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Vinylic Trifluoromethylselenolation via Pd-Catalyzed C–H Activation

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Abstract: Trifluorometylselenolation via C–H activation is barely described in literature. In particular, no such vinylic functionalization has been yet described. Herein, a palladium-catalyzed trifluoromethylselenolation of vinylic C–H bonds is described. The 5-methoxy-8-aminoquinoline has been used as auxiliary directing group to perform this reaction. The reaction gives excellent yields with α-substituted compounds whatever the substituents and a microwave activation can be used to accelerate the reaction. With β-substituted substrates lower yields, but still satisfactory, are obtained. This methodology was also successfully extended to other fluoroalkylselenyl groups.

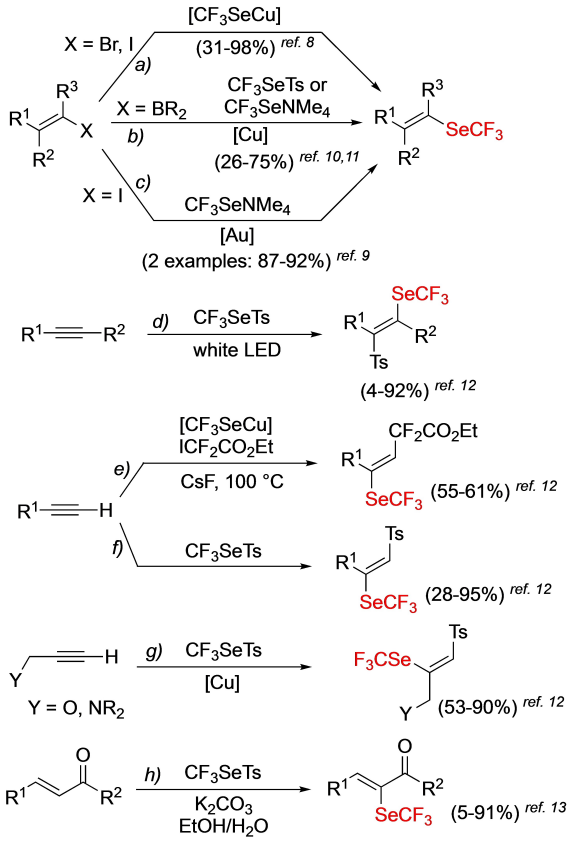
Introduction

Because of the intrinsic properties of the fluorine atom,[1] fluorinated compounds have gained momentum these last decades. Thus, molecules bearing fluoro-substituents are present in a large panel of applications, due to the specific properties brought by fluorinated moieties.[2] In order to tune such physico-chemical characteristics, the development of new emerging fluorinated groups has been very active these last years.[3] In this area, the association of fluoroalkyl moieties with chalcogens has been more specifically studied, partly due to the high lipophilicity of these groups.[3–4]

Although selenylated molecules find applications in various fields from materials to life sciences,[5] the chemistry of CF_3Se group remains still underdeveloped. However, its high lipophilicity (Hansch-Leo parameter $\pi_R = 1{,}61$)[4c] could be of high interest, in particular in medicinal chemistry. Indeed, some trifluoromethylselenolated molecules have recently shown promising results as potential anticancer agents.[6]

Consequently, methods to synthesize trifluoromethylselenolated molecules are still highly required to favor their development.[7] Vinylic compounds bearing a CF_3Se constitute original and useful fluorinated building-blocks. Nevertheless, synthetic methods to obtain such substrates remains limited (Scheme 1).[7a]

Coupling reactions of vinylic bromides or iodides have been described by using CF_3SeCu species, but these reactions require



Scheme 1. Previous syntheses of CF_3Se-vinyl products.

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stoichiometric amount of metal and the fastidious preliminary preparation of the starting material (Scheme 1a).[8] A gold-catalyzed coupling between two vinyl iodides and CF_3SeNMe_4 reagent, which is sensitive and synthesized under drastic conditions, has also been performed (Scheme 1c).[9] Few couplings with vinyl-boronic substrates have also been described either with CF_3SeNMe_4 reagent[10] or with CF_3SeTs reagent but only on very few examples (Scheme 1b).[11] Furthermore, this method also requires the prior synthesis of boronic derivatives. Radical, electrophilic or copper-mediated additions onto alkynes have been also performed, but in this case, another group is concomitantly added (e.g. Ts or CF_2CO_2Et) (Scheme 1e–g).[12] Finally, Morita-Baylis-Hillman like reactions between enones and CF_3SeTs have been described with medium yields (Scheme 1 h).[13]

In view of these previous works, a direct trifluoromethylselenolation of non-prefunctionalized olefins is still required to easily obtain CF_3Se-vinylic compounds.

