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Tailoring the Reactivity of the Langlois Reagent and Styrenes With Cyanoarenes Organophotocatalysts under Visible-Light.

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Abstract. The selective one-step access to fluoroalkylated hexestrol derivatives, nonsteroidal estrogens, is achieved in good to excellent isolated yields under organophotoredox conditions by using the stable and easy to handle Langlois reagent. Furthermore, the challenging selective hydrotrifluoromethylation of styrenes proceeds under mild reaction conditions without the requirement for any additive. We assume that the solvent drives the reaction pathway towards either the reduction or the dimerization of the radical intermediate generated after initial addition of the fluoroalkyl radical to the styrene. The versatility of the developed system is also extended to encompass radical-radical cross-coupling as exemplified here using cyanopyridine. Mechanistic investigations including luminescence and EPR spectroscopy allow to shed the light on the different mechanisms.

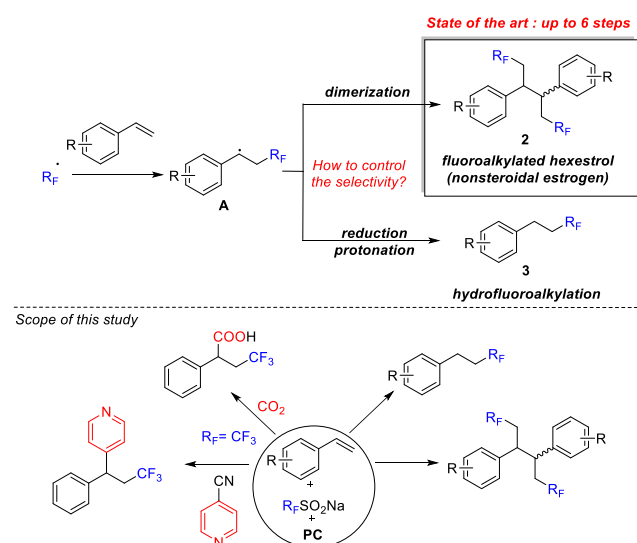
Keywords: Trifluoromethylation; Organophotocatalysis; Cyanoarenes; Styrenes; Radicals

Introduction

Over the past few years, the functionalization of styrene-based compounds has generated a lot of interest in the scientific community due to the impact it generates in areas such as medicinal chemistry and material science.^[1] In addition, the direct incorporation of trifluoromethyl groups and derivatives has witnessed widespread interest over the last decades.^[2] Indeed, fluoroalkylation of organic molecules is finding numerous applications in cutting-edge technologies from life sciences to material applications^[3] as the presence of a fluoroalkyl group on a molecule can alter its physico-chemical properties and provide it with higher lipophilicity as well as greater metabolic stability.^[4] The development of selective fluorinative strategies for the functionalization of styrene molecules is therefore highly desirable.

In this context, transition metal catalyzed direct trifluoromethylation has been employed for a long time to forge C-fluoroalkyl bonds.^[2b]

Figure 1. Reactivity of fluoroalkyl radical with styrene and scope of this study.



More recently, photocatalysis^[5] turned out to be an attractive alternative to leverage the orthogonality of transition metal catalysis through the selective generation of a fluoroalkyl radical, which, in the presence of a suitable reactant, can lead to the desired product.^[6] Although a plethora of methodologies have been developed in the last decade for the selective fluoroalkylation of aliphatic alkenes and alkynes under photoredox conditions^[7], the use of styrene reactants turns out to be highly challenging. Indeed, unlike aliphatic alkenes, unproductive polymerization or oxidation processes are favored, which constitutes a major hurdle towards more elaborate radical-based functionalizations. While nucleophilic trapping has been used for the functionalization of styrene, the

hydrotrifluoromethylation of styrene derivatives has been scarcely studied. This challenge has been addressed by Choi *et al.*^[8] who used inorganic electride as a radical generator (3 equivalents) in their procedure to achieve this transformation. More recently, the group of Noël^[9] used an iridium-based photocatalyst in the presence of 4-hydroxythiophenol as an external hydrogen donor in batch or continuous flow. It should be mentioned that both procedures require the use of gaseous trifluoromethyl iodide.

In parallel to hydrotrifluoromethylation reactions, the selective dimerization of trifluoromethyl styrenes is another interesting area as it allows the direct and straightforward access to fluoroalkylated hexestrol derivatives.^[10] Those compounds are known to be nonsteroidal estrogens^[11a] that so far have been exclusively isolated as byproducts in marginal amounts or after laborious 6-step synthetic sequences.^[6,12] In this context, a direct and straightforward strategy towards either fluoroalkylated hexestrol derivatives or for the hydrotrifluoromethylation of styrenes will constitute an important step forward, especially using cheap and easy-to-handle fluoroalkyl sources.

We recently started a new research program that aims to use organic photocatalysts for the fluorination/fluoroalkylation of organic molecules.^[13] As a new step forward, we demonstrate herein that cyanoarenes^[14,5a] are efficient organophotocatalysts to selectively achieve the unprecedented synthesis of fluoroalkylated hexestrol derivatives or the hydrofluoroalkylation of styrenes depending on the solvent choice. Indeed, we demonstrate herein that solvent can directly impact the reaction mechanism and drive it either towards either the reduction or dimerization process. Furthermore, we demonstrate that our system could also be further applied to other types of radical styrene substitutions, including carboxylative trifluoromethylation and radical-radical cross-coupling with cyanopyridine, enabling unprecedented access to complex molecular structures.^[15]

Results and Discussion

We started our study by investigating the direct access to fluoroalkylated hexestrol derivatives. Styrene was selected as model substrate in the presence of the cheap and easy-to-handle trifluoromethylating Langlois reagent (sodium trifluoromethanesulfinate, CF_3SO_2Na).^[16] This latter exhibits an oxidation potential of 1.05 V in DMF (vs. SCE). In this context, we selected **PC1** with a redox potential ($E_{1/2}$ (**PC1**[•]/**PC1**^{•-})) of +1.10 V, which makes it able to oxidize the Langlois reagent under photoactivation conditions.^[17] We were glad to observe that running the reaction upon blue LED irradiation at room temperature in MeCN allowed the formation of the desired product **2e** in an overall excellent yield of 95%. The reaction does not require the presence of any additives and gives rise, beside the *meso* form, to a pair of *d,l* enantiomers (with

