

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

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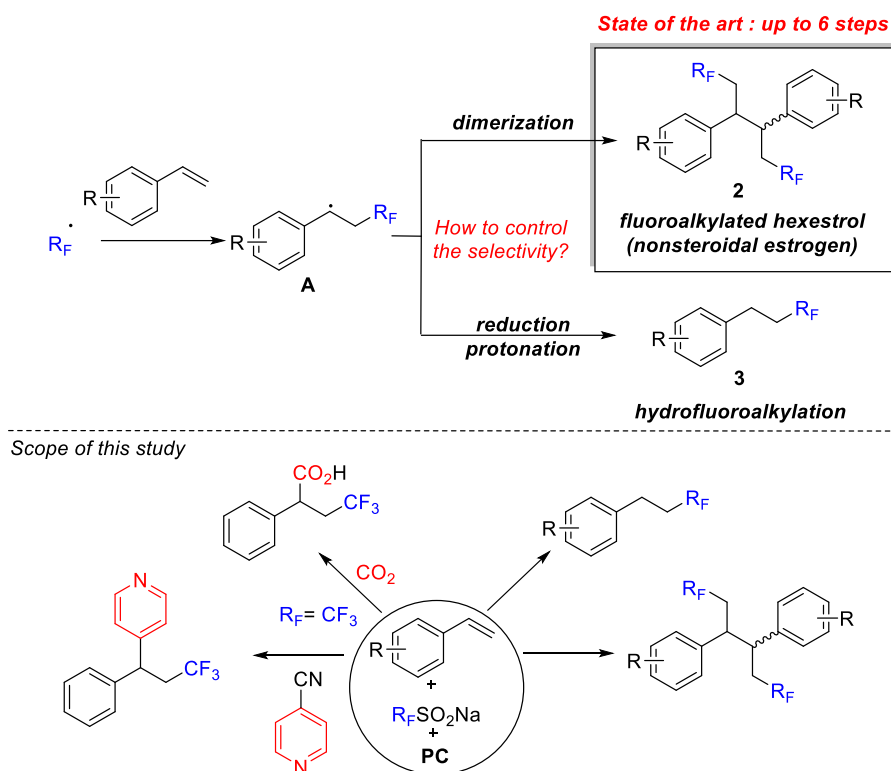
ABSTRACT: The unprecedented selective and straightforward one-step access to fluoroalkylated hexestrol derivatives, nonsteroidal estrogens, is achieved in good to excellent isolated yields under organophotoredox conditions by using the stable and easy to handle Langlois reagent. Furthermore, the challenging selective hydrotrifluoromethylation of styrenes proceeds under mild reaction conditions without the requirement of 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.

INTRODUCTION

The direct incorporation of trifluoromethyl group and derivatives has witnessed widespread interest over the last decades¹. Nowadays, the fluoroalkylation of organic molecules is finding numerous applications in cutting-edge technologies from life sciences to material applications.² Indeed, the presence of a fluoroalkyl group on a molecule can alter its physico-chemical properties and increases its lipophilicity as well as its metabolic stability.³ The development of selective transformations affording such fluorinated 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.^{1b} More recently, photocatalysis⁴ has turned out to be an interesting alternative to leverage the orthogonality of transition metal catalysis through the selective generation of a fluoroalkyl radical, which, in the presence of an appropriate reactant, will yield to the desired product.⁵ Although a plethora of methodologies have been developed in the last decade for the selective fluoroalkylation of aliphatic alkenes and alkynes under photoredox conditions⁶, the use of styrene reactants turns out to be particularly challenging. Indeed, unproductive polymerization or oxidation is favored in the latter compared to aliphatic alkenes, which constitutes a major hurdle towards more elaborate functionalization based on radical additions. 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.*⁷ who used inorganic electride as a radical generator (3 equivalents) in their procedure to achieve this transformation. More recently, the group of Noël⁸ 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 made use of gaseous trifluoromethyl iodide.

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



In parallel to hydrotrifluoromethylation reactions, selective dimerization of trifluoromethyl styrenes constitutes another interesting task. Indeed, this allows a direct and straightforward strategy to access fluoroalkylated hexestrol derivatives known as nonsteroidal estrogens⁹ that so far have been exclusively isolated as byproducts and only in marginal amounts in synthetic protocols or in up to 6 step syntheses.^{9a,10} In this context, a direct and straightforward synthetic strategy towards either fluoroalkylated hexestrol derivatives or for the hydrotrifluoromethylation of styrenes will constitute an important step forward, especially if using cheap and easy to handle fluoroalkyl sources (**Figure 1**).

