RESEARCH ARTICLE

Gold(I/III)-Catalyzed Trifluoromethylthiolation and Trifluoromethylselenolation of Organohalides

Sagar R. Mudshinge,[a] Yuhao Yang,[a] Bo Xu,[b] Gerald B. Hammond,*[a] and Zhichao Lu*[a]

[a] Dr. Z. Lu, and Prof. G. B. Hammond
Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States
E-mail: zhichao.lu@louisville.edu; gb.hammond@louisville.edu.
[b] Prof. Bo Xu
College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

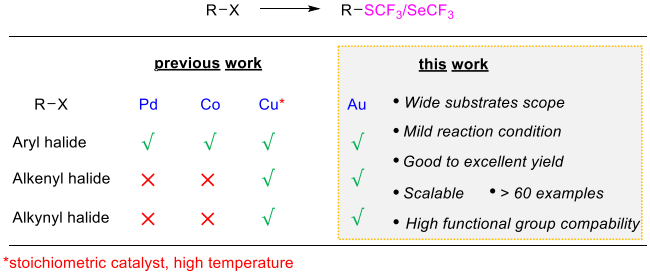
Abstract: The first C−SCF_3/$SeCF_3$ cross-coupling reactions using gold redox catalysis [(MeDalphos)AuCl], $AgSCF_3$ or Me_4NSeCF_3, and organohalides as substrates are reported. The new methodology enables a one-stop shop synthesis of aryl/alkenyl/alkynyl trifluoromethylthio- and selenoethers with a broad substrate scope (> 60 examples with up to 97% isolated yield). The method is scalable, and its robustness is evidenced by the late-stage functionalization of various bioactive molecules, which makes this reaction an attractive alternative in the synthesis of trifluoromethylthio- and selenoethers for pharmaceutical and agrochemical research and development.

Introduction

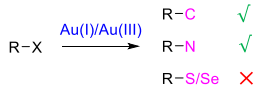
The introduction of fluorine or fluorinated functional groups into organic molecules continues to command attention in the world of pharmaceuticals, agrochemicals, and functional materials. In particular, CF_3S and CF_3Se are of significant interest[1] due to their inherently high Hansch lipophilicity parameters (CF_3S: π_R = 1.44, CF_3Se: π_R = 1.29) vs. (CF_3O: π_R = 1.04, CF_3: π_R = 0.88, F: π_R = 0.14)[2] and strong electron-withdrawing effects (Hammett constants CF_3S: σ_p = 0.50, CF_3Se: σ_p = 0.45) vs. (CF_3O: σ_p = 0.35, CF_3: σ_p = 0.54, F: σ_p = 0.06)[3]. The unique Hansch parameters of CF_3S and CF_3Se provide the medicinal chemist with a convenient tool for adjusting the lipophilicity of bioactive molecules, whereas their electron-withdrawing properties and considerable steric hindrance enhance the metabolic stability of the molecules containing these fluorinated groups. Not surprisingly, synthetic methodologies that introduce SCF_3 and $SeCF_3$ are being actively pursued.[1b, 1c, 4] Among them, the direct trifluoromethylthiolation and trifluoromethylselenolation of organohalides with palladium,[5] nickel,[6] and copper[7] have gained the most traction[8] (Scheme 1A). Despite their gains, palladium, nickel, and copper-based methods involve harsh reaction conditions (high temperature, air- or moisture- sensitivity), limited substrate scope, or high catalyst loading. An even more crippling drawback is that none of these metals can single-handedly catalyze the synthesis of aryl, alkenyl, and alkynyl trifluoromethylthio- and selenoethers. Palladium and nickel have been reported only for the synthesis of aryl trifluoromethylthio- and selenoethers whereas more than one equivalent of copper with a ligand at high temperature is needed for the synthesis of trifluoromethylthio- and selenoether derivatives.[1]

