Chemistry–A European Journal
Full Paper
doi.org/10.1002/chem.202100053
Chemistry Europe
European Chemical Societies Publishing

Synthetic Methods

(Trifluoromethylselenyl)methylchalcogenyl as Emerging Fluorinated Groups: Synthesis under Photoredox Catalysis and Determination of the Lipophilicity

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Abstract: The synthesis of molecules bearing (trifluoromethylselenyl)methylchalcogenyl groups is described via an efficient two-step strategy based on a metal-free photoredox catalyzed decarboxylative trifluoromethylselenolation with good yields up to 88%, which raised to 98% in flow chemistry conditions. The flow methods allowed also to scale up the reaction. The mechanism of this key reaction was studied. The physicochemical characterization of these emerging groups was performed by determining their Hansch–Leo lipophilicity parameters with high values up to 2.24. This reaction was also extended to perfluoroalkylselenolation with yields up to 95%. Finally, this method was successfully applied to the functionalization of relevant bioactive molecules such as tocopherol or estrone derivatives.

Introduction

Since the fluorine discovery by Henri Moissan one century ago,[1] fluorinated compounds have known a growing interest.[2] Throughout these years, such substrates have demonstrated their successful usage in a large panel of applications, with a wide diversity from materials to life sciences.[3]

Nowadays, introduction of fluorinated substituents onto molecules is quite a staple in the design of new compounds for targeted applications. This is mainly due to the exclusive characteristics of fluorinated groups which confer to molecules specific properties in particular concerning physicochemical and electronic aspects.[4]

In the objective to continue to propose new fluorinated moieties with modulative properties, the concept and development of "emerging fluorinated groups" appeared these last years, in particular by introducing heteroatoms.[5] In this field, chalcogens are the most considered. Indeed, trifluoromethylchalcogenyl groups possess, inter alia, high Hansch–Leo lipophilicity parameters.[6]

If fragments with oxygen and sulfur were well studied,[5,7] selenium derivatives were less developed until recently,[8] maybe due to the toxicity associated to selenium.[9] However, selenium is an essential trace element for human biochemistry[10] and seleno-proteins play a crucial role in physiology for live species.[11] In recent years, selenylated molecules have found promising applications in various fields such as, for instance, materials or drug design.[12] Thus, recently, nonsteroidal anti-inflammatory derivatives bearing a CF_3Se group have been tested as potential anticancer agents with promising results.[13]

In our ongoing efforts to design new fluorinated moieties with expected unknown properties, in particular concerning lipophilicity, we considered more sophisticated groups by merging another chalcogen with CF_3Se group. In order to avoid weak chalcogen–chalcogen bonds and to introduce some structural modularity, a methylene bridge between both heteroatoms was envisaged. Therefore, we focused our interest onto (trifluoromethylselenyl)methylchalcogenyl groups (CF_3SeCH_2E; E = O, S, Se).

Results and Discussion

The synthesis of molecules bearing these substituents was first considered. Visible light photocatalysis has emerged over the last decade as a powerful tool for the synthesis of various substrates in eco-friendly conditions.[14] More specifically, photoredox-catalyzed decarboxylation is an approach which was widely described and, in particular, the use of R-ECH_2CO_2H substrates as starting materials was considered.[15] Indeed, such

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.202100053.

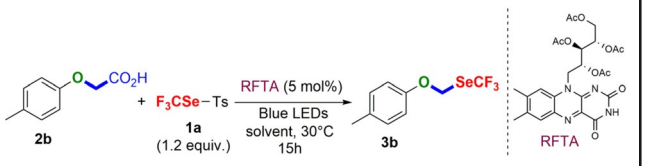
substrates are easy to obtain by carboxymethylation of corresponding chalcogenols with haloacetate reagents. This strategy was perfectly adapted to our objective. The interest for such approach was confirmed during our study by the work of Zhang et al. which described the photoredox-catalyzed decarboxylative trifluoromethylselenolation of aliphatic carboxylic acids.[16] Two examples of naphthyl-ECH_2SeCF_3 (E = O, S) compounds were described with medium yields. Nevertheless, this method is based on the use of $[CF_3Se][NMe_4]$ as anionic trifluoromethylselenolating reagent. This reagent suffers from some stability issues and its synthesis requires tedious conditions.[8b,17] Furthermore, this decarboxylation required the use of one equivalent of NFSI as oxidant.

Trifluoromethylselenotoluenesulfonate (CF_3SeTs, **1a**) was recently described as an electrophilic trifluoromethylselenolative reagent.[18] Visible-light activation of this substrate to perform radical trifluoromethylselenolations was also performed.[19] Consequently, the use of this reagent in the photoredox decarboxylation was postulated as a valuable alternative, which would avoid the addition of an oxidant. Such hypothesis was confirmed by the recently published decarboxylative cyanation of carboxylic acids based on the use of TsCN as reagent[20] and an inexpensive and non-toxic derivative of vitamin B_2 as organic photocatalyst.[21]

Therefore, photoredox-catalyzed decarboxylative trifluoromethylselenolation was optimized with compound **2b** as model substrate and riboflavin tetraacetate (RFTA) as photocatalyst.

