3 \\ AgSeCF_3 + Ar\text{-}I \overset{\times}{\xrightarrow[\text{phen}]{}} ArSeCF_3 \end{gathered} \tag{1}$$

$$AgSeCF_3 + CuI + phen \longrightarrow \underset{\mathbf{5}}{[(phen)Cu(SeCF_3)]_2} \tag{2}$$

the trifluoromethylselenolation of the $AgSeCF_3$ with aryl iodides in the presence of phen did not proceed at all; In contrast, the reaction of $AgSeCF_3$ and CuI (1.0 equiv) with phen (1.0 equiv) was found to give an dinuclear copper trifluoromethylselenate intermediate $[(phen)Cu(SeCF_3)]_2$ (**5**) (eq 2). The facile transmetalation of the $-SeCF_3$ group from silver to copper center explains the increased efficiency in silver promoted copper-catalyzed trifluoromethylselenolation. Complex **5** has been determined by X-ray crystallography (see the Supporting Information).

We then evaluated the relevance of complex **5** as intermediate in the copper-catalyzed trifluoromethylselenolation of aryl halides. Reactions of **5** with 1 equiv of *p*-tolyl iodide in DMF for 16 h formed the trifluoromethylselenolate product *p*-tolyl(trifluoromethyl)selane in 85% yield (^{19}F NMR) (eq 3). This result is consistent with its catalytic version (87% yield; Table 1, entry 3) suggesting the plausible intermediacy of **5** in the catalytic cycle.



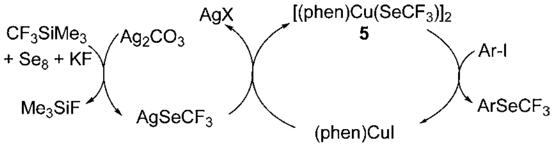
(3)

$$\begin{array}{l} \text{CuI + phen + Se}_8 \\ \text{+ CF}_3\text{SiMe}_3\text{ + KF} \end{array} \xrightarrow[80\ ^\circ\text{C, 16 h}]{\text{DMF}} \underset{\mathbf{5}}{[(\text{phen})\text{Cu}(\text{SeCF}_3)]_2} \qquad (4)$$

Additionally, we found that the reactive intermediate **5** can also be obtained from the stoichiometric reaction of CuI with Se_8, KF, CF_3SiMe_3, and phen (eq 4). This result may explain how catalytic trifluoromethylselenolation can be performed in the absence of Ag_2CO_3, albeit with reduced efficiency (Table 1, entry 1).

On the basis of the results described above, a tentative reaction pathway for this copper-catalyzed trifluoromethylselenolation is shown in Scheme 4. The transmetalation of the in situ generated silver trifluoromethylselenate $AgSeCF_3$ with copper iodide to form the copper trifluoromethylselenate **5**, followed by the reaction of **5** with iodoarenes to release the $ArSeCF_3$ products and to regenerate copper iodide for the next catalytic cycle.

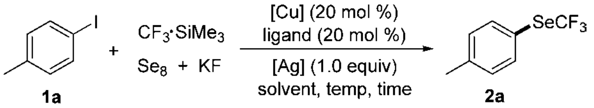
Scheme 4. Proposed Reaction Pathway



To probe whether any radical intermediates are generated, a radical clock probe, 1-(allyloxy)-2-iodobenzene **6**,[24] was used as the substrate in the trifluoromethylselenolation (Scheme 5). The reaction proceeded smoothly to produce the trifluoromethylselenolation product **7** in 80% yield (^{19}F NMR). No cyclized product, 3-methyl-2,3-dihydrobenzofuran **8**, was observed by GC/MS.

