PERSPECTIVES

Visible light-catalyzed fluoroalkylation reactions of free aniline derivatives

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Abstract

The electron-rich nature of aminoaromatic compounds and the electrophilic character of fluoroalkyl R_F radicals allow for a special match in substitution reactions. We herein present visible light photocatalyzed fluoroalkylation reactions of aniline derivatives, with a study of the reaction mechanisms. The examples evaluated make use of different photocatalysts, such as polypyridyl complexes of Ir or Ru transition metals, organic dyes such as Rose Bengal, phthalocyanine-metal organocatalysts, or visible-light activated complexes. Different visible light sources that span from the blue region of the electromagnetic spectrum to low power red light irradiation sources deliver the excited photocatalysts that ensue into the production of fluoroalkyl R_F radicals. In turn, many sources of R_F radicals can be employed, such as fluoroalkyl halides, Togni's reagents, Umemoto's reagent, etc. All these protocol variants demonstrate the expansion of the methodology and the versatility of photocatalytic techniques applied to a special family of organic compounds such as aminoaromatic substrates, which has been studied by different groups. Contributions from our own laboratory will be given.

Graphic abstract
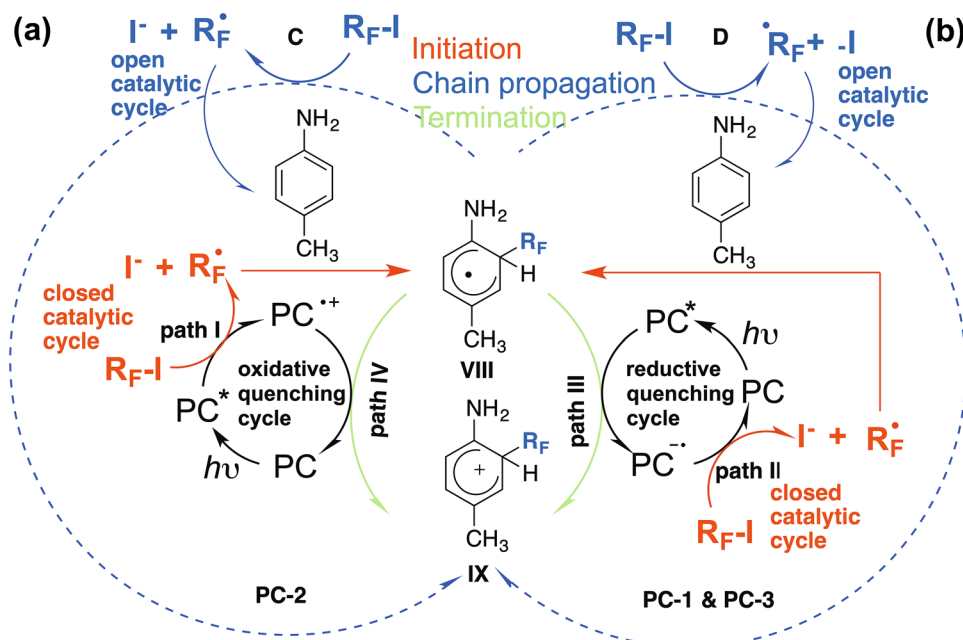
Dedicated to Prof. Angelo Albini in the occasion of his 75th birthday.

Extended author information available on the last page of the article

1 Introduction

The late-stage introduction of perfluoroalkyl R_F groups into organic substrates is a subject of great interest, specially so for compounds with biological relevance, as the properties imparted by R_F groups substantially modify the physical chemical characteristics and sometimes biological potency of the substituted bioactive candidates [1–6]. For this very same reason, introducing the fluoroalkyl group onto bioactive compounds *later* in the reaction sequence becomes a primordial target.

The aniline motive is found in many pharmaceuticals with a great variance of activities. As an example, sulfa drugs containing *N*-substituted sulfonamide moieties at the *para* position of an aniline ring (NH_2ArSO_2NHR) have long been used as antibacterial agents. Halogenated derivatives of *N*-substituted-4-aminobenzenesulfonamides and triazine sulfa drug derivatives, have found important activity towards carbonic anhydrase isozymes [7, 8] and as anticancer agents [9]. Candidates such as anilino enaminones are considered potential anticonvulsant agents, and the fluoro, trifluoromethyl, and trifluoromethoxy derivatives are also very active

compounds [10]. In the same lines, widely prescribed anesthetics such as procaine and benzocaine contain aminoaromatic (vide infra) functionalities.

The electron-rich nature of aminoaromatic compounds and the electrophilic character of fluoroalkyl R_F radicals allow for a special match in substitution reactions [11–13]. This reactivity marriage has encouraged profuse studies, and come up with different protocols and alternative approaches to substitute free aniline derivatives with R_F moieties.

There are plenty of methods devoted to achieving the perfluoroalkylation of aniline derivatives. Early thermal protocols such as the use of perfluoroalkyl halides in the presence of Cu_2O in DMSO as solvent at high temperatures, (Scheme 1a) [14] or sulfinatodehalogenation reactions of aniline derivatives with perfluoroalkyl chlorides (Scheme 1b) [15–17], or the direct irradiation of mixtures of perfluoroalkyl(di)iodides and aminoaromatics [18], all afford perfluoroalkyl-substituted anilines.

Transition metal-mediated cross coupling reactions can also be used to achieve aryl-R_F compounds. Recently, the transition-metal-catalyzed fluoroalkylations with aryl halides or aryl metals have come up as effective protocols to
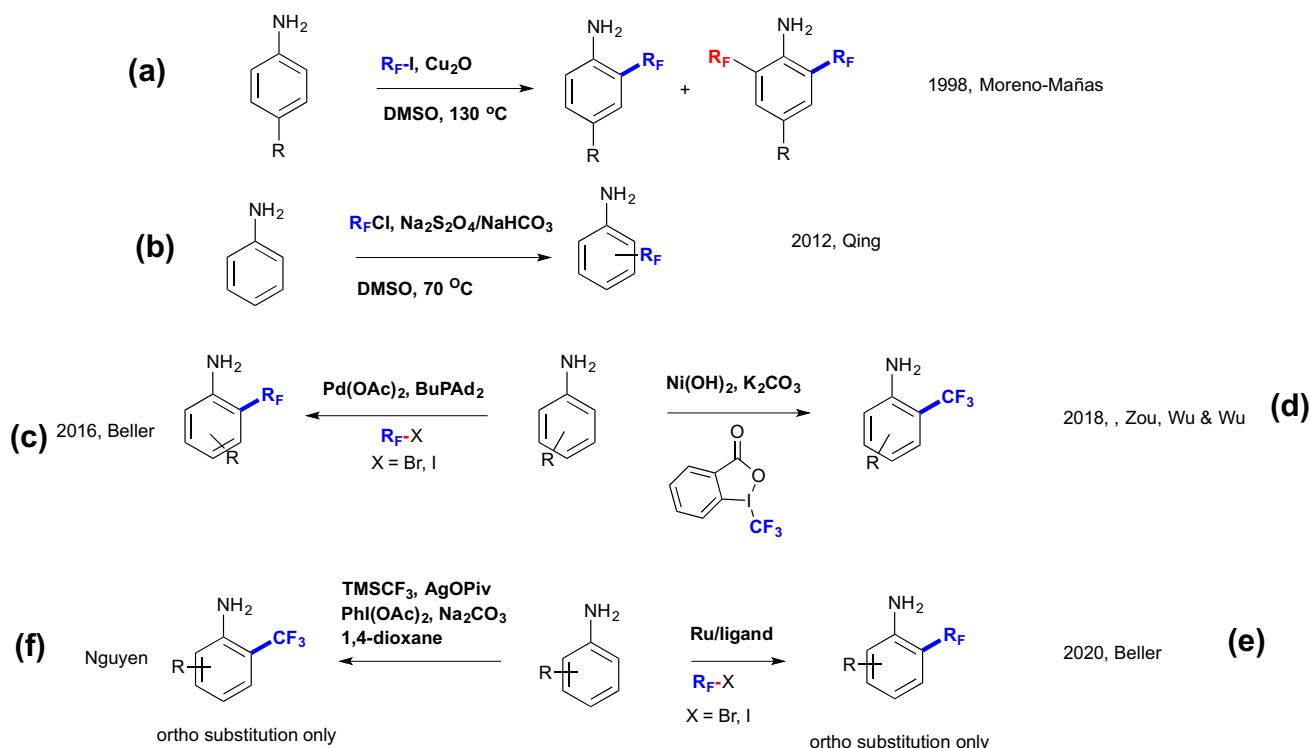
Scheme 1 Thermal methods for perfluoroalkylation of aniline derivatives