Our goal is to develop a 'one-stop shop' synthesis of aryl/alkenyl/alkynyl trifluoromethylthio- and selenoethers using gold catalysis. Although gold-catalysis has made significant strides in the construction of C-C and C-X bonds, progress in gold-catalyzed cross-coupling reactions has been hampered by the 'bottleneck' oxidative addition of organohalides.[9] Attempts to overcome this hurdle through the use of strong external oxidants or an aryl diazonium salt as an electrophile to form the active Au(III)-Ar intermediates have been reported, but these strategies have limited the range of compatible coupling partners and have diminished functional group tolerance.[10] Recently, Bourissou and co-workers reported that a hemilabile (P,N) ligand (MeDalPhos) triggered the key oxidative addition of aryl/alkynyl/alkenyl halides to gold(I) under ambient conditions.[11] The resulting active gold (III) complex enabled C-C,[11a, 11b] and C-N[11d, 12] cross-coupling reactions under mild conditions. However, the Au-catalyzed reactions of organosulfur compounds—known to be catalyst poisons and highly aurophilic—are difficult. Even though stoichiometric gold-mediated cysteine bioconjugation[13] and hybrid nanocluster construction[14] have been reported, gold-catalyzed C-S/Se cross-couplings are still elusive (Scheme 1B). We now report the first gold-catalyzed C−SCF_3/$SeCF_3$ cross-coupling reactions enabled by the commercially available, air and moisture-stable (MeDalphos)AuCl complex. Our methodology provides an operationally simple, mild, and efficient synthesis of aryl/alkenyl/alkynyl trifluoromethylthio- and selenoethers featuring a broad substrate scope (both acidic and basic substrates are tolerated and > 60 examples with up to 97% isolated yield are reported). Furthermore, our method is scalable, and its robustness is evidenced by the late-stage functionalization of various bioactive molecules (Scheme 1A).

A. Transition metal-catalyzed direct trifluoromethyl- thiolation/selenolation:



B. Au(I)/Au(III)-catalyzed C-X coupling triggered by MeDalPhos ligand:

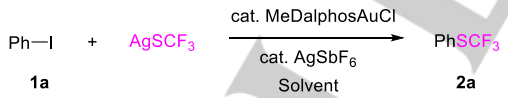


Scheme 1. Au(I)/Au(III)-catalyzed C-SCF_3/$SeCF_3$ coupling reactions.

Results and Discussion

Our initial focus was the conversion of aryl halides to the corresponding $ArSCF_3$. We used phenyl iodide **1a** as the model substrate in conjunction with the Au pre-catalyst (MeDalphos)AuCl (Table 1). We selected $AgSCF_3$ as the nucleophilic SCF_3 source because $AgSCF_3$ is readily available and stable. Furthermore, as a silver salt, it can also serve as a gold pre-catalyst activator, thus eliminating the need for additional silver activators. The reaction, conducted in dichloroethane at rt for 24 hours, delivered the trifluoromethylate **2a** in 80% yield with 20% starting material remaining (entry 2). Solvents played a vital role as the reaction did not proceed when a polar solvent like acetonitrile or dimethylformamide was utilized (see SI for more details). A significant counterion effect was observed during the silver activator screening as the silver activator with lower gold affinity[15] counterion exhibited faster kinetics[11d, 16] (see entries 5, 6, and 7, SbF_6^- >BF_4^- >NTf_2^-). The screening of silver activators revealed that 0.2 equivalent of $AgSbF_6$ gave the highest conversion (entry 5 *vs.* entry 8). A 5 mol% of gold pre-catalyst was optimal as the reaction yield decreased dramatically with lesser amounts (entry 5 vs. entry 9). Concentration (0.2 M) was also crucial (compare entry 1 vs. entries 10, 11). Control experiments demonstrated that both the gold catalyst and the silver activator were essential (entries 12, 13, 14). The reaction without silver activator barely proceeded (entry 13), and only gave a 23% yield of product after the reaction time was extended to 24 hours; this result indicated that $AgSCF_3$ could activate the gold pre-catalyst, albeit at a much slower rate than $AgSbF_6$ (entry 13). The reaction without gold catalyst did not proceed at all, even after 30 hours (entry 14). However, when the gold pre-catalyst was introduced to the reaction mixture, the reaction resumed and was completed in 2 hours with full conversion. The reaction yield was further improved when 0.2 mmol of **1a** was employed (entry 15). After exhaustive reaction condition screenings, we found that reacting 0.2 mmol of phenyl iodide **1a** with 5 mol% of (MeDalphos)AuCl pre-catalyst, 1.05 equiv of $AgSCF_3$, and 0.2 equiv of $AgSbF_6$ in 1 mL dichloroethane (DCE) gave the best yield of the desired product **2a** (entry 15). It should be noted that when another nucleophilic SCF_3 reagent like Me_4NSCF_3 was utilized, the reaction gave a lower yield (entry 16, see SI for more details).

