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Copper catalyzed oxidative coupling reactions for trifluoromethylselenolations – synthesis of R-SeCF₃ compounds using air stable tetramethylammonium trifluoromethylselenate†

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The aerobic, room-temperature coupling of tetramethylammonium trifluoromethylselenate with readily available boronic acids, boronic esters, and terminal alkynes has been developed. The method permits direct access to valuable trifluoromethylselenoarenes and alkynes under mild conditions. A convenient one-pot reaction, a scale up procedure as well as an extension to perfluoroalkylselenates are also presented to further demonstrate the synthetic utility of this reaction.

Fluorine is the most electronegative element and plays an important role in contemporary chemical research and development. Fluorinated groups can be found on the market in blockbuster drugs and highly effective agrochemicals and also have applications in material sciences.¹ Compounds possessing fluorinated moieties have gained increased attention during the past few years, as their strong lipophilic and electron-withdrawing abilities allow modulation of their physicochemical properties (*i.e.*, log *P*, p*K*_a, solubility). This often leads to enhanced bioactivity and bioavailability compared to parent non-fluorinated compounds. Therefore, methods for the introduction of these groups into organic molecules are of great interest for pharmaceutical and agrochemical industries as well as material sciences.

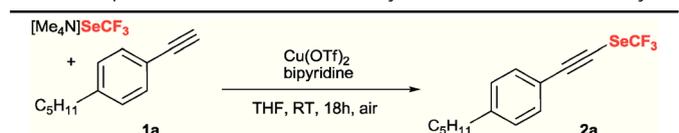
Selenium is an essential element in nature, as a vital part of antioxidant enzymes.² Organoselenium compounds are even more easily oxidized compared to their sulfur counterparts, leading to a richer hypervalent chemistry.³ The odor of selenols and diselenides partially prevented the in-depth investigation of methodologies for preparing selenium-containing molecules. In particular the production of trifluoromethylated selenoethers still represents a challenge, even though these compounds might have promising properties.

Therefore, we decided to develop a mild, safe and odor-free method for the synthesis of fluorinated selenoethers.

Trifluoromethylselenolated compounds are usually prepared by trifluoromethylation of electrophilic sources of selenium, but this requires the preparation of the corresponding diselenide or selenium chloride.⁴ Another more modular approach would be the direct formation of the C–SeCF₃ bond. In principle, (F₃CSe)₂ and F₃CSeCl could serve as electrophilic reagents, and F₃CSeH as a nucleophilic reagent. These reagents have boiling points of 72 °C, 31 °C, and –14.5 °C, respectively, as well as high toxicity, making their use cumbersome. Therefore, MSeCF₃ salts, where M is a metal, have been investigated, and the coupling of copper derivatives with alkyl and aryl halides has been reported in 1985 by Yagupolskii, and revised very recently by Weng and co-workers.⁵ This approach is restricted to the metal used.

Based on Naumann's work,⁶ we identified tetramethylammonium trifluoromethylselenate ([Me₄N]SeCF₃) as a promising reagent, readily prepared from red selenium and the Ruppert–Prakash reagent (TMSCF₃). The chemistry of this reagent has not been well established. Therefore, we decided to evaluate the reactivity and stability of [Me₄N]SeCF₃ and to apply it for the challenging introduction of the SeCF₃ group into different molecules.

Table 1 Optimization of the trifluoromethylselenolation of terminal alkynes



Entry	Time (h)	Yield ^b (%)
1	Standard conditions ^a	93
2	No air (Ar atmosphere)	<1
3	O ₂ atmosphere	94
4	No copper	nr
5	No ligand	9
6	10 mol% Cu(OTf) ₂	<5
7	2 equiv. Cs ₂ CO ₃	33

^a Standard conditions: alkyne **1a** (0.10 mmol), [Me₄N]SeCF₃ (0.11 mmol), Cu(OTf)₂ (0.10 mmol) and bipyridine (0.11 mmol) in THF (1 mL) were stirred at RT for 18 h. Full optimization table in the ESI. ^b Yields were determined by ¹⁹F NMR analysis with PhCF₃ as the internal standard.