form fluoroalkylated compounds [19–21]. However, these latter strategies make use of pre-functionalized starting substrates.

Homolytic aromatic substitution approaches consisting of Pd-catalyzed electron-transfer reactions of amino-substituted arenes with fluoroalkyl groups (Scheme 1c) [22, 23], the Ni(II)-catalyzed fluoroalkylation of anilines with Togni's reagent (Scheme 1d) [24], or the more recent transition metal-mediated thermal regioselective C_{Ar}-H perfluoro-alkylation strategies developed by Beller and collaborators (Scheme 1e) [25], and the silver-catalyzed trifluoromethyla-tion of anilines (Scheme 1f) [26, 27] have augmented the chemists' armamentarium to substitute electron-rich sub-strates such as anilines with R_F groups.

Other free radical pathways are available for anilines tri-fluoromethylation and fluoroalkylation reactions through direct C–H functionalization by photoredox catalysis or electrochemistry [28–37]. Notably, photocatalytic methods gather a cluster of advantages over conventional methods that range from the absence of chemical radical initiators, tolerance of different functional groups pre-assembled on the aniline scaffolds, milder reaction conditions as vis-ible light energy in replacement of high temperatures, and organo(metallic) photoactive catalysts in catalytic or sub-stoichiometric quantities. The notorious absence of strong oxidants or reducing species in photocatalytic reactions is accounted for by the prominent redox properties of photo-catalysts in their excited states, which render them much stronger oxidants or reducing agents.

In the next sections, a study of the different visible light photocatalyzed fluoroalkylation reactions of aniline deriva-tives is conducted, with emphasis on their reaction mecha-nisms, to show the reader the different approaches under-taken by the authors to attain substitution of free anilines with R_F groups. At the end of the manuscript, a comparison of visible light photocatalytic techniques is made, employing a unique substrate and a single perfluoroalkyl radical source. Although the different approaches illustrated all afford good substitution yields, considerations regarding regioselectiv-ity, employment or absence of photocatalyst, heteroleptic or organic photocatalysis, and fluoroalkyl radical source, will make each strategy unique. Contributions from our own laboratory will be given.

2 Discussion

As observed before, the photoredox perfluoroalkylation of aniline derivatives has been performed with different pho-tocatalysts and can be considered a convenient and environ-mentally benign strategy for the syntheses of these com-pounds, even more so taking into account the possibility

of a late fluoroalkyl-group functionalization, which is very appealing to the pharmaceutical industry.

Zhu, Ma and colleagues [38] have reported the visible light photocatalyzed trifluoromethylation of free aniline derivatives employing Togni's reagent, $Ir(ppy)_3$ as photo-catalyst, in DMF as solvent under blue LED irradiation. The scope of the reaction is depicted in Scheme 2.

Both electron withdrawing and donating groups on ani-lines afforded reasonable-good yields of trifluoromethylated products. The authors [38] studied the reaction mechanism through a series of experiments. Kinetic isotope effects anal-yses, radical trapping experiments, and theoretical calcula-tions threw some light into the reaction mechanism. Single electron transfer from excited $Ir(ppy)_3$* to Togni's reagent generates Ir(IV) and the radical anion of the Togni's rea-gent, which decomposes to CF_3 radicals and 2-iodobenzo-ate. These CF_3 radicals add to the aniline derivative to form a cyclohexadienyl-substituted radical intermediate which is oxidized to a carbocation intermediate by the upper oxida-tion state of the photocatalyst (i.e., Ir(IV)). Deprotonation of the carbocation intermediate affords the substituted product (Scheme 3).

In 2015, our group [39] developed a Rose Bengal-photo-catalyzed perfluoroalkylation reaction of aniline derivatives with perfluoroalkyl iodides R_F-I, in the presence of Cs_2CO_3 as additive, in MeCN as solvent irradiating with a compact fluorescent lamp (CFL). The reaction scope is depicted in Scheme 4.

Aniline, *N*-methylaniline, and *N,N*-dimethylaniline gave good yields of perfluoroalkylated products. Anilines with electron-donating groups (CH_3, OCH_3) gave excellent yields of R_F-substituted products. Aniline with electron-poor groups (NO_2) afforded low yields of products.

The authors attempted the perfluorobutylation of two bioactive compounds, mefenamic acid (anti-inflammatory drug), and benzocaine (anesthetic), obtaining good yields of the fluorinated compounds, as shown in Scheme 4. Also large-scale reactions of aniline derivatives worked very well.

The authors [39] attempted to study the reaction mecha-nism, and proposed the catalytic cycle shown in Scheme 5.

In the proposed mechanism visible light-excited photo-catalyst Rose Bengal (RB*) has enough reductive poten-tial to reduce n-C_4F_9-I (DG = − 1.53 V) to C_4F_9 radicals, which add to the aniline derivative to yield a cyclohex-adienyl-substituted radical intermediate (I, Scheme 5), which in turn, by an oxidative ET to n-C_4F_9-I, generates the Wheland intermediate which suffers deprotonation by the base. The photoactive photocatalyst RB is re-generated from its radical cation by reduction with carbonate anion, yielding carbonate radical anion and thermoneutral RB. In another study [40], we postulated an alternative regen-eration of the photoactive catalyst Rose Bengal which is

