

Review

Hydrotrifluoromethylation of Styrene and Phenylacetylene Derivatives under Visible-Light Photoredox Conditions

Amel Souibgui ^{1,2,3}, Mongi ben Mosbah ^{2,4}, Ridha ben Salem ² , Younes Moussaoui ^{2,3,*}  and Anis Tlili ^{1,*} 

- ¹ Institute of Chemistry and Biochemistry (ICBMS–UMR CNRS 5246), University Lyon, Université Lyon 1, CNRS, CPE-Lyon, INSA43 Bd du 11 Novembre 1918, 69622 Villeurbanne, France
- ² Organic Chemistry Laboratory (LR17ES08), Faculty of Sciences of Sfax, University of Sfax, Sfax 3029, Tunisia
- ³ Faculty of Sciences of Gafsa, University of Gafsa, Gafsa 2112, Tunisia
- ⁴ Laboratory for the Application of Materials to the Environment, Water and Energy (LR21ES15), Faculty of Sciences of Gafsa, University of Gafsa, Gafsa 2112, Tunisia
- * Correspondence: y.moussaoui2@gmx.fr (Y.M.); anis.tlili@univ-lyon1.fr (A.T.)

Abstract: Photoredox processes have emerged recently as a powerful tool for methodology developments. In this context, the hydrotrifluoromethylation of alkenes and alkynes using visible light photoredox methodologies has proven its efficiency these last years. This micro-review summarizes the latest developments in this field.

Keywords: hydrotrifluoromethylation; photocatalysis; visible light; styrene; phenylacetylene



Citation: Souibgui, A.; ben Mosbah, M.; ben Salem, R.; Moussaoui, Y.; Tlili, A. Hydrotrifluoromethylation of Styrene and Phenylacetylene Derivatives under Visible-Light Photoredox Conditions. *Chemistry* **2022**, *4*, 1010–1015. <https://doi.org/10.3390/chemistry4030068>

Academic Editors: Gianguido Ramis, Antonio Tripodi and Barbara Bonelli

Received: 6 July 2022

Accepted: 25 August 2022

Published: 6 September 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The incorporation of fluorinated motifs has gained widespread interest in the last decade [1]. This is mainly due to the increasing numbers of agrochemicals compounds or drugs that contains at least one fluorine atom [2–4]. The unique physico-chemical properties induced by fluorine or fluorinated motifs are the driving force for such interest. On the other hand, the renaissance of photocatalysis has emerged recently as robust tool for the construction of complex molecules through one electron process and turned out to be an interesting alternative to leverage the orthogonality of transition metal catalysis [5–11]. Regarding the hydrotrifluoromethylation of unsaturated compounds, several methodologies have been developed under photo-redox conditions. In the case of styrene and phenylacetylene derivatives, hydrotrifluoromethylation has turned out to be a more challenging transformation since unproductive polymerization or oxidation of the starting material are favored byproducts. The selective hydrotrifluoromethylation of styrene and arylacetylene derivatives have been addressed recently [12–14]. The key to success is controlling the key steps in the photoredox process employed. These developed methodologies allow one-pot access to aliphatic as well as vinylic trifluoromethylated compounds in an attractive and convenient way. Although these methods remain scarce, we highlight in this micro-review the recent general developed methods for the hydrotrifluoromethylation of aromatic alkenes and alkynes under visible-light photoredox processes.

2. Hydrotrifluoromethylation of Styrene Derivatives

The selective hydrotrifluoromethylation of styrenes derivatives has been disclosed by the group of Nicewicz in 2013 [15]. The use of commercially available and easy to handle Langlois's reagent **2**, CF₃SO₂Na, is highly advantageous. The generation of trifluoromethyl radical relies on the SET of the trifluoromethylating reagent by Fukuzumi organophotocatalyst *N*-Me-9-mesityl acridinium under blue LEDs irradiation (Figure 1). The reaction was performed in the presence of thiophenol as H-atom donor. The desired products **3a–g** were obtained in low to very good yields and the reactions tolerate the presence of chlorine, free alcohol (products **3b–3e**) as well as NPhth (**3f**) derivatives.