Our group recently started a new research program aiming to use organic photocatalysts for the fluorination/fluoroalkylation of organic molecules.¹¹ As a new step forward, we demonstrate herein that cyanoarenes^{12,4a} are efficient organophotocatalysts to achieve the unprecedented synthesis of fluoroalkylated hexestrol derivatives or the hydrofluoroalkylation of styrenes depending on the solvent choice. Indeed, we show herein that solvent can directly impact the reaction mechanism and drives it either towards the reduction or dimerization process. Furthermore, we demonstrate that our system could

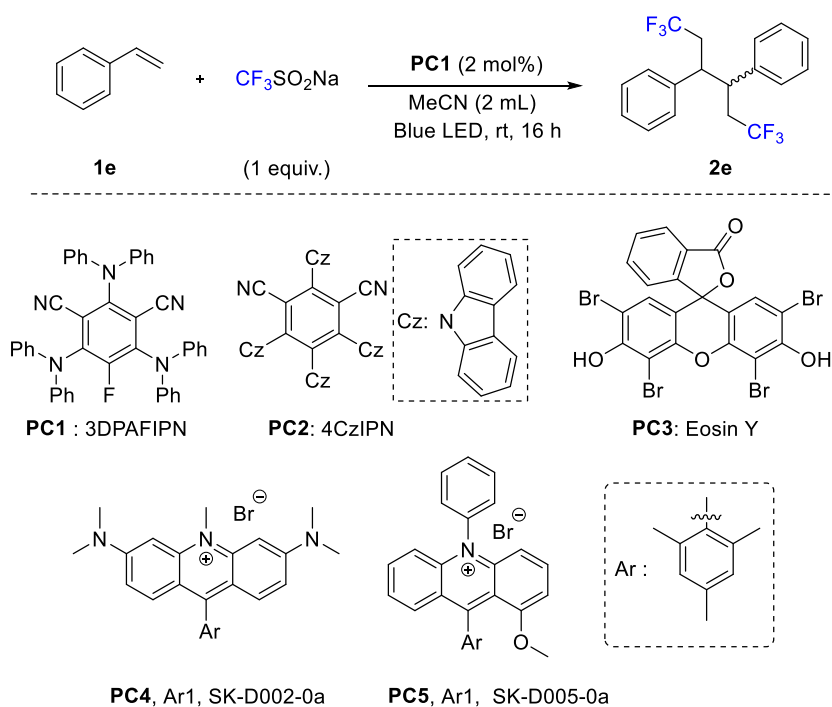
also be further exploited in other types of radical styrenes substitution, including carboxylative trifluoromethylation and radical-radical cross coupling with cyanopyridine, enabling unprecedented direct access to complex molecular structures.

RESULTS and DISCUSSION

We started our study by investigating the direct access to fluoroalkylated hexestrol derivatives. To do so, we selected styrene **1e** as model substrate in the presence of Langlois reagent (sodium trifluoromethanesulfinate, $\text{CF}_3\text{SO}_2\text{Na}$) as a cheap and easy to handle trifluoromethylating reagent.¹³ This latter exhibits an oxidation potential of 1.05 V (vs. SCE). In this context we selected **PC1** with a reduction potential ($E_{\text{red}}^{1/2}$ (**PC1/PC1^{•-}**) of -1.59 which makes it able to oxidize the Langlois reagent under photoactivation conditions.¹⁴ The reaction was performed in MeCN as solvent upon blue LED irradiation at room temperature and the desired product was observed 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 variations on the reaction outcome and to screen other organophotocatalysts. In a first serie of experiments, we therefore considered the effects of solvent variations. Only traces of the desired product were obtained when substituting MeCN with MeOH (10%, **Table 1**, entry 2) while no detectable formation of the target product was observed in toluene (**Table 1**, entry 3). Only DMF was also effective under our conditions since an excellent yield of 85% was reached (table 1, entry 4). Afterwards, other organophotocatalysts were tested. **PC2** (4CzIPN) was to some extent also effective under our conditions although product formation yield dropped in this case 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 derivatives¹⁵ were also investigated: in the present case **PC4** allows to obtain the desired product in only 30% yield while higher efficiency was observed with **PC5** affording a 60 % yield (**Table 1**, entry 8). Noteworthy, blank experiments in the absence of light and/or organophotocatalyst did not

allow desired product formation (**Table 1**, entries 9 & 10) ascertaining the crucial role of photoinduced electron transfer processes in the reaction

