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Forging C-SeCF₃ Bonds with Trifluoromethyl Tolueneselenosulfonate under Visible-Light.

Dan Louvel,^[a] Clément Ghiazza, ^[a] Vincent Debrauwer, ^[a] Lhoussain Khrouz, ^[b] Cyrille Monnereau,^[b] and Anis Tlili*^[a]

Dedicated to Prof. Pierre Dixneuf for his seminal contribution to the field of homogeneous catalysis



Abstract: This account highlights some of our recent work on photoinduced trifluoromethylselenolation reactions. This research program relies primarily on the design of a new key shelf-stable selenating reagent that can be involved in various radical processes In particular, we demonstrated that trifluoromethylselenolation of arenes, alkenes, alkynes as well as aliphatic organic building blocks can be readily achieved under visible-light irradiation. Mechanistic investigations based on ¹⁹F NMR studies, EPR spectroscopy, cyclic voltammetry and luminescence studies allowed us to shed the light on the different proposed mechanisms in the designed methodologies. The applicative potential of these strategies was further demonstrated through the synthesis of bioactive analogue containing SeCF₃ motif.

1. Introduction

Organofluorine chemistry has been a very active research topic in modern organic chemistry, constantly driven by the interesting properties of fluorinated molecules in a diversity of cutting-edge applications.¹ Today, the incorporation of fluorinated building blocks is routinely used in academia as well as for industrial applications. Major breakthroughs have been reported for the direct incorporation of fluorine and trifluoromethyl groups. It has been shown that the association of chalcogen to trifluoromethyl group confers very high lipophilicity to the target molecule,² a sought-after property in the design of bioactive compounds, in particular. In this context, several bioactive compounds have been recently reported, in most cases with trifluoromethoxy group as a fluorinated unit.³ The lack of efficient reagent and methods for the trifluoromethylthiolation⁴ and trifluoromethylselenolation⁵ has been a major hurdle towards the extension of this field of research to other fluoroalkylchalcogen containing compounds. In the last decade, several research groups have attempted to tackle this challenge.

For what particularly concerns trifluoromethylselenolation pathways reactions. two maior for direct trifluoromethylselenolations were studied in the literature. On the one hand nucleophilic trifluoromethylselenolation reactions were mainly performed by using ammonium trifluromethylselenide and discrete copper complexes developed by the group of Weng as nucleophilic reagents.⁶ On the other hand, electrophilic version of this transformation could be achieved by using trifluoromethaneselenenyl chloride7, however, the low boiling point and high toxicity constitute strong limiting factors to the upscale use of this selenating agent. In order to tackle this

- D. Louvel, Dr. C. Ghiazza, V. Debrauwer, Dr. A. Tilli
 Institute of Chemistry and Biochemistry (ICBMS–UMR CNRS 5246)
 Univ Lyon, Université Lyon 1, CNRS, CPE-Lyon, INSA
 43 Bd du 11 Novembre 1918, 69622 Villeurbanne, France
 E-mail: anis.tilii@univ-lyon1.fr
- [b] L. Khrouz, Dr. C. Monnereau Univ Lyon, Ens de Lyon, CNRS UMR 5182, Université Lyon 1, Laboratoire de Chimie, F-69342, Lyon, France

challenge, we succeeded to design a new shelf-stable reagent, tolueneselenosulfonate (TsSeCF₃), trifluoromethyl and demonstrated that it could constitute an advantageous substitute to CF₃SeCl in electrophilic trifluoromethylselenolation reactions. This reagent (reagent 1 in scheme I) could readily be obtain by reaction of an in situ formed trifluoromethylselenyl chloride reacted with toluensulfinate . Higher fluorinated homologues II and III were been also synthesized (Scheme 1).8 In ongoing efforts to demonstrate further the versatility of our reagent in the modern toolbox of fluoroalkylchalcogen chemistry, we recently succeeded to implement new radical trifluoromethylselenolation reactions, in particular under safe, mild and environmentally friendly photoactivation conditions. The purpose of the account is to highlight our recent results in radical trifluoromethylselenolation under visible-light irradiation.9





Dan Louvel graduated from the ECPM at the university of Strasbourg, France in 2019. He completed his M.Sc. internship under the guidance of Dr Nicolas Duguet, working on the chemistry of β -hydroxy hydroperoxides. He is now doing his Ph.D. at the University of Lyon, France, under the supervision of Dr A. Tlili. His Ph.D. project focuses on photoredox catalysis/small molecules activations, with particular focus on fluorine chemistry.



