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Title: Direct Trifluoromethyl- and Fluoroalkylselenolations of Alkynyl Copper (I) compounds.

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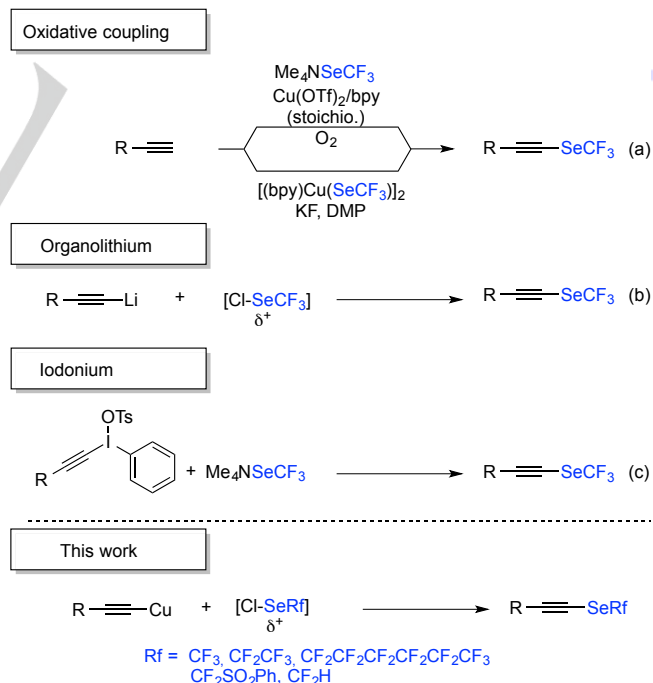
Clément Ghiazza^[a], Thierry Billard^[a,b], Anis Tlili^{*[a]}

Abstract: The successful perfluoroalkylselenolation of alkynyl copper (I) compounds is described herein. The reaction occurs under oxidant free conditions at room temperature. This convenient one-pot procedure is based on the *in-situ* generation of trifluoromethylselenenyl chlorides. The developed system shows high functional group tolerance and also promotes the employment of fluoroalkyl derivatives.

The introduction of fluorine or fluorine-containing groups into organic molecules has gained considerable importance over the last years. Especially the newly gained properties of such molecules have fostered developments in their synthesis.^[1] Consequently, it is not surprising today that fluorinated molecules are finding a plethora of applications in all areas of life science.^[2] Especially in drug discovery fluorination has become an essential tool as it can be associated with a variety of dramatic effects on a molecule's properties such as better lipophilicity, higher selectivity, increased efficacy or easier administration.^[1d] In this context, the development of trifluoromethylthiolating reagents has attracted much attention in order to access a large panel of trifluoromethylthiolated compounds (Hansch-Leo parameter, $\pi_R = 1.44$).^[3] Motivated by their advantageous, the introduction of other trifluoromethyl chalcogen groups has gained interest recently.^[4] This includes the trifluoromethylselenenyl group which possesses a high Hansch-Leo parameter ($\pi_R = 1.29$).^[5]

From a retrosynthetic perspective, the direct introduction of SeCF_3 group is the more elegant approach. From this point of view, several methodologies have been developed using σ -bonded copper trifluoromethylselenenyl^[6] or ammonium trifluoromethylselenenyl salts^[7] as a nucleophilic trifluoromethylselenenyl source. In complementarity, we recently revisited the use of trifluoromethylselenenyl chlorides as an electrophilic source. It is noteworthy that the key of success here is the *in-situ* generation of this volatile electrophilic reagent. After observing general activity with this reagent in aromatic electrophilic substitution^[8] as well as in the presence of organomagnesium or organolithium compounds,^[5] we attempted to evaluate its reactivity towards the formation of $\text{C}(\text{sp})\text{-SeCF}_3$ bonds. Regarding the state of the art for the direct