Table 1. Reaction optimization

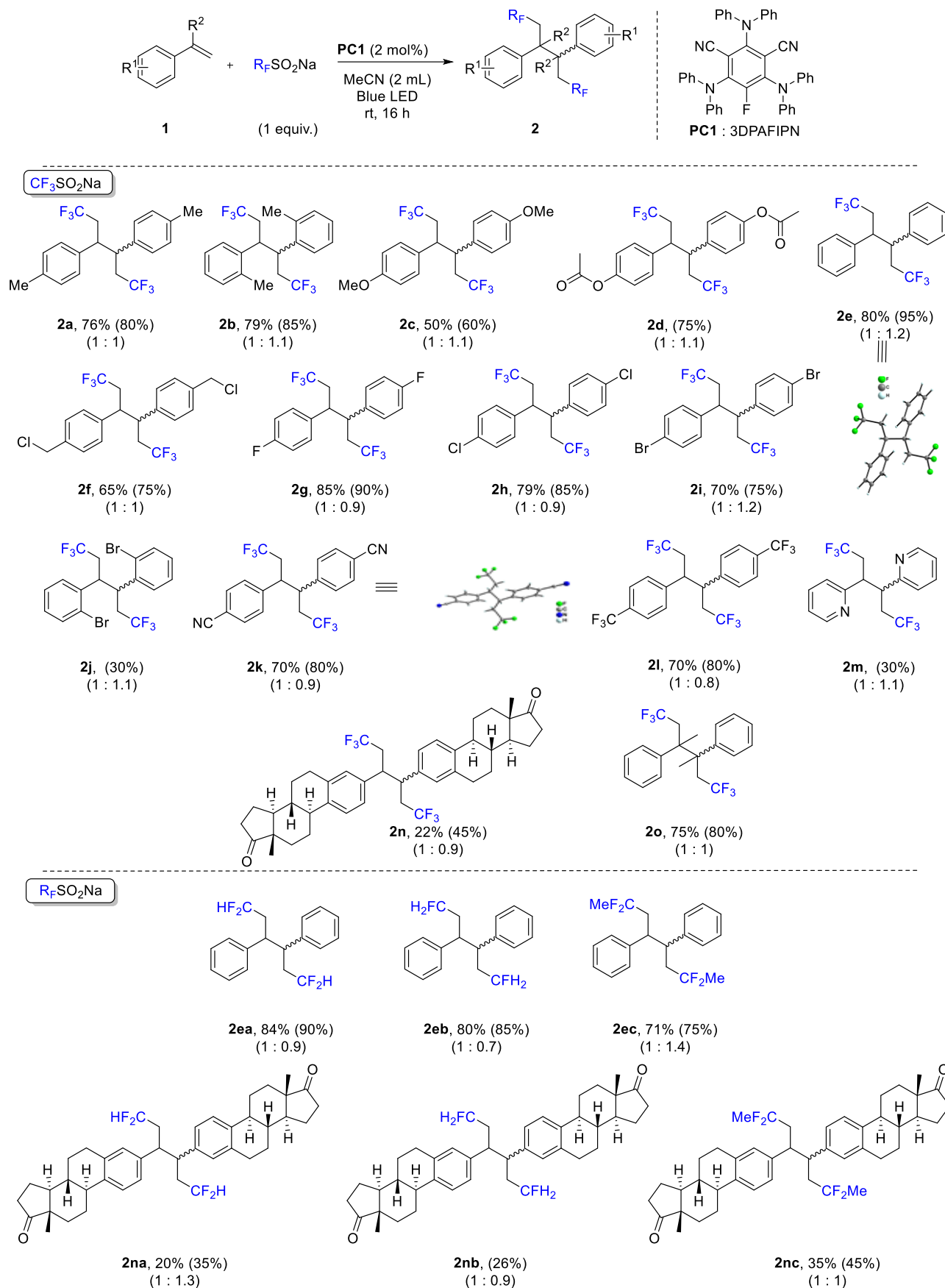


Entry ^[a]	Deviation from standard conditions	Yield [%] ^[b]
1	None	95 (80)
2	MeOH instead of MeCN	10
3	PhMe instead of MeCN	0
4	DMF instead of MeCN	85
5	PC2 instead of PC1	75
6 ^[c]	PC3 instead of PC1	0
7	PC4 instead of PC1	30
8	PC5 instead of PC1	60
9	No light	0
10	No PC1	0

[a] Reactions were performed with styrene **1** (0.2 mmol, 1 equiv.), $\text{CF}_3\text{SO}_2\text{Na}$ (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 ^{19}F NMR spectroscopy with PhOCF_3 as internal standard; [c] Under green LED irradiation. Isolated yield shown in parentheses.