Results and Discussion

These last years, direct functionalization through transition metal-catalyzed C–H activation has known a rapid infatuation to become a standard reaction which is now well-documented.[14] Nevertheless, despite the efficiency of such reactions, their applications have remained unexploited in CF_3Se chemistry, until recently.[7e]

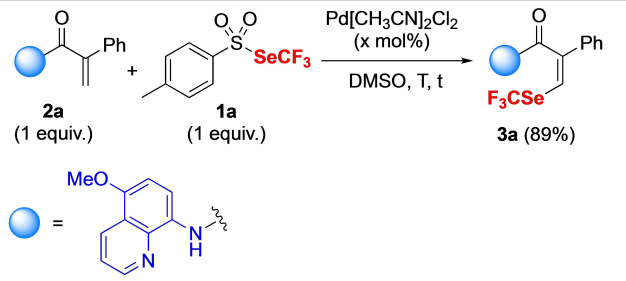
As trifluoromethyl toueneselenosulfonate (**1 a**) has proven its high efficiency to perform various trifluoromethylselenolation reactions,[15] we have lately described its use in metal-catalyzed C–H functionalization of aromatic compounds, with good results.[16] In this previous work, the 5-methoxy-8-aminoquinoline turned out to be the most efficient directing group, the methoxy substituent preventing the trifluoromethylselenolation of the 5-position of the quinoline core. The better catalyst was determined as $Pd[CH_3CN]_2Cl_2$ (20 mol%) at 70 °C in DMSO.

Buoyed by this first successful result, we decided to extend this aromatic C–H functionalization to vinylic substrates. To this end, conditions elaborated in aromatic series were firstly applied to acrylamide **2 a** as model substrate (Table 1, entry 1).[16] The observed result was already good, but in order to try to optimize the reaction, further reaction conditions were then screened (Table 1).

Decreasing the reaction time from 24 h to 16 h (entries 1–2) did not affect the yield. Interestingly, only 10 mol% of Pd catalyst appeared to be sufficient (entry 3), but with 5 mol%, a lower yield was observed (entry 6) which was not increased with higher temperature (entry 7). A shorter reaction led to a moderate yield (entry 4). Similarly, heating to only 50 °C was less favorable for the reaction (entry 5). Finally, it was controlled that Pd catalyst was crucial for the reaction (entry 8). Thus, the optimal conditions were 10 mol% of Pd catalyst, at 70 °C, for 16 h (entry 3).

In order to increase the kinetic of the reaction, microwave activation was also considered (entries 9–11). Using optimal

Table 1. Reaction conditions for C–H trifluoromethylselenolation of **2 a**.



Entry	$Pd[CH_3CN]_2Cl_2$ [mol%]	T [°C]	t [h]	**3 a** [%][a]
1	20	70	24	89
2	20	70	16	93
3	10	70	16	97
4	10	70	3	65
5	10	50	16	63
6	5	70	16	61
7	5	100	16	61[b]
8	0	70	16	0
9	10	70 (μW)[c]	2	73
10	10	100 (μW)[c]	1	99
11	5	100 (μW)[c]	1	56

Conditions: CF_3SeTs (**1 a**, 0.2 mmol), **2 a** (0.2 mmol), $Pd[CH_3CN]_2Cl_2$ (x mol%), anhydrous DMSO (2 mL, 0.1 M). [a] Determined by ^{19}F NMR with $PhOCF_3$ as internal standard. [b] Minor fluorinated by-products observed by ^{19}F NMR. [c] μW: microwave.