Table 1. Reaction condition optimization for Au(I)/Au(III)-catalyzed trifluoromethylation of phenyl iodide[a]



1a **2a**

Entry	Deviation	Yield (**2a**, %)[b]
1[a]	no	95
2	rt, 24 h	80
3	0.5 mL THF as solvent, rt, 24 h	2
4	0.5 mL CH_3CN as solvent, rt, 24 h	0
5	0.2 equiv $AgSbF_6$, 60 °C, 1h	80
6	0.2 equiv $AgBF_4$, 60 °C, 1h	57
7	0.2 equiv $AgNTf_2$, 60 °C, 1h	42
8	0.1 equiv $AgSbF_6$, 60 °C, 1h	31
9	2 mol% MeDalPhosAuCl, 60 °C, 1h	32
10	0.25 mL DCE, 70 °C	88
11	1 mL DCE, 70 °C	90
12[c]	No MeDalPhosAuCl, No $AgSbF_6$, 70 °C, 1 h	0
13[d]	No $AgSbF_6$, 70 °C, 1 h	1
14[e]	No MeDalPhosAuCl, 70 °C, 30 h	0
15	Scaled up with 0.2 mmol **1a**, 1h	100
16[f]	Me_4NSCF_3 was used instead of $AgSCF_3$	81

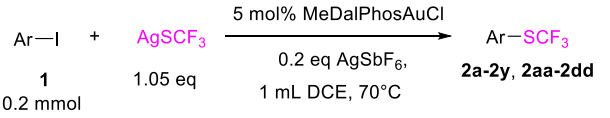
[a]Conditions: Unless otherwise noted, reactions were conducted as follows: An 8-mL reaction vial was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv) and 0.5 mL DCE. PhI (0.1 mmol) was added, and the resulting mixture was stirred at rt for 1 min. $AgSbF_6$ (0.2 equiv) was then added, and the reaction was stirred at rt for 1 min before stirring at 70 °C for 1 h. [b]Yields were determined by GC. [c]24 h, 0% yield; [d]24 h, 23% yield; [e]when 5 mol% Au was re-introduced, the reaction gave 100% yield in 2 h. [f] Me_4NSCF_3 (0.2 equiv) and $AgSbF_6$ (1.2 equiv) were applied.

With optimized reaction conditions in hand, we explored the reaction scope for the trifluoromethylthiolation of aryl halides. As illustrated in Table 2, the reaction furnished trifluoromethylthiolated products in good to excellent yields. Aryl iodides with diverse functionalities such as ethers (**2b-2d**, **2n, 2bb-2dd**), halides (**2e-2g**, **2cc**), ketones (**2j**, **2x**, **2cc**), aldehyde (**2k**), nitro (**2l**, **2dd**), nitrile (**2m**), esters (**2p**), amine (**2q**), phenol (**2r**), carboxylic acids (**2s**, **2cc**), triflate (**2t**), amide (**2dd**), and medicinally important fluorine functionalities (**2n**, **2o**) were well-tolerated. It should be noted that our protocol tolerated both acidic (**2s**, **2cc**) and basic (**2q**) functional groups, a feat that has not been achieved with other transition metal catalysts. Both electron-rich and electron-deficient aromatic iodides, as well as a polyaromatic (**2 v**), were efficiently converted in good yields. The reactions with electron-rich aryl iodides were faster than with their electron-withdrawing counterparts (**2b** vs. **2e**, **2j**, **2m**, **2s**). *Ortho*-substituted aryl iodides gave a decreased yield vis-à-vis *para-/meta*-substituted derivatives (**2d** vs. **2b**, **2c**). Two CF_3S groups were installed in high yield in just one single step when 1,8-diiodonaphthalene was employed (**2v**), demonstrating the potential for multiple trifluoromethylthiolation of polyiodoarenes. Heteroaryl iodides substrates, including thiophene (**2w**), furan (**2x**), and pyridine (**2y**), were also suitable substrates that produced the corresponding trifluoromethylthiolates in very good yields. All together, these results underscored the mild conditions and excellent functional group tolerance of our methodology. Our protocol also showed high chemoselectivity as the trifluoromethylthiolation only occurred at the $C(sp^2)$-I site, leaving other common coupling sites, such as bromide (**2g**), chloride (**2f**), triflate (**2t**), boronic ester (**2u**) intact. Particularly, the selective trifluoromethylthiolation of $C(sp^2)$–I over $C(sp^2)$–Br is noteworthy because differentiation of C–I versus C–Br is a significant challenge that has eluded other transition metal-catalysis (for any type of bond formation). These intact coupling sites provide useful handles for orthogonal functionalization.