trifluoromethylselenolation of terminal alkynes, few reports have been disclosed recently. The group of Rueping^[9] reported an oxidative coupling in the presence of stoichiometric amounts of copper/ligand (copper(II)triflate/2,2'-bipyridine) in conjunction with tetramethylammonium trifluoromethylselenate. Interestingly, molecular oxygen was used as oxidant (Scheme 1, a). Moreover the group of You and Weng reported a discrete copper trifluoromethylselenenyl complex $[(\text{bpy})\text{Cu}(\text{SeCF}_3)_2]$ able to promote the trifluoromethylselenolation of terminal alkynes.^[10] Herein the presence of potassium fluoride as base (5 equiv.) as well as DMP (Dess-Martin periodinane, more than 3 equiv.) are primordial (Scheme 1, a). Furthermore, our group demonstrated that lithiated terminal alkynes undergo trifluoromethylselenolation at -78°C . Even though high yields have been obtained, a limitation in the reaction scope has been observed (Scheme 1, b). It should be mentioned also that alkynyl trifluoromethyl selenide can be obtained *via* the direct trifluoromethylselenolation of alkynyl(phenyl) iodoniums using tetramethylammonium trifluoromethylselenate. However, the pre-synthesis of the iodonium starting material is major drawback (Scheme 1, c).^[11]



Scheme 1. State of the art of the trifluoromethylselenolation of alkynes

With our continuous interest to develop and discover new methodologies,^[12] we report herein a new approach for the $\text{C}(\text{sp})\text{-SeCF}_3$ bond formation based on the employment of

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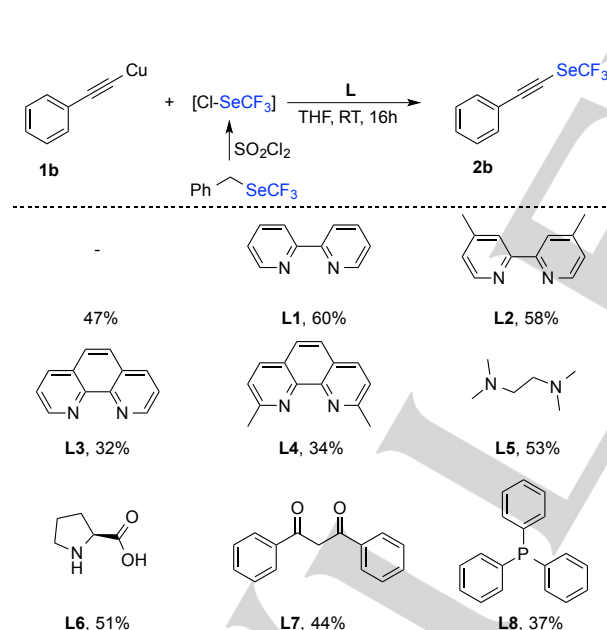
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alkynyl copper compounds.^[13] The developed methodology reveal a large substrate scope and encompass selenyldifluoromethyl moieties (SeCF_2H , $\text{SeCF}_2\text{SO}_2\text{Ph}$) as well as higher fluorinated homologues. The key point is the *in-situ* generation of perfluoroalkylselenenyl chloride.

Initial investigation focused on the identification of the best catalyst system. By employing (phenylethynyl) copper without any additional ligand the desired product was obtained in 47% yield. In order to improve the reaction we decided to test ancillary ligands that are commonly used in copper catalyzed cross-coupling reactions.^[13] In this context we investigated 4 different known families of ligand. (Scheme 2) Starting with amines, by adding 1 equivalent of bipyridine (bpy, **L1**) the desired product was formed in higher yield of 60%. No further improvement was observed when 4,4'-Dimethyl-2,2'-dipyridyl was used (**L2**) since only 58% was achieved. 1,10-phenanthroline derivatives (**L3** and **L4**) were not suitable since less than 34% of the desired product was formed. TMEDA also was less efficient than **L1** and only 53% was observed. The use of L-proline, dibenzoylmethane as well as triphenylphosphine demonstrated obviously the presence of new species in fluorine NMR. We confirmed the α -trifluoromethylselenenol of **L7** with less than 10% yield.^[14]

Scheme 2. Ligand optimisation for the trifluoromethylselenenol of (phenylethynyl) copper



^[a] Reactions were performed with BnSeCF_3 (0.3 mmol, 1 equiv.), SO_2Cl_2 (0.3 mmol, 1 equiv.) and dry DMF (1 mL). The reaction mixture was stirred for 5 hours at room temperature. The mixture was added to another schlenk tube containing alkynyl copper (I) (0.3 mmol), L (0.3 mmol). Yields determined by ^{19}F NMR spectroscopy with PhOCF_3 as an internal standard.

