European Journal of Organic Chemistry

Benign Perfluoroalkylation of Aniline Derivatives through Photoredox Organocatalysis under Visible Light Irradiation

--Manuscript Draft--

Manuscript Number:	ejoc.201501189
Article Type:	Short Communication
Corresponding Author:	Al Postigo, Ph.D. UNIVERSIDAD DE BUENOS AIRES BUENOS AIRES, ARGENTINA
Corresponding Author E-Mail:	apostigo@ffyb.uba.ar
Other Authors:	Sebastian Barata-Vallejo, Ph.D.
	Damian E. Yerien, Biochemist
Keywords:	perfluoroalkylation; cesium carbonate; photoredox catalysis; dye-catalyzed; perfluoroalkyl radicals
Manuscript Classifications:	Catalysis; Organic Chemistry: Compound Classes; Organic Chemistry: Methodology and Reactions; Sustainable Chemistry
Suggested Reviewers:	Armido Studer, Professor Full Professor, Westfalische Wilhelms Universitat Munster studer@wwu.de expert on radical chemistry
	Henri DOUCET, Ph.D. PROFESSOR, University of Rennes 1 henri.doucet@univ-rennes1.fr expert on organocatalysis
	William R. Dolbier, Ph.D. Professor, University of Florida wrd@chem.ufl.edu EXPERT ON FLUORINE CHEMISTRY
	Timothy Noeel, Ph.D. Professor, Ghent University t.noel@tue.nl EXPERT ON PHOTOCATALYSIS
Opposed Reviewers:	
Abstract:	In this work, we present a room light- or solar-initiated transition metal-free radical homolytic aromatic substitution (HAS) reaction of aniline derivatives with perfluoroalkyl moieties employing perfluoroalkyl halides as readily-available perfluoroalkyl sources in the presence of cesium carbonate as base and inexpensive Rose Bengal as organophotocatalyst in MeCN as solvent, rendering perfluoroalkyl-substituted aniline derivatives in good-to-excellent yields, even upon scaling up. Although the mechanism of this reaction is still under investigation, we shall present some evidence based on competitive substitution rate experiments that cast some light into the reaction intermediates.
Author Comments:	Please find as attachment a manuscript entitled: "Benign Perfluoroalkylation of Aniline Derivatives through Photoredox Organocatalysis under Visible Light Irradiation" by Sebastián Barata-Vallejo, Damian E. Yerien, and Al Postigo, to be considered for publication in European Journal of Organic Chemistry. In this work, we have developed a photocatalytic CAr-Rf bond formation reaction (Homolytic Aromatic Substitution, HAS) with an inexpensive organic dye, Rose Bengal, in the absence of transition metals, through irradiation at ambient temperature with a household fluorescent light bulb (visible light) and readily-available perfluoroalkyl iodides. The reaction can also be conducted under solar exposure, and can be scaled up, which renders this method convenient, benign and energy saving. This method was applied to the synthesis of a variety of perfluoroalkyl-substituted aniline derivatives, which had previously been