Our protocol provides an easy-to-use synthetic tool for the late-stage modification of drug molecules, as evidenced by the smooth conversion of **2cc**-**2dd** in high yields. For example, we obtained the trifluoromethylthiolated fenofibric acid (**2cc**) in a 95% isolated yield. Fenofibric acid is used to treat increased cholesterol and fatty substance levels in the blood. It possesses various functionalities (e.g., chloride, ketone, ether, and carboxylic acid) that remained intact using our mild protocol. Recently, it was found that fenofibric acid could reduce Covid-19 infections by up to 70%. Coupled with its extensive history of clinical use and relatively good safety profile, fenofibric acid derivatives could be used as potential therapeutic agents to treat SARS-CoV-2 infection.[17] A similar outcome was observed in the

reaction with nimesulide (**2dd**), a nonsteroidal anti-inflammatory drug repurposed for Covid-19 infection treatment,[18] which was converted to the corresponding product in 92% isolated yield. These examples further validate our trifluoromethylthiolation protocol as suitable for the late-stage, protecting-group-free modification of bioactive molecules. The robustness and scalability of this protocol were further evaluated using 1 mmol of aryl iodide **1aa** (430 mg) and a lesser amount of gold pre-catalyst (2.5 mol%). The corresponding product **2aa** was obtained in excellent yield (92%) without demanding precautions, albeit a longer reaction time of 6 h was necessary.

Table 2. Substrates scope of trifluoromethylthiolation of aryl Halides[a,b]

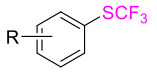


1
0.2 mmol

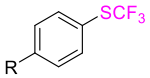
1.05 eq

2a-2y, **2aa-2dd**

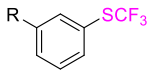
Aryl iodides with various functionalities:



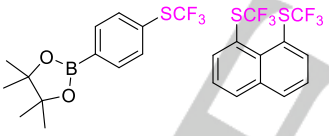
2a, R = H, 1 h, 61% (95%)[c]
2b, R = 4-MeO, 1.5 h, 92% (96%)[c]
2c, R = 3-MeO, 1.5 h, 90% (95%)[c]
2d, R = 2-MeO, 1.5 h, 79% (82%)[c]
2e, R = 4-F, 7 h, (91%)[c]
2f, R = 4-Cl, 4 h, 87% (91%)[c]
2g, R = 4-Br, 4 h, 91% (97%)[c]



2h, R = t-Bu, 0.75 h, 92% (96%)[c]
2i, R = Ph, 2 h, 93%
2j, R = Acetyl, 3 h, 91% (97%)[c]
2k, R = CHO, 1.5 h, 90% (100%)[c]
2l, R = NO_2, 24 h, 67%
2m, R = CN, 24 h, 85% (100%)[c]
2n, R = OCF_3, 8 h, 62% (93%)[c]
2o, R = CF_3, 2 h, (100%)[c]



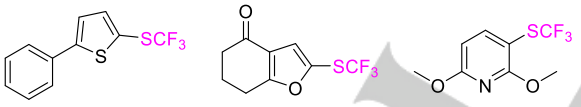
2p, R = COOMe, 4 h, 87% (93%)[c]
2q, R = NH_2, 19 h, 80% (86%)[c]
2r, R = OH, 1 h, 92% (98%)[c]
2s, R = COOH, 10 h, 93% (100%)[c]
2t, R = OTf, 19 h, 87% (99%)[c]



2u, 6 h,90% (100%)[c]

2v, 1 h, 92%[d]

Heteroaryl iodides :

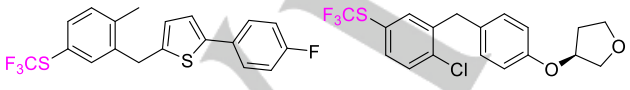


2w, 2 h, 96%

2x, 3 h, 95%

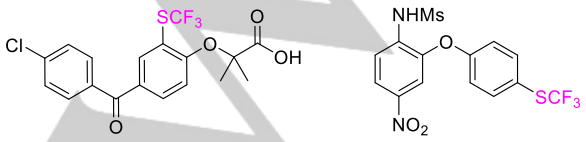
2y, 1.5 h, 86%

late-stage modification of bioactive molecules:



Canagliflozin intermediate
2aa, 1 h, 93%[e]