With the best conditions in hand, we turned our attention to study 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**). 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 tolerance of the reaction 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: both 4-cyanostyrene and 4-trifluoromethylstyrene allowed the formation of 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 low yield of 30% (2m). Interestingly, we also demonstrated that our protocol is tolerant to complex molecular structures and estrone derivatives **2n** was obtained in 45% yield. Moreover, 1,1-disubstituted styrene could also be smoothly transformed to the desired product **2o** in excellent yield of 80%. Then, we turned our attention to study the impact of the starting sulfinate on the reaction outcome (**Scheme 1**), since the use of a variety of different sulfinate precursors opens many perspectives on a molecular diversity of accessible structures point of view. Indeed, we demonstrated that hexestrol derivatives containing CF₂H, CH₂F as well as MeCF₂ and *p*-BrBnCF₂ could also be obtained in good to excellent yield (**Scheme 1**, **2ea-2ec**). Once again, the same protocol could be extended to complex molecular structures (**Scheme 1**, **2na-2nc**).



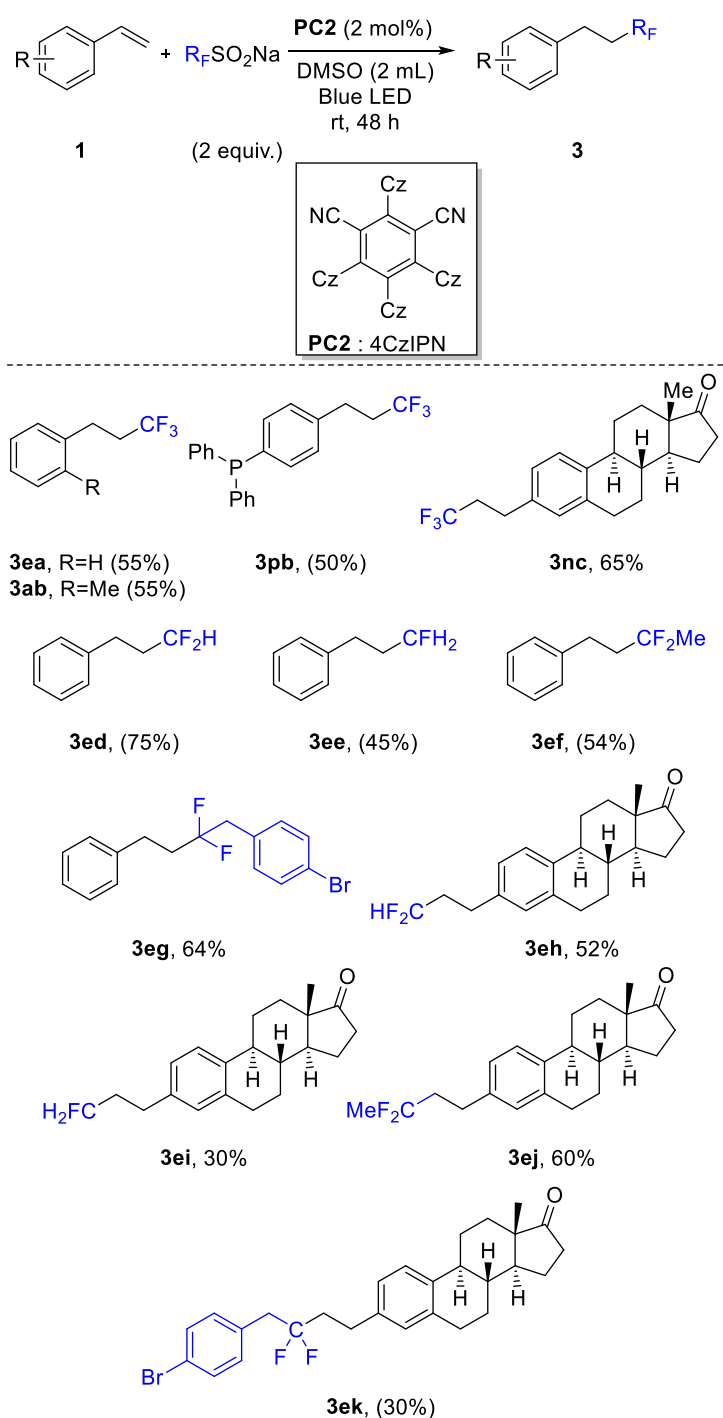
Scheme 1. Reaction scope for the synthesis of fluoroalkylated hexestrol derivatives. Reactions were performed with styrene derivatives **1** (0.2 mmol, 1 equiv.), R_FSO₂Na (0.2 mmol, 1 equiv.), **PC1** (2 mol%) and ACN (2 mL). The reaction mixture was stirred at room temperature for 16 hours under blue LED