Reaction led to the expected product **3b** with 45% yield in acetonitrile (Table 1, entry 1). Doubling the photocatalyst amount did not bring any improvements (Table 1, entry 2). A more polar solvent as DMSO decreased considerably the yield (Table 1, entry 3) and protic solvents were deleterious for the reaction (Table 1, entries 4, 5). The addition of Cs_2CO_3 as base decreased the observed yield (Table 1, entry 6). Interestingly, a dilution by half of the reacting medium gave rise to a better result of 82% (Table 1, entry 7), as previously observed in the literature.[20] This may be due to the high molar absorption coefficient of RFTA. Even in these diluted conditions, the use of more polar solvents clearly did not favor the reaction (Table 1, entries 8, 9). No significant modifications were observed with an increase of reaction time (Table 1, entry 10). Finally, the compulsory uses of photocatalyst and blue LED irradiation were confirmed (Table 1, entries 11, 12).

Table 1. Reaction between **1a** and **2b** under photoredox conditions.



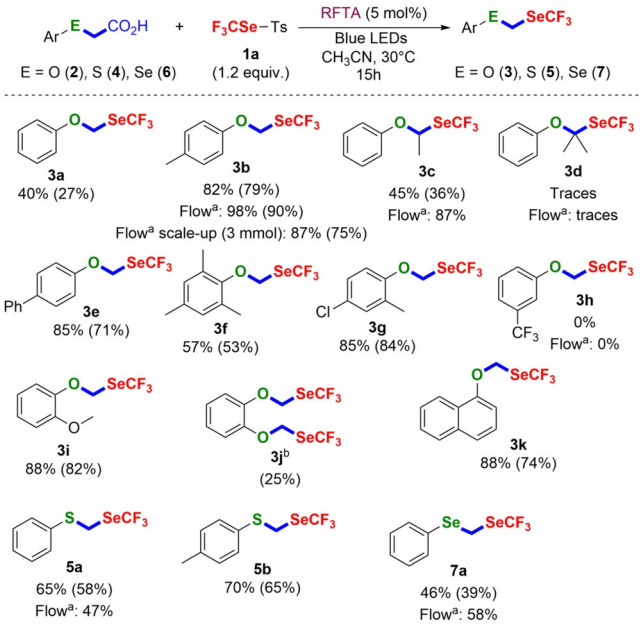
Entry	Solvent	[**2b**] [M]	**3b** [%][a]
1	CH_3CN	0.1	45
2	CH_3CN[b]	0.1	46
3	DMSO	0.1	12
4	MeOH	0.1	–
5	H_2O	0.1	–
6	CH_3CN[c]	0.1	38
7	CH_3CN	0.05	82
8	DMF	0.05	17
9	DMAc	0.05	–
10	CH_3CN[d]	0.05	78
11	CH_3CN[e]	0.05	–
12	CH_3CN[f]	0.05	–

[a] Yield determined by ^{19}F NMR with $PhOCF_3$ as internal standard. [b] With 10 mol% of RFTA. [c] With 1 equiv of Cs_2CO_3. [d] 24 h. [e] Without RFTA. [f] Without irradiation.

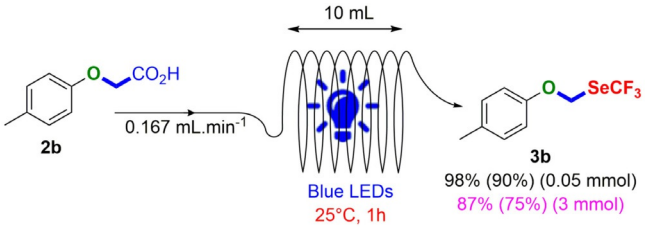
With these optimal conditions in hand (Table 1, entry 7), several compounds were synthesized in batch and in flow conditions (Scheme 1).

Globally, good results were obtained. If a slight steric hindrance did not have significant influence (**3c**), a more important one precluded the formation of the expected compound (**3d**). The presence of electron-donating group on the aromatic ring seems to favor the reaction (**3b**, **3e-g**, **3i**). In contrast, strong electron-withdrawing group as CF_3 did not provide the expected product (**3h**). The reaction appears to be compatible with the presence of chlorine atom onto the aryl moiety (**3g**). Similar result was observed in naphthyl series (**3k**). Very original bis-adduct was also obtained, starting from the corresponding bis-carboxylic acid, albeit with moderate yield (**3j**). This reaction proved not limited to the oxygen atom and other chalcogens were also considered. Similar results were obtained with sulfur (**5a-b**) or selenium (**7a**). Everything else being equal, the yields are similar to those of oxygen.