Empagliflozin intermediate
2bb, 6 h,92%



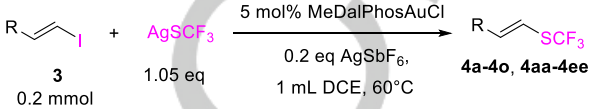
From Fenofibric acid
2cc, 2 h, 95%

From nimesulide
2dd, 1 h, 92%

[a]Reaction conditions: Unless otherwise noted, reactions were conducted as follows: An 8-mL reaction vial was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv) and 1 mL DCE. Aryl iodide **1** (0.2 mmol) was added and the resulting mixture was stirred at rt for 1 min. $AgSbF_6$ (0.2 equiv) was then added and the reaction was stirred at rt for 1 min before stirring at 70 °C; [b]Isolated yields; [c]NMR yields in parenthesis with benzotrifluoride as an internal standard; [d]10 mol% MeDalPhosAuCl, 0.4 equiv of $AgSbF_6$, and 2.1 equiv of $AgSCF_3$ was applied; [e] 92% isolated yield was obtained when 1 mmol **1aa**, 2.5 mol% MeDalPhosAuCl, 0.2 equiv of $AgSbF_6$, 1.05 equiv of $AgSCF_3$ and 5 mL DCE was applied.

Few methods have been reported for the reaction with vinyl halides.[19] Our protocol converted a variety of vinyl iodides into vinyl trifluoromethyl thioethers at low reaction temperature (Table 3).

Table 3. Substrates scope of trifluoromethylthiolation of vinyl halides[a,b]

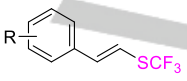


3
0.2 mmol

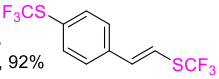
1.05 eq

4a-4o, **4aa-4ee**

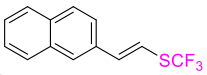
Vinyl idodide with various functionalities:



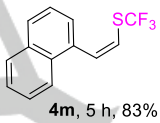
4a, R = H, 15 min, 80%
4b, R = 4-Me, 15 min, 83%
4c, R = 3,5-di-*t*-Bu, 30 min, 92%
4d, R = 4-F, 1 h, 87%
4e, R = 4-Cl, 30 min, 90%
4f, R = 2-Br, 30 min, 95%
4g, R = 3-Br, 30 min, 97%
4h, R = 4-CN, 45 min, 94%
4i, R = 4-COOMe, 1 h, 93%
4j, R = 4-OCF_3, 30 min, 90%



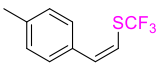
4k, 2 h, 79%[c]



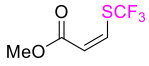
4l, 3 h, 88%



4m, 5 h, 83%

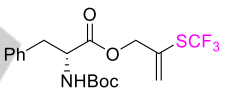


4n, 1 h, 85%

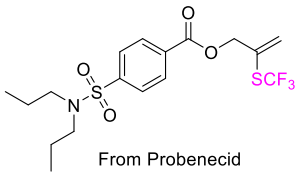


4o, 30 min, 98 %[b]

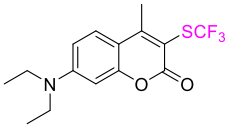
Late-stage modification of bioactive molecules:



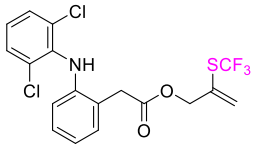
From Boc-D-phenylalanine
4aa, 18 h, 85%



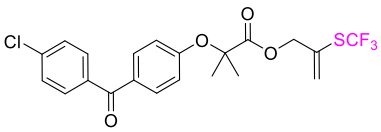
From Probenecid
4bb, 15 h, 91%



From Coumarin 1
4cc, 8 h, 86%



From Diclofenac
4dd, 24 h, 64%



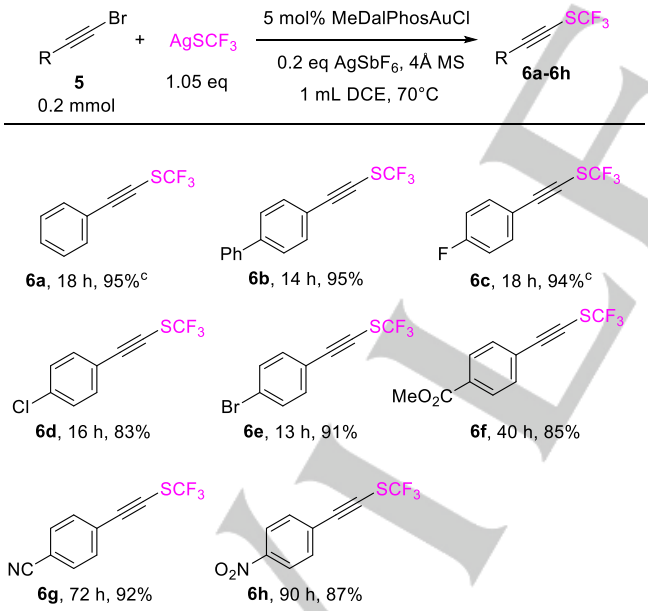
From Fenofibric acid
4ee, 12 h, 89%

[a]Reaction conditions: Unless otherwise noted, reactions were conducted as follows: An 8-mL reaction vial was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv) and 1 mL DCE. Vinyl iodide **3** (0.2 mmol) was added, and the resulting mixture was stirred at rt for 1 min. $AgSbF_6$ (0.2 equiv) was then added and the reaction was stirred at rt for 1 min before stirring at 60 °C; [b]Isolated yields; [c]NMR yields in parenthesis with benzotrifluoride as an internal standard; [d]10 mol% MeDalPhosAuCl, 0.4 equiv of $AgSbF_6$, and 2.1 equiv of $AgSCF_3$ was applied.

As in the case of the trifluoromethylthiolation of aryl iodides, the reaction conditions tolerated various functional groups, such as vinyl halides (**4d-4g, 4ee**), nitrile (**4h**), esters (**4i, 4o**, **4aa-4ee**), amides (**4aa**, **4bb**), amines (**4cc**, **4dd**) ether (**4ee**) and

trifluoromethoxyl ether (**4j**). Both electron-withdrawing/-donating substituents and their position on the aromatic ring of styrenyl iodides did not influence the reaction outcome. Various alkyl (**4o**, **4aa**-**4ee**), and aryl (**4a**-**4n**), di- (**4a**-**4n**, **4aa**, **4bb**, **4dd**, **4ee**), and tetrasubstituted (**4cc**) vinyl iodides all gave the corresponding products in excellent yields, without affecting the initial Z/E isomer ratio. The complete retention of the olefin geometry suggests that the reaction proceeds via an oxidative addition–reductive elimination pathway. Both internal (**4aa**-**4ee**) and terminal (**4a**-**4o**) vinyl iodides, either in *cis*- or *trans*- configuration (**4m** vs. **4l**), worked very well. An extended reaction time was necessary when working with internal vinyl iodides, probably because of the steric effect in the oxidative addition step (**4aa**-**4ee**). It was remarkable that double trifluoromethylthiolation took place in high yield when aryl and vinyl iodides appeared in the same molecule (**4k**). We next tested our protocol with a vinyl iodide-containing bioactive molecule. These reactions gave the corresponding vinyl trifluoromethylthioethers in good to excellent isolated yields (**4aa**-**4ee**). For instance, we obtained the trifluoromethylthiolated probenecid (**4bb**) in a 91% isolated yield. Probenecid is a prototypical uricosuric agent used to treat patients with renal impairment. On the other hand, a diclofenac tethered vinyl iodide was converted to the corresponding product in 64% yield. Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat mild-to-moderate pain and helps to relieve symptoms of arthritis. A fenofibric acid-tethered vinyl iodide was smoothly converted to the trifluoromethylthiolated fenofibrate derivative in 89% isolated yield. All together, those examples demonstrated the robustness and efficiency of our protocol.

Table 4. Substrates scope of trifluoromethylthiolation of alkynyl halides[a,b]

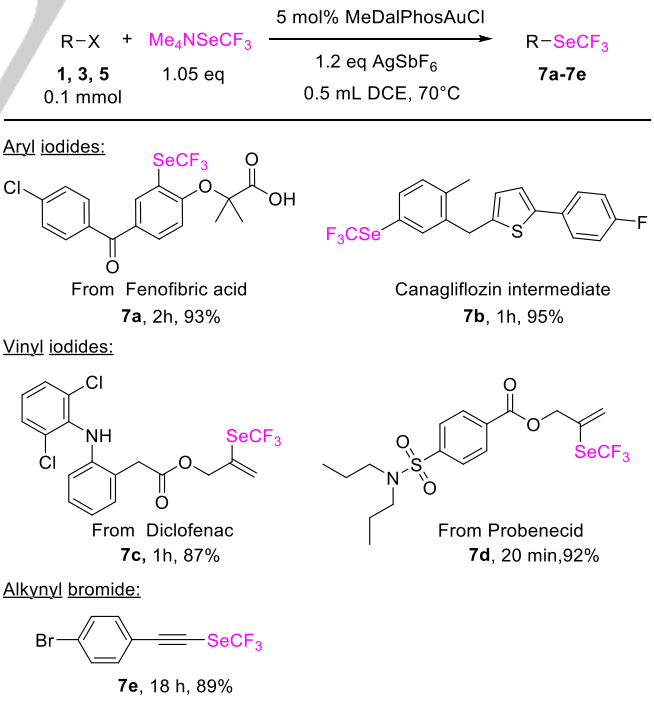


[a]Reaction conditions: Unless otherwise noted, reactions were conducted as follows: An 8-mL reaction vial was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv), 4 Å molecular sieves (20 mg), and 1 mL DCE. Alkynyl bromide **5** (0.2 mmol) was added, and the resulting mixture was stirred at rt for 1 min. $AgSbF_6$ (0.2 equiv) was then added and the reaction was stirred at rt for 1 min before stirring at 60 °C; [b]Isolated yields; [c]NMR yields in parenthesis with benzotrifluoride as an internal standard.