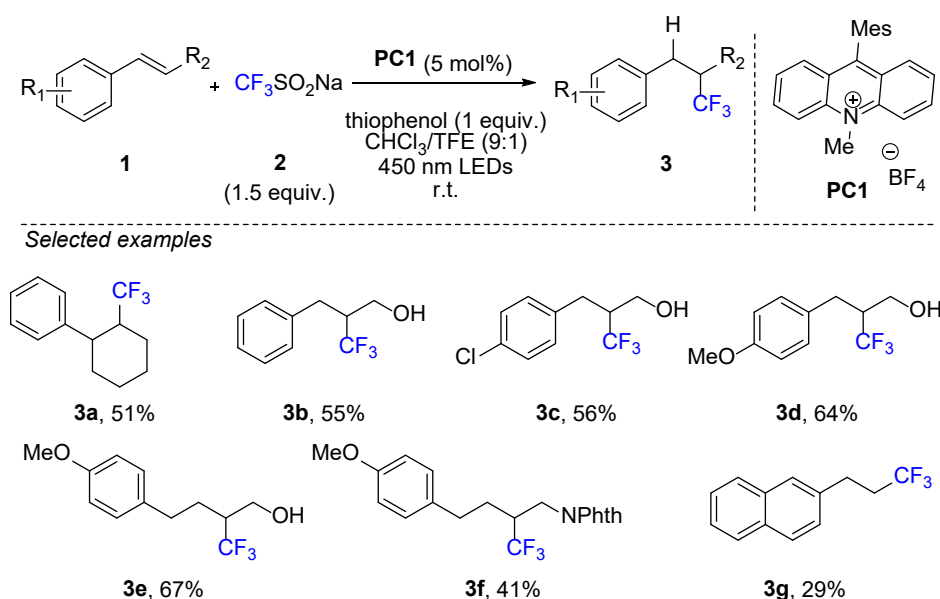


Figure 1. Hydrotrifluoromethylation of styrenes developed by the group of Nicewicz.

The Noël group developed another strategy for the hydrotrifluoromethylation of styrene derivatives. Their visible light protocol is based on the use of CF_3I as a trifluoromethylation reagent in the presence of $\text{fac-Ir}(\text{ppy})_3$ photocatalyst upon 24W CFL [16]. Herein, 4-hydroxythiophenol (4-HTP) was used as H-atom donor (Figure 2). The desired compounds were obtained in very good to excellent yields and the reaction conditions tolerated the presence of several functional groups, including free alcohols (**4c**), halogens bromo (**4d**) and chloro (**4e**), as well as heterocyclic starting materials such as 4-vinylpyridine (**4f**). Interestingly, the authors demonstrated that the hydrotrifluoromethylation could be performed using continuous-flow photo-micro-reactors, thus reducing the reaction time from 18 h to 50 min with similar reaction outcome (product **4a** obtained in 77% yield).