In addition, this transformation was also performed with the use of continuous-flow reactor (Scheme 2). This technic is perfectly well adapted to photochemical transformations and



Scheme 1. Synthesis of CF_3SeCH_2E-molecules (E = O, S, Se). Yields determined by ^{19}F NMR with $PhOCF_3$ as the internal standard; in parentheses, isolated yields. [a] Flow rate of 167 μL min^{-1} (residence time of 1 h) at 25 °C. [b] with 2.4 equiv of **1a**.



Scheme 2. Synthesis of ((*p*-tolyloxy)methyl)(trifluromethyl)selane (**3 b**) using continuous flow.

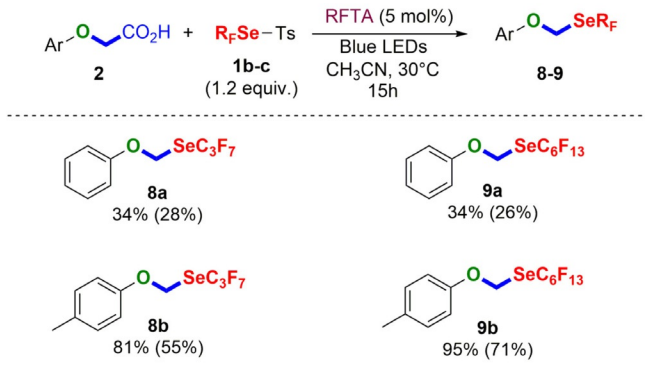
scale-up experiments are facilitated under safer reaction conditions.[22] After slight modifications of the reaction conditions, with a flow rate of 167 µL min^{-1}, the irradiation could be decreased to only 1 h of residence time, and the expected CF_3Se-product **3 b** was obtained in 98% yield. Furthermore, flow photoredox reactions are easier to scale-up than in batch conditions. Thus, the same experiment was performed on a larger scale (half a gram of starting carboxylic acid −3 mmol) without any significant loss of the yield. In general, continuous flow provided a better yield (Scheme 1), in particular in the case of the more sterically hindered adduct **3 c** (87% yield in flow, vs. 45% in batch).

Other fluoroalkylselenotoluenesulfonates reagents were also developed by one of our group with higher homolog of the fluorinated part.[18a] Consequently, the reaction was extended to others fluorinated reagents **1 b**,**c** (Scheme 3).

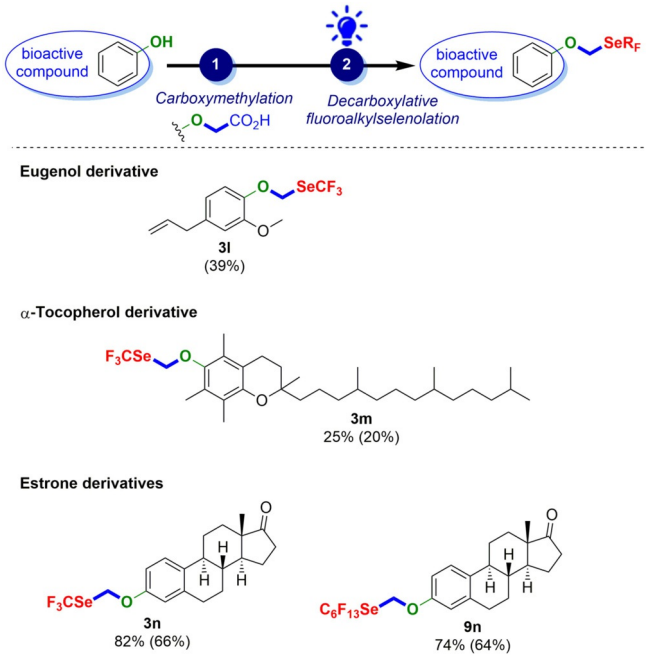
Similar results to CF_3 series were obtained with C_3F_7 and C_6F_{13} moieties. These examples constitute the first examples of photoredox-catalyzed decarboxylative perfluoroalkylselenolation.

Finally, this method was applied to some relevant bioactive compounds. Thus, eugenol, major component of clove bud oil used as local antiseptic and anesthetic, α-tocopherol, component of vitamin E used as antioxidant, and estrone, a steroid estrogen hormone, were functionalized with R_FSeCH_2O groups (Scheme 4).

Eugenol derivative (**3 l**) was obtained in only moderate yield. A complex mixture was observed at the end of the reaction with some by-products arising from radical trifluoromethylselenolation of double bond, as previously described.[19b] Derivatization of tocopherol led also to a moderate result (**3 m**) which could be explained by steric hindrance as demonstrated in Scheme 1. Nevertheless, the result remains interesting in view of the complexity of molecule. Finally, with estrone good yield was observed in both trifluoromethyl (**3 n**) and tridecafluorohexyl series (**9 n**). This result demonstrates that not hindered aromatic ring favors the reaction and confirms the hypothesis put forward with tocopherol.



Scheme 3. Synthesis of R_FSeCH_2O-molecules. Yields determined by ^{19}F NMR with $PhOCF_3$ as the internal standard; in parentheses, isolated yields.