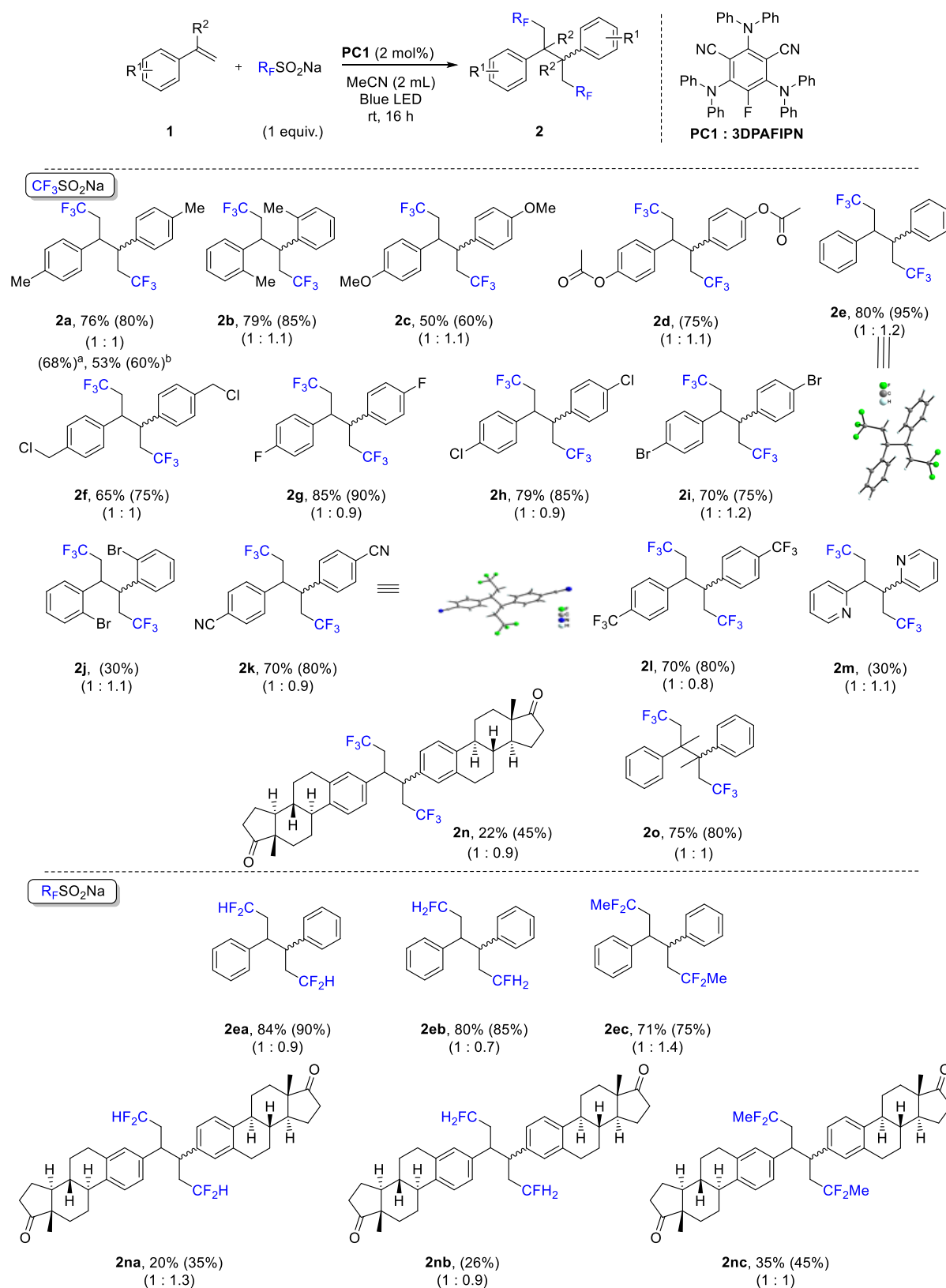
a ratio of 1:1.2). Although an excellent yield was already obtained in those native conditions, we decided to investigate the impact of different parameters on the reaction outcome but also to screen other organophotocatalysts. We first considered the effects of solvent. Only traces of the desired product were detected when substituting MeCN by MeOH (10%, table 1 entry 2) while no noticeable formation of the target product was observed in toluene (table 1, entry 3). Only DMF was effective under our conditions and delivered an excellent yield of 85% (table 1, entry 4). Afterwards, other organophotocatalysts were tested. **PC2** (4CzIPN) was to some extent also competent under our conditions although product formation dropped to 75% (table 1, entry 5). Surprisingly, Eosin Y was not effective, and no product formation was observed (table 1, entry 6). Sparr's organophotocatalysts which have shown similar reactivity to that of cyanoarenes derivatives^[18] were also investigated: while **PC4** allows to obtain the desired product in only 30% yield, a higher conversion of 60% was observed with **PC5** (table 1, entry 8). Noteworthy, blank experiments in the absence of light and/or organophotocatalyst did not allow the formation of the desired product (Table 1, entries 9 & 10) ascertaining the crucial role of photoinduced electron transfer processes in the reaction.

Table 1. Reaction optimization

Entry ^[a]	Deviation from standard conditions	Yield [%] ^[b]
1	None	95 (80)
2	MeOH instead of MeCN	10
3	PhMe instead of MeCN	0
4	DMF instead of MeCN	85
5	PC2 instead of PC1	75
6 ^[c]	PC3 instead of PC1	0
7	PC4 instead of PC1	30
8	PC5 instead of PC1	60
9	No light	0
10	No PC1	0

[a] Reactions were performed with styrene **1** (0.2 mmol, 1 equiv.), CF₃SO₂Na (0.2 mmol, 1 equiv.), **PC1** (2 mol%) and MeCN (2 mL) unless otherwise noted. The reaction mixture was stirred at room temperature for 16 hours under blue LED irradiation and inert conditions; [b] Yields determined by ¹⁹F NMR spectroscopy with PhOCF₃ as internal standard; [c] Under green LED irradiation. Isolated yield shown in parentheses.

With the best conditions in hand, we turned our attention to studying the scope of the reaction. Styrenes substituted with electron donating groups including methyl, methoxy or acetoxy were effectively transformed under our conditions and the desired products were obtained in good to excellent yields, up to 85% (Scheme 1, compounds **2a-c**).