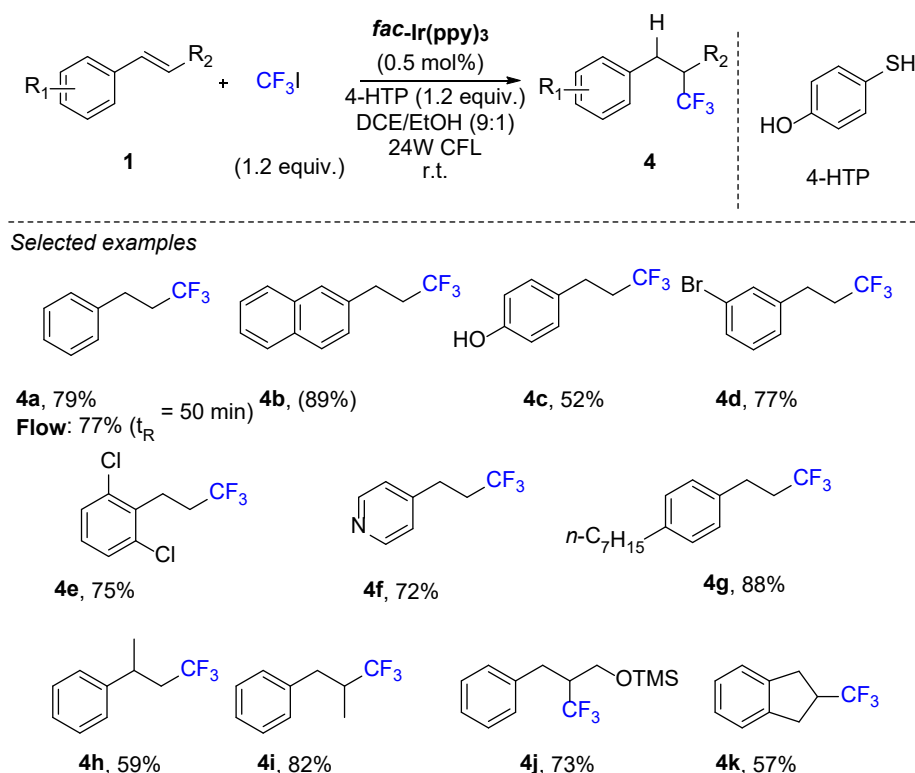


Figure 2. Hydrofluoroalkylation of styrenes developed by the group of Noël.

Afterwards, our group developed a direct strategy for the hydrotrifluoromethylation of styrene derivatives [17]. Interestingly, this strategy does not require the additive of thiophenol as HAT donor. The key to success was to perform the reaction in DMSO. The reactions have been conducted with 4-CzIPN as an organophotocatalyst under blue LED irradiation at room temperature for 48 h. Desired products **5aa–5cd** have been obtained in moderate to excellent yields. Interestingly, several Langlois sulfinate analogues have been successfully used under these conditions including CF_2H (products **5ba** and **5ca**), CFH_2 (products **5bb** and **5cb**), CF_2Me (products **5bc** and **5cc**) and $p\text{-BrPhCH}_2\text{CF}_2$ (products **5bd** and **5cd**). It should be mentioned that to some extent, the reaction tolerates the presence complex structure of the estrone derivatives (Figure 3).