Clément Ghiazza obtained is Master's degree in organic chemistry at the University of Lyon in 2016. He pursued a Ph.D. under the supervision of Dr. Anis Tlili and Dr. Thierry Billard at the same university during which he was involved in the development of new fluoroalkylselenolation methods. Clément is currently holding a postdoctoral fellowship from the Alexander von Humboldt foundation in the group of Dr. Josep Cornella at the Max Planck Institut für



Kohlenforschung. Clément was awarded the Dina Surdin prize by the French Chemical Society – Organic Chemistry Division (SCF – DCO) in 2020.

PERSONAL ACCOUNT

Vincent Debrauwer studied chemistry at CPE Lyon (FR) where he graduated in 2017. He completed his master internship at the University of Lyon under the supervision of Dr. Anis Tlili working in new method of trifluoromethylselenolation. Since 2018, he is working as PhD student at University of Strasbourg (FR) in Dr. Nicolas Blanchard research group. His research focuses on fluorine chemistry and palladium catalysed stereoselective transformations.

Lhoussain Khrouz is Engineer at the Ecole Normale Supérieure de Lyon (France), where he is responsible for EPR spectroscopy since 2010. Nowadays, he collaborates in several multidisciplinary projects of chemistry or physico-chemistry topics requiring EPR studies.

Cyrille Monnereau was born in Nantes, France, where he studied and received his MS and PhD, under the supervision of Dr Fabrice Odobel in 2005. His thesis work dealt with the synthesis and study of molecular materials for nonlinear optics. After two consecutive postdoctoral stays in the group of Pr Roeland J.M. Nolte (Radboud University, Nijmegen, NL), then Pr. Olivia Reinaud (Université Paris Descartes, France), where he investigated

supramolecular systems using spectroscopic techniques, he got recruited (2009) at the Ecole Normale Supérieure de Lyon, France, where he is now an associate professor. His research interests are in the design and study of organic molecules with specific photophysical/photochemical properties.

Anis Tilii is CNRS Research Fellow. After studying chemistry in the université de Bourgogne, Anis gained a master's degree in the same university with Pr. S. Jugé (Dijon, France). Afterwards, he completed his PhD in the group of Dr. M. Taillefer (Montpellier, France) in late 2011. Subsequently, he joined the group of Pr. M. Beller (LIKAT, Rostock Germany) for a postdoctoral stay before taking up a second collaborative postdoctoral position



(CEA/ICSN, Paris). In 2014 he was appointed a CNRS research Fellow in Lyon. His current research interests lie in the area of homogeneous catalysis/photoredox catalysis, with particular focus on fluorine chemistry. Anis was awarded recently a JSP Fellow for the 53rd Bürgenstock Conference (2018) and was selected to participate to EuCheMS Young Investigators Workshop in Oxford in 2018.







2. Trifluromethylselenolation of arenes

2.1. Aryl lodonium salts

In order to evaluate the effectiveness of our shelf-stable reagent in trifluoromethylselenolation reactions, we first started to investigate C(sp₂)-SeCF₃ bond formation processes. In this context, we selected aryl iodonium salt 1 (Scheme 2) as aryl partner.¹⁰ This choice was motivated by their straightforward synthesis as well as their stability. Moreover, it is well established in the literature that reduction of such starting materials proceeds in a straightforward manner to quantitatively generate aryl radicals, and can be photo-chemically achieved. It indeed turned out that high conversion vields were obtained when the reactions were performed starting with unsymmetrical aryl(2,4,6-trimethylphenyl)iodonium salts 1 in EtOH as solvent in photocatalyst the presence of Ir-based ((Ir[dF(CF₃)ppy]₂(dtbpy))PF₆, 3 mol%) under blue LED irradiation. It is particularly worth noting that very good to excellent yields were obtained for both electron donating and electron withdrawing aryl partners (Scheme 1). Unfortunately, the purification of almost all synthesized compounds was tedious. A major issue was the presence of the remaining mesitylene iodide by-product generated following the reduction of the starting iodonium salts that was observed even after chromatography columns. While an appropriate distillation of the reaction crude could have been an appropriate option to tackle this issue, we were not able to isolate synthetically useful amounts given the small quantity involved under our reaction conditions.