Scheme 4. Functionalization of some bioactive compounds. Yields determined by ^{19}F NMR with $PhOCF_3$ as the internal standard; in parentheses, isolated yields.

To better understand this decarboxylative trifluoromethylselenolation, a mechanistic study has been performed. As both light and photocatalyst were required for the reaction (Table 1, entries 11, 12, and Scheme 5), a radical-based mechanism was hypothesized. This hypothesis was confirmed by a reaction quenched in presence of TEMPO (Scheme 5).

Due to the high oxidation potential of the excited state of RTFA ($E = +1{,}67$ V vs. SCE),[23] we envisioned an oxidative quenching cycle with carboxylic acids **2**–**4**–**6** ($E = +1.16$ V vs.

	82%
without LED irradiation	0%
without RFTA	0%
in presence of TEMPO (5 equiv.)	0%

Scheme 5. Control reactions.

SCE).[24] To confirm this hypothesis, fluorescence quenching experiments were performed with *p*-methylphenoxyacetic acid **2b** and trifluoromethylselenotoluenesulfonate **1a** (Figure 1). The quenching constant of **1a** was calculated to be almost ten times less important ($k_{q(1a)} = 4.7\times10^{8}\,M^{-1}s^{-1}$) than the quenching constant with **2b** ($k_{q(2b)} = 3.5\times10^{9}\,M^{-1}s^{-1}$). This result indicated that RFTA* is mostly quenched by the carboxylic acid substrate. Finally, the quantum yield of the reaction was measured (see Supporting Information for more details). The maximum value $\Phi = 0.23$ indicated that a photocatalytic pathway is favored over a radical chain mechanism.

Based on these studies, a plausible mechanism was proposed (Scheme 6). First, the excited photocatalyst (RFTA*) performs a PCET (proton coupled electron transfer) with carboxylic acid **2**, **4**, or **6**, leading to [RFTA-H] and O-centered radical intermediate **I**, which evolves into carbon-centered radical **II** after a fast decarboxylation step. Intermediate **II** then reacts with reagent **1a** to form the desired product. The resulting Ts$^{\bullet}$ radical is then reduced into TsH by [RFTA-H]$^{\bullet}$, which regenerates the photocatalyst.

In order to further study the properties of the (trifluoromethylselenyl)methylchalcogenyl groups, their Hansch-Leo lipophilicity parameters were determined. As previously described,[6b] octanol-water partition coefficient (log*P*) of substituted benzene **3a**, **5a** and **7a** were measured and compared to benzene (Figure 2). The measures were replicated several times and the mean values were obtained with a good standard deviation.

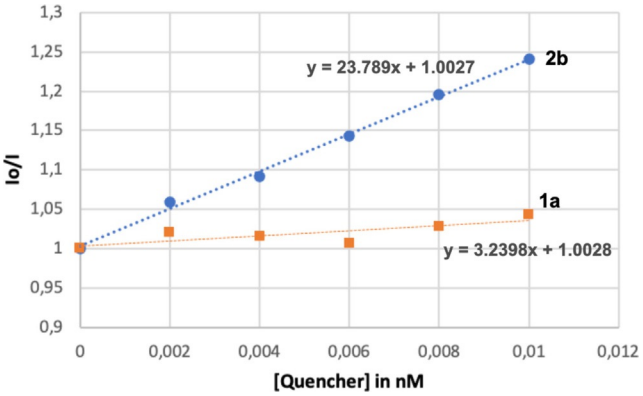
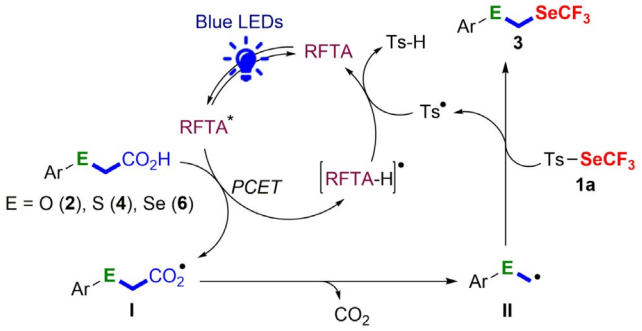


Figure 1. Fluorescence quenching experiments.



Scheme 6. Proposed mechanism.