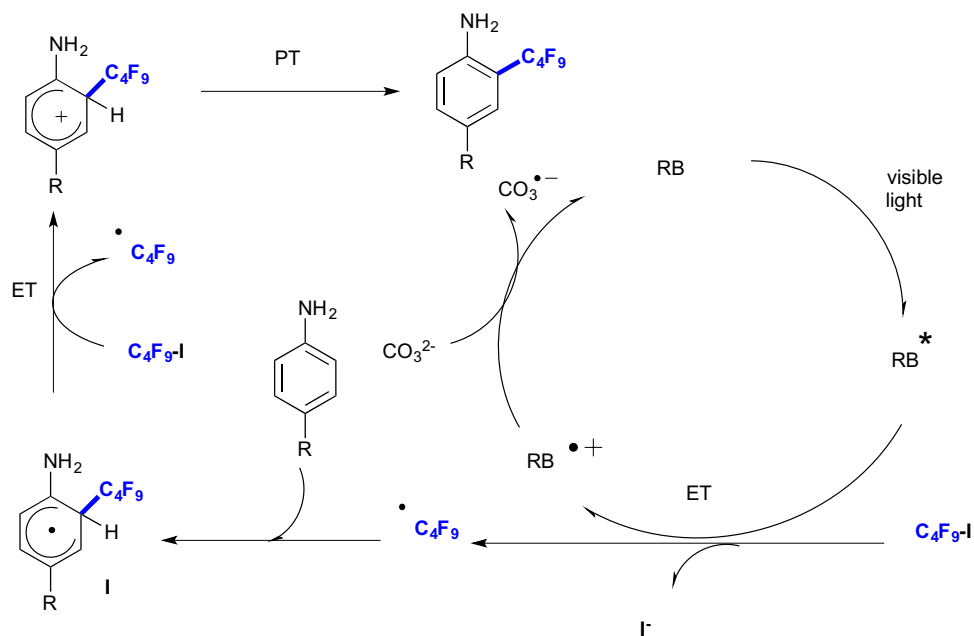**Scheme 2** Selected examples for the scope of trifluoromethylation of free aniline derivatives

51% 58% 60% 52% 81%

80% 76% 56% 70% 38%
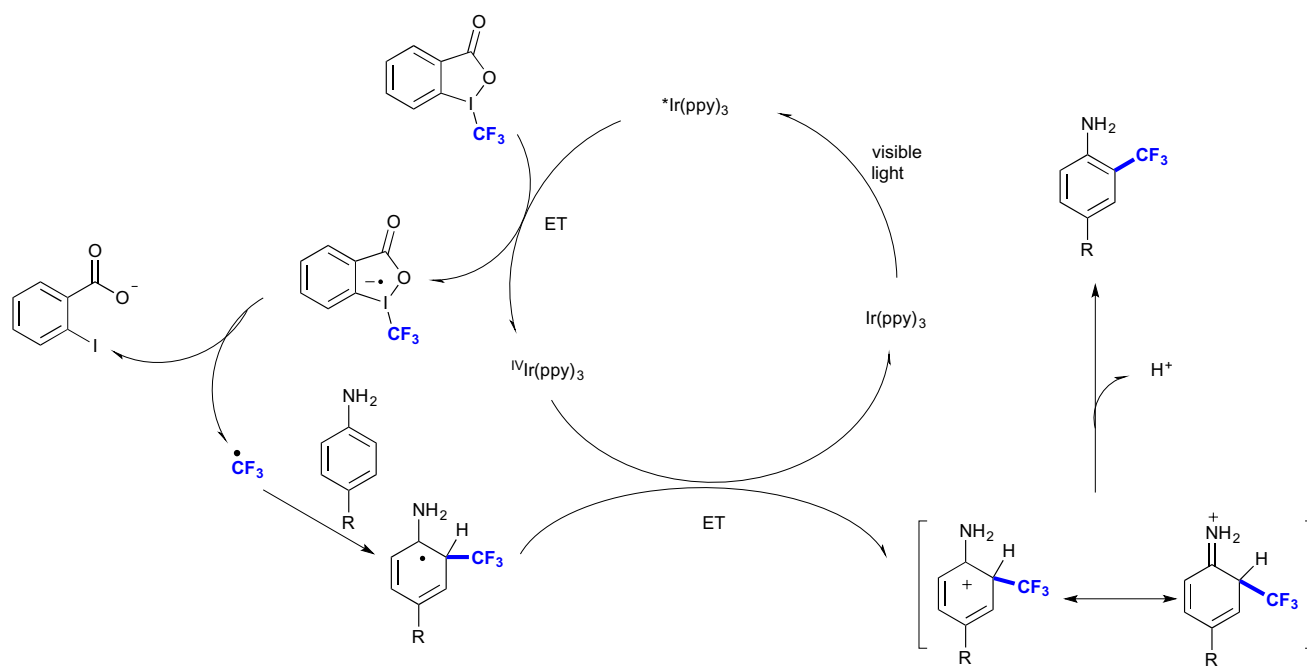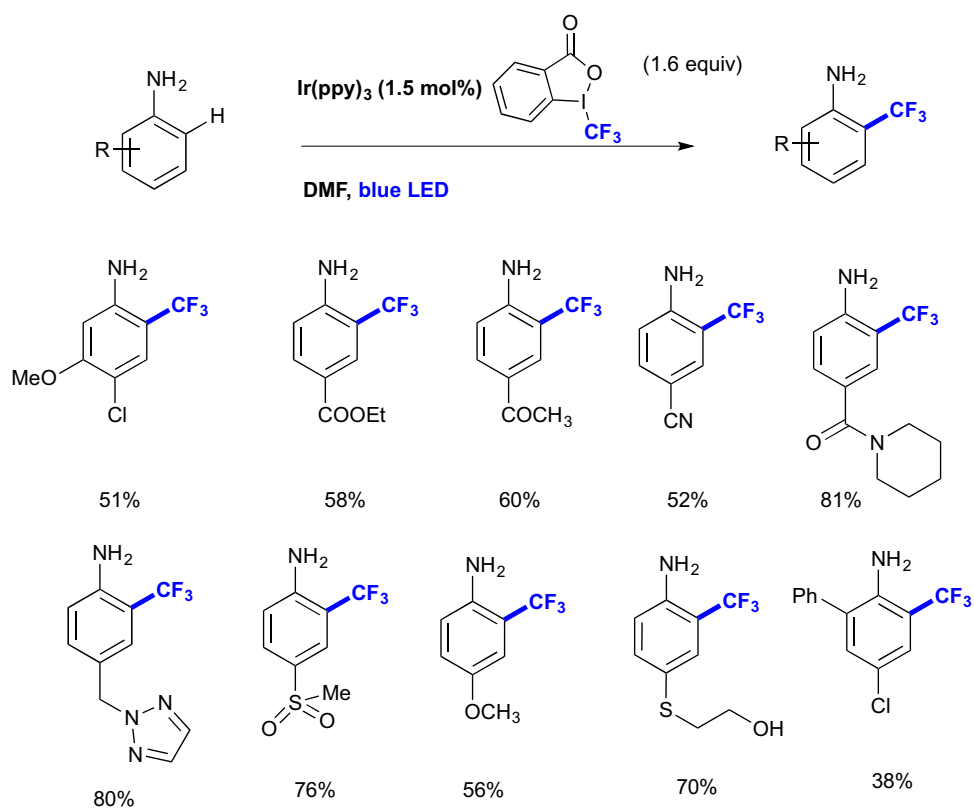
Scheme 3 Proposed reaction mechanism
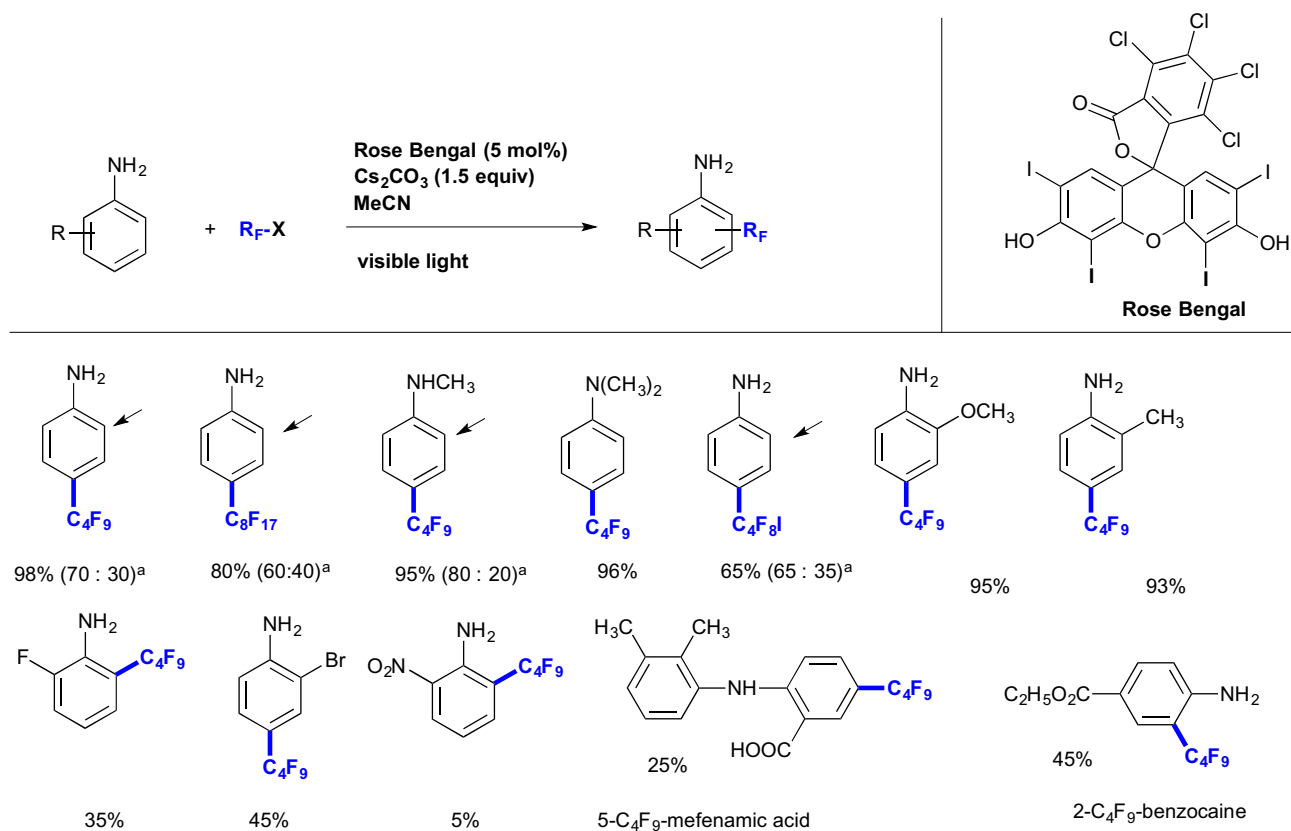
Scheme 4 Selected examples for the Rose Bengal-photocatalyzed fluoroalkylation of aniline derivatives