Our protocol also works with alkynyl halides. We initially tried alkynyl iodide but found a low yield of the trifluoromethylthiolation product. Instead, homocoupling was the main reaction. However, alkynyl bromides gave satisfactory results with our modified protocol after adding molecular sieves to the reaction to avoid the hydration side reaction. As displayed in Table 4, various substituted phenyl acetylene iodides were examined, and all of them gave good yields. Different functional groups like halides (**6c**-**6e**), ester (**6f**), nitrile (**6g**), and nitro (**6h**) were well-tolerated. The reaction was significantly affected by the substituent electronics of the phenyl ring. Substrates with electron-withdrawing functionalities needed significantly extended reaction times (**6f**, **6g**, **6h**).

Trifluoromethylselenide (−$SeCF_3$) represents a fluorinated variant that has been actively studied due to its similar properties with the trifluoromethylthioether group (-SCF_3).[5c, 6d] But trifluoromethylselenides are relatively scarce, probably because of the limited synthetic options available. In this context, we were delighted to observe an efficient trifluoromethylselenolation with the above three categories of halides (aryl, alkenyl and alkynyl). We first examined our protocol using $AgSeCF_3$ as the trifluoromethylselenating reagent. However, the trifluoromethylselenolation reaction with 4-*tert*-butylphenyl iodide gave poor conversion. However, when 1.05 equivalent of Me_4NSeCF_3 was employed instead of $AgSeCF_3$ and 1.2 equivalent of $AgSbF_6$ was utilized as the silver activator, the same reaction showed complete conversion (see SI for more details). To demonstrate the practicality of this method, we selected several drug molecule substrates equipped with an aryl iodide moiety (**7a**, **7b**) or tethered to a vinyl iodide (**7c**, **7d**) (Table 5). All the reactions worked very well with excellent isolated yields. The new protocol also worked with alkynyl bromide, delivering the corresponding trifluoromethylselenide in an excellent yield (**7e**). This broad spectrum application by just one catalyst has never been reported with other transition-metal catalysts.

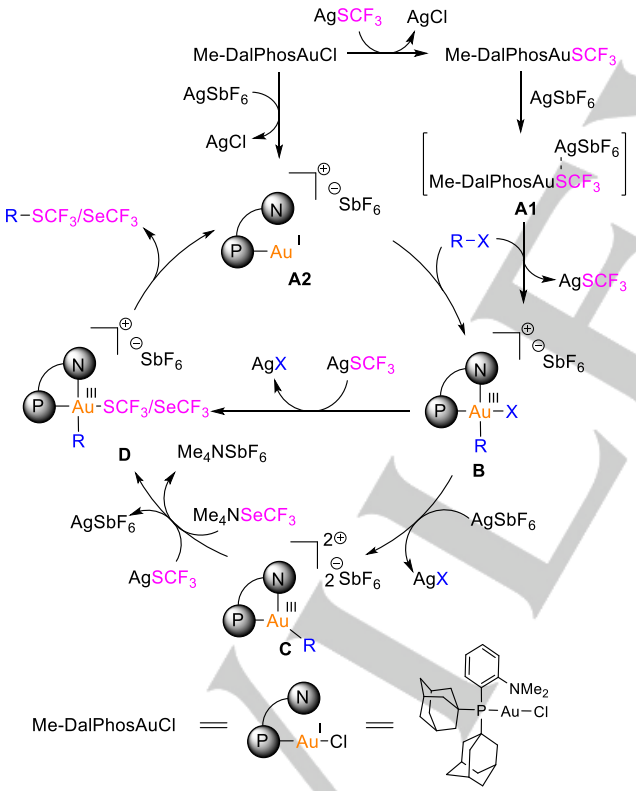
Table 5. Substrates scope of trifluoromethylselenolation of aryl/alkenyl/alkynyl Halides[a,b]