Scheme 1. Reaction scope. Reactions were performed with styrene derivatives **1** (0.2 mmol, 1 equiv.), R_FSO_2Na (0.2 mmol, 1 equiv.), **PC1** (2 mol%) and ACN (2 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 ^{19}F NMR spectroscopy with

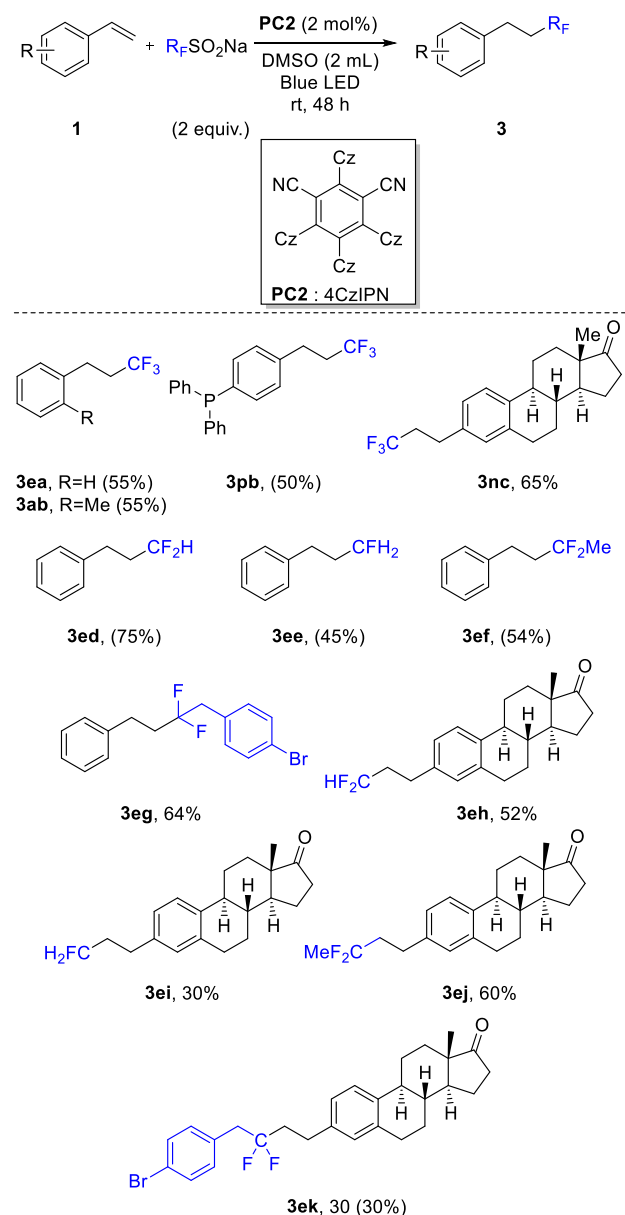
PhOCF₃ as internal standard are shown in parentheses. *meso* and *d,l* enantiomers ratio was calculated from the crude. ^a 0.5 mmol scale. ¹ 1 mmol scale.

Steric hindrance was also tolerated, as the presence of methyl in *ortho* position of the styrene allow to obtain the desired product in an excellent yield of 88% (Scheme 1, compound **2b**). Interestingly, the *meso* form of compound **2e** turned out to be solid. Hence, X-ray analysis allowed us to fully confirm the expected structure of **2e** (Scheme 1). Afterwards, the reaction tolerance towards the presence of halogen substituents was also investigated, either using a C(Csp³)-Cl or C(Csp²)-Cl, Br or F containing reactants. Good to excellent yields were obtained with halogenated styrenes substituted in para position (compounds **2f-i**). 2-Bromostyrene was also effective under our reaction conditions and the desired product was obtained in a synthetically useful yield of 30% (compound **2j**). We showed that our procedure also tolerates electron deficient styrenes with both 4-cyanostyrene and 4-trifluoromethylstyrene affording the corresponding hexestrol derivatives in good to excellent yield (compounds **2k** & **2l**). Heterocyclic 2-vinylpyridine also allows to obtain the desired product albeit in a lower yield of 30% (**2m**). Interestingly, we also demonstrated that our protocol can be applied to complex molecular structures with estrone derivative **2n** obtained in 45% yield. Moreover, 1,1-disubstituted styrene could also be smoothly transformed to the desired product **2o** in an excellent yield of 80%.

Then, we evaluated the impact of the starting sulfinate on the reaction outcome (Scheme 1), since the use of several sulfinate precursors would open many perspectives from a molecular diversity point of view. Hexestrol derivatives containing CF₂H, CH₂F as well as MeCF₂ and *p*-BrBnCF₂ could be obtained in good to excellent yield (Scheme 1, **2ea-2ec**) and the same protocol could be extended to complex molecular structures (Scheme 1, **2na-2nc**).

After having demonstrated the general efficiency and robustness of our functionalization/dimerization protocol to directly access fluorinated hexestrol derivatives, we turned our attention towards the selective hydrotrifluoromethylation of styrenes. This strategy relies on the working hypothesis that the selective reduction of the generated benzylic radical obtained after addition of trifluoromethyl radical to styrene should be a crucial step to avoid subsequent dimerization of this highly reactive intermediate. It has been reported recently that the difunctionalization of styrenes derivatives could be performed with **PC2** (4CzIPN) in DMSO through the generation of benzylic

anion from its corresponding benzylic silanes derivatives.^[19] Under our conditions, the reduction of the radical intermediate A (Figure 3, *vide infra*) should be even thermodynamically favoured given the electron withdrawing nature of the trifluoromethyl group, yielding to a benzylic anion that should afford the desired hydrotrifluoromethylation product after protonation, avoiding the use of an external additive (HAT donor).^[13]



Scheme 2 Reaction scope. Reactions were performed with styrene derivatives **1** (0.2 mmol, 1 equiv.), **R_FSO₂Na** (0.4 mmol, 2 equiv.), **PC2** (2 mol%) and DMSO (2 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.

To our satisfaction, we were able to confirm this working hypothesis by simply switching MeCN to DMSO under the exact same reaction conditions as our functionalization/dimerization procedure. Under these conditions, **3ea** was obtained in 40% yield. After optimization, we demonstrated that using **PC2** (2 mol%) and an excess of the Langlois reagent (2 equiv.) in DMSO for 48 hours at room temperature afforded **3ea** in 55% yield.

With these optimized conditions in hand, we next studied the scope of the hydrotrifluoromethylation of styrenes with the Langlois reagent. *Ortho*-substituted styrene allowed the formation of the desired product in 55% yield (product **3ab**). The presence of diphenylphosphine in *para* position was also tolerated under our conditions and afforded desired product **3pb** in 50% yield. Desired product **3nc**, issued from the functionalization of estrone derivative, was obtained in a good yield of 65%.

To demonstrate further the utility of this new methodology we decided to investigate the sulfinate scope. All tested sulfonates were effective under our reaction conditions and the desired products were obtained in moderate to very good yield either starting with simple styrene or the estrone derivatives. As a major outcome of this work, new compounds containing CF₂H, CFH₂, MeCF₂ and CF₂ArBr could be obtained for the first time under our protocol demonstrating again the robustness of the developed methodology.