Attempts to improve the reaction outcome we turned our attention to study further the different parameters (Table 1). While the desired product was obtained in 60% yield in the presence of **L1** after 16h (Entry 1). The yield could be further increased to 81% by extending the reaction time (Entry 2). Afterwards, several solvents have been examined including DCM (Entry 4), CH_3CN (Entry 5), 1,4-dioxane (Entry 6). Only low

conversions and yields have been observed. The use of DMSO was deleterious to the reaction outcome since only 3% of the product was observed. DMF furnished the product in slightly better yield of 64 % (Entry 8). The product could be formed in 80 % with a slight excess of the trifluoromethylselenenolating reagent (Entry 10). Finally, once again the background reaction in absence of any additional ligand demonstrated lower product formation (Entry 11).

With the best condition in hand (Entry 10), we turned our attention to study the scope and limitation of the reaction with a particular focuses of studying different functional groups as demonstrated in Scheme 3. In general, when aryl acetylene derivatives were evaluated, the reaction was tolerant to both electrons withdrawing or donating substituents and the desired products were obtained in moderate to excellent yields. Moreover, the reaction turns out to be tolerant also to aliphatic alkynyl derivatives with basically similar reactivity. In more detail, when ((3-hydroxyphenyl)ethynyl) copper was evaluated, we were glad to observe only the C-Se CF_3 bond formation (product **2a**) and no trifluoromethylselenenol of the free oxygen was detectable.

Table 1. Optimization of the reaction conditions for the trifluoromethylselenenol of (phenylethynyl)copper

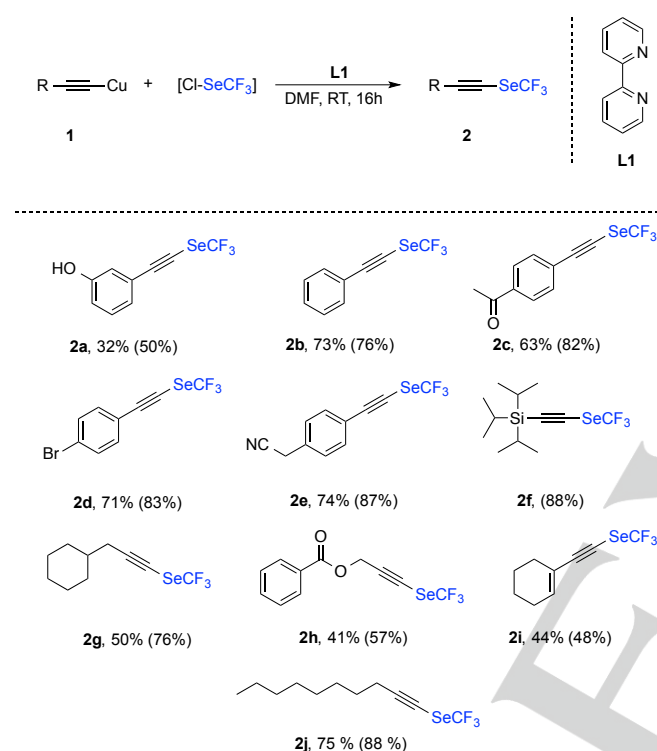
Entry	Deviation from standard conditions	Yield % ^[a]
1	None	60
2	Reaction time 64h	81
3	50 °C	65
4	DCM instead of THF	29
5	CH_3CN instead of THF	45
6	1,4-dioxane instead of THF	32
7	DMSO instead of THF	3
8	DMF instead of THF	64
9	1.1 equiv. of $[\text{Cl-SeCF}_3]$ in DMF	71
10	1.2 equiv. of $[\text{Cl-SeCF}_3]$ in DMF	80
11	No L1 in DMF with 1.2 equiv. of $[\text{Cl-SeCF}_3]$	65