[a]Reaction conditions: Unless otherwise noted, reactions were conducted as follows: A 8-mL reaction vial was loaded with MeDalPhosAuCl (5 mol%), Me_4NSCF_3 (1.05 equiv), and 0.5 mL DCE. Organohalide (0.2 mmol) was added, and the resulting mixture was stirred at rt for 1 min. $AgSbF_6$ (1.2 equiv) was then

added, and the reaction was stirred at rt for 1 min before stirring at 70 °C; [b]Isolated yields;

Based on previous reports on MeDalPhos-enabled gold-catalyzed C−X cross-coupling[1-12, 20] and other transition metal-catalyzed trifluoromethylthiolation mechanisms[5a, 7a, 21], we proposed the reaction mechanism displayed in Scheme 2. Firstly, MeDalPhosAuCl is activated by $AgSCF_3$ to generate the MeDalPhosAuSCF$_3$, as verified by ^{31}P and ^{19}F NMR (see SI for more details). This intermediate is too inert and has to be activated by $AgSbF_6$ (see SI for more details) to form the active intermediate **A1** for the oxidative addition with organohalides, which then forms the Au(III) intermediate **B** with the aryl/vinyl/alkynyl group *trans* to the nitrogen.[11] Next, the intermediate **B** undergoes transmetalation with $AgSCF_3$ to deliver the intermediate **D**, which then undergoes reductive elimination to furnish the C−SCF$_3$ bond formation, regenerating the Au(I) intermediate **A2** for the next catalytic cycle. The intermediate **B** could also undergo another halide abstraction with $AgSbF_6$ and deliver a more electrophilic Au(III) species **C**, which then reacts with $AgSCF_3$ or Me_4NSeCF_3 to form the intermediate **D**. This scenario is especially true for the trifluoromethylselenolation reaction in which the cationic Au(I) intermediate **A2**, instead of **A1**, is generated from the halide abstraction of MeDalPhosAuCl by $AgSbF_6$.



Scheme 2. Plausible mechanism for the Au(I)/Au(III)-catalyzed C-SCF$_3$ /SeCF$_3$ cross-coupling reactions.

The following NMR studies also substantiated the putative catalytic cycle. First, 1-iodo-4-trifluoromethoxybenzene was added to the preformed MeDalPhosAuSCF$_3$ solution in CD_2Cl_2 at room temperature. We found that no reaction happened even when the reaction temperature was raised to 70 °C and the reaction time was extended to 17 hours. However, the subsequent addition of the $AgSbF_6$ to the reaction mixture at room temperature gave a 3% yield of product and 6% of intermediate **B**, but 76% of the iodide starting material remained. Meanwhile. the MeDalPhosAuSCF$_3$ signal in F-NMR disappeared, and two new peaks appeared. Merely heating the reaction to 70 °C converted intermediate **B** and all the remaining starting material to the product in 70% NMR yield after 1 hour (see SI for more details).

Conclusion

In conclusion, we have developed the first gold-catalyzed C−SCF$_3$/SeCF$_3$ cross-coupling reaction. The generality of this protocol facilitates an efficient 'one-stop shop' synthesis of a diverse array of C−SCF$_3$/SeCF$_3$ cross-coupled products. This synthetic protocol is characterized by a broad functional group compatibility, mild reaction conditions, simple procedure, and overall excellent yields. The scalability and robustness of this reaction, as demonstrated by the late-stage functionalization of bioactive molecules, proves that our method is a competitive alternative to the synthesis of trifluoromethylthio- and selenoethers, which may stimulate further applications in pharmaceutical and agrochemical research and development.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cross-coupling, gold catalysis, organohalides, trifluoromethylthiolation, trifluoromethylselenolation

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RESEARCH ARTICLE

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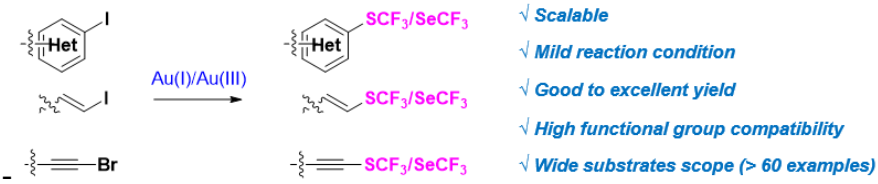

The first gold(I/III)-catalyzed direct trifluoromethylthiolation and trifluoromethylselenolation of organohalides is reported. This mild and efficient protocol enjoys a broad substrate scope and high yield(> 60 examples with up to 97% isolated yield). Its robustness was demonstrtated by the late-stage functionalization of various bioactive molecules, which makes this reaction applicable to pharmaceutical and agrochemical research and development.