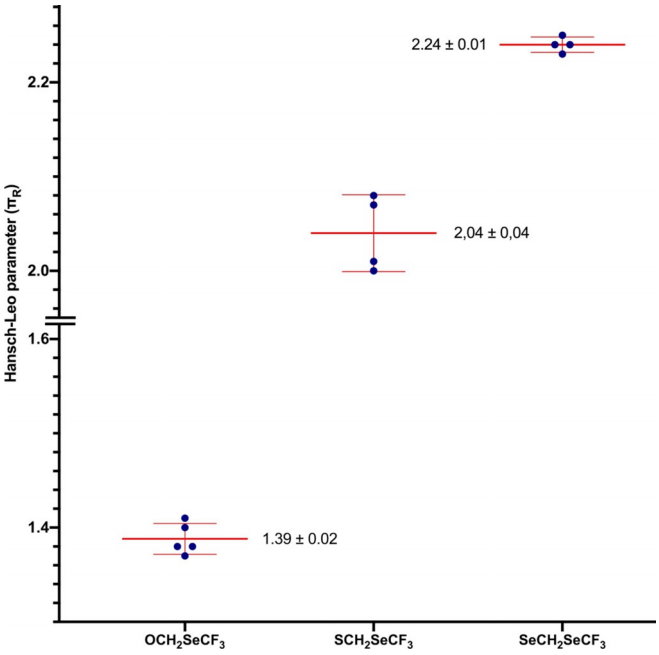


Figure 2. Hansch–Leo lipophilicity parameters (π_R) of CF_3SeCH_2E groups. Scatter dot plot with means and standard deviations.

Compared to CF_3E groups, lipophilicity of CF_3SeCH_2E groups is systematically increased (Table 2). Furthermore, the values grow with atomic number of chalcogen (E). The evolution of the Hansch–Leo parameters demonstrates an additive effect of both chalcogen atom and CH_2 moiety leading to a continuous increase of π_R parameters (Figure 3). Compared to CH_2SeCF_3, the addition of a second chalcogen generally increases π_R apart for oxygen because of the hydrophilic character of OCH_2 moiety. Nevertheless, ECH_2SeCF_3 groups are more lipophilic than corresponding ECF_3. Thus, the $SeCH_2SeCF_3$ moiety appears to be very lipophilic with a $\pi_R = 2.24$ which constitutes one of the highest determined values for fluorinated groups.

Table 2. Hansch–Leo lipophilicity parameters (π_R) observed by merging chalcogen(s) and CF_3 group.

ECH_3	π_R[6]	ECF_3	π_R[6]	ECH_2SeCF_3	π_R[a]
CH_3	0.56	CF_3	0.88	CH_2SeCF_3	1.63
OCH_3	−0.02	OCF_3	1.04	OCH_2SeCF_3	1.39
SCH_3	0.61	SCF_3	1.44	SCH_2SeCF_3	2.04
$SeCH_3$[b]	0.74	$SeCF_3$[c]	1.61	$SeCH_2SeCF_3$	2.24

[a] Determined in this paper, see supporting information. [b] log*P* calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994–2020 ACD/Labs). [c] Re-evaluated value, see Supporting Information.

Conclusions

(Trifluoromethylselenyl)methylchalcogenyl groups are innovative fluorinated substituents with high Hansch–Leo lipophilicity parameters. Their introduction onto organic molecules is easy

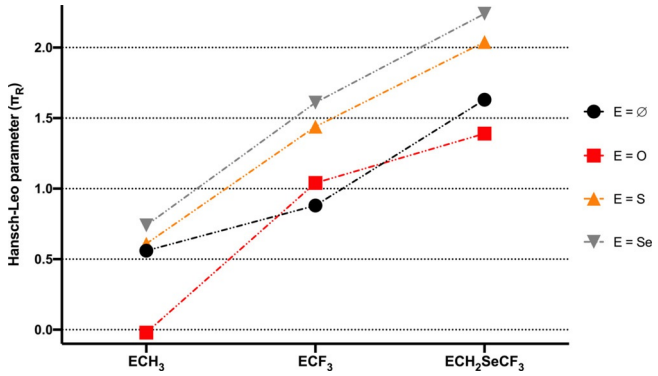


Figure 3. Hansch–Leo lipophilicity parameters (π_R) evolution.

to perform in two steps starting from corresponding chalcogenols via an efficient metal-free photoredox decarboxylative trifluoromethylselenolation as key step. This synthesis was optimized in flow conditions allowing rapid process easy to scale-up. These results demonstrate that not only the association of chalcogens and trifluoromethyl moiety remains a pertinent strategy to develop new fluorinated emerging groups with specific properties but also confirm, as already widely described in the literature, that photoredox catalysis and flow chemistry constitute very efficient and well-adapted approaches in modern fluorine chemistry.

Experimental Section

Decarboxylative perfluoroalkylselenolation in batch conditions

To a tube equipped with a magnetic stir bar are added $TsSeR_F$ (**1**; 0.18 mmol, 1.2 equiv), carboxylic acid (**2**, **4**, **6**; 0.15 mmol, 1 equiv) and RFTA (0.008 mmol, 0.05 equiv) in 3 mL of dry CH_3CN (previously sparged with N_2). The tube is sealed with an adapted septum and the mixture is sparged for 5 min with a N_2 balloon. The reaction mixture is then stirred for 15 h at 30 °C under blue light irradiation. Conversion is checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture is partitioned between Et_2O or pentane and water, the combined organic layers are washed with 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**, **7**, **8**, **9**).