Scheme 2. [a] Reactions were performed with TsSeCF₃ (0.36 mmol, 2 equiv.), aryl iodonium salt **1** (0.18 mmol, 1 equiv.), [Ir] (3 mol%) and EtOH (1.7 mL). The reaction mixture was stirred at room temperature for 16 hours under blue LED irradiation and inert conditions. Yields shown are those of isolated products; yields determined by ¹⁹F NMR spectroscopy with PhOCF₃ as internal standard are shown in parentheses.

2.2. Aryl diazonium slats

To circumvent the limitation encountered with aryl iodonium derivatives, we turned our attention to arene diazonium salts, another much studied class of reagents in recent years, as starting aryl partners. Their straightforward synthesis from their corresponding, widely available anilines makes them particularly attractive in view of enlarging the scope of accessible products. Moreover, the formation of gaseous by product (N₂) in the course of the photoinduced reduction process should be beneficial in order to achieve our goal. After optimizing the reaction conditions, it turned out that the cheap and environmentally benign organic dye Eosin Y is the best catalyst to convert arene diazonium salts to their corresponding trifluoromethylselenolated analogues in the presence of reagent I.¹¹ The reactions were this time performed under white LED irradiation in DMSO as solvent and at room temperature. Depending on the starting diazonium salt, the desired product was obtained in moderate to excellent isolated vields. Herein, both electron rich or electron poor starting materials were smoothly converted. To some extent, we showed that steric hindrance was not problematic under these conditions. Interestingly, broad functional groups tolerance was also observed: in particular, halogenated starting materials including the highly reactive aryl iodide were tolerated. Furthermore, taking advantage of the base-free reaction conditions, highly electrophilic substituent including carboxylate and amide were also compatible with our conditions. Finally, we were also able to demonstrate the efficiency of the protocol toward heterocyclic compounds, of particular interest and relevance for the design of new bioactive molecules (Scheme 3).





Scheme 3. [a] Reactions were performed with TsSeCF₃ (0.6 mmol, 3 equiv.), arene diazonium (0.2 mmol, 1 equiv.), Eosin Y (5 mol%), and DMSO (2 mL). The reaction mixture was stirred at room temperature for 16 hours under white LED irradiation and inert conditions. Yields shown are those of isolated products; yields determined by ¹⁹F NMR spectroscopy with PhOCF₃ as internal standard are shown in parentheses.

In order to expand the scope of the reaction, and in particular to bring adjustability to the lipophilicity of the target molecules, we decided to investigate the feasibility of substituting reagent I with higher fluorinated analogues, reagents II and III (Scheme 4). Overall, we demonstrated that good reactivity could be obtained starting with reagents II and III although with generally slightly lower yields than with reagent I.





mL). The reaction mixture was stirred at room temperature for 16 hours under inert conditions. Yields shown are those of isolated products; yields determined by ^{19}F NMR spectroscopy with PhOCF3 as internal standard are shown in parentheses.

In order to shed some light on the reaction mechanism, fluorine NMR monitoring of the reaction, cyclic voltammetry, Stern Volmer quenching of the Eosin Y luminescence as well as EPR signature of the radicals produced in the course of the reaction were successively investigated. Although reduction of reagent I (E: -0.60 V vs SCE) with the excited Eosin Y is thermodynamically favored, Stern-Volmer (SV) quenching experiment did not clearly indicate the occurrence of electron transfer. In contrast, we confirmed that the photoreduction of diazonium salt was occurring in our conditions, following ET from Eosin Y. In particular, working at higher concentration of the diazonium salt led to rapid and irreversible degradation of the photocatalyst indicative of a reaction between the photoinduced aryl radicals and Eosin Y. Measurement of the radical generation quantum yield indicated a value that slightly exceeds unity (Φ =1.07) suggesting that a radical-chain process might be the most plausible pathway for the reaction to proceed. Monitoring the stability of reagent I upon white LED irradiation confirmed the quick formation of (CF₃Se)₂ upon homolysis of S-Se bond within 1 hour. Furthermore, EPR spectroscopy confirmed the presence of selenyl radical, as well as a possible trigonal selenium reaction intermediate (Scheme 5).