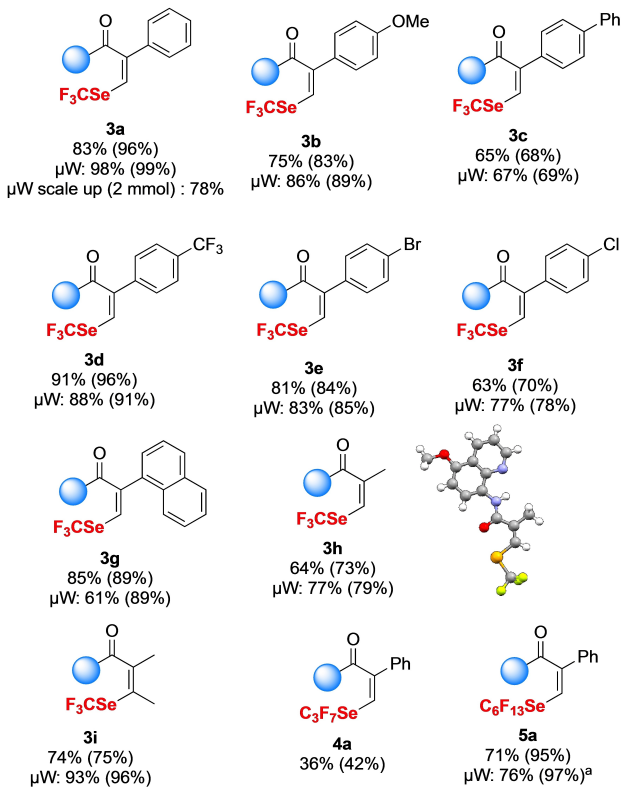
conditions previously determined, a good yield was obtained in only 2 h (entry 9). The same yield than with conventional heating was achieved at 100 °C in only 1 h (entry 10). With only 5 mol% of Pd catalyst, the yield remained modest (entry 11).

With these conditions in hand (Table 1, entries 3 or 10), the scope of the reaction was screened (Scheme 2).

Generally, the reaction led to good yields. With arenes in α-position, no significative effect was observed regardless of the aromatic substituents (electron-donor or -acceptor) (**3 a**–**g**). The chloro or bromo groups were not affected by the reaction conditions and remained unaffected during the C–H trifluoromethylselenolation (**3 e**–**f**). With alkyl substituents on the double bond, the yields remained good with mono- or bis-substituted substrates (**3 h**–**i**). In case of **3 i**, the obtained result is even excellent compared to the analogous trifluoromethylthiolation reaction.[17] Similar results were observed with standard heating or under microwave irradiation, the only difference being the reaction time (16 h vs. 1 h). The reaction was also scaled up to 2 mmol scale, under microwave irradiation, with similar yield and no observed degradations (**3 a**). Concerning the stereochemistry, only the Z products were obtained as shown by the X-ray structure of **3 h**.

The same conditions were also successfully extended to perfluoroalkylselenolations, as illustrated with heptafluoropropylselenolated (**4 a**) and tridecafluorohexylselenolated (**5 a**) compounds which were obtained in modest to good yields.

Because product **3 i**, bearing substituents both in α- and β-positions, has been obtained with excellent yield, we decided to explore the C–H trifluoromethylselenolation of β-substituted acrylamides, which have not been described for trifluoromethylthiolation.[17]



Scheme 2. Scope of C–H trifluoromethylselenolation. Isolated yields. In parentheses, yields determined by ^{19}F NMR with $PhOCF_3$ as internal standard. *Conditions*: CF_3SeTs (**1 a**, 0.2 mmol), **2** (0.2 mmol), $Pd[CH_3CN]_2Cl_2$ (10 mol%), anhydrous DMSO (2 mL, 0.1 M), 70 °C, 16 h or µW, 100 °C, 1 h. [a] 1 h30 instead of 1 h.

The reaction was then investigated with cinnamamide **6 a** as model substrate (Table 2).

With the previous conditions optimized for α-substituted substrates, only 12% of trifluoromethylselenolation was observed (entry 1). Longer reaction time did not significantly improve the reaction efficiency (entry 2). With 20 mol% of Pd catalyst, a doubling of the yield was observed (entry 3). Again, a longer time reaction did not bring a significant improvement (entry 4). However, the accurate control of the temperature was essential for the optimization of the process: while detrimental effects were observed at 115 °C and 130 °C (entries 6–7), we were pleased to see that product **3 a** was formed in 53% NMR yield at 100 °C (entry 5). Finally, a new increase of catalyst loading was not significantly beneficial (entry 8). Noteworthy, the use of $Pd(OAc)_2$ as catalyst or an excess of **1 a** led to similar results.

Because the microwave irradiation was beneficial, in term of kinetic, for the trifluoromethylselenolation of α-substituted substrates described above, such an activation was also considered with β-substituted compounds (Table 3).

As in conventional heating, accurate control of the temperature appeared to be fundamental (entries 1–3). Doubling of catalyst loading led to an increased, but still modest, yield (entry 5). Contrary to previous conditions (Table 2, entry 8), 30% of catalyst favored significantly the results (entries 7–8). Nevertheless, globally, microwave irradiation did not improve the kinetic of the reaction and even seemed deleterious to the reaction.

With the best conditions (Table 2, entry 5), the trifluoromethylselenolation of β-substituted substrates was investigated (Scheme 3).