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Alkynes are versatile building blocks in organic and polymer chemistry, and a wide range of metal-catalyzed methods are known for their functionalization.⁷ Despite numerous reports on the functionalization of selenoalkynes,⁸ trifluoromethylselenoalkynes are virtually unknown.³ⁱ Oxidative coupling of alkynes with heteronucleophiles is challenging due to the competitive Glaser coupling. However, encouraging preliminary results lead us to investigate the trifluoromethylselenolation of alkynes using $[\text{Me}_4\text{N}]\text{SeCF}_3$. To our delight, the reaction proceeded smoothly under aerobic, copper(II)-mediated conditions, with THF being the solvent of choice. However, various other solvents could also be used (Table 1, full optimization table in the ESI†). The reaction can be performed under air or under oxygen with equal success. Low conversion was observed under an argon atmosphere or in the absence of a ligand (Table 1, entries 2 and 5). Using substoichiometric amounts of copper did not result in full conversion of starting materials. Interestingly, using either

bpy or dtbpy as ligand for both Cu(I) and Cu(II) mediated reactions provided similar results. That was unexpected as it was shown by Weng that these ligands tend to form respectively dimeric or monomeric copper(I) complexes with the SeCF_3 anion in the solid state.^{5c} These results point to an oxygen-promoted Cu(III) intermediate.⁹

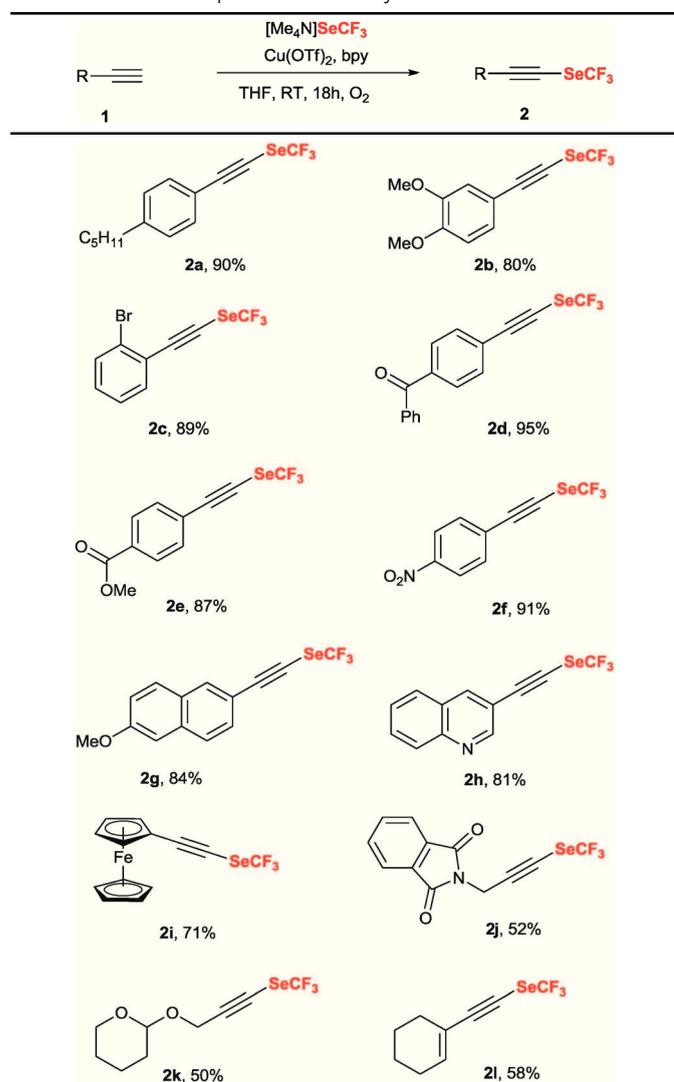
The scope of this reaction proved to be very general, as aromatic and heteroaromatic alkynes **1a–i** gave excellent yields of the cross-coupling products **2a–i**, disregarding the substitution pattern (Table 2). Aliphatic alkynes **1j–l** were also suitable substrates, although giving the expected products **2j–l** in lower yields due to incomplete conversion. However, this oxidative coupling represents the first procedure for the introduction of the SeCF_3 moiety into alkynes.¹⁰

With these encouraging results in hand, we wondered whether this methodology could be applied to the coupling with boronic acid **3a** (Table 3, full optimization table in the ESI†).¹¹ To our delight, we found that these Chan–Lam-type conditions gave the corresponding trifluoromethylselenoarene **4a** in good yield. This time, DMF was the solvent of choice, and once again, although the reaction worked best under an oxygen atmosphere, the product was obtained in comparable yield under air (Table 3, entries 3 and 1). Addition of base or molecular sieves did not improve the yield (Table 3, entries 7 and 8).