Scheme 5. Proposed radical intermediates with EPR spectroscopy

In light of these experiments, we were able to propose the following mechanism. Homolysis of the S-Se bond is taking place upon white LED irradiation yielding tosyl radical and trifluoromethylselenyl radical. This later could dimerize very quickly and react with the reduced diazonium salt (reduction by the excited Eosin Y) forming a new trigonal radical species **A**. The latter was then at the origin of a chain propagation mechanism, intermediate **A** being responsible for the reduction of the starting diazonium salt yielding an aryl radical and cationic trigonal species **B**. Possible closure of the mechanism was suggested to occur after terminal reaction with DMSO (Scheme 6).¹²





Scheme 6. Proposed mechanism for the trifluoromethylselenolation of aryl diazonium salts.

3. Trifluromethylselenolation of alkenes and alkynes

Given that the aforementioned study seemingly indicates that homolysis of TsSeCF3 is taking place upon white LED irradiation of the latter, we decided to investigate the reactivity of the formed radicals in the presence of unsaturated compounds. Herein, we demonstrated that β -fluoroalkylselenolated sulfones could be obtained by reaction our photoactivated selenating agent with alkenes and alkynes.13 To this end, we started our study with alkenes (Scheme 7). Styrene derivatives, terminal as well as aliphatic alkenes and cyclic alkenes were converted smoothly to their corresponding products in good to excellent yields. Interestingly, excellent trans-diasteroselectivity was achieved when the reactions were performed with internal alkenes. Also, starting with E- or Z-alkene lead to the same mixture of diastereoisomers, suggesting a thermodynamic control in the product formation and thus a sequential rather than concerted addition of the two radicals on the double bond. Higher fluorinated analogues were also tolerated under these conditions.

Afterwards, we extended the methodology to alkynes (Scheme 8). Although we demonstrated earlier that terminal alkynes could reacts with reagent I yielding trifluoromethylselenylated vinyl sulfone in THF without the requirement of light irradiation, the reaction was not effective for internal alkynes and only marginal conversion was obtained with aliphatic ones.¹⁴ Under white LED irradiation we could circumvent these limitations, as shown in scheme 7 and a variety of terminal and internal alkynes could be converted to their vinyl sulfones products in very good to excellent yields. Here again, it should be mentioned that the

thermodynamically more stable (*E*)-product was primarily formed.



Scheme 7. [a] Reactions were performed with TsSeCF₃ (0.25 mmol, 1.25 equiv.), alkene (0.2 mmol, 1 equiv.) and DMSO (1.5 mL). The reaction mixture was stirred at room temperature for 16 hours under white LED irradiation and inert conditions. Yields shown are those of isolated products; yields determined by ¹⁹F NMR spectroscopy with PhOCF₃ as internal standard are shown in parentheses.



Scheme 8. [a] Reactions were performed with TsSeR_F (0.25 mmol, 1.25 equiv.), alkyne (0.2 mmol, 1 equiv.) and DMSO (1.5 mL). The reaction mixture was stirred at room temperature for 16 hours under white LED irradiation and inert conditions. Yields shown are those of isolated products; yields determined by ¹⁹F NMR spectroscopy with PhOCF₃ as internal standard are shown in parentheses.

Mechanistic investigations were undertaken, using either NMR spectroscopy or UV-vis spectroscopy to monitor consumption of

the reagent (and, in the case of NMR, formation of the product). First, ¹⁹F NMR monitoring of the conversion of reagent I and the formation of the desired product after different irradiation periods with a monochromatic (λ =385nm) light source with controlled incident power allowed us to establish a photochemical quantum yield of 7.8. Second, using UV-visible absorption spectroscopy decrease of the absorption band of reagent I was used also to determine the temporal conversion efficiency, this time pointing towards a photochemical quantum yield of 10.3, in overall good agreement with the NMR measurements, and unquestionably indicative of a chain propagation process. Finally, EPR spectroscopy demonstrated the presence of two radical intermediates (scheme 9). The first one, with a signature typical of an initial carbon centered radical C (scheme 9) resulted from the addition of the generated tosyl radical to the radical scavenger. A second species could be attributed either to a trifluoromethylselenyl radical intermediate, originating from the homolytic cleavage of TsSeCF₃, or alternatively to trigonal selenyl radical D (Scheme 9) as a plausible intermediate of the reaction mechanism. .