Decarboxylative trifluoromethylselenolation in flow conditions

To a tube under argon were added the carboxylic acid (**2**, **4**, **6**; 0.1 mmol, 1 equiv), $TsSeCF_3$ (**1a**; 0.12 mmol, 1.2 equiv) and RFTA (5.0 μmol, 0.05 equiv). CH_3CN (2 mL) was added and the solution is degassed with argon for 10 min and stirred at room temperature until full dissolution of reagents. Then, using an easy-Photochem E-series system from Vapourtec with a 10 mL reactor irradiated with a 450 nm LED system, 1 mL of the solution (0.05 mmol) was pumped at a flow rate of 167 $\mu L\,min^{-1}$ at 25 °C. The reaction mixture is collected and partitioned between Et_2O or pentane and water, the combined organic layers are washed with 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.

Luminescence quenching experiments

A stock solution of photocatalyst was prepared by dissolving RFTA (3 mg, 5 μmol) in 10 mL of MeCN. Of this solution, 1 mL were further diluted with MeCN to give a total volume of 10 mL ([RFTA] = 5×10^{-5} M). A stock solution of carboxylic acid **2b** was prepared by dissolving **2b** (100 mg, 600 μmol) in 20 mL of MeCN ([**2b**] = 3×10^{-2} M). A stock solution of $TsSeCF_3$ **1a** was prepared by dissolving **1a** (181 mg, 600 μmol) in 20 mL of MeCN ([**1a**] = 3×10^{-2} M). For each experiment, 6 samples were prepared in the dark. Quartz cuvettes (3.5 mL) were filled with photocatalyst stock solution (0.3 mL), quencher stock solution (0 mL, 0.2 mL, 0.4 mL, 0.6 mL, 0.8 mL, 1.0 mL) and MeCN (2.7 mL, 2.5 mL, 2.3 mL, 2.1 mL, 1.9 mL, 1.7 mL) to obtain a total volume of 3 mL. The final concentrations were [RFTA] = 5 10^{-6} M and [Quencher] = 2×10^{-3} M, 4×10^{-3} M, 6×10^{-3} M, 8×10^{-3} M, 1×10^{-2} M. For each sample, emission spectra were acquired between 400 nm and 600 nm (excitation at 450 nm). Rates of quenching (k_q) were determined using Stern–Volmer kinetics: $I_0/I = k_q\tau_0[\text{quencher}] + 1$, where I_0 is the luminescence intensity without the quencher, I is the intensity with the quencher, and τ_0 is the excited state lifetime of the photocatalyst.

Determination of Hansch–Leo parameters (π_R)

To a 10 mL pear-shaped flask was added octanol (ca. 2 mL), water (ca. 2 mL) and the molecule to study (ca. 2 μL). The resulting biphasic mixture was hand-shacked for 5 min and then the flask was centrifuged for 5 min to enable complete phase separation. Using two syringes with needles, a sample was carefully taken from each layer. In particular for taking a water sample aliquot, a long needle with trocar was used. Upon reaching the water phase, the trocar was removed, the aliquot was taken with syringe and the needle quickly removed from the solution. Then a small amount of water phase was discarded (to ensure all traces of octanol were out of the needle). The needles were carefully wiped with dry tissue before the sample was transferred into the HPLC vial. Samples were injected in HPLC (eluent MeOH/H_2O) with an UV detector. Log *P* was determined as the logarithm of the ratio between the peak areas of molecules in octanol and water. The Hansch–Leo parameter was calculated as $\pi_R = \log P(\text{molecule}) - \log P(\text{benzene})$.

Acknowledgements

This work was supported by a grant from the French National Research Agency (ANR 18-CE07-0039-01). The NMR Centre of the university of Lyon is thanked for their contribution. The authors are grateful to the CNRS and the French Ministry of Research for financial support. The French Fluorine Network (GIS-FLUOR) is also acknowledged for its support.

Conflict of interest

The authors declare no conflict of interest.