We also investigated different nucleophiles (see ESI†) and realized that next to boronic acid **3a**, boron pinacol ester **5a** and boronic acid neopentyl glycol ester **6a** gave similar results with over 80% yield, whereas MIDA and DEAM boronates **7a** and **8a** as well as organotin reagent **10a** were inferior, with low to moderate yields. On the other hand, no desired product was observed if potassium trifluoroborate **9a** was used. Given the range of substrates, we believe this methodology which does not require aromatic halides as starting materials, or the use of a glove-box, poisonous gases or high temperatures will be widely applicable.¹²

With the optimized conditions in hand, we examined the scope of this reaction (Table 4). Both electron-rich and electron deficient aromatic boronic acids and pinacol esters took part in

Table 2 Reaction scope for terminal alkynes



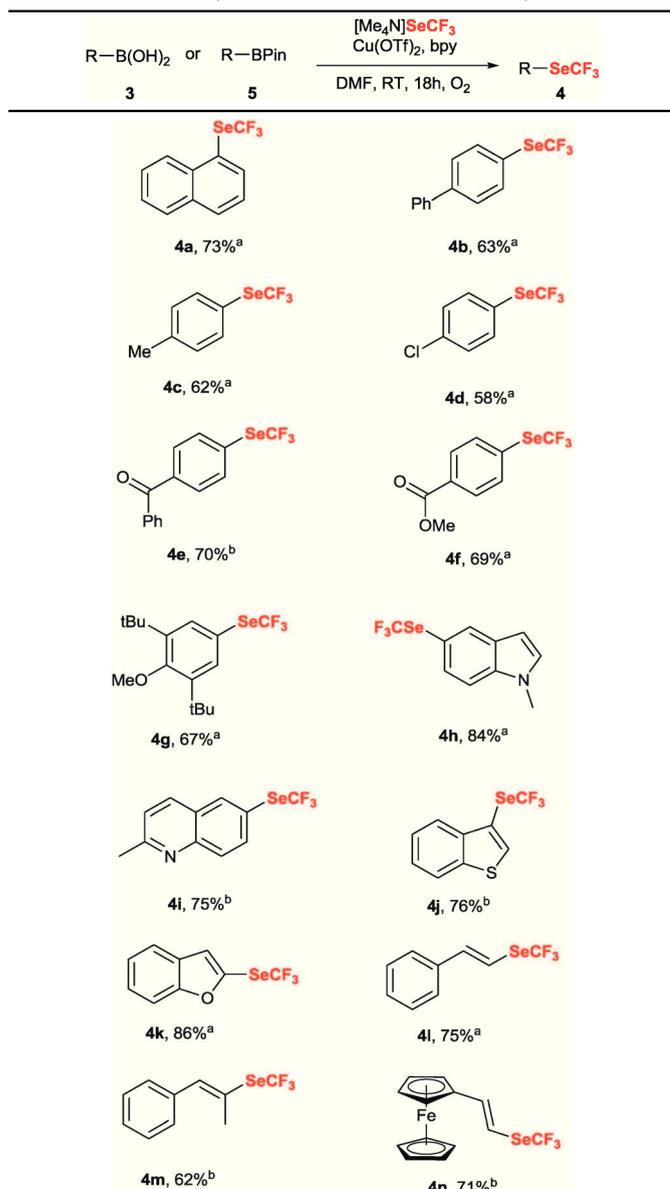
Reaction conditions: alkyne **1** (0.10 mmol), $[\text{Me}_4\text{N}]\text{SeCF}_3$ (0.11 mmol), $\text{Cu}(\text{OTf})_2$ (0.10 mmol) and bipyridine (0.11 mmol) in THF (1 mL) were stirred at RT for 18 h. Yield of isolated products.