^[a] Reactions were performed with BnSeCF_3 (0.3 mmol, 1 equiv.), SO_2Cl_2 (0.3 mmol, 1 equiv.) and dry DMF (1 mL) unless otherwise noted. The reaction mixture was stirred for 5 hours at room temperature. The mixture was added to another schlenk tube containing alkynyl copper (I) (0.3 mmol), L1 (0.3 mmol) and the reaction media was stirred for 16h at room temperature. Yields determined by ^{19}F NMR spectroscopy with PhOCF_3 as an internal standard.

In similar way, when the (phenylethynyl) copper substituted in *para* position with an acetyl group was evaluated, the desired product **2c** was obtained with an excellent yield of 82% (^{19}F NMR) with full selectivity. Furthermore, bromo as well as cyano containing starting materials were also tolerated under our reaction conditions, the desired product could be obtained in excellent yield (products **2d**, **2e**). Interestingly, the trifluoromethylselenenol of (triisopropylsilyl)acetylene copper occur with an excellent yield of 88% (product **2f**). Noteworthy,

the products **2d** and **2f** could be used in follow up reactions under transition metal catalysis. Finally, aliphatic alkynyl copper underwent trifluoromethylselenolation in moderate to excellent yields (**2g**, **2h**, **2i**, **2j**). More specifically, the ester derivatives **2h** is also tolerated and undergo selective trifluoromethylselenolation with good yield. Finally, this process is highly selective toward alkynes. Indeed, no addition of chlorotrifluoroselenyl to the double bond of product **2i** is detectable under this condition.

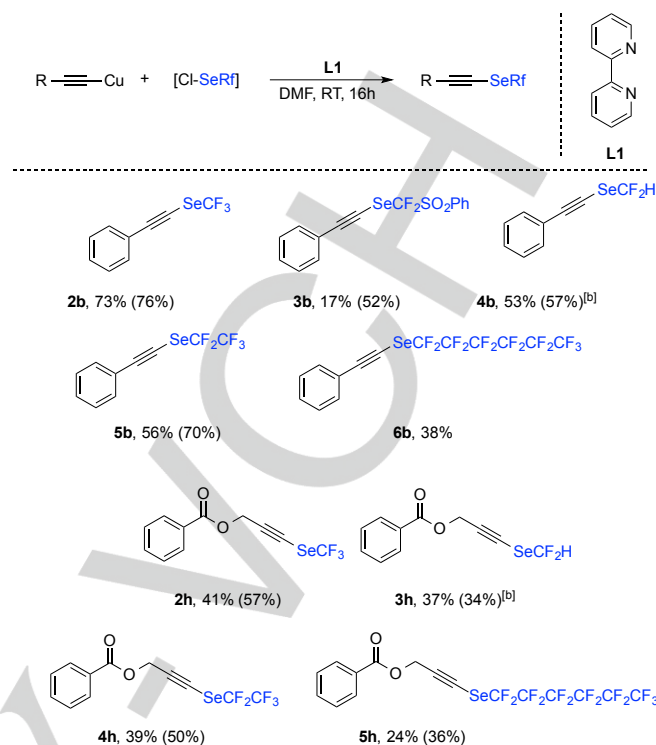
Scheme 3. Trifluoromethylselenolation of alkynyl copper compounds.^[a]



^[a] Reactions were performed with $BnSeCF_3$ (0.4 mmol, 1.2 equiv.), SO_2Cl_2 (0.4 mmol, 1.2 equiv.) and dry DMF (1 mL). The reaction mixture was stirred for 5 hours at room temperature. The mixture was added to another schlenk tube containing alkynyl copper (I) (0.33 mmol), **L1** (0.33 mmol). The reaction media was stirred for 16 h at room temperature. Yields shown are those of isolated products; yields determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard are shown in parentheses.