Keywords: decarboxylation · fluorine · lipophilicity · photoredox · selenium

[1] a) H. Moissan, *C. R. Hebd. Seances Acad. Sci.* **1886**, *102*, 1543 – 1544; b) H. Moissan, *C. R. Hebd. Seances Acad. Sci.* **1886**, *103*, 202 – 205; c) H. Moissan, *C. R. Hebd. Seances Acad. Sci.* **1886**, *103*, 256 – 258; d) H. Moissan, *Ann. Chim. Phys.* **1887**, *6*, 472 – 537; e) H. Moissan, *C. R. Hebd. Seances Acad. Sci.* **1899**, *128*, 1543 – 1545.
[2] P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2013**.
[3] a) M. Pagliaro, R. Ciriminna, *J. Mater. Chem.* **2005**, *15*, 4981 – 4991; b) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496 – 3508; c) D. Chopra, T. N. G. Row, *CrystEngComm* **2011**, *13*, 2175 – 2186; d) P. Jeschke, *Pest Manage. Sci.* **2010**, *66*, 10 – 27; e) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16 – 29; f) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467; g) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422 – 518; h) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822 – 5880; i) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797 – 11819; j) M. Cheng, C. Guo, M. L. Gross, *Angew. Chem. Int. Ed.* **2020**, *59*, 5880 – 5889; *Angew. Chem.* **2020**, *132*, 5932 – 5942; k) B. M. Johnson, Y.-Z. Shu, X. Zhuo, N. A. Meanwell, *J. Med. Chem.* **2020**, *63*, 6315 – 6386; l) J. Han, A. M. Remete, L. S. Dobson, L. Kiss, K. Izawa, H. Moriwaki, V. A. Soloshonok, D. O'Hagan, *J. Fluorine Chem.* **2020**, *239*, 109639.
[4] B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3 – 11.
[5] *Emerging Fluorinated Motifs: Synthesis Properties and Applications* (Eds.: D. Cahard, J. A. Ma), Wiley-VCH, Weinheim, **2020**.
[6] a) A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525 – 616; b) Q. Glenadel, E. Ismalaj, T. Billard, *Eur. J. Org. Chem.* **2017**, 530 – 533.
[7] a) F. R. Leroux, B. Manteau, J.-P. Vors, S. Pazenok, *Beilstein J. Org. Chem.* **2008**, *4*, 13; b) T. Besset, P. Jubault, X. Pannecoucke, T. Poisson, *Org. Chem. Front.* **2016**, *3*, 1004 – 1010; c) A. Tlili, F. Toulgoat, T. Billard, *Angew. Chem. Int. Ed.* **2016**, *55*, 11726 – 11735; *Angew. Chem.* **2016**, *128*, 11900 – 11909;; d) H.-Y. Xiong, X. Pannecoucke, T. Besset, *Chem. Eur. J.* **2016**, *22*, 16734 – 16749; e) F. Toulgoat, T. Billard in *Modern Synthesis Processes and Reactivity of Fluorinated Compounds: Progress in Fluorine Science* (Eds.: H. Groult, F. Leroux, A. Tressaud), Elsevier Science, London, **2017**, pp. 141 – 179; f) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731 – 764.
[8] a) A. Tlili, E. Ismalaj, Q. Glenadel, C. Ghiazza, T. Billard, *Chem. Eur. J.* **2018**, *24*, 3659 – 3670; b) T. Billard, F. Toulgoat in *Emerging Fluorinated Motifs: Synthesis Properties and Applications* (Eds.: D. Cahard, J. A. Ma), Wiley-VCH, Weinheim, **2020**, pp. 691 – 721.
[9] M. J. Yaeger, R. D. Neiger, L. Holler, T. L. Fraser, D. J. Hurley, I. S. Palmer, *J. Vet. Diagn. Invest.* **1998**, *10*, 268 – 273.
[10] a) M. P. Rayman, *Lancet* **2000**, *356*, 233 – 241; b) EFSA Panel on Dietetic Products, Nutrition and Allergies, *EFSA Journal* **2014**, *12*, 3846; c) European Food Safety Authority, *EFSA Supporting Publications* **2017**, *14*, e15121E.
[11] a) K. M. Brown, J. R. Arthur, *Public Health Nutr.* **2001**, *4*, 593 – 599; b) S. Gromer, J. K. Eubel, B. L. Lee, J. Jacob, *Cell. Mol. Life Sci.* **2005**, *62*, 2414 – 2437; c) V. M. Labunskyy, D. L. Hatfield, V. N. Gladyshev, *Physiol. Rev.* **2014**, *94*, 739 – 777; d) E. Mangiapane, A. Pessione, E. Pessione, *Curr. Protein Peptide Sci.* **2014**, *15*, 598 – 607; e) R. Mousa, R. Notis Dardashti, N. Metanis, *Angew. Chem. Int. Ed.* **2017**, *56*, 15818 – 15827; *Angew. Chem.* **2017**, *129*, 16027 – 16037.