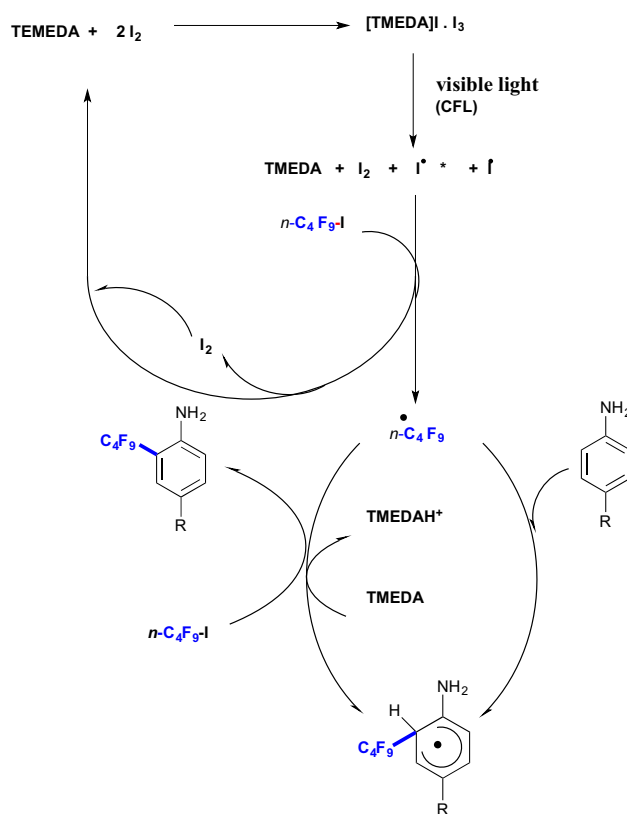**Scheme 5** Proposed reaction mechanism

ensued by the reductive ET from cyclohexadienyl-substituted radical intermediate **I** to the radical cation of Rose Bengal.

Replacing the inorganic base Cs_2CO_3 for *N,N,N',N'*-tetramethylethylenediamine (TMEDA), we uncovered that in the presence of molecular iodine and absence of organic dye Rose Bengal as photocatalyst, the complex formed between TMEDA and I_2 (i.e., [(TMEDA)I.I_3]) was capable of producing R_F radicals when irradiation took place with a compact fluorescent lamp (CFL) [41]. Thus, the visible light-activated complex [(*N,N,N`,N`*-tetramethylethylenediamine)I.I_3] (i.e., [(TMEDA)I.I_3]) in the presence of perfluoroalkyl iodides, R_F-I produced R_F radicals efficiently, making possible substitution reactions on amino-aromatics. A brief scope of the reaction is illustrated in Scheme 6 [41].

It is observed from Scheme 6 that for 2,5-dimethoxyaniline and 2,3-dimethylaniline, the reactions are quite regioselective in the sense that mostly one perfluoroalkylated product is obtained when using *n*-C_nF_{2n}Y-I (n = 4, 6, 10, Y = F or I).

The authors [41] postulated a reaction mechanism based on an electron catalysis, by which, upon visible light-decomposition of [(TMEDA)I.I_3] complex into iodine atoms (plus molecular iodine and TMEDA), these latter react with R_F-I, to produce R_F radicals (and molecular iodine, which re-combines with TMEDA). R_F radicals substitute the aniline derivative, generating a cyclohexadienyl-substituted radical intermediate which, by ulterior ET to R_F-I is converted to a Wheland intermediate (and more R_F radicals that re-enter the chain reaction).