After observing general reactivity with aliphatic as well as aromatic alkynyl copper (I) derivatives, we turned our attention to evaluate for the first time the fluoroalkylselenolations of alkynyl copper derivatives (Scheme 4). We were glad to observe the incorporation of $SeCF_2SO_2Ph$ in satisfactory yield (52%, product **3b**). Noteworthy, easily follow up reactions could be easily be designed.^[12e] The challenging $SeCF_2H$ alkyne product was also obtained in good yield (57%, product **4b**). Moreover, the system turned to be tolerant to higher homologues and products **5b** and **6b** were obtained in moderate to good yield. Furthermore, the alkyne benzoate derivatives were also successfully employed and the corresponding desired product were obtained in low to good yields.

Scheme 4. Fluoroalkylselenolations of alkynyl copper compounds.^[a]



^[a] Reactions were performed with $BnSeCF_3$ (0.24 mmol, 1.2 equiv.), SO_2Cl_2 (0.24 mmol, 1.2 equiv.) and dry DMF (1 mL). The reaction mixture was stirred for 5 hours at room temperature. The mixture was added to another schlenk tube containing alkynyl copper (I) (0.2 mmol), **L1** (0.2 mmol) and the reaction media was stirred for 16 h at room temperature. Yields shown are those of isolated products; yields determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard are shown in parentheses. ^[b] Reactions performed in dry THF (1 mL).

In conclusion, we demonstrated herein that the direct trifluoromethylselenolation of alkynes could be successfully promoted by making use of alkynyl copper (I) compounds. The system shows high functional group tolerance in comparison with the reported systems and the desired product were obtained in good yields. Moreover, aliphatic as well as aromatic alkynes were effective under our reaction conditions. Furthermore, we demonstrated that the procedure could be extended to fluoroalkyl derivatives. The evaluation of other nucleophile as well as catalytic version of such transformation is under way and will be reported in due course.

Experimental Section

Typical procedure: Synthesis of {2-[(trifluoromethyl)selenanyl]ethynyl}benzene **2b**: to a flame-dried-flask equipped with a magnetic stirrer are added $BnSeCF_3$ (0.4 mmol, 1.2 equiv.), SO_2Cl_2 (0.4 mmol, 1.2 equiv.) and dry DMF (1 mL). The reaction mixture was stirred for 5 hours at room temperature under nitrogen. The mixture was added to another flame-dried-flask containing phenylacetylene copper (I) (0.33 mmol, 1 equiv.), **L1** (0.33 mmol, 1 equiv.) and the reaction media was stirred for 16 h at room temperature under nitrogen.

Conversion is checked by ^{19}F NMR with PhOCF_3 as internal standard. The reaction mixture is partitioned between DCM and water. The aqueous layer is extracted with DCM and the combined organic layers are washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The crude residue is purified by flash chromatography to afford the desired product ^1H NMR (300 MHz, CDCl_3) δ = 7.49 (m, 2H), 7.39–7.33 (m, 3H). ^{19}F NMR (282 MHz, CDCl_3) δ = -36.14 (s, 3F).

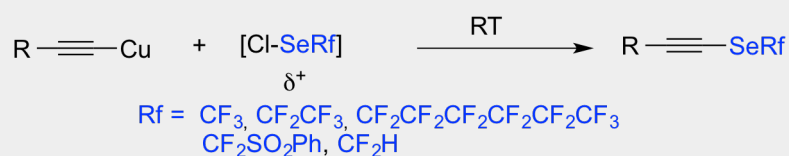
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Keywords: Copper • Trifluoromethylselenolation • Alkynes • Fluorine • Selenium

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The successful fluoroalkylselenolation of alkynyl copper (I) is described herein. The system shows high functional group tolerance and the applicability of the procedure is extended to various fluoroalkyl derivatives. This convenient one-pot procedure occurs under oxidant free conditions at room temperature.