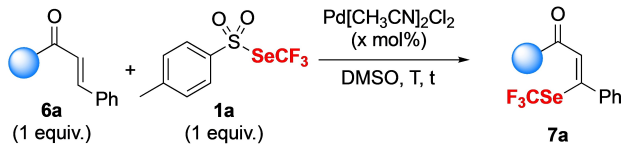
In the case of β-arylated substrates, satisfactory yields were observed, whatever the electronic character of substituents (**7 a**–**f**). Again, the reaction was also compatible with chloro substituent, which remained unaffected (**7 b**). Steric hindrance appeared to not have significative influence (**7 c**–**e**). Remarkably, the reaction conditions were also compatible with an aliphatic substituent in β-position, as exemplified by product **7 g**.

Concerning the stereochemistry, only the Z products were also obtained as shown by the X-ray structure of **7 f**.

In a mechanistic point of view, no further experiments have been conducted but a similar mechanism to that demonstrated in aromatic C–H functionalization could be envisaged, the formation of intermediate $CF_3SeSeCF_3$ being also observed in these reactions.[16]

Finally, a post-functionalization of **3 a** was performed. Thus, the methanolysis was successfully realized to provide the corresponding ester **8 a** (Scheme 4) with good yield. Such a

Table 2. Reaction conditions for C–H trifluoromethylselenolation of **6 a**.



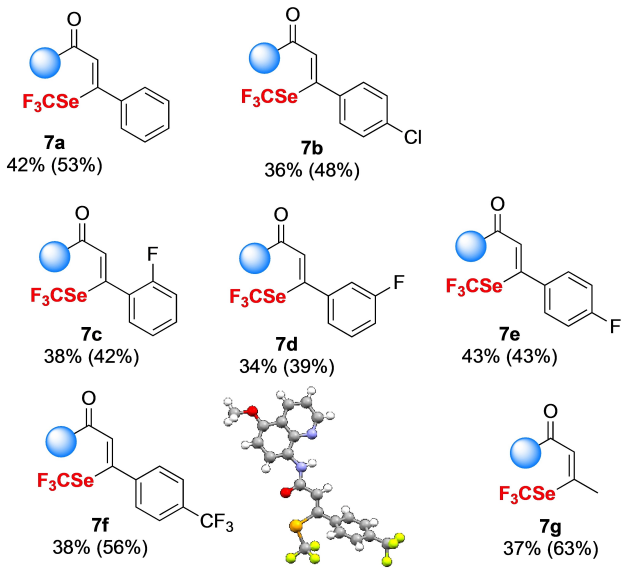
Entry	$Pd[CH_3CN]_2Cl_2$ [mol%]	T [°C]	t [h]	**7 a** [%][a]
1	10	70	16	12
2	10	70	24	13
3	20	70	24	27
4	20	70	72	32
5	20	100	24	53
6	20	115	24	41[b]
7	20	130	24	23[b]
8	30	100	24	57

Conditions: CF_3SeTs (**1 a**, 0.2 mmol), **6 a** (0.2 mmol), $Pd[CH_3CN]_2Cl_2$ (x mol%), anhydrous DMSO (2 mL, 0.1 M). [a] Determined by ^{19}F NMR with $PhOCF_3$ as internal standard. [b] Fluorinated by-products observed.

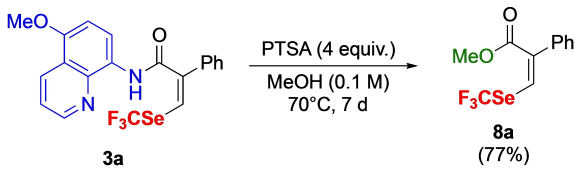
Table 3. C–H trifluoromethylselenolation of **6 a** under microwave activation.

Entry	$Pd[CH_3CN]_2Cl_2$ [mol%]	T [°C]	t [h]	**7 a** [%][a]
1	10	100	2	10
2	10	110	2	22
3	10	120	2	8
4	20	110	2.5	26
5	20	110	3	34
6	20	110	6	31
7	30	110	3	45
8	30	110	5	45

Conditions: CF_3SeTs (**1 a**, 0.2 mmol), **2 a** (0.2 mmol), $Pd[CH_3CN]_2Cl_2$ (x mol%), anhydrous DMSO (2 mL, 0.1 M). [a] Determined by ^{19}F NMR with $PhOCF_3$ as internal standard.