irradiation and inert conditions. Yields shown are those of isolated products; yields determined by ^{19}F NMR spectroscopy with PhOCF_3 as internal standard are shown in parentheses. *meso* and *d,l* enantiomers ratio was calculated from the crude.

After having demonstrated the general efficiency and robustness of the proposed protocol for the unprecedented direct and straightforward access to fluorinated hexestrol derivatives, we turned our focus to develop a similar strategy towards the selective hydrotrifluoromethylation of styrenes. This strategy relies on the working hypothesis that selective reduction of the benzylic radical generated by addition of trifluoromethyl radical to styrene should be a crucial step to avoid the dimerization of the formed intermediate. It has been shown 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.¹⁶ In this context, the reduction of the radical intermediate (intermediate A on **figure 3**, *vide infra*) should be even more accessible thermodynamically given the electron withdrawing nature of the trifluoromethyl group, yielding a benzylic anion that after protonation should afford the desired hydrotrifluoromethylation products, avoiding the use of external additive (HAT donor). To our satisfaction, we were able to confirm this working hypothesis when the reaction was performed using DMSO as a solvent instead of MeCN. Under these conditions, still using **PC1** as a photocatalyst, **3ea** was obtained in 40% yield. After a quick optimization it turned out that compound **3ea** could be obtained with a better yield of 55% by using **PC2** (2 mol%) with an excess of the Langlois reagent (2 equiv.) in DMSO and longer reaction times.

With these optimized conditions in hands, 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 the desired product **3pb** was obtained in 50% yield. The use of estrone derivatives allowed to obtain the desired product **3nc** with a good yield of 65%. To demonstrate further the utility of this new methodology we decided to investigate the same scope of different sulfinate salts as used in the

above-described synthesis of the fluorinated hexestrol derivatives. Once more, 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 CF_2H , CFH_2 , MeCF_2 and CF_2ArBr could be obtained for the first time under our protocol demonstrating again the robustness of the developed methodology.



Scheme 2. Reaction scope. for the hydrotrifluoromethylation of styrene. Reactions were performed with styrene derivatives **1** (0.2 mmol, 1 equiv.), $\text{R}_\text{F}\text{SO}_2\text{Na}$ (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 ^{19}F NMR spectroscopy with PhOCF_3 as internal standard are shown in parentheses.

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 ^{19}F NMR), EPR spectroscopy and isotopic labelling. Fluorimetric titrations were first performed to bring evidence for the occurrence of an electron transfer (ET) process between **PC1** and Langlois reagent in MeCN (the weak luminescence of the 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.¹⁷ 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 $\text{CF}_3\text{SO}_2\text{Na}$ led to similar observations. This suggest 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 ^{19}F NMR following of 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-d_3 or **PC2**: DMSO-d_6), using our recently reported NMR actinometric set-up¹⁸, that we recently adapted to the study of photoinduced ET mediated chemical transformations (please see 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-d_3 , figure S1A, SI) or compound **3ea** (in DMSO-d_6 , figure S1B, SI), in a kinetic that could be in both cases satisfactorily fitted to a first-order trend. Very similar quantum yield was obtained in both cases: conditions I, $\Phi_p = 0.7 \times 10^{-2}$;¹⁹ conditions II, $\Phi_p = 1.3 \times 10^{-2}$; Interestingly this

extremely low value agrees well with the very inefficient ET process suggested throughout the spectrofluorometric experiments. It is particularly remarkable, considering the inefficiency of the process, that the reaction yields in both cases one single product that can be isolated in a synthetically relevant yield, which underlines the exquisite selectivity of the associated chemical transformation. With these results, several questions raised to be able to propose plausible mechanisms in both reactions, SET oxidation of the Langlois reagent is thermodynamically favored. Thus, generating trifluoromethyl radical that could collapse to the styrene to form a new C-centred-benzylic radical. This C-centred intermediate **A** (**Figure 1**) should not be involved anymore in SET reactions with the catalyst since dimerization allow the formation of the desired fluorinated hexestrol derivatives. Given the nature of the stepwise mechanism the involvement of 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. To do so, 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 favored. As a matter of fact, 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. Complementary experiments were carried out using CF₂HSO₂Na as sulfinate source, which also demonstrated the formation of a single major adduct either with DMPO (adduct **C**, $g=2.0064$, $a_N=14.1G$, $a_H=18.6G$ $a_F=0.6G$) or PBN (adduct **D**, $g=2.006$, $a_N=14.62G$ $a_H=2.8G$, $a_F=0.98G$) confirming again the generation of the perfluoroalkyl radical (**Figure 2**, b & c).²⁰