Table 3 Optimization of the trifluoromethylselenolation of boronic acids

Entry	Time (h)	Yield ^b (%)
1	Standard conditions ^a	88
2	No air (Ar atmosphere)	20
3	O ₂ atmosphere	90
4	No copper	nr
5	No ligand	26
6	10 mol% $\text{Cu}(\text{OTf})_2$	7
7	2 equiv. Cs_2CO_3	67
8	4 Å MS	81

^a Standard conditions: boronic acid **1a** (0.10 mmol), $[\text{Me}_4\text{N}]\text{SeCF}_3$ (0.11 mmol), $\text{Cu}(\text{OTf})_2$ (0.10 mmol) and bipyridine (0.11 mmol) in DMF (1 mL) were stirred at RT for 18 h. Full optimization table in the ESI. ^b Yields were determined by ¹⁹F NMR analysis with PhCF_3 as internal standard.

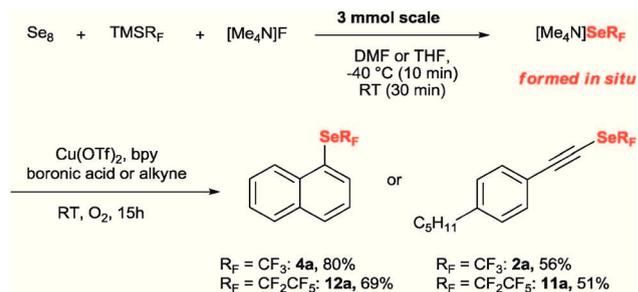
Table 4 Reaction scope for boronic acids and boronic pinacol esters



Reaction conditions: boronic acid **3** or boronic acid pinacol ester **5** (0.10 mmol), [Me₄N]SeCF₃ (0.11 mmol), Cu(OTf)₂ (0.10 mmol) and bipyridine (0.11 mmol) in DMF (1 mL) were stirred at RT for 18 h. Yield of isolated products. ^a Boronic acid was used. ^b Boronic acid pinacol ester was used.

the reaction to give the corresponding products **4a–g** in good yields. Heteroaromatic compounds gave the corresponding trifluoromethylselenolated compounds **4h–k** in good to excellent yields. Vinyl boronic acid **4l** and pinacol esters **4m** and **4n** were also good substrates which underline the applicability of this new method to effectively synthesize SeCF₃-containing molecules.

Although [Me₄N]SeCF₃ could be easily synthesized and isolated from commercially available starting materials, we questioned whether the development of a one-pot procedure could be possible. To prove the synthetic utility of our method, we therefore performed a 3 mmol scale experiment in which tetramethylammonium trifluoromethylselenate was formed *in situ* from its components.



Scheme 1 One-pot procedure. Yields of isolated products.

After reaction completion and standard work-up, we could isolate the trifluoromethylselenolated products **2a** and **4a** in 56% and 80% yield, respectively (Scheme 1). A similar experiment was conducted using the perfluoroethyl analogue, providing the corresponding products **11a** and **12a** in good yields. Therefore, this methodology is expected to be applicable for the synthesis of a wide range of selenoethers. As a proof of synthetic usefulness, oxidation of **4a** to the corresponding selenoxide proceeded uneventfully in 86% yield (see ESI[†]).

In summary, we have developed a new oxidative trifluoromethylselenolation of boron derivatives and alkynes. This reaction proceeds in various solvents, under air, and at room temperature, and tolerates a wide range of substrates, thus possibly making it valuable for late-stage functionalization of complex organic molecules. Next to the use of air and moisture stable tetramethylammonium trifluoromethylselenate ([Me₄N]SeCF₃), the reaction can also be performed starting from selenium and TMSCF₃. Furthermore, the scale up of the reaction as well as the introduction of perfluoroalkylselenate groups has been demonstrated. Thus the development of such a practical methodology will provide new classes of compounds relevant for pharmaceutical and agrochemical industries as well as material sciences.

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