Scheme 7 Proposed reaction mechanism

Scheme 6 Selected examples of the perfluoroalkylation reaction of aniline derivatives employing [(TMEDA)I.I_3] complex in the presence of *n*-C_nF_{2n+1}-I
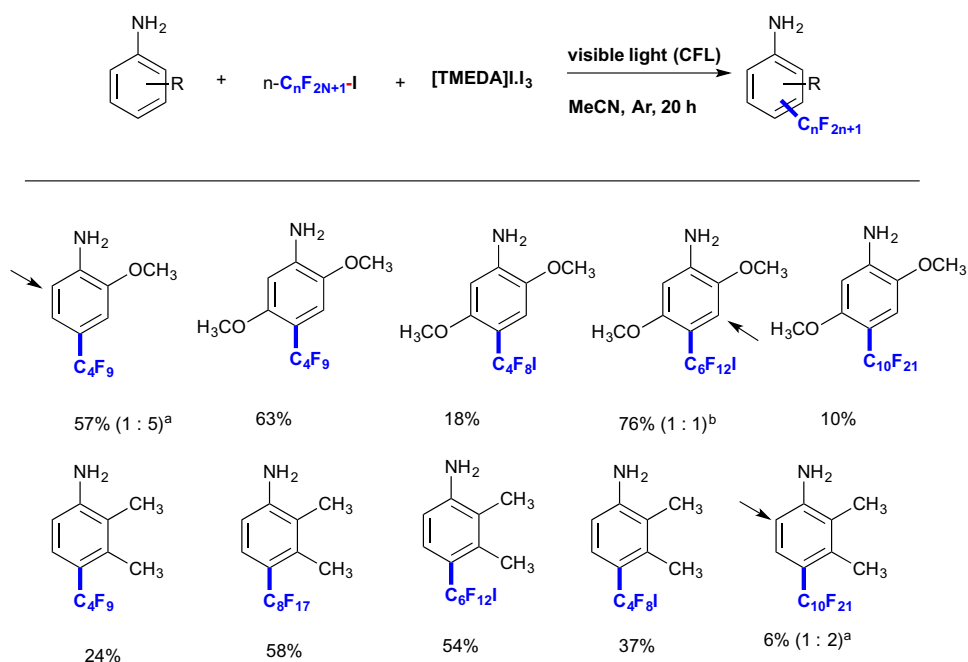
a.-*ortho : para* ratio. b.- *meta : para* ratio.

The carbocation is deprotonated by TMEDA to render the substituted thermoneutral product (Scheme 7) [41].

Zhang et al. [42] have developed an efficient method from free anilines to obtain perfluoroalkylated aniline derivatives via a photoredox catalysis process. This reaction allows the use of an important variety of substituted anilines, including those with electron attracting groups, obtaining perfluoroalkylated products with high efficiency and good regioselectivity. The optimization study was carried out with 4-iodoaniline and perfluorohexyl iodide. The selection of aniline as a substrate is because amino group was considered a versatile group for further transformations. The reaction was carried out with different catalysts: $Ru(bpy)_3(PF_6)_2$, $Ru(bpy)_3Cl_2$, fac-$Ir(ppy)_3$. Irradiation was done by a blue light-emitting diode (LED) bulb (12 w) for 24 h. Different bases (K_2CO_3, $NaHCO_3$, Cs_2CO_3, Na_2CO_3, Na_2HPO_4) and solvents (DCE, DCM, DMF, dioxane, DMSO) were tested.

The best results were obtained using fac-$Ir(ppy)_3$ as catalyst and K_2CO_3 and DCE as base and solvent. When the reaction was carried out without a photocatalyst or light source, there was no reaction, demonstrating that a visible-light-promoted photoredox process is involved. The scope of the transformation is illustrated in Scheme 8.

A variety of anilines were tested to check the extent of the reaction. Good to excellent yields were obtained from substrates with electron-poor substituents and electron donors. Yields were good even with anilines substituted with electron-withdrawing groups. These results highlight the good tolerance of the reaction conditions. Perfluoroalkylated products containing aryl halides and aryl boronates allow a good opportunity for further transformations. When 3-amino-4-iodobenzoate was used as a substrate, a mixture of regioisomers was obtained in a 1/1 ratio (*ortho/para*). The method allows to prepare other perfluoroalkylated anilines, with high yields. Trifluoromethyliodide is a useful

Scheme 8 Visible-light-mediated direct perfluoroalkylation of free anilines[a]
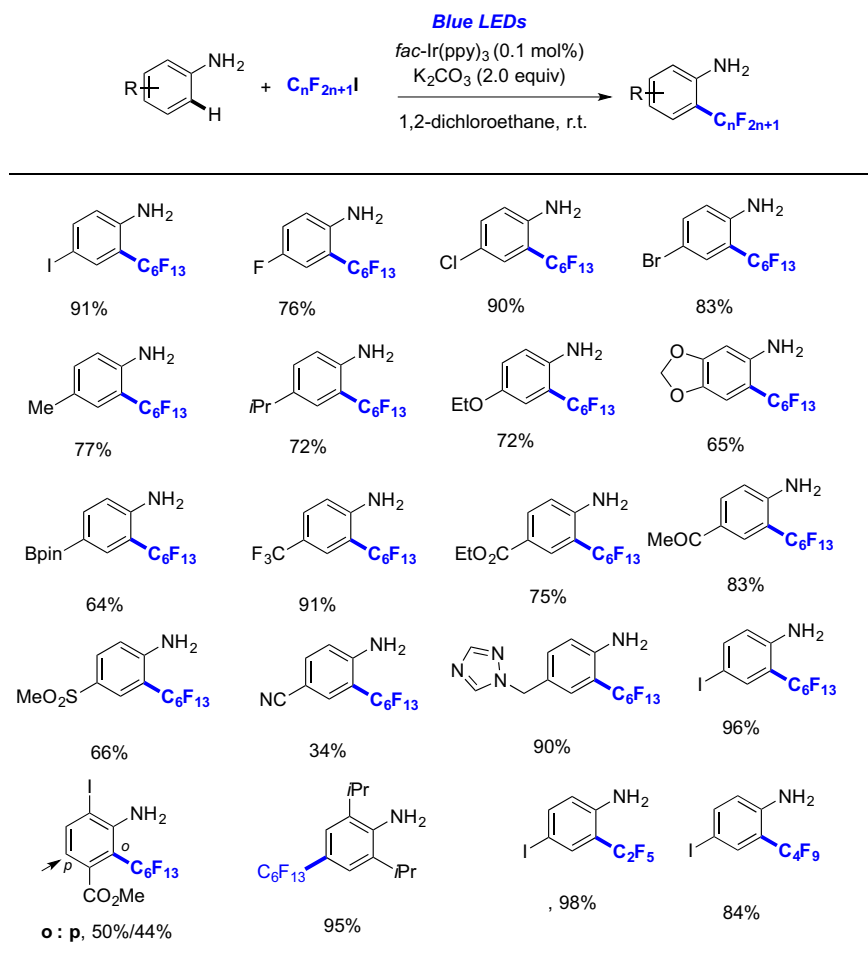
[a]Reaction conditions (unless otherwise specified): aniline 1 (1.2 mmol, 3.0 equiv), 2 (0.4 mmol, 1.0 equiv), K_2CO_3 (2.0 equiv), fac-$Ir(ppy)_3$ (0.1 mol %), 1,2-dichloroethane (4 mL), argon atmosphere, blue LEDs, room temperature, 24 hours. All reported yields are those of the isolated products.