	synthesized under harsh reaction conditions, in somewhat low yields and poor regioselectivity. As far as we know, this is the first report on a high-yielding, almost quantitative, perfluoroalkylation reaction of aniline derivatives where a photoredox organocatalyst functions as an Electron Transfer Reductant. We deem this work important both from the synthetic point of view, as well as mechanistic, since we provide evidence for the nature of the transition state/intermediate through reaction rates, and precludes the proton transfer-electron transfer route (PT-ET) for the re-aromatization of the radical intermediate formed upon addition of the Rf radical to the arene, which had previously been suggested by other authors in the presence of Cs2CO3. We provide evidence that Cs2CO3 acts as both an ET initiator/mediator in the photocatalytic cycle In this manner, we present twenty (20) new compounds properly characterized, obtained by a facile and reproducible photocatalytic methodology. We are currently extending the current procedure to other families of organic compounds such as heteroaromatics. We look forward to hearing from you, and in the meantime, remain faithfully Professor Dr. Al Postigo Faculty of Pharmacy and Biochemistry University of Buenos Aires
Section/Category:	
Additional Information:	
Question	**Response**
Dedication	
Justification	In this work, we have developed a photocatalytic CAr-Rf bond formation reaction (Homolytic Aromatic Substitution, HAS) with an inexpensive organic dye, Rose Bengal, in the absence of transition metals, through irradiation at ambient temperature with a household fluorescent light bulb (visible light) and readily-available perfluoroalkyl iodides. The reaction can also be conducted under solar exposure, and can be scaled up, which renders this method convenient, benign and energy saving. This method was applied to the synthesis of a variety of perfluoroalkyl-substituted aniline derivatives, which had previously been synthesized under harsh reaction conditions, in somewhat low yields and poor regioselectivity. As far as we know, this is the first report on a high-yielding, almost quantitative, perfluoroalkylation reaction of aniline derivatives where a photoredox organocatalyst functions as an Electron Transfer Reductant. We deem this work important both from the synthetic point of view, as well as mechanistic, since we provide evidence for the nature of the transition state/intermediate through reaction rates, and precludes the proton transfer-electron transfer route (PT-ET) for the re-aromatization of the radical intermediate formed upon addition of the Rf radical to the arene, which had previously been suggested by other authors in the presence of Cs2CO3. We provide evidence that Cs2CO3 acts as both an ET initiator/mediator in the photocatalytic cycle In this manner, we present twenty (20) new compounds properly characterized, obtained by a facile and reproducible photocatalytic methodology. We are currently extending the current procedure to other families of organic compounds such as heteroaromatics. We look forward to hearing from you, and in the meantime, remain faithfully Professor Dr. Al Postigo Faculty of Pharmacy and Biochemistry University of Buenos Aires
Submitted solely to this journal?	Yes
Has there been a previous version?	Yes
Please state previous 1) Manuscript ID and 2) journal. 3) If the paper was reviewed, please include a point-by-point response to the reviewer comments. as follow-up to "Has there been a previous version?"	1)EMID:62b47d74caf39c1d-201505610 2)Angewandte Chemie International Edition 3)Comments from referees: Reviewer 1: (This reviewer suggests publication in EJOC) "A run-of-the-mill work! In this paper, a method for aromatic perfluoroalkylation. The authors have investigated a photoredox organocatalysis protocol for the introduction of

perfluoroalkyl groups into electron-rich arenes. The similar strategy using photoredox transformations were already reported by many groups. The regioselectivity of aromatic substitution is quite poor. Furthermore, all the products are too specialized and not of general interest to readers of Angew.Chem. Regrettably, I do not find enough urgency nor importance in this paper in order to be acceptable for publication in Angew. Chem.

Response to referee:
Quote: "...The similar strategy using photoredox transformations were already reported by many groups". End quote.
As a matter of fact, there has not been a transition metal-free photoredox strategy employing an organic dye and readily-available perfluoroalkyl iodides as perfluoroalkylating agents for homolytic aromatic substitution. However, the employment of transition metal-photoorganocatalysis for the trifluoromethylation and perfluoroalkylation reactions of both aliphatic and aromatic substrates is well established in the literature. The present methodology is quite convenient, since the organic dye (as photocatalyst) allows the use of sunlight as inexpensive irradiation source, and the perfluoroalkyl iodide as perfluoroalkylating agent (c.f.: S. P. Pitre, Ch. D. McTiernan, H. Ismaili, J. C. Scaiano, ACS Catalysis, 2014, 4, 2530, and N. J. W. Straathof, H. P. L. Gemoets, X. Wang, J. C. Schouten, V. Hessel and T. Noeel, Chem. Sus. Chem., 2014, 7, 1612.).

Quote: “The regioselectivity of aromatic substitution is quite poor”. End quote.
This observation is totally correct. As a matter of fact, we are working towards strategies to increase the regioselectivity in the perfluoroalkylation reactions of heteroarenes. At present, we have results with a combination of photocatalysts and reaction conditions. However, these are preliminary results that need further experiments.

Reviewer 2:
Reviewer 2: There has been a plethora of reactions allowing for the direct perfluoroaklyation of electron rich aromatics via CH activation. The variant of such reaction presented here is a so-called metal free approach conducted under visible light activation in the presence of Rose Bengal as the photoredox organocatalyst. All these ingredients have been used independently by other groups but I guess the originality of this contribution is to assemble these components to affect perfluoroalkylation. From a synthetic viewpoint, this method does not appear overwhelmingly advantageous as a mixture of regioisomers is obtained for the most challenging substrates (The table should draw the exact isomer formed for reactions leading to a single regioisomer); synthetically, the next challenge is to define reactivity that would allow clean control of regiochemistry on demand and this is not addressed in this paper; this being said, the fact that this transformation is conducted at room temperature is a beneficial characteristic. So the key informative section of the paper is the mechanistic interpretation mainly based on Hammett type analysis looking at the influence of electronic on the aniline substrates. The mechanism as suggested seems plausible but some additional arguments/experiments on the role of Cs2CO3 acting both as a base and an electron transfer would be useful.