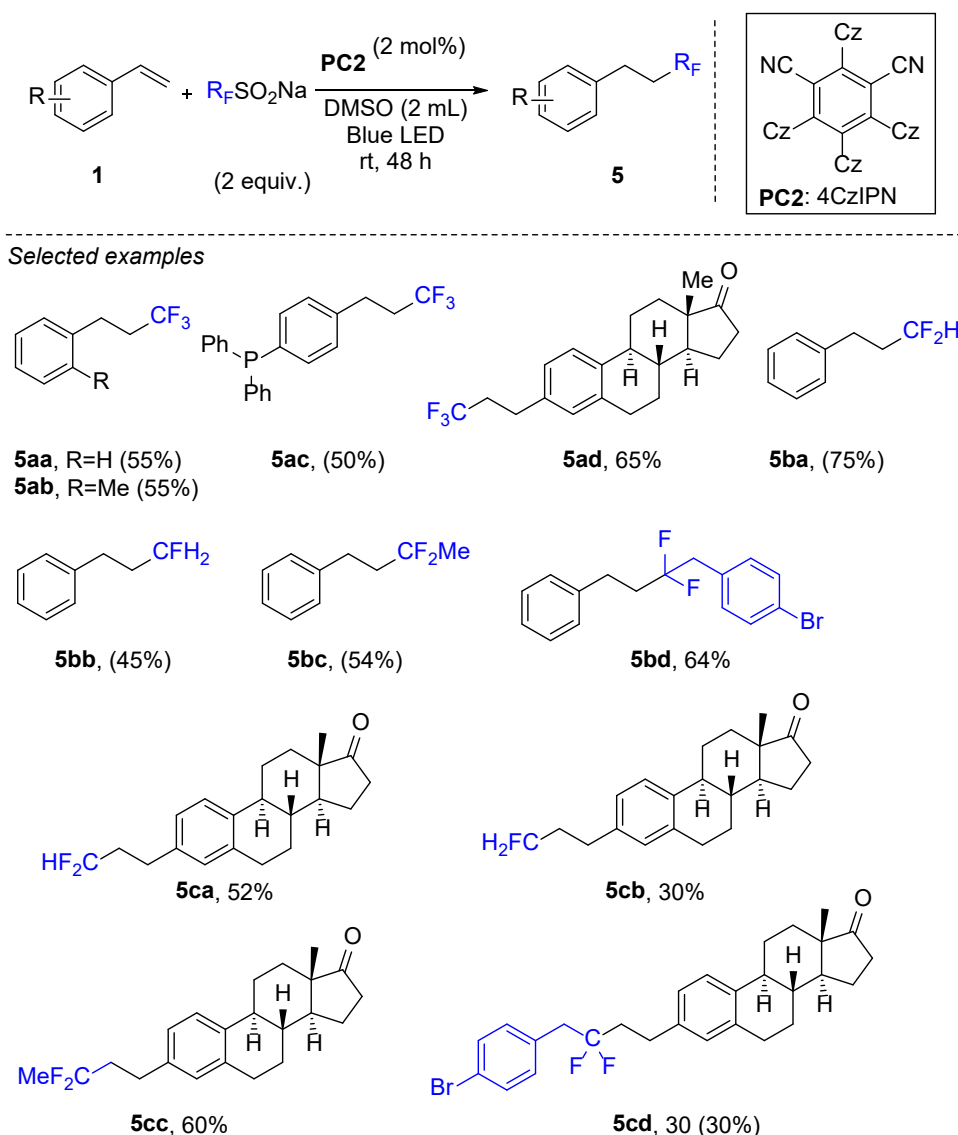


Figure 3. Hydrofluoroalkylation of styrenes developed by the group of Tlili.

From a mechanistic standpoint, and in contrast to previously described methods, no additive was required. Mechanistic investigation including luminescence, EPR spectroscopy confirmed the SET oxidation of the Langlois reagent with the excited organophotocatalyst 4CzIPN. Afterwards, the formed trifluoromethyl radical collapses to the styrene to afford radical **A** that could be reduced with radical anion photocatalyst producing anion **B** and furnishing the organophocatalyst at its ground state. Finally, protonation of the formed anion allows the formation of the desired product. Herein, it should be mentioned that

simply adding CO₂ allows the carboxylation of anion intermediate **B**. Moreover, adding deuterated water in the media allows the incorporation of the deuterium atom (Figure 4).

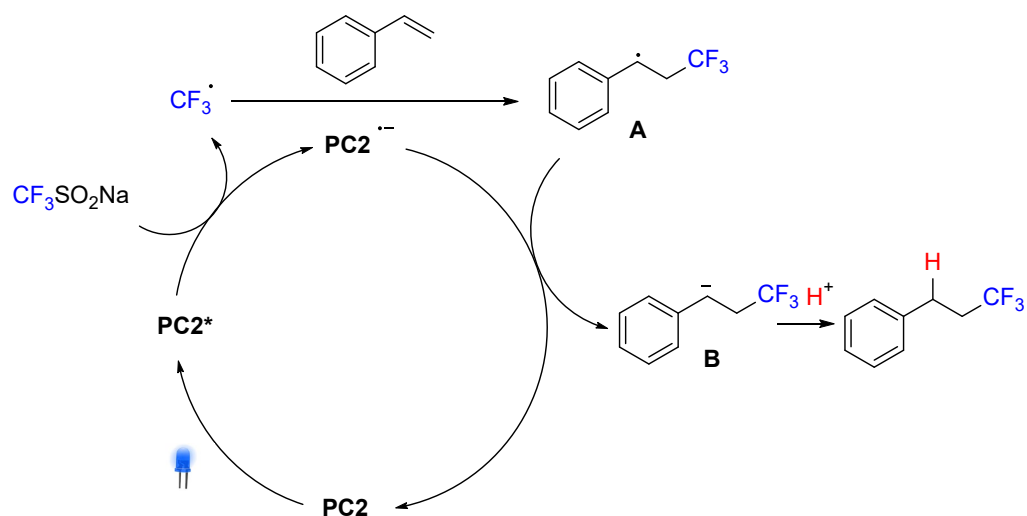
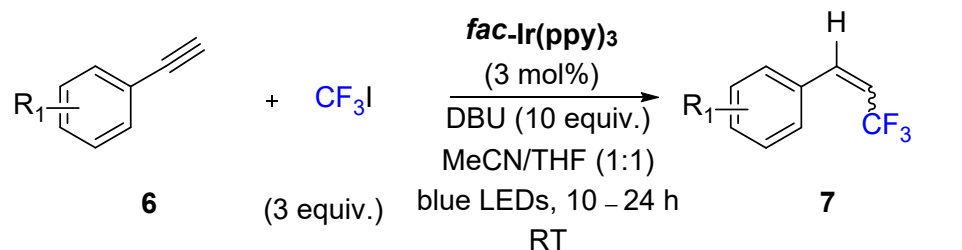


Figure 4. Proposed mechanism for the Hydrofluoroalkylation of styrenes developed by the group of Tlili.