Scheme 9. Proposed radical intermediates with EPR spectroscopy

From a mechanistic point of view, the homolysis of the S-Se bond plays a key role in our reaction. Indeed, the tosyl radical collapses to the unsaturated compounds and the selenyl radical dimerizes to form $(SeCF_3)_2$. Radical intermediate **C** reacts with the dimer to form a new trigonal radical species **D**. Herein a homolysis of the Se-Se bond could take place to deliver the desired product and regenerate a selenyl radical able to react with reagent **I** and promote the radical chain propagation (Scheme 10).



Scheme 10. Proposed mechanism for the trifluoromethylselenolation of alkenes and alkynes derivatives.

4. Trifluromethylselenolation of alkyl radicals

In order to enlarge the scope of reactivity of our shelf-stable reagent we decided to investigate the direct trifluoromethylselenolation of alkyl derivatives. For this purpose, it is well established in the literature that alkyl silanes and alkyl trifluoroborates are effective sources of alkyl radicals. This section highlights our finding in direct trifluoromethylselenolation of alkyl silanes and alkyltrifluoroborates derivatives in the presence of Fukuzumi acridinium organophotocatalyst under blue LED irradiation.¹⁵

4.1. Alkylsilane derivatives

The trifluoromethylselenolation of benzylic alkylsilane derivatives were undertaken in MeOH as solvent in the presence of **Mes-Acri⁺** (Fukuzumi catalyst – 5 % mol.), under blue LED irradiation. In order to obtain photoconversion yield, the use of potassium persulfate was necessary. The reaction does not require inert conditions. Depending on the substrate the desired products were formed in low to excellent yields (Scheme 11). Again, we demonstrated that the reaction could also operate with higher fluorinated analogues



Scheme 11. Reactions were performed with TsSeR_F (0.4 mmol, 1 equiv.), alkylsilane derivatives (0.4 mmol, 1 equiv.), PC (5 mol%), and DMSO (2 mL). The reaction mixture was stirred at room temperature for 16 hours under inert conditions. Yields shown are those of isolated products; yields determined by ¹⁹F NMR spectroscopy with PhOCF₃ as internal standard are shown in parentheses.

In order to investigate the possibility of an electron transfer between the alkyl silane and the excited photocatalyst we

performed luminescence quenching studies. Incremental addition of benzyltrimethylsilane to a methanolic solution of the Fukuzumi's catalyst resulted in a marked quenching that could be plotted according to Stern-Volmer equation, indicating an electron transfer between this electron donor and the photocatalyst. This finding was confirmed by EPR spectroscopy upon mixing the photocatalyst with trimethylbenzylsilane in methanol under blue LED irradiation. In these condictions, a radical adduct consistent with benzyl radical was trapped by both PBN and DMPO. Performing the reaction with all reactants and in the concentration conditions used for trifluoromethylselenolation of benzylsilanes only small amounts of either Ts or SeCF3 could be observed, while the benzyl radical signal disappeared indicative of the efficient conversion of the latter. It should be mentioned that the main observed species under these conditions is MeO seemingly indicative of a possible redox reaction involving the solvent

The obtained information allows us to propose the following mechanism: upon excitation with light, the excited photocatalyst is able to oxidize the alkyl silanes forming a new radical **MesAcri** And a benzylsilane radical cation (BnSiMe₃⁺). As disclosed in the literature, the formation of the alkyl radical is not favorable in a unimolecular fashion.¹⁶ Thus, a methanol assisted desilylation will deliver the corresponding radical. Afterwards, the formed alkyl radical reacts with reagent I to furnish the desired product and tosyl radical. The sacrificial oxidant potassium persulfate enables regeneration of the photocatalyst at the ground state which is mandatory to fulfil substrate conversion since light on/off experiments support stepwise mechanism (Scheme 12).



Scheme 12. Proposed mechanism for the trifluoromethylselenolation of alkylsilanes derivatives

4.1. Alkyltrifluoroborate derivatives

Under similar conditions of photocatalyst and light wave, and substituting MeOH by DMSO, we have been able to encompass potassium alkyltrifluoroborate salts. In striking contract to alkylsilanes derivatives, we were able to perform the reaction without using any external sacrificial oxidant, while maintaining recovery of the desired products in low to good yields (Scheme 13).