Response to referee:

We are working towards the improvement of the regioselectivity in the perfluoroalkylation reactions. We have had preliminary results with the perfluoroalkylation of heteroarenes and a combination of organic dyes and reaction conditions.

Quote: “The mechanism as suggested seems plausible but some additional arguments/experiments on the role of Cs2CO3 acting both as a base and an electron transfer would be useful.” End quote.

Intrigued by the role of Cs2CO3 in the ET process (see entries 1 & 21, Table 1, where either thermally of photochemically, C4F9 radical production is achieved with the reaction mixture Cs2CO3/C4F9I/aniline), we have attempted UV-visible experiments (Figure 5, Supporting Information) in order to uncover the presence of a charge transfer complex between the reactants, including Cs2CO3, but we did not observe

	any spectral shift in the wavelength maximum. We have also performed the illuminated reaction of aniline, C4F9I, in the absence of both RB and Cs2CO3 (24 hrs), and obtained a very low yield of substitution product (5%), demonstrating that laboratory light alone is not sufficient to produce enough C4F9 radicals to effect substitutuion. We have also performed an experiment employing the photocatalyst, C4F9I, and aniline substrate, in MeCN as solvent, turning on and off the lamp at different intervals. This experiment was aimed at elucidating the role of Rose Bengal (RB), whether it acts as a radical initiator or as a photocatalyst. From Figure 3, inserted in the manuscript, we uncovered the role of RB as photocatalyst, since during the intervals maintaining the lamp off (dark conditions), no substitution product is accumulated. We are planning to expand our mechanistic interpretation in a full paper. We have also studied the employment of additives such as TMEDA or tetramethyl guanidine-TMG (F. Sladojevich, E. McNeill, J. Borgel, S.-L. Zheng, T. Ritter, Angew. Chemie. Int. Ed. 2015, 54, 1-6.).
Have you used the "**CSEARCH Robot Referee**" for this submission?	Yes
Please upload the report as an extra Supporting Information file. as follow-up to "Have you used the "**CSEARCH Robot Referee**" for this submission?"	OK

Benign Perfluoroalkylation of Aniline Derivatives through Photoredox Organocatalysis under Visible Light Irradiation

Sebastián Barata-Vallejo,[a] Damian E. Yerien,[a] and Al Postigo*[a]

Abstract: In this work, we present a room light- or solar-initiated transition metal-free radical homolytic aromatic substitution (HAS) reaction of aniline derivatives with perfluoroalkyl moieties employing perfluoroalkyl halides as readily-available perfluoroalkyl sources in the presence of cesium carbonate as base and inexpensive Rose Bengal as organophotocatalyst in MeCN as solvent, rendering perfluoroalkyl-substituted aniline derivatives in good-to-excellent yields, even upon scaling up. Although the mechanism of this reaction is still under investigation, we shall present some evidence based on competitive substitution rate experiments that cast some light into the reaction intermediates.

Introduction

The anilino moiety is well represented in pharmaceuticals with a large array of activity. For instance, sulfa drugs are a well known class of antibacterial agents containing *N*-substituted sulfonamide groups on the *para* position of an aniline ring (NH_2ArSO_2NHR). Recently, halogenated derivatives of *N*-substituted-4-aminobenzene sulfonamides as well as triazine sulfa drug derivatives have found remarkable activity towards carbonic anhydrase *iso*zymes [1,2] and anticancer activity [3] as well. Compounds such as anilino enaminones have found applications as potential anticonvulsant agents, and the fluoro-, trifluoromethyl-, and trifluoromethoxy- derivatives have shown substantial enhanced activity [4]. Also, largely prescribed anethetics such as procaine and benzocaine contain aminoaromatic functionalities.

The introduction of a fluoroalkyl moiety into a pharmacophore is often known to increase activity, resistance to oxidation, and lipophilicity/bioavailability. However, it is now widely accepted that compounds with certain functional groups such as anilines, and hydrazines have a much greater associated risk towards formation of reactive metabolites in drug candidates than compounds that do not contain such "structural alerts". The incorporation of fluoroalkyl moieties into anilino substrates [5] can therefore be conceived to hamper the formation of these metabolites due to their uneasiness towards oxidation.