To shed light on the origin of the observed reactivities, we turned our focus to study the different reactions' mechanisms by spectrofluorimetry, chemical actinometry (using ¹⁹F NMR), EPR spectroscopy and isotopic labelling. Fluorimetric titrations were first performed in an attempt to bring evidence for the occurrence of an electron transfer (ET) process between **PC1** and Langlois reagent in MeCN (the weak luminescence of photocatalyst **PC2** in DMSO turned out to be incompatible with such measurements). Stern Volmer experiments were in all cases performed in thoroughly deaerated solution of the photocatalyst, as the presence of oxygen was seen to markedly quench the fluorescence of **PC1**, as a consequence of a reported reverse Intersystem Crossing (rISC) mechanism.^[20] Unfortunately, to our surprise, no sign of luminescence quenching was observed even upon addition of large excess (up to 10⁻¹M) of Langlois reagent. Similar experiments carried out with styrene as a potential electron donor/acceptor, or with a mixture of styrene and CF₃SO₂Na led to similar results. This suggests that if ET takes place, it occurs with very low efficiency, several orders of magnitude below classical diffusion control processes.

We thus turned our attention to evaluating the photochemical quantum yields of the studied reactions, namely (i) the hydrotrifluoromethylation of styrene in

DMSO (conditions I) and (ii) the formation of trifluoromethylated styrene dimer in acetonitrile (conditions II). Both studies were performed by using ¹⁹F NMR to follow the reaction ensuing irradiation of a NMR tube containing the reaction mixture (reagent **1e**, **PC1** or **PC2** and Langlois reagent) in the corresponding deuterated solvent (**PC1**: MeCN-d₃ or **PC2**: DMSO-d₆), using our recently reported NMR actinometric set-up^[21], that we adapted to study photoinduced ET mediated chemical transformations^[8a] (SI for details about the procedure).

In both cases, transformations operated very cleanly upon prolonged irradiation of the NMR sample to provide either compound **2e** (in MeCN-d₃, figure S1A, SI) or compound **3ea** (in DMSO-d₆, figure S1B, SI), in a kinetic that could be in both cases satisfactorily fitted to a first-order trend. Very similar quantum yield were obtained in both cases: conditions I, Φ_p = 0.7x10⁻²;^[22] conditions II, Φ_p = 1.3x10⁻²; Interestingly this extremely low value matches with the very inefficient ET process suggested throughout the spectrofluorometric experiments. It is particularly remarkable, considering the inefficiency of the process, that both reactions afford a single product that can be isolated in synthetically relevant yield, which underlines the exquisite selectivity of the associated chemical transformation.

With these results, several questions had to be addressed to be able to propose plausible mechanisms for both reactions. SET oxidation of the Langlois reagent is thermodynamically favoured and generates a trifluoromethyl radical that could collapse to the styrene to form a new C-centred-benzylic radical. This C-centred intermediate **A** (Figure 1) cannot be involved in another SET process with the catalyst since dimerization affords the desired fluorinated hexestrol derivatives. Given the nature of the stepwise mechanism, another species is required to regenerate the organophotocatalyst. Herein, the solvent or SO₂ generated after oxidation of the Langlois reagent could be involved. With respect to the hydrotrifluoromethylation of styrene, the involvement of a HAT process with DMSO or reduction of the C-centred radical **A** generated from addition of the trifluoromethyl radical to styrene are plausible mechanisms.

Therefore, investigation was devoted to characterizing the radical intermediates involved in our reaction by EPR spectroscopy, using radical trapping agents. As mentioned earlier, SET from the Langlois reagent derivatives to the catalyst is thermodynamically favoured. Consequently, a single trifluoromethyl adduct **B** (Figure 2, a) was obtained with DMPO when the Langlois reagent was irradiated with blue LED in the presence of **PC1** in MeCN (g=2.0065, a_N=13.6G a_H=15.85 G, a_{3F}=0.93G), with features compatible with those reported for CF₃ radicals, constituting a first direct evidence for the occurrence of a SET step between the excited photocatalyst and Langlois reagent. Additional experiments were carried out using CF₂HSO₂Na as sulfinate source, which also demonstrated the formation of a single major adduct either with DMPO (adduct **C**,

$g=2.0064$, $a_N=14.1\text{G}$, $a_H=18.6\text{G}$ $a_F=0.6\text{G}$) or PBN (adduct **D**, $g=2.006$, $a_N=14.62\text{G}$ $a_H=2.8\text{G}$, $a_F=0.98\text{G}$) confirming again the generation of the perfluoroalkyl radical (Figure 2, b & c).^[23]