Scheme 9 Visible-light-mediated direct perfluoroalkylation of free anilines[a]
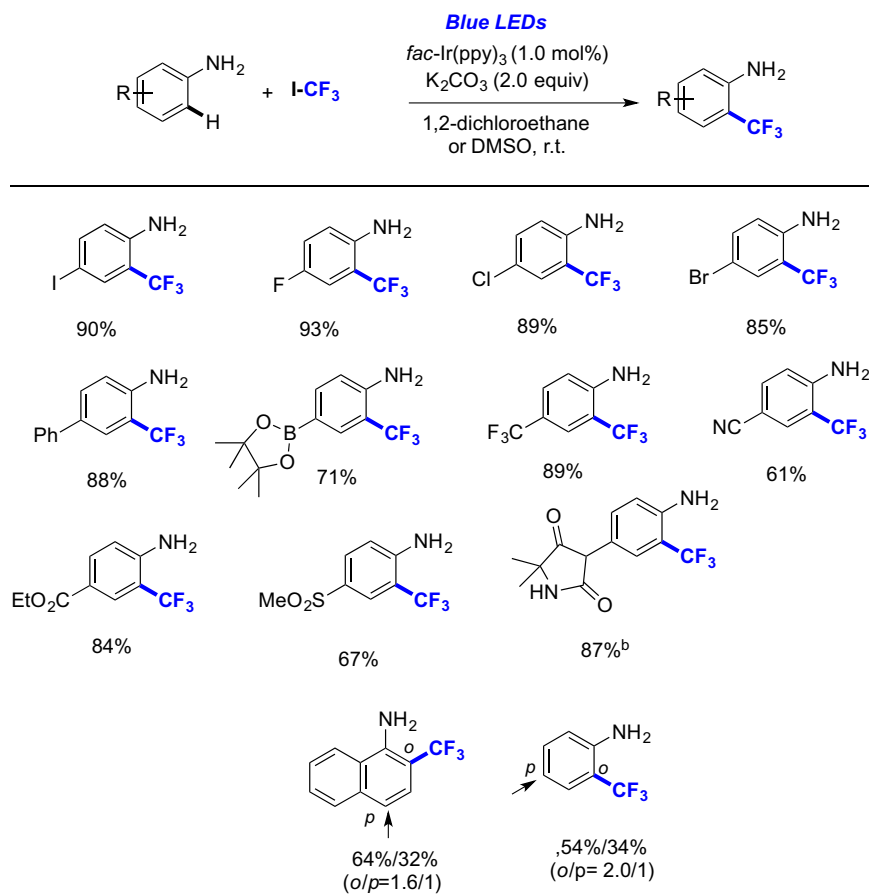
a.-Reaction conditions (unless otherwise specified): free anilines 1 (1.2 mmol, 3.0 equiv), CF₃I 4 (a solution in 1,2-dichloroethane, 0.4 mmol, 1.0 equiv), K₂CO₃ (2.0 equiv), fac-Ir(ppy)₃ (1 mol %), 1,2-dichloroethane (4 mL, together with CF₃I solution), argon atmosphere, blue LEDs, room temperature, 24 hours. All reported yields are those of the isolated products. b.- The reaction was conducted in DMSO with a solution of CF₃I in DMSO.

Scheme 10 Proposed reaction mechanism
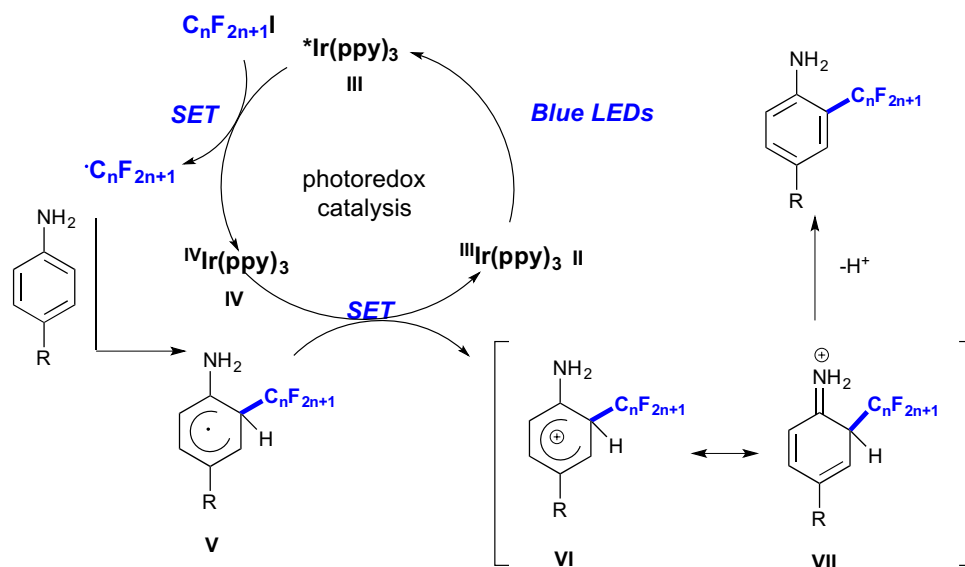
trifluoromethylating reagent, however, due to its gaseous state at room temperature, its accurate measurement is difficult. The authors found that a CF$_3$I solution in DCE or DMSO could be stored at room temperature without losing titer, allowing for convenient handling. Under these modified conditions trifluoromethylation of various anilines was carried out in good to high yields. Good tolerance to the various functional groups was demonstrated (Scheme 9). When aniline was used as a substrate, a mixture of regioisomers was obtained in a ratio of 1.6/1 (ortho/para). The same was observed when using naphthylamine.

A possible mechanism in shown in Scheme 10. The photoredox catalytic cycle is initiated, upon irradiation of Ir(ppy)$_3$ with blue LEDs, from the excited state of the photocatalyst *[Ir(ppy)$_3$] (**III**).The perfluoroalkyl radical is then generated by single electron transfer from **III** to R$_F$I and Ir(IV)(ppy)$_3$ (**IV**). This formed radical reacts with the aniline to give intermediate **V**, which is oxidized by **IV**, to Wheland intermediate **VI** followed by abstraction of a proton by the base to give the perfluoroalkylated product.

In another report [43] the unprecedented perfluoroalkylation reaction of aniline derivatives employing this time low power red-light irradiation sources (red LEDs) and commercially available zinc phthalocyanine as photocatalyst has been presented. Perfluoroalkyl iodides were employed as perfluoroalkyl radical sources, ascorbic acid, sodium acetate and 2,4,6-collidine as additives in MeCN:DMF mixture of solvents. Irradiation took place with 635 nm red LEDs. The scope of the transformation regarding aniline derivatives is illustrated in Scheme 11.

It is observed from Scheme 11, that substitutions of electron-rich anilines are carried out efficiently and in a regioselective manner, purporting that C$_4$F$_9$ radical production under red-light photocatalysis is an convenient and competent methodology.

The reaction mechanism was inspected through a series of experiments. Radical scavenger TEMPO suppressed the reaction completely. The presence of 1,4-dinitrobenzene, a well-known radical anion scavenger, affords a notorious decrease in the perfluorobutylation of aniline (30% product yield). The reaction in the presence of oxygen, afforded only a slight decrease in product yield. In the absence of illumination, the reaction (dark reaction) does not afford product, whereas the reaction carried out under white light illumination led to 30% yield of substitution product, probably from white-light-induced homolysis of C$_4$F$_9$-I bond. The reaction under red light irradiation in the absence of photocatalyst (i.e., zinc phthalocyanine) afforded less than 5% yield of substitution product. These results indicate that excitation of PC under red-light is required for substitution to proceed. A proposed mechanism is depicted in Scheme 12.