Scheme 13. Reactions were performed with TsSeR_F (0.4 mmol, 1 equiv.), potassium alkyltrifluoroborate derivatives (0.4 mmol, 1 equiv.), PC (5 mol%), and DMSO (2 mL). The reaction mixture was stirred at room temperature for 16 hours under inert conditions. Yields shown are those of isolated products; yields determined by ¹⁹F NMR spectroscopy with PhOCF₃ as internal standard are shown in parentheses.

Fluorescence quenching experiments confirmed an electron alkytrifluroborates transfer between the and the organophotocatalyst. This finding was further supported by EPR spectroscopy since benzyl radical could be trapped with PBN or DMPO. It should be mentioned that in contrast to the previous reaction with methanol we could observe that an electron transfer also occurs between the excited photocatalyst and DMSO, which results in the built up of a complex signal typical of Fukuzumi's catalyst in its radical form. In the reaction conditions, we could also observe the formation of SeCF₃ radical through photoinduced electron transfer reagent I which can recombine with the benzyl radical, which formation through photoinduced electron transfer with Fukuzumi catalyst was also attested in the corresponding experiment. lt turns out that the homorecombination of SeCF₃ radical into a (SeCF₃)₂ dimer constitute a dead end of the catalytic cycle.

Following these mechanistic investigations, we were able to propose the following mechanism. The excited **Mes-Acri⁺** is able to oxidize the alkyltrifluoroborate through SET. Afterwards, the organophotocatalyst is restored after reduction of reagent I. Ultimately the generated SeCF₃ radical can recombine with the alkyl radical to form the desired product (Scheme 14).



Scheme 14. Proposed mechanism for the trifluoromethylselenolation of alkyltrifluoroborates derivatives

5. Perspective and future developments

As already mentioned in the introduction, the synthesis of bioactive compounds containing SeCF₃ motif should be a hot future improvement topic iassociated with in trifluromethylselenolation reactions. The lack of methodology affording the synthesis of such compounds, and the consequent current lack of relevant biological studies and data supporting their potential biological relevance, hampered their more widespread development. In this context, based on the abovementioned methodologies and in the framework of a collaboration with researchers from Novartis we established a study aiming at the synthesis of selenylated analogues of trifluoromethoxylated relevant molecules and the evaluation of their physicochemical and ADME properties.¹⁷ In particular, the access to the selenvlated analogue of Riluzole¹⁸ (treatment for amyotrophic lateral sclerosis - ALS) could be performed by using our photoredox process in synthetically useful yield (Scheme 15). We demonstrated that chalcogen replacement modulates physico-chemical and ADME properties without introducing intrinsic liabilities. We believe that such finding will foster future developments towards the synthesis of bioactive compounds containing the SeCF₃ motif.



Scheme 15. Synthesis of analogue of bioactive compound

6. Conclusion

In summary we have been able to demonstrate that, upon light activation, using trifluoromethyl tolueneselenosulfonate as a radical source, radical trifluoromethylselenolation proceeds smoothly. Reaction generally requires the use of a benign organophotocatalyst, but radical trifluoromethylselenolation can also occur in certain specific cases in the absence of photocatalyst. Indeed, upon white LED irradiation the homolysis of S-Se bond is taking place spontaneously. Although, the dimerization of the SeCF3 radical proceeds very quickly, the presence of radical intermediate allows the formation of C-SeCF₃ through trigonal species. Furthermore, we also demonstrated that aliphatic sources of radical including alkylsilanes and potassium alkyltrifluoroborate salts could undergo trifluromethylselenolation under blue LED irradiation. We have been able to demonstrate the utility of the developed methodology for the synthesis of a variety of analogues of bioactive compounds, with fluoroalkyl attached to either aromatic or aliphatic positions. We have been able to demonstrate the utility of one of the developed methodologies for the synthesis of bioactive compounds analogues, with highly promising results in biological studies that will definitely pave the way towards future developments.

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we report herein our recent work on photoinduced trifluoromethylselenolation reactions. The key to success is the design of a new key shelf-stable selenating reagent that can be involved in various radical processes. Herein we discuss the recent methodologies that we developed for the trifluoromethylselenolation of arenes, alkenes, alkynes as well as aliphatic compounds under visible light irradiation.

D. Louvel,^[a] C. Ghiazza,^[a] V. Debrauwer,^[a] L. Khrouz,^[b] C. Monnereau,^[b] and A. Tilii $*^{[a]}$

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Forging C-SeCF3 Bonds with Trifluoromethyl Tolueneselenosulfonate under Visible-Light.