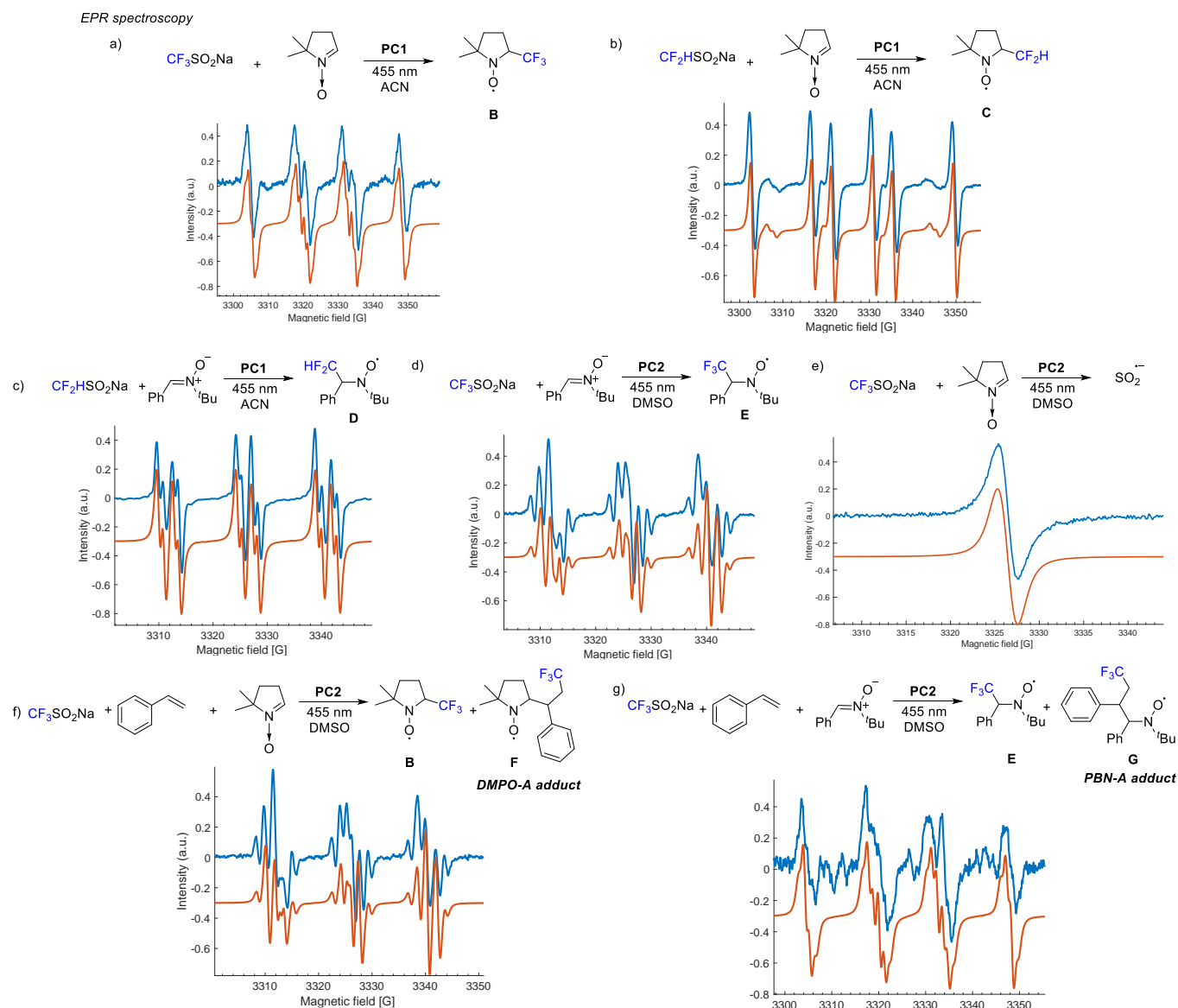


Figure 2. EPR spin-trapping spectra upon irradiation ($\lambda=455\text{ nm}$) in the presence of BPN or DMPO in MeCN or DMSO at room temperature. Blue = experimental, red = simulated.

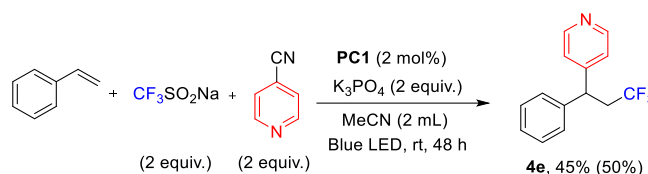
Similarly we were also able to demonstrate that using **PC2** in DMSO allows the formation of a trifluoromethyl radical adduct with PBN **E** (figure 2, d) ($g=2.0062$, $a_N=14.23\text{G}$ $a_H=2.15\text{G}$, $a_{3F}=1.55\text{ G}$).^[24] Surprisingly, performing the same reaction with DMPO as a spin-trapping agent allowed us to observe the formation of a different species with features compatible with $\text{SO}_2^{\cdot-}$ ($g=2.0061$) (figure 2, e), while no clear signature could be observed for the trifluoromethyl radical. This species may result from

the reduction of SO_2 generated after oxidation of the Langlois reagent. Reduction of SO_2 is favoured either with **PC1** or **PC2** since both radical anions of these two photocatalysts could reduce SO_2 ($E_{\text{red}} = -0.8\text{ V}$).^[25] Furthermore, $\text{SO}_2^{\cdot-}$ is prone to evolve by dimerization, yielding dithionite $\text{S}_2\text{O}_4^{2-}$ as a white solid which was observed at the end of the reaction.^[26] To get more insight on the missing signature of the trifluoromethyl radical under this condition, we decided to investigate the same SET reaction but this time in the presence of

styrene (**Figure 2, f**). In addition to the signal of adduct **B** obtained in the previous irradiation experiment, we detected the formation of DMPO-A adduct **F** as plausible intermediate in our reaction ($g=2.0061$, $a_N=14G$ $a_H=16G$, present in 20%). Similarly, the same signature was observed with PBN where the corresponding adduct **G** (PBN-A adduct, $g=2.006$, $a_N=14.8G$ $a_H=2.2G$, present in 40%) was observed in the presence of the previously characterized **E** (**Figure 2, g**).^[27]

The aforementioned results allowed us to propose the following mechanisms. Regarding the synthesis of fluorinated hexestrol derivatives, SET oxidation of the Langlois reagent by the excited **PC1** allow the formation of CF_3 radical. This latter collapses to the styrene to generate intermediate **A**. Then **A** dimerizes yielding both *meso* and *d,l* enantiomers. The catalyst is regenerated through reduction of SO_2 (generated as a side product in Langlois reagent oxidation, in the first step of the photocatalytic cycle) yielding dithionite as by-product of the reaction.

Interestingly we also demonstrated that it is possible to take advantage of the presence of intermediate **A** to facilitate the reduction of cyanopyridines by **PC1**⁻ (**Figure 3, II**).^[28] This alternative reactivity allows difunctionalization of styrene via a three component sequence and desired compound **4e** was obtained in 50% yield using K_3PO_4 as a base (**Scheme 3**).^[29]



Scheme 3 Reaction was performed with styrene **1** (0.2 mmol, 1 equiv.), CF_3SO_2Na (0.4 mmol, 2 equiv.), **PC1** (2 mol%) 4-cyanopyridine (0.4 mmol, 2 equiv.), K_3PO_4 (0.4 mmol, 2 equiv.) and MeCN (2 mL). The reaction mixture was stirred at room temperature for 48 hours under blue LED irradiation and inert condition. Yield shown is of isolated product. Yield determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as internal standard is shown in parenthesis

Regarding the hydrotrifluoromethylation of styrene, **PC2** is also able to oxidize the Langlois reagent to generate intermediate **A**, which in DMSO will be reduced as a closing step of the photocatalytic cycle, yielding a benzylic anion **H**, which can be protonated to afford the target compound. Reactions performed in $DMSO-d_6$ rule out the possibility that DMSO is involved in a HAT process, as product **3ea** was formed as sole product, without any sign of deuteration (**Figure 3, III.1**). Herein the formation of the carbanion is more plausible.^[13] This hypothesis was further confirmed when the reaction was performed under a CO_2 atmosphere where compound **5a** was obtained in 45% yield. This constitutes a strong indication that the reaction proceeds through nucleophilic attack of CO_2 by the anionic intermediate **H**. (**Figure 3, III.2**).^[30] It should be mentioned that performing the same reaction in ACN did not allow any formation of compound **5a**. Finally, performing the reaction in the presence of 3 equiv. of D_2O allows the incorporation of deuterium with compound **[D]3ea** obtained in 45% yield (77% incorporation of deuterium) (**Figure 3, III.**) reinforcing the formation of the carbanion intermediate.