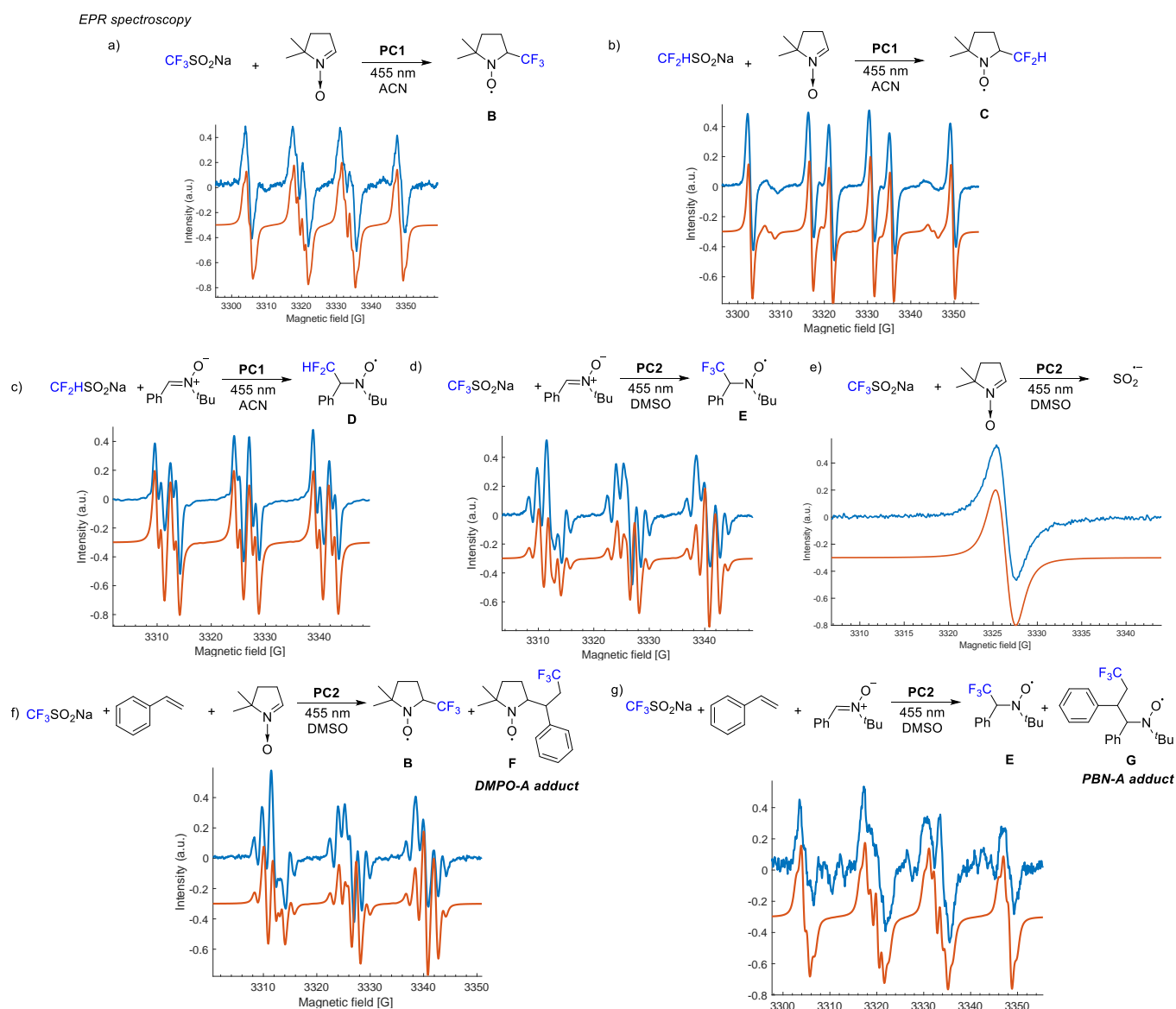
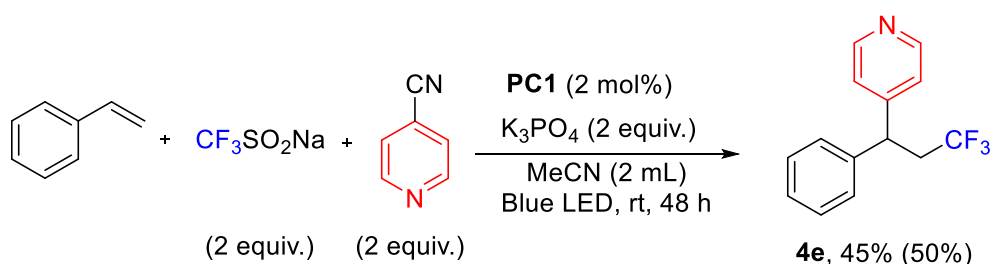