3. Hydrotrifluoromethylation of Phenylacetylenes Derivatives

Regarding the hydrotrifluoromethylation of alkynes, Cho's group disclosed in 2014 a general method to access trifluoromethylated alkenes (products **7a–7e**) (Figure 5) [18]. Trifluoromethyl iodide was used as trifluoromethylation reagent in conjunction with *fac*-Ir(ppy)₃ under blue LEDs irradiation. The reaction requires the use of 10 equivalents of DBU, providing a mixture of *E* and *Z* alkenyl-CF₃ compounds in good to excellent yields.



Selected examples

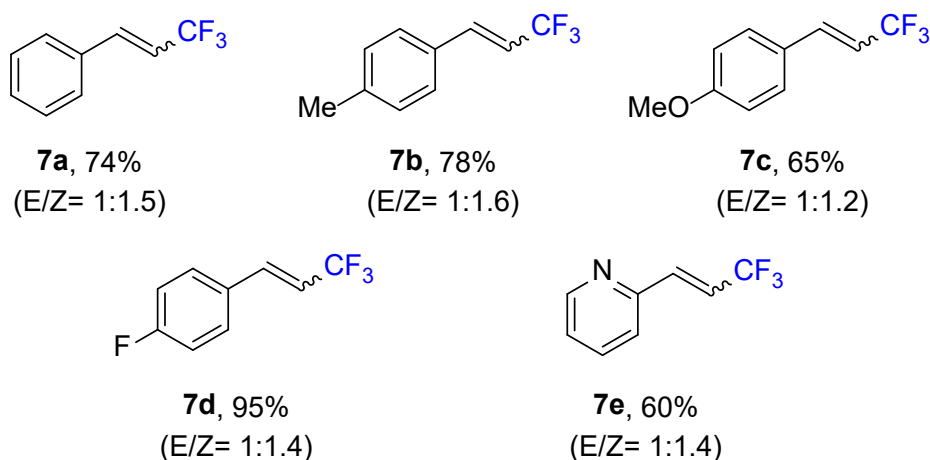


Figure 5. Hydrofluoroalkylation of alkynes developed by Cho's group.

The authors proposed the following mechanism (Figure 6). DBU reduces the excited photocatalyst yielding DBU⁺ and [Ir(ppy)][−]. The photocatalyst radical anion reduces the

CF_3I yielding trifluoromethyl radical that collapses to the phenylacetylene, yielding to a vinyl radical. The desired product could be obtained through radical abstraction from the amine radical cation. It should be mentioned that another plausible mechanism was also disclosed. Indeed, the abstraction of the iodide by the trifluoromethylvinyl radical can also furnish the alkenyl iodide. Herein, deiodination would take place by the radical anion $[\text{Ir}(\text{ppy})_3]^-$ (Figure 6).

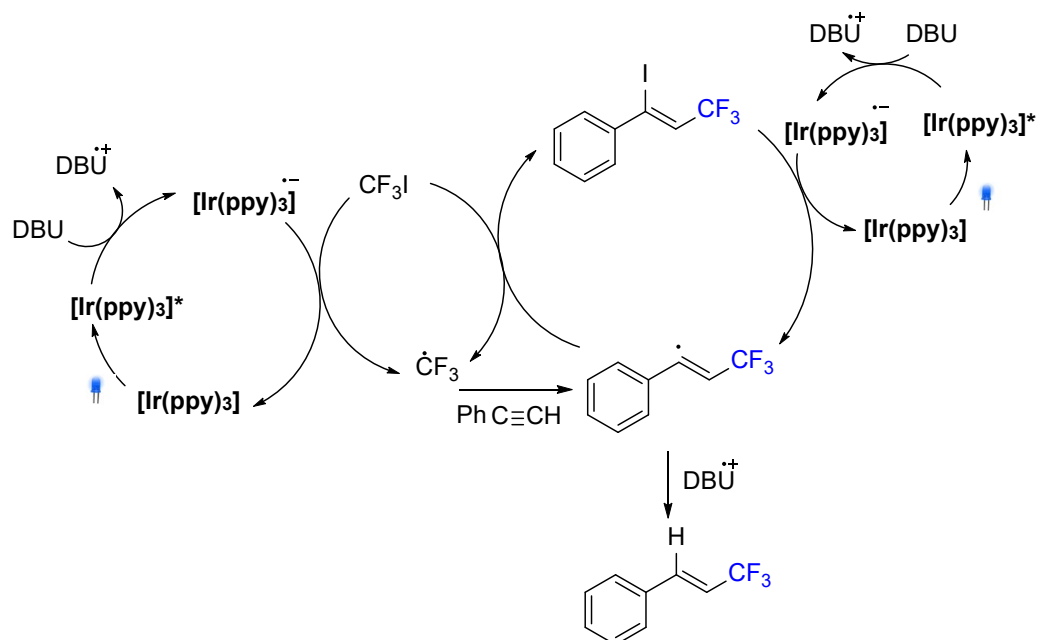
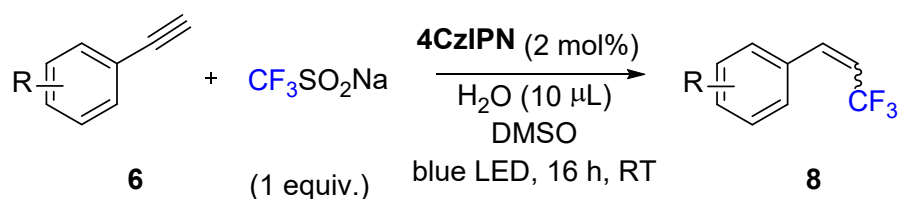