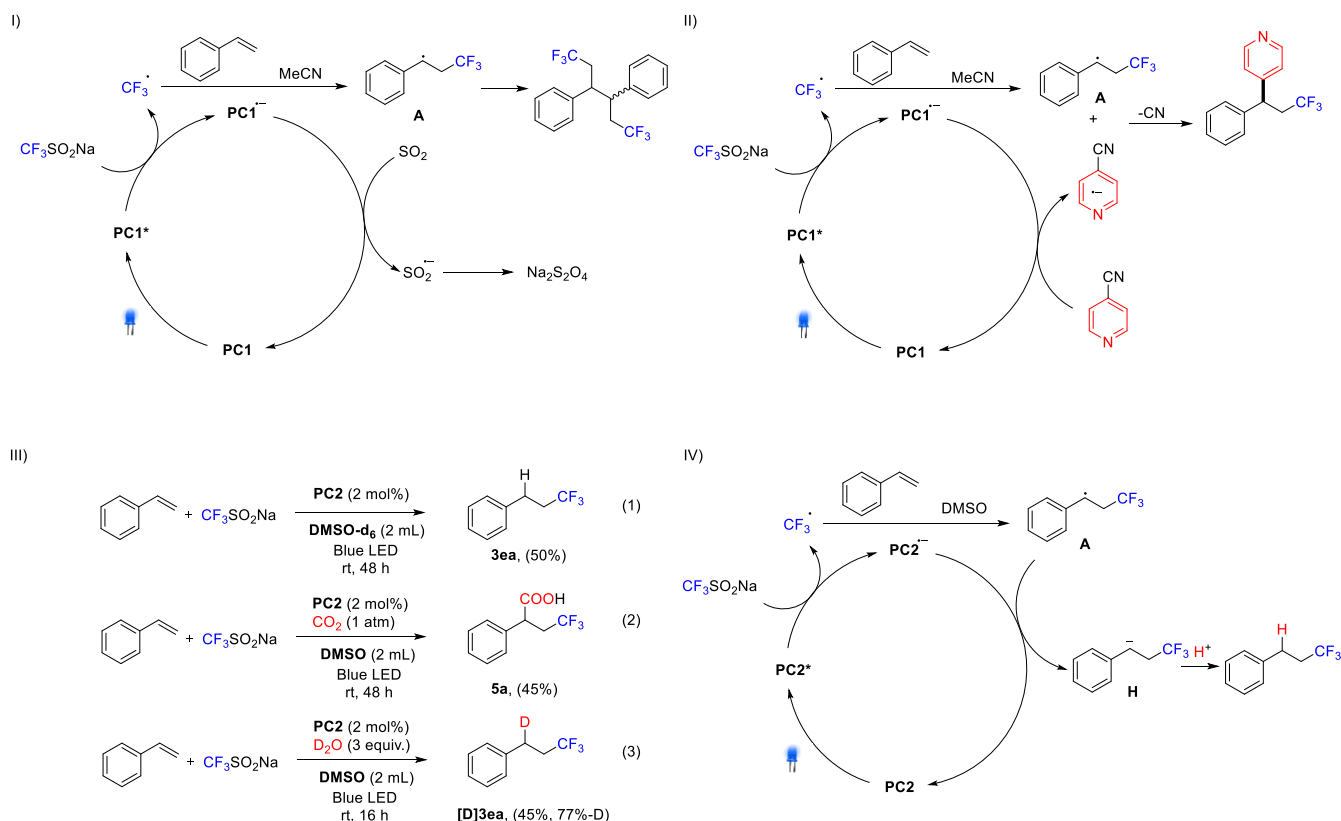


Figure 3. I. Proposed mechanism for the synthesis of fluorinated hexestrol derivatives. II. Proposed mechanism for the difunctionalization of styrene through radical-radical cross coupling process with 4-cyanopyridine. III. Deuteration experiment and trapping of the carbanion intermediate. IV. Proposed mechanism for the hydrotrifluoromethylation

with a magnetic stir bar are added styrene **1** (0.2 mmol, 1 equiv.), sodium triflate (0.2 mmol, 1 equiv.), 3DPAFIPN (0.004 mmol, 2mol%), and anhydrous acetonitrile (2 mL). The reaction is stirred at 25°C under blue led irradiation for 16 hours. Conversion is checked by ¹⁹F NMR with PhOCF₃ as internal standard. The reaction mixture is partitioned between Et₂O and brine. The aqueous layer is extracted with Et₂O and the combined organic layers are dried over MgSO₄, filtered and concentrated to dryness. The crude residue is purified by chromatography to afford the desired product **2**.

Typical procedure for the synthesis of the hydrofluoroalkylation of styrenes: to a sealed 8 mL tube under nitrogen atmosphere equipped with a magnetic stir bar are added styrene **1** (0.2 mmol, 1 equiv.), sodium triflate (0.4 mmol, 2 equiv.), 4CzIPN (0.004 mmol, 2mol%), and anhydrous dimethyl sulfoxide (2 mL). The reaction is stirred at 25°C under blue led irradiation for 48 hours. Conversion is checked by ¹⁹F NMR with PhOCF₃ as internal standard. The reaction mixture is partitioned between Et₂O and brine. The aqueous layer is extracted with Et₂O and the combined organic layers are dried over MgSO₄, filtered and concentrated to dryness. The crude residue is purified by chromatography to afford the desired product **3**.

Conclusion

In summary, we demonstrated that cyanoarenes are effective organophotocatalysts for the selective and synthesis of hexestrol derivatives by using the Langlois reagent and its derivatives in conjunction with styrenes. In addition, subtle variations of the initial reaction conditions allowed us to achieve hydrotrifluoromethylation of styrenes, which proceeds smoothly without the need of hydrogen atom donor. Mechanistic investigation including EPR spectroscopy, luminescence studies as well as isotope labelling experiments allows us to propose plausible mechanisms for those different reactions, which, depending of the solvent used may proceed through a radical or anionic intermediate species. Those observations led to the development of a trifluoromethylation/carboxylation as well as a three component difunctionalization of styrene that proceeds via a radical-anion or radical-radical coupling processes, respectively.