[12] a) L. V. Romashov, V. P. Ananikov, *Chem. Eur. J.* **2013**, *19*, 17640 – 17660; b) Q. Li, Y. Zhang, Z. Chen, X. Pan, Z. Zhang, J. Zhu, X. Zhu, *Org. Chem. Front.* **2020**, *7*, 2815 – 2841; c) W. Guo, Y. Fu, *Chem. Eur. J.* **2020**, *26*, 13322 – 13331; d) G. Mugesh, W.-W. du Mont, H. Sies, *Chem. Rev.* **2001**, *101*, 2125 – 2180; e) N. Singh, A. C. Halliday, J. M. Thomas, O. V. Kuznetsova, R. Baldwin, E. C. Y. Woon, P. K. Aley, I. Antoniadou, T. Sharp, S. R. Vasudevan, G. C. Churchill, *Nat. Commun.* **2013**, *4*, 1332; f) J. B. T. Rocha, B. C. Piccoli, C. S. Oliveira, *ARKIVOC* **2017**, 457 – 491; g) *Organoselenium Compounds in Biology and Medicine: Synthesis Biological and Therapeutic Treatments* (Eds.: V. K. Jain, K. I. Priyadarsini), Royal Society of Chemistry, Croydon, **2018**; h) Z. Chen, H. Lai, L. Hou, T. Chen, *Chem. Commun.* **2020**, *56*, 179 – 196; i) A. D. Landgraf, A. S. Alsegiani, S. Alaqel, S. Thanna, Z. A. Shah, S. J. Sucheck, *ACS Chem. Neurosci.* **2020**, *11*, 3008 – 3016; j) V. Alcolea, S. Pérez-Silanes, *Eur. J. Med. Chem.* **2020**, *206*, 112673.
[13] X. He, M. Zhong, S. Li, X. Li, Y. Li, Z. Li, Y. Gao, F. Ding, D. Wen, Y. Lei, Y. Zhang, *Eur. J. Med. Chem.* **2020**, *208*, 112864.
[14] a) *Visible Light Photocatalysis in Organic Chemistry* (Eds.: C. R. J. Stephenson, T. P. Yoon, D. W. C. MacMillan), Wiley-VCH, Weinheim, **2018**; b) P. Li, J. A. Terrett, J. R. Zbieg, *ACS Med. Chem. Lett.* **2020**, *11*, 2120 – 2130.
[15] Q. Q. Zhou, Y. Wei, L. Q. Lu, W. J. Xiao in *Science of Synthesis: Photocatalysis in Organic Synthesis Vol. 1*, Thieme Chemistry, Stuttgart, **2018**, pp. 167 – 218.
[16] Q.-Y. Han, K.-L. Tan, H.-N. Wang, C.-P. Zhang, *Org. Lett.* **2019**, *21*, 10013 – 10017.
[17] W. Tyrra, D. Naumann, Y. L. Yagupolskii, *J. Fluorine Chem.* **2003**, *123*, 183 – 187.
[18] a) Q. Glenadel, C. Ghiazza, A. Tlili, T. Billard, *Adv. Synth. Catal.* **2017**, *359*, 3414 – 3420; b) C. Ghiazza, A. Tlili, T. Billard, *Beilstein J. Org. Chem.* **2017**, *13*, 2626 – 2630; c) C. Ghiazza, V. Debrauwer, T. Billard, A. Tlili, *Chem. Eur. J.* **2018**, *24*, 97 – 100; d) X. Zhao, X. Wei, M. Tian, X. Zheng, L. Ji, Q. Li, Y. Lin, K. Lu, *Tetrahedron Lett.* **2019**, *60*, 1796 – 1799; e) J. Liu, M. Tian, A. Li, L. Ji, D. Qiu, X. Zhao, *Tetrahedron Lett.* **2021**, *66*, 152809.
[19] a) C. Ghiazza, V. Debrauwer, C. Monnereau, L. Khrouz, M. Médebielle, T. Billard, A. Tlili, *Angew. Chem. Int. Ed.* **2018**, *57*, 11781 – 11785; *Angew. Chem.* **2018**, *130*, 11955 – 11959; b) C. Ghiazza, L. Khrouz, C. Monnereau, T. Billard, A. Tlili, *Chem. Commun.* **2018**, *54*, 9909 – 9912; c) C. Ghiazza, C. Monnereau, L. Khrouz, M. Médebielle, T. Billard, A. Tlili, *Synlett* **2019**, *30*, 777 – 782; d) D. E. Yerien, S. Barata-Vallejo, A. Postigo, *J. Fluorine Chem.* **2020**, *240*, 109652.
[20] N. P. Ramirez, B. König, J. C. Gonzalez-Gomez, *Org. Lett.* **2019**, *21*, 1368 – 1373.
[21] J. B. Metternich, R. J. Mudd, R. Gilmour in *Science of Synthesis: Photocatalysis in Organic Synthesis Vol. 1*, Thieme Chemistry, Stuttgart, **2018**, pp. 391 – 404.
[22] a) J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025 – 2052; b) Y. Su, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Eur. J.* **2014**, *20*, 10562 – 10589; c) Z. J. Garlets, J. D. Nguyen, C. R. J. Stephenson, *Isr. J. Chem.* **2014**, *54*, 351 – 360; d) M. B. Plutschack, C. A. Correia, P. H. Seeberger, K. Gilmore in *Organometallic Flow Chemistry* (Ed.: T. Noël), Springer International Publishing, Cham, **2016**, pp. 43 – 76; e) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276 – 10341.
[23] A. H. Tolba, F. Vávra, J. Chudoba, R. Cibulka, *Eur. J. Org. Chem.* **2020**, 1579 – 1585.
[24] M. Galicia, F. J. González, *J. Electrochem. Soc.* **2002**, *149*, D46.

Manuscript received: January 6, 2021
Accepted manuscript online: February 4, 2021
Version of record online: March 3, 2021