Figure 6. Hydrotrifluoromethylation of alkynes developed by Cho's group.

In parallel to the work of Cho's group, we recently turned our attention to study the effectiveness of the protocol developed based on the use of organophotocatalysts in our laboratory for the hydrotrifluoromethylation of styrene derivatives toward phenylacetylene derivatives (Figure 7) [19]. The hydrotrifluoromethylation of phenylacetylene yields the desired product **8a** in 60% with a mixture of E/Z isomers. Herein, adding a few equivalents of water was necessary to obtain the best reaction outcome. Unfortunately, the use of other arylacetylene derivatives **8b** and **8c** furnished only traces to very low yields.



Selected examples

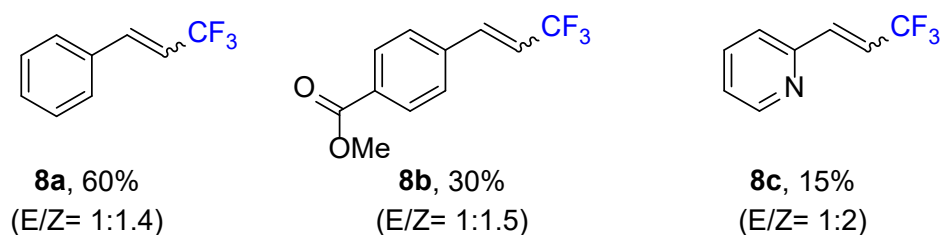


Figure 7. Hydrofluoroalkylation of styrenes developed by the group of Tlili.

4. Conclusions

In conclusion, the use of visible-light photoredox has demonstrated its robustness for the hydrotrifluoromethylation of styrene and phenyl acetylene derivatives by using commercially available and easily accessible photoredoxcatalysts. The developed protocols are also easy to implement and make use also of easy-to-handle commercially available starting materials. The use of HAT allows us to obtain a better reaction outcome. Future developments should take this important point into consideration and more convenient HAT precursors should be used. Furthermore, the use of a more efficient catalyst, especially with higher TONs, should be considered for future developments. Finally, the use of these methodologies for the synthesis of bio-active compounds will definitely foster the emergence of molecules of interest bearing trifluoromethyl or fluoroalkyl motif.

Author Contributions: The manuscript was written through the contribution of all the co-authors. All authors have read and agreed to the published version of the manuscript.