Experimental Section

Typical procedure for the synthesis of hexestrol derivatives **2**: to a sealed 8 mL tube under nitrogen atmosphere equipped

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References

- [1] For a selection of books, reviews and papers: (a) H. A. Wittcoff, B. G. Reuben, and J. S. Plotkin, *Industrial organic chemicals*, Wiley, Hoboken, NJ, 2004; (b) R. I. McDonald, G. Liu, and S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981–3019; (c) J. Gui, C. M. Pan, Y. Jin et al., *Science* **2015**, *348*, 886–891.; (d) M. Gaydou, T. Moragas, F. Juliá-Hernández, and R. Martin, *J. Am. Chem. Soc.* **2017**, *139*, 12161–12164; (e) S. Aoshima and S. Kanaoka, *Chem. Rev.* **2009**, *109*, 5245–5287.; (f) S. R. Chemler and P. H. Fuller, *Chem. Soc. Rev.* **2007**, *36*, 1153–1160.; (g) A. Minatti and K. Muñoz, *Chem. Soc. Rev.* **2007**, *36*, 1142–1152.; (h) G. Urgoitia, R. SanMartin, M. T. Herrero, and E. Domínguez, *ACS Catal.* **2017**, *7*, 3050–3060.; (i) T. Wang and N. Jiao, *J. Am. Chem. Soc.* **2013**, *135*, 11692–11695.
- [2] T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; b) O. A. Toma-shenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; c) L. Chu, F.-L. Qing, *Acc. Chem. Res.* **2014**, *47*, 1513–1522; d) J. Charpentier, N. Fruh, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682; e) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683–730.
- [3] P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd Edition; Wiley–VCH: Weinheim, Germany, **2013**.
- [4] a) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305–321.
- [5] For selected reviews on photoredox catalysis see: a) A. Tlili, S. Lakhdar, *Angew. Chem. Int. Ed.* **2021**, *70*, 10.1002/anie.202102262; *Angew. Chem.* **2021**, *133*, 10.1002/anie.202102262 b) A. Vega-Peçaloza, J. Mateos, X. Companyó, M. Escudero-Casao, L. Dell’Amico, *Angew. Chem. Int. Ed.* **2021**, *60*, 1082 – 1097; *Angew. Chem.* **2021**, *133*, 1096–1111; c) Y. Lee, M. S. Kwon, *Eur. J. Org. Chem.* **2020**, 6028 –6043; d) B. Zilate, C. Fischer, C. Sparr, *Chem. Commun.* **2020**, *56*, 1767–1775; e) Stephanie G. E. Amos, Marion Garreau, Luca Buzzetti and Jerome Waser, *Beilstein J. Org. Chem.* **2020**, *16*, 1163–1187; f) J. J. Molloy, T. Morack, R. Gilmour, *Angew. Chem. Int. Ed.* **2019**, *58*, 13654 – 13664; *Angew. Chem.* **2019**, *131*, 13789 – 13800; g) L. Marzo, S. K. Pagire, O. Reiser, B. König, *Angew. Chem. Int. Ed.* **2018**, *57*, 10034–10072; *Angew. Chem.* **2018**, *130*, 10188–10228; h) M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898–6926; j) N. A. Romero, D. A. Nicewicz, *Chem Rev.* **2016**, *116*, 10075–10166; j) D. P. Haria, B. König, *Chem. Commun.* **2014**, *50*, 6688–6699.
- [6] T. Koike, M. Akita, *Chem.* **2018**, *4*, 409–437.
- [7] a) T. Courant, G. Masson, *J. Org. Chem.* **2016**, *81*, 6945–6952; for selected other references see a) S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O’Duill, K. Wheelhouse, G. Rassias, M. Médebielle, V. Gouverneur, *J. Am. Chem. Soc.* **2013**, *135*, 2505–2508; c) D. J. Wilger, N. J. Gesmundo, D. A. Nicewicz, *Chem. Sci.*, **2013**, *4*, 3160–3165; d) E. Merino, C. Nevado, *Chem. Soc. Rev.*, **2014**, *43*, 6598–6608; e) D. P. Tiwari, S. Dabral, J. Wen, J. Wiesenthal, S. Terhorst, C. Bolm *Org. Lett.* **2017**, *19*, 4295–4298; f) T. Koike, M. Akita, *Acc. Chem. Res.* **2016**, *49*, 1937–1945; g) D. Kaiser, I. Klose, R. Oost, J. Neuhaus, N. Maulide, *Chem. Rev.* **2019**, 8701–8780; h) K. Zhao, Z.-Y. Zhang, X.-L. Cui, Y.-X. Wang, X.-D. Wu, W.-M. Li, J.-X. Wu, L.-L. Zhao, J.-Y. Guo, T.-P. Loh, *Org. Lett.* **2020**, *22*, 9029–9035; i) T.-H. Zhu, Z.-Y. Zhang, J.-Y. Tao, K. Zhao, T.-P. Loh, *Org. Lett.* **2019**, *21*, 6155–6159; j) K. Zhao, J.-Y. Guo, T. Guan, Y.-X. Wang, J.-Y. Tao, Y. Zhang, Q.-H. Zhang, K. Ni, T.-P. Loh, *Org. Chem. Front.*, **2021**, *8*, 4086–4094; k) L. Zhy, L.-S. Wang, B. Li, B. Fu, C. -P. Zhang, W. Li, *Chem. Commun.*, **2016**, *52*, 6371–6374; l) S. Tanaka, Y. Nakayama, Y. Konishi, T. Koike, M. Akita, *Org. Lett.* **2020**, *22*, 7, 2801–2805.
- [8] S. Choi, Y. J. Kim, S. M. Kim, J. W. Yang, S.W. Kim, E. J. Cho, *Nat. Commun.* **2014**, DOI:10.1038/ncomms5881.
- [9] N. J. W. Straathof, S. E. Cramer, V. Hessel, T. Noel, *Angew. Chem. Int. Ed.* **2016**, *55*, 15549–15553; *Angew. Chem.* **2016**, *128*, 15778–15782.
- [10] For a selection of reviews and papers: (a) C. K. Prier, D. A. Rankic, and D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.; (b) S. Tojo, K. Morishima, A. Ishida, T. Majima, S. Takamuku, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 958–966.; (c) S. L. Mattes, S. Farid, *J. Am. Chem. Soc.* **1986**, *108*, 7356–7361.; (d) J. Shey, C. M. McGinley, K. M. McCauley, A. S. Dearth, B. T. Young, W. A. van der Donk, *J. Org. Chem.* **2002**, *67*, 837–846.; (e) A. J. Fry, J. M. Proter, P. F. Fry, *J. Org. Chem.* **1996**, *61*, 3191–3194.; (f) M. Silvi, C. Verrier, Y. P. Rey, L. Buzzetti, P. Melchiorre, *Nat. Chem.* **2017**, *9*, 868–873. (g) K. Hironaka, S. Fukuzumi, T. Tanaka, *J. Chem. Soc. Perkin. Trans. II.* **1984**, 1705–1709.
- [11] a) C. K. Rhee, K. Chae, L. A. Levy, K. S. Korach, *Bioorg. & Med. Chem. Lett.* **1995**, *5*, 133–138; b) A. Deb, S. Manna, A. Modak, T. Patra, S. Maity, D. Maiti, *Angew. Chem. Int. Ed.* **2013**, *52*, 9747–9750; *Angew. Chem.* **2013**, *125*, 9929–9932.
- [12] a) B. Yang, X.-H. Xu, F.-L. Qing, *Org. Lett.* **2015**, *17*, 1906–1909; b) H. Rudler, A. Parlier, C. Denneval, P. Herson, *J. Fluor. Chem.* **2010**, *131*, 738–741.
- [13] a) D. Louvel, A. Chelagha, J. Rouillon, P.-A. Payard, L. Khrouz, C. Monnereau, A. Tlili *Chem. Eur. J.* **2021**, 10.1002/chem.202101056; b) D. Louvel, C. Ghiazza, V. Debrauwer, L. Khrouz, C. Monnereau, A. Tlili, *Chem. Rec.* **2021**, *21*, 417–426; c) C. Ghiazza, V. Debrauwer, C. Monnereau, L. Khrouz, M. Médebielle, T. Billard, A. Tlili, *Angew. Chem. Int. Ed.* **2018**, *57*, 11781; *Angew. Chem.* **2018**, *130*, 11955; d) C. Ghiazza, C. Monnereau, L. Khrouz, M. Médebielle, T. Billard, A. Tlili, *Synlett* **2019**, *30*, 777; e) C. Ghiazza, L. Khrouz, C. Monnereau, T. Billard, A. Tlili, *Chem. Commun.* **2018**, *54*, 9909; f) C. Ghiazza, L. Khrouz, T. Billard, C. Monnereau, A. Tlili, *Eur. J. Org. Chem.* **2020**, *2020*, 1559.
- [14] E. Speckmeier, T. G. Fischer, K. Zeitler, *J. Am. Chem. Soc.* **2018**, *140*, 15353 – 15365.