Initially, the red-light-photoexcited PC accepts one electron from 2,4,6-collidinium ascorbate to form the anion radical of the photocatalyst (Stern Volmer results confirm that fluorescence of PC* is suppressed by 2,4,6-collidinium ascorbate), along with formation of ascorbate radical anion Asc$^{\cdot-}$, and concomitant loss of H$^+$ and one electron. This process has a favorable Gibbs energy ($\Delta G_{ET} = -0.775$ V) The anion radical of the photocatalyst should reduce R$_F$-I to R$_F$ radicals, which in turn substitute the aniline derivative. Further comparative mechanistic studies on perfluoroalkylation of anilines derivatives under red-light photocatalysis was carried out by Yerien and colleagues, where radical
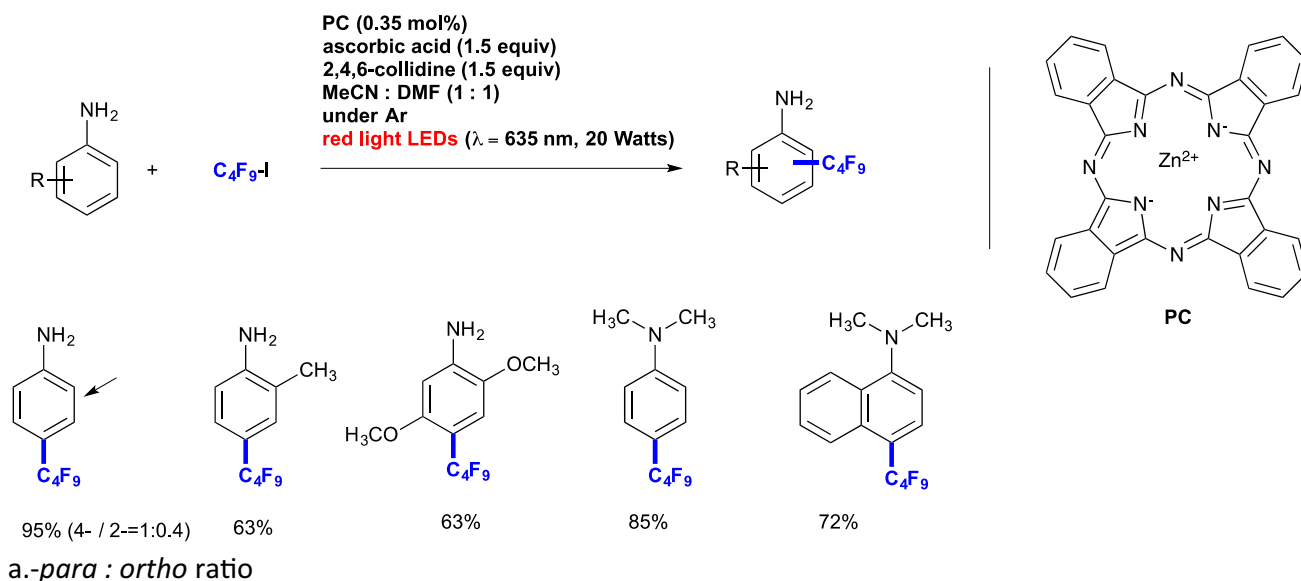
Scheme 11 Selected examples for the perfluorobutylation of aniline derivatives under red-light photocatalysis
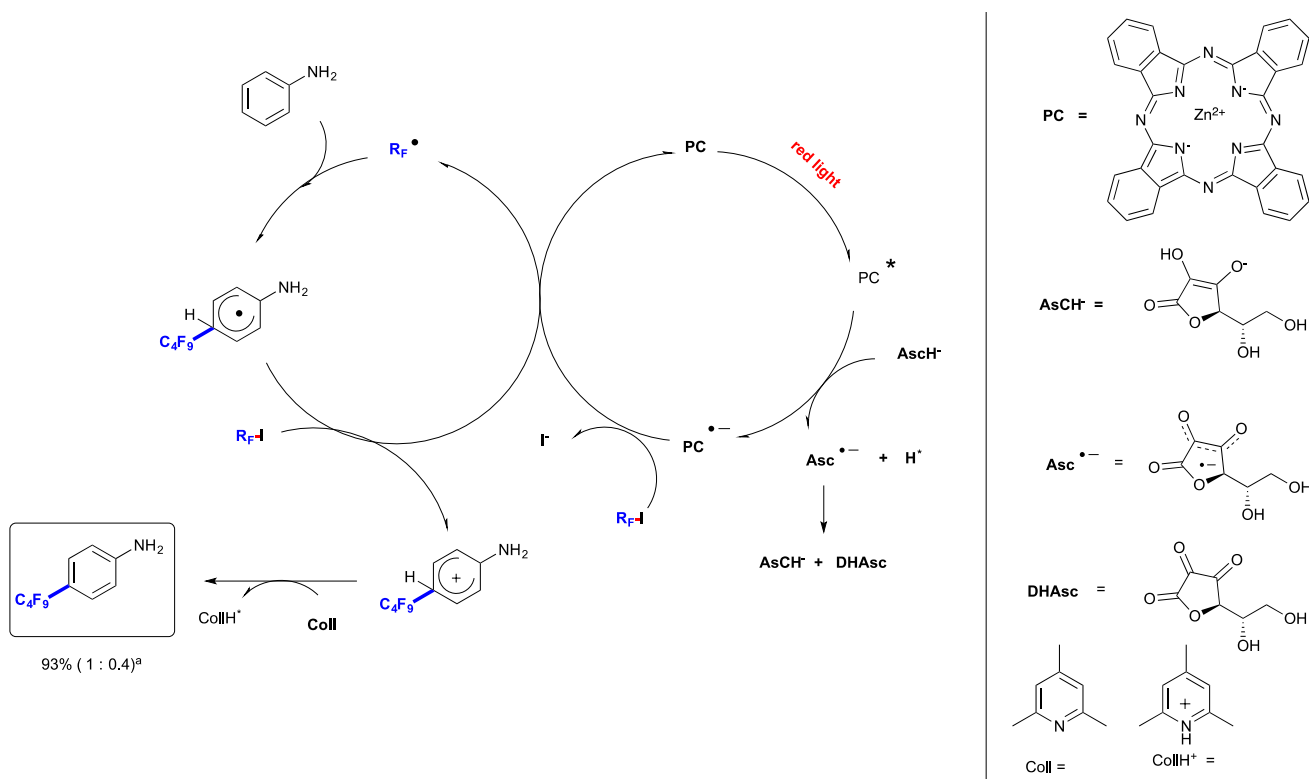
Scheme 12 Proposed reaction mechanism

chain lengths were compared between different photocatalysts [40].

In a parallel study [40] the efficiency of different photocatalysts (Rose Bengal, (Ir[(dF(CF$_3$)ppy]$_2$(dtbbpy)$^+$, and zinc phthalocyanine) on the perfluorobutylation of

4-methylaniline was compared, employing different light sources (green LEDs, violet LEDs, and red LEDs, respectively). The perfluorobutylation of 4-methylaniline under Rose Bengal photocatalysis is made possible through an oxidative quenching cycle of the photocatalyst, whereas