Scheme 3. Scope of C–H trifluoromethylselenolation of β-substituted compounds. Isolated yields. In parentheses, yields determined by ^{19}F NMR with $PhOCF_3$ as internal standard. *Conditions*: CF_3SeTs (**1 a**, 0.2 mmol), **6** (0.2 mmol), $Pd[CH_3CN]_2Cl_2$ (20 mol%), anhydrous DMSO (2 mL, 0.1 M), 100 °C, 24 h.



Scheme 4. Post-functionalization of **3 a**.

compound constitutes a pertinent building-blocks for further synthetic plans.

Conclusion

With this work, the C–H trifluoromethylselenolation of sp^2 carbon atoms, previously described in aromatic series, has been efficiently extended to vinylic substrates. The obtained results were satisfactory to excellent, whatever the substitution of the double bond. Such results will contribute to confirm the installation of the trifluoromethyl tolueneselenosulfonate (**1 a**) as an essential reagent for trifluoromethylselenolation, in general, and for C–H functionalization in particular. Furthermore, this method has been successfully extended to perfluoroalkylselenolation reactions. No doubt that this family of reagents should become a useful tool in the toolbox of emerging fluorinated groups.

Experimental Section

General procedure for the trifluoromethylselenolation of compounds α-substituted (2): To a 10 mL tube equipped with a magnetic stir bar were added $TsSeCF_3$ (**1 a**, 0.2 mmol, 1 equiv.), benzamide (**2**, 0.2 mmol, 1 equiv.) and $Pd[CH_3CN]_2Cl_2$ (0.02 mmol, 0.1 equiv.) in anhydrous DMSO (2 mL, 0.1 M). The tube was sealed, and the mixture was stirred at 70 °C for 16 h. Conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture was partitioned between DCM and water, the combined organic layers were washed with water then brine, dried over $MgSO_4$, filtered, and concentrated under moderate vacuum. The crude residue was then purified by flash chromatography to afford the desired product (**3**-**5**).

General procedure for the trifluoromethylselenolation of compounds α-substituted (2) under microwave irradiation: To a 10 mL microwave tube equipped with a magnetic stir bar were added $TsSeCF_3$ (**1 a**, 0.2 mmol, 1 equiv.), benzamide (**2**, 0.2 mmol, 1 equiv.) and $Pd[CH_3CN]_2Cl_2$ (0.02 mmol, 0.1 equiv.) in anhydrous DMSO (2 mL, 0.1 M). After stirring at room temperature, the mixture was subjected to microwave irradiation at 100 °C during 1 h. The mixture was then cooled to room temperature, the conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture was partitioned between DCM and water, the combined organic layers are washed with water then brine, dried over $MgSO_4$, filtered, and concentrated under moderate vacuum. The crude residue is then purified by flash chromatography to afford the desired product (**3**-**5**).

General procedure for the trifluoromethylselenolation of compounds β-substituted (6): To a 10 mL tube equipped with a magnetic stir bar were added $TsSeCF_3$ (**1 a**, 0.1 mmol, 1 equiv.), benzamide (**6**, 0.1 mmol, 1 equiv.) and $Pd[CH_3CN]_2Cl_2$ (0.02 mmol, 0.2 equiv.) in anhydrous DMSO (1 mL, 0.1 M). The tube was sealed, and the mixture was stirred at 100 °C for 24 h. Conversion is checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture was partitioned between DCM and water, the combined organic layers were washed with water then brine, dried over $MgSO_4$, filtered, and concentrated under moderate vacuum. The crude residue was then purified by flash chromatography to afford the desired product (**7**).

Deposition Number(s) 2175829 (for **3 h**), 2175830 (for **7 f**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: C–H functionalization · fluorine · selenium · trifluoromethylselenolation · trifluoromethylselenosulfonate

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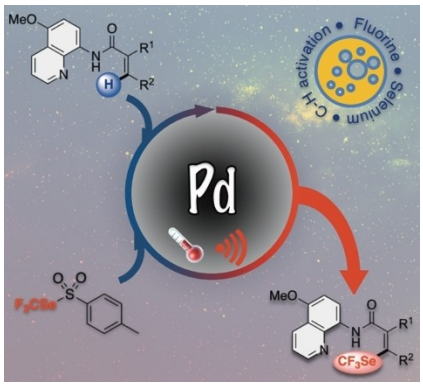
RESEARCH ARTICLE

Trifluoromethylselenolation of vinylic substrates was performed through a palladium-catalyzed C–H activation. This reaction was based on the use of 5-methoxy-8-amino-quinoline as directing group and trifluoromethyl tolueneselenosulfonate as trifluoromethylselenolating reagent. This method was also extended to fluoroalkylselenolation reactions.



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