- [15] D. Louvel, A. Souibgui, A. Taponard, J. Rouillon, M. ben Mosbah, Y. Moussaoui younes, G. Pilet, L. Khrouz, C. Monnereau, A. Tlili, *ChemRxiv*. 10.33774/chemrxiv-2021-3g3d1
- [16] a) M. Tordeux, B. R. Langlois, C. Wakselman, *J. Org. Chem.* **1989**, *54*, 2452–2453; b) B. R. Langlois, E. Laurent, N. Roidot, *Tet. Lett.* **1991**, *32*, 7525–7528; c) For a review see: C. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 2895 – 2906.
- [17] For selected recent examples for the use of cyanoarenes as oxidant for the Langlois reagent see: a) Q.-F. Bao, Y. Xia, M. Li, Y.-Z. Wang, Y.-M. Liang, *Org. Lett.* **2020**, *22*, 7757–7761; b) R. Abrams, J. Clayden, *Angew. Chem. Int. Ed.* **2020**, *59*, 11600–11606; *Angew. Chem.* **2020**, *132*, 11697–11703; c) J. Luo, J. Zhang, *ACS Catal.* **2016**, *6*, 873 – 877.
- [18] C. Fischer, C. Kerzig, B. Zilate, O. S. Wenger, C. Sparr, *ACS Catal.* **2020**, *10*, 210 – 215.
- [19] J. Hou, A. Ee, H. Cao, H. W. Ong, J. H. Xu, J. Wu, *Angew. Chem. Int. Ed.* **2018**, *57*, 17220 – 17224; *Angew. Chem.* **2018**, *130*, 17466 – 17470.
- [20] a) M. A. Bryden, E. Zysman-Colman, *Chem. Soc. Rev.*, **2021** doi.org/10.1039/D1CS00198A; b) T. Y. Shang, L. H. Lu, Z. Cao, Y. Liu, W. M. He, B. Yu, *Chem. Commun.* **2019**, *55*, 5408 – 5419.
- [21] J. Rouillo, C. Arnoux, C. Monnereau, *Anal. Chem.* **2021**, *93*, *5*, 2926–2932.
- [22] photoconversion quantum yield is calculated based on the amount of product **2e** formed versus the amount of absorbed photons. As formation of one molecule of **2e** involves the coupling of two radical intermediates, and thus the photoconversion of two molecules of reactant, quantum yield of radical intermediate formation, and thus of SET, is about twice this value, ie $\Phi_{\text{SET}} = 1.4 \times 10^{-2}$ assuming that radical recombination step proceeds quantitatively (no by product in NMR)
- [23] M. D. Kosobokov, M. O. Zubkov, V. V. Levin, V. A. Kokorekin, A. D. Dilman, *Chem. Commun.*, **2020**, *56*, 9453-9456.
- [24] A. Klein, D. A. Vicic, C. Biewer, I. Kieltisch, K. Stirnat, C. Hamacher, *Organometallics* **2012**, *31*, 5334–5341.
- [25] a) F. Magno, G. A. Mazzocchin, G. Bontempelli, *J. Electroanal. Chem.*, **1974**, *57*, 89; b) D. Knittel, *Electroanal. Chem.*, **1985**, *195*, 345.
- [26] I. Streeter, A. J. Wain, J. Davies, R. G. Compton, *J. Phys. Chem. B* **2005**, *109*, 18500-18506.
- [27] A. A. Zemtsov, S. S. Lunkov, V. V. Levin, A. D. Dilman, *Eur. J. Org. Chem.* **2021**, 1007–1010.
- [28] C. Zhou, T. Lei, X. Z. Wei, C. Ye, Z. Liu, B. Chen, C. H. Tung, L. Z. Wu, *J. Am. Chem. Soc.* **2020**, *142*, 16805–16813.
- [29] The synthesis of β -CF₃ pyridines was developed by the group of Chu by using the Togni II reagent and stoichiometric amount of Hantzsch ester (1. equiv.) see: D. Chen, T. Long, S. Zhu, J. Yang, L. Chu, *Chem. Sci.*, **2018**, *9*, 9012-9017; the group of Shen demonstrated recently that PC2 allow the intermolecular pyridylation/phosphinoxylation of alkenes b) J. Shen, Y. Zhang, Y. Yu, M. Wang, *Org. Chem. Front.*, **2021**, *8*, 901-907.
- [30] The dicarbotrifluoromethylation of styrenes with the Langlois reagent and CO₂ was developed by the Martin group with Ir-based photocatalyst please see: V. R. Yatham, Y. Shen, R. Martin, *Angew. Chem. Int. Ed.* **2017**, *56*, 10915-10919; *Angew. Chem.* **2017**, *129*, 11055-11059.

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