Figure 2. EPR spin-trapping spectra upon irradiation ($\lambda = 455\text{ nm}$) in the presence of BPN or DMPO in MeCN or DMSO at room temperature. Blue = experimental, red = simulated.

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) ($g=2.0062$, $a_N=14.23\text{G}$ $a_H=2.15\text{G}$, $a_{3F}=1.55\text{G}$).²¹ 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 SO_2^- ($g=2.0061$) (**figure 2, e**), while no clear signature could be observed for the trifluoromethyl radical. This latter, may result from the reduction of SO_2 generated after reduction of the Langlois reagent. The reduction of SO_2 is favored either

with **PC1** or **PC2** since both radical anions of these two photocatalysts could reduce SO_2 ($E_{\text{red}} = -0.8 \text{ V}$).²² 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 a distinctive feature that we observed at the end of the reaction.²³ In order to get more insight especially on the missing signature of the trifluoromethyl radical under this condition, we decided to investigate the same SET reaction, this time in the presence of styrene (**Figure 2, f**). In addition to a signal of adduct **B** obtained in the previous irradiation experiment we observed the formation of **DMPO-A** adduct **F** as plausible intermediate in our reaction ($g=2.0061$, $a_{\text{N}}=14\text{G}$ $a_{\text{H}}=16\text{G}$, present in 20%). Similarly, same signature was observed with PBN where corresponding adduct **G** (**PBN-A** adduct, $g=2.006$, $a_{\text{N}}=14.8\text{G}$ $a_{\text{H}}=2.2\text{G}$, present in 40%) was observed in conjunction with that of the previously characterized **E** (**Figure 2, g**).²⁴

Considering the obtained results, we were able to propose the following mechanisms. Regarding the synthesis of fluorinated hexestrol derivatives, SET oxidation of the Langlois reagent by **PC1** at its excited state allow the formation of CF_3 radical. This latter collapses to the styrene yielding 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 showed also that it is possible to take advantage of the presence of intermediate **A** to facilitate the reduction of cyanopyridines by $\text{PC1}^{\cdot -}$ (**Figure 3, II**).²⁵ This alternative reactivity allows difunctionalization of styrene through three component reactions. Indeed, the desired compound **4e** was obtained in 50% yield in one step procedure in the presence of K_3PO_4 as the base (**Scheme 4**).²⁶



Scheme 4. Reaction was performed with styrene **1** (0.2 mmol, 1 equiv.), CF₃SO₂Na (0.4 mmol, 2 equiv.), **PC1** (2 mol%) 4-cyanopyridine (0.4 mmol, 2 equiv.), K₃PO₄ (0.4 mmol, 2 equiv.) and ACN (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 ¹⁹F NMR spectroscopy with PhOCF₃ as internal standard is shown in parentheses.

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 further evolve by protonation to yield the target compound. Reactions performed in DMSO-d₆ 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 proved when the reaction was performed under a CO₂ atmosphere. Herein, compound **5a** was obtained in 45% yield which constitutes a strong indication that the reaction proceeds through nucleophilic attack of CO₂ by the anionic intermediate **H**. (**Figure 3**, III.2).²⁷ 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 D₂O allows the incorporation of deuterium and compound [D]**3ea** was obtained in 45% yield (**Figure 3**, III.3) (77% incorporation of deuterium) demonstrating once again the formation of the carbanion intermediate