Funding: Financial support from the CNRS and the Agence Nationale de la Recherche (ANR-JCJC-2020-CDI-DEOX) is gratefully acknowledged. A.S. thanks the Tunisian Ministry of Higher Education and Research for financial support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* **2008**, *37*, 308–319. [[CrossRef](#)] [[PubMed](#)]
2. *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*; Haufe, G.; Leroux, F. (Eds.) Elsevier Science: London, UK, 2018; pp. 459–518.
3. Leo, A.; Hansch, C.; Elkins, D. Partition coefficients and their uses. *Chem. Rev.* **1971**, *71*, 525–616. [[CrossRef](#)]
4. Hagemann, W.K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369. [[CrossRef](#)] [[PubMed](#)]
5. Tlili, A.; Lakhdar, S. Acridinium Salts and Cyanoarenes as Powerful Photocatalysts: Opportunities in Organic Synthesis. *Angew. Chem. Int. Ed.* **2021**, *60*, 19526–19549. [[CrossRef](#)] [[PubMed](#)]
6. Vega-Peçaloza, A.; Mateos, J.; Companyó, X.; Escudero-Casao, M.; Dell'Amico, L. A Rational Approach to Organo-Photocatalysis: Novel Designs and Structure–Property Relationships. *Angew. Chem. Int. Ed.* **2021**, *60*, 1082–1097. [[CrossRef](#)] [[PubMed](#)]
7. Marzo, L.; Pagire, S.K.; Reiser, O.; König, B. Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis? *Angew. Chem. Int. Ed.* **2018**, *57*, 10034–10072. [[CrossRef](#)] [[PubMed](#)]
8. Shaw, M.H.; Twilton, J.; MacMillan, D.W.C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898–6926. [[CrossRef](#)] [[PubMed](#)]
9. Romero, N.A.; Nicewicz, D.A. Organic Photoredox Catalysis. *Chem Rev.* **2016**, *116*, 10075–10166. [[CrossRef](#)] [[PubMed](#)]
10. Poliakov, M.; George, M.W. Manufacturing chemicals with light: Anyrole in the circular economy? *Phil. Trans. R. Soc.* **2020**, *378*, 20190260. [[CrossRef](#)] [[PubMed](#)]
11. Yungyeong, L.; Min, S.K. Emerging Organic Photoredox Catalysts for Organic Transformations. *Eur. J. Org. Chem.* **2020**, *2020*, 6028–6043.
12. Courant, T.; Masson, G. Recent Progress in Visible-Light Photoredox-Catalyzed Intermolecular 1,2-Difunctionalization of Double Bonds via an ATRA-Type Mechanism. *J. Org. Chem.* **2016**, *81*, 6945–6952. [[CrossRef](#)] [[PubMed](#)]
13. Koike, T.; Akita, M. Fine Design of Photoredox Systems for Catalytic Fluoromethylation of Carbon–Carbon Multiple Bonds. *Acc. Chem. Res.* **2016**, *49*, 1937–1945. [[CrossRef](#)] [[PubMed](#)]
14. Choi, S.; Kim, Y.J.; Kim, S.M.; Yang, J.W.; Kim, S.W.; Cho, E.J. Hydrotrifluoromethylation and iodotrifluoromethylation of alkenes and alkynes using an inorganic electride as a radical generator. *Nat. Commun.* **2014**, *5*, 4881. [[CrossRef](#)] [[PubMed](#)]
15. Wilger, D.J.; Gesmundo, N.J.; Nicewicz, D.A. Catalytic hydrotrifluoromethylation of styrenes and unactivated aliphatic alkenes via an organic photoredox system. *Chem. Sci.* **2013**, *4*, 3160. [[CrossRef](#)]
16. Straathof, S.N.J.W.; Cramer, E.; Hessel, V.; Noel, T. Practical Photocatalytic Trifluoromethylation and Hydrotrifluoromethylation of Styrenes in Batch and Flow. *Angew. Chem. Int. Ed.* **2016**, *55*, 15549–15553. [[CrossRef](#)] [[PubMed](#)]
17. Louvel, D.; Souibgui, A.; Taponard, A.; Rouillon, J.; ben Mosbah, M.; Moussaoui, Y.; Pilet, G.; Khrouz, L.; Monnereau, C.; Vantourout, J.C.; et al. Tailoring the Reactivity of the Langlois Reagent and Styrenes with Cyanoarenes Organophotocatalysts under Visible-Light. *Adv. Synth. Catal.* **2022**, *364*, 139–148. [[CrossRef](#)]
18. Iqbal, N.; Jung, J.; Park, S.; Cho, E.J. Controlled Trifluoromethylation Reactions of Alkynes through Visible-Light Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2014**, *53*, 539–542. [[CrossRef](#)] [[PubMed](#)]
19. Souibgui, A.; ben Mosbah, M.; Moussaoui, Y.; Tlili, A. *unpublished results*.