Scheme 13 Proposed reaction mechanisms for the perfluorobutylation of 4-methylaniline under oxidative (**A**) and reductive (**B**) quenching cycles of the photocatalysts, employing (Ir[(dF(CF$_3$)ppy]$_2$(dtbbpy)$^+$ (PC-1), zinc phthalocyanine (PC-3) and Rose Bengal (PC-2)
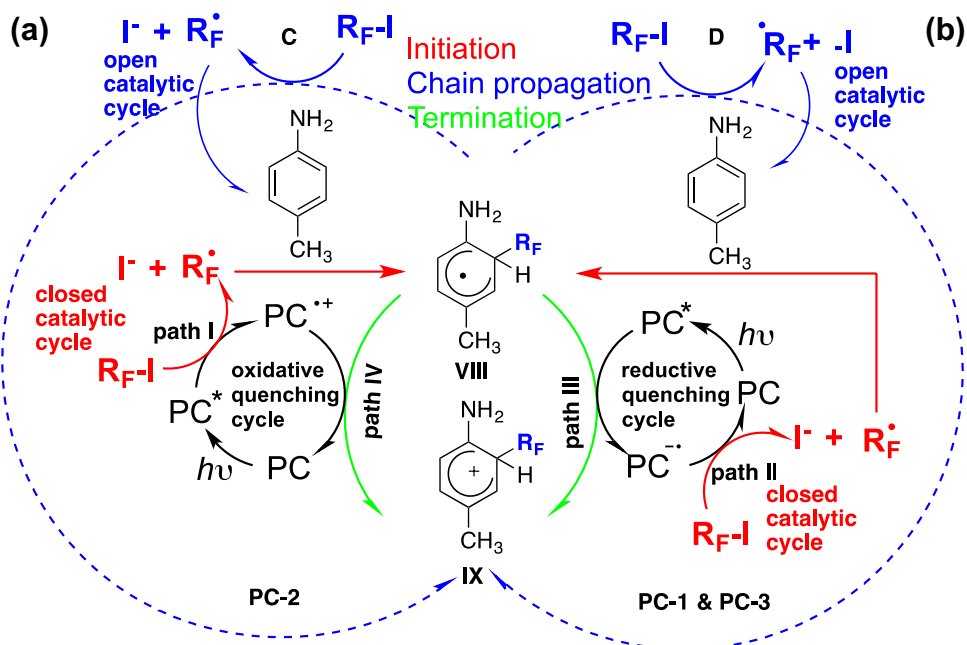
the same reaction under Ir[(dF(CF$_3$)ppy]$_2$(dtbbpy)$^+$, or zinc phthalocyanine photocatalysts are conducted under reductive quenching cycles of the photocatalysts. A pictorial representation of the photoredox cycles within each photocatalyst is given in Scheme 13.

From Scheme 13, it is observed that, under the oxidative quenching cycle (left, part **A**, Scheme 13) of Rose Bengal (PC-2) as photocatalyst, R$_F$ radicals are produced through the reductive ET from excited RB* to R$_F$-I, leading to the radical cation of Rose Bengal, which is re-generated into its photoactive state through the ET reduction of intermediate **VIII** (cf. Scheme 5). Two catalytic cycles can be distinguished: a closed course, in which R$_F$ radicals are produced through the initial ET reduction by PC* (path **I**, Scheme 13), and an open catalytic cycle (path **C**, Scheme 13) where further R$_F$ radicals are generated through the ET reduction by intermediate **VIII**. Oxidation of intermediate **VIII** to intermediate **IX** is accomplished, in the oxidative quenching cycle, by oxidation from the radical cation of the photocatalyst (Rose Bengal radical cation).

Regarding the reductive quenching cycles of (Ir[(dF(CF$_3$)ppy]$_2$(dtbbpy)$^+$ (PC-1) and zinc phthalocyanine photocatalysts (PC-3) (B, Scheme 13), the closed catalytic courses (path **II**, Scheme 13) comprise the reduction of R$_F$-I through the lower oxidation state of the photocatalysts (PC-1 and PC-3), which are produced by the reductive ET from intermediate **VIII** to the excited state of PC* (path **III**, Scheme 13). On the other hand, the open catalytic cycles with PC-1 and PC-3 are attained when intermediate **VIII** reduces R$_F$-I to R$_F$ radicals by ET (path **D**, Scheme 13).

Table 1 summarizes the photochemical parameters for the photocatalyzed perfluorobutylation of 4-methylaniline under three photocatalytic systems (employing PC-1, -2, and -3).

As observed from Table 1, the largest reaction quantum yield for the perfluorobutylation of 4-methylaniline is obtained with (Ir[(dF(CF$_3$)ppy]$_2$(dtbbpy)$^+$ (PC-1) photocatalyst, followed by that with Rose Bengal (PC-2). The lowest reaction quantum yield is obtained when zinc phthalocyanine (PC-3) photocatalysis was employed. The excited state

quenching fraction Q refers to the proportion of the excited state of the PC which is used in the very productive photocatalytic cycle (generation of R$_F$ radicals). As observed from Table 1, both PC-1 and -3 have productive excited states involved in the production of R$_F$ radicals, whereas for Rose Bengal (PC-2), only 34% of its excited state is devoted to the production of R$_F$ radicals (the other 66% of the excited state are likely involved in radiative or internal conversion processes). Regarding the radical chain lengths L, PC-1 (i.e., (Ir[(dF(CF$_3$)ppy]$_2$(dtbbpy)$^+$) affords the longest radical chain, purporting on the efficiency of the open catalytic cycle (path **D**, Scheme 13). The lowest radical chain is that for PC-3 (i.e., zinc phthalocyanine), where path **D**, Scheme 13, seemed not to play a relevant role when PC-3 is employed. Experimental evidence supports these observations when comparing photoreaction times (PC-3 needs prolonged reaction times, as compared to PC-1 and -2) [40].

3 Conclusions

On account of the excellent electronic match between anilines and the electrophilic nature of fluoroalkyl radicals R$_F$, substitution reactions with R$_F$ groups can be accomplished efficiently and in high yields by radical methodologies. On the other hand, photocatalytic methods have been established as convenient tools to generate the incipient fluoroalkyl radical that ensues substitution of the aniline scaffold, being a mild, environmentally benign method as compared to other radical-generating strategies. We have shown different visible-light photocatalytic methods to achieve fluoroalkylation of free aniline derivatives. Diverse photocatalysts have been explored, such as polypyridyl complexes of Ir and Ru transition metals, 18-π electron planar metal-*iso*indole systems such as zinc phthalocyanine, and organic dyes such as Rose Bengal have all been successfully employed as photocatalysts. These photocatalysts can undergo either oxidative or reductive quenching cycles. Also, light sources spanning from the blue region of the electromagnetic spectrum to red light from power LEDs have been used. Mechanistic aspects have been discussed for each photoredox transformation. A comparative study of the photocatalytic mechanisms employing different photocatalysts within a unique fluoroalkylation reaction of an aniline derivative has thrown light into the open and closed catalytic cycles operating within each photocatalytic mechanism, bringing out the lengths of radical chains and catalytic efficiency for each photoredox transformation.

Future work or studies in the area should be directed to studying the visible light photocatalyzed fluoroalkylation of free aniline derivatives employing more environmentally convenient protocols such as reactions in water, photocatalyst recycling, and employing photocatalysts that operate in

Table 1 Measured values of Stern–Volmer constants (K_{SV}), reaction quantum yields (ϕ), excited state quenching fractions of PC (Q), and radical chain lengths (L), employing PC-1–3

Entry	PC	K_{SV}[a]	ϕ[b]	Q[c]	L[d]
1	1	402	3.81 ± 0.16	0.979	3.9
2	2	4.3	0.51 ± 0.03	0.340	1.5
3	3	162	0.17 ± 0.01	0.951	0.18

[a]Stern–Volmer constant, in M^{-1}

[b]Quantum yields at the maximum absorption wavelength of the PC

[c]Excited state quenching fractions of PC

[d]Radical chain lengths

photocatalytic cycles with long radical chains to minimize irradiation time and photocatalyst degradation/consumption. Also, a study on photocatalyst efficiency should come up with the best photoredox choice for accomplishing the fluoroalkylation of free aniline derivatives.

Declarations

Conflict of interest The authors herein declare no conflict of interests.

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