Next, the catalytic trifluoromethylselenolation of **3j** was carried out in the presence of a radical scavenger, cyclohexa-1,4-

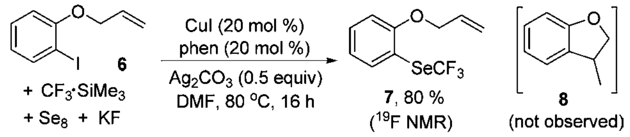
Table 1. Optimization of Trifluoromethylselenolation Conditions[a]



entry	[Cu]	ligand	[Ag]	solvent	temp (°C)	time (h)	yield[b] (%)
1	CuI	phen		DMF	80	16	50
2				DMF	80	16	0
3	CuI	phen	Ag_2CO_3	DMF	80	16	87
4			Ag_2CO_3	DMF	80	16	0
5	CuBr	phen	Ag_2CO_3	DMF	80	16	46
6	CuSCN	phen	Ag_2CO_3	DMF	80	16	75
7	$Cu(OTf)_2$	phen	Ag_2CO_3	DMF	80	16	77
8	CuI	Me_2phen	Ag_2CO_3	DMF	80	16	<1
9	CuI	bpy	Ag_2CO_3	DMF	80	16	12
10	CuI	TMEDA	Ag_2CO_3	DMF	80	16	6
11	CuI	2,6-lutidine	Ag_2CO_3	DMF	80	16	<1
12	CuI	phen	$AgNO_3$	DMF	80	16	13
13	CuI	phen	AgF	DMF	80	16	31
14	CuI	phen	AgOTf	DMF	80	16	17
15	CuI	phen	Ag_2CO_3	DMSO	80	16	38
16	CuI	phen	Ag_2CO_3	NMP	80	16	39
17	CuI	phen	Ag_2CO_3	CH_3CN	80	16	6
18	CuI	phen	Ag_2CO_3	CH_2Cl_2	40	16	0
19	CuI	phen	Ag_2CO_3	CH_3OH	80	16	0
20	CuI	phen	Ag_2CO_3	diglyme	80	16	38
21	CuI	phen	Ag_2CO_3	THF	80	16	13
22	CuI	phen	Ag_2CO_3	toluene	80	16	<1
23	CuI	phen	Ag_2CO_3	DMF	110	16	26
24	CuI	phen	Ag_2CO_3	DMF	50	16	29
25	CuI	phen	Ag_2CO_3	DMF	80	8	69

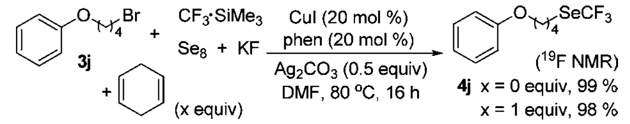
[a] Reaction conditions: **1a** (0.10 mmol), Se_8 (0.20 mmol), KF (0.3 mmol), $CF_3{\cdot}SiMe_3$ (0.30 mmol), [Cu] (0.020 mmol), ligand (0.020 mmol), [Ag] (0.10 mmol), solvent (1.5 mL), under N_2 atmosphere. [b] Yields were determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as internal standard.

Scheme 5. Radical Clock Probe Experiment



diene (CHD). The experiments showed that the reaction rates and selectivities for trifluoromethylselenolation were not affected. (Scheme 6).

Scheme 6. Radical Scavenger Experiment



The absence of cyclization product **8** and the lack of any effect on product yields with the addition of CHD suggest that the trifluoromethylselenolation are not in favor of the possible involvement of radical species.

In summary, we have developed a general and practical strategy for the trifluoromethylselenolation of aryl, heteroaryl and alkyl halides by Cu(I) catalyst. The catalytic system is compatible with a wide range of functional groups, such as nitro, nitrile, methoxy, chloro, amide, ester, thioether, and ether. Silver plays an important role in promoting the reaction by transferring the $SeCF_3$ group to copper species. An dimeric copper trifluoromethylselenate $[(phen)Cu(SeCF_3)]_2$ (**5**) was successfully isolated as an intermediate and characterized by X-ray diffraction. Further applications of this methodology to other distinctive substrates and substituents are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for products and mechanistic study experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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