Proposed mechanisms

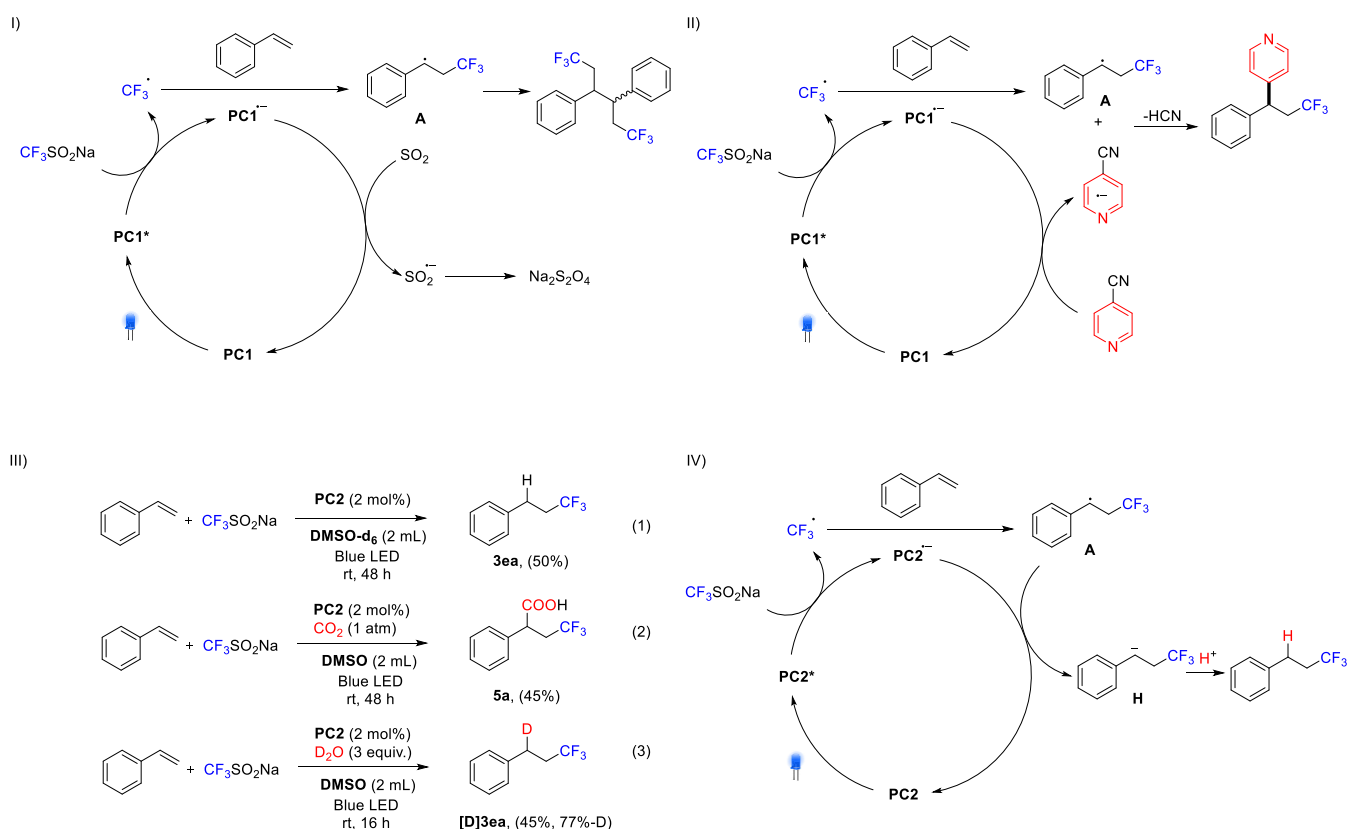


Figure 3. I. Proposed mechanism for the synthesis of fluorinated hexestrol derivatives. II. Proposed mechanism for the difunctionalization of styrene through radical-radical cross coupling process with 4-cyanopyridine. III. Deuteriation experiment and trapping of the carbanion intermediate. IV. Proposed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

Conclusion

In summary we demonstrated that cyanoarenes are effective organophotocatalysts for the unprecedented selective and straightforward synthesis of hexestrol derivatives by using Langlois reagents and its derivatives in conjunction with styrenes. Furthermore, we were able to demonstrate that subtle variations of the initial reaction conditions, make it possible to drive its evolution towards hydrotrifluoromethylation of styrenes, which proceeds smoothly without the need of hydrogen atom donor. Our system was also efficient for the carboxylation of CO_2 as well as a three component difunctionalization of styrene through radical-radical cross coupling process. Mechanistic investigation including EPR spectroscopy, luminescence 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.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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