One general strategy to achieve fluoroalkyl-group substitution is the radical homolytic aromatic substitution reaction (HAS) [6]. HAS with the CF_3 group has been well documented [7], however, fewer examples have been informed for HAS perfluoroalkylation [8-11]. HASs with perfluoroalkyl groups can be classified into thermal and photoinduced methods. Thermal methods can make use of transition metal-catalysis [12-16] and several perfluoroalkyl sources (Figure 1) or else be non-metal catalyzed, among which, the use of the Baran reagent [17] or perfluoroalkylsulfinate salts [18] in the presence of organic peroxide [19] or azo initiators [20] (Figure 1) render perfluoroalkyl-substituted arenes efficiently. Also electrophilic perfluoroalkylating reagents in the presence of metals effect C-H bond radical substitutions with R_f groups [15,21].

Photoinduced methods either through direct homolysis of X-C_nF_{2n+1} bonds [22,23], or by means of photoinduced electron transfer (PET) reactions [24] are capable of generating perfluoroalkyl radicals C_nF_{2n+1} even in aqueous systems [25] (Figure 1). Since the pioneering work of MacMillan for the trifluoromethylation reactions of arenes through the use of transition-metal photo-organocatalysts [26], only a few reports on photocatalytic perfluoroalkylations of arenes have been documented [27].

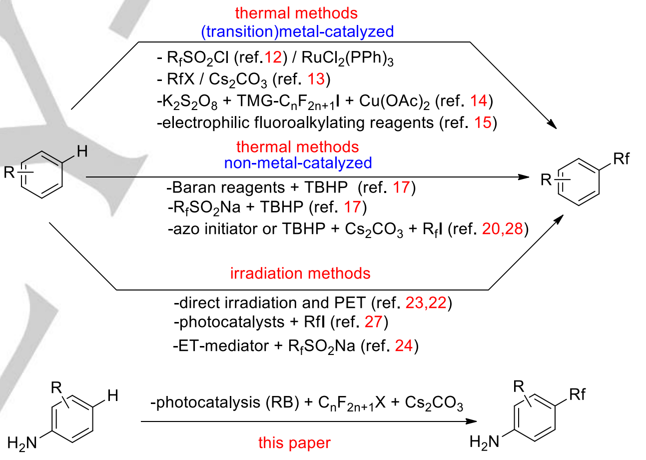


Figure 1. Methods for C-H (HAS) radical perfluoroalkylation of arenes

Among the reported synthetic methods described to obtain perfluoroalkyl-substituted anilines by HAS reactions, the Cu(I) oxide- [29] and the zinc-SO_2-mediated methodologies [30a,b] afford *2*- and *4*-substituted perfluoroalkyl anilines in moderate yields in organic solvents [30c]. These methods, however, lack in regioselectivity and employ harsh reaction conditions.

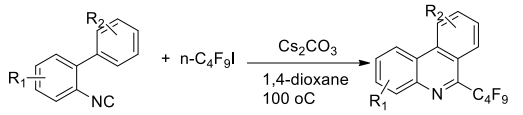
We have employed the photoinduced methodology (Photoinduced Electron Transfer, PET) in the past to effect the HAS on activated aromatic amines to synthesize Ar-R_f, in water or aqueous organic solvent mixtures [22]. Compounds such as *N,N*-dimethylaminoaromatic substrates efficiently substitute a ring H-atom by a perfluoroalkyl group. We have postulated a PET mechanism [22] between the excited aromatic amine and *n*-C_4F_9I which affords a radical ion pair (radical cation of the amine and radical anion of R_fX), from where C_4F_9 radicals are obtained, which ultimately substitute the ring systems. However, the PET substitution reaction of secondary and primary aromatic amines with perfluoroalkyl moieties is very sluggish, probably due to deprotonation of the resulting radical cations ([31], [32]) diverting the aromatic-ring R_f group substitution pathways [33].

It has recently been informed the perfluorobutylation of *iso*nitriles leading to the synthesis of phenanthridines-R_f employing Cs_2CO_3 according to Scheme 2 [28].

---

[a] Sebastián Barata-Vallejo, Damian E. Yerien, and Al Postigo
Departamento de Química Orgánica
Facultad de Farmacia y Bioquímica-Universidad de Buenos Aires
Junin 954 CP1113-Buenos Aires-Argentina
E-mail: apostigo@ffyb.uba.ar

Supporting information for this article is given via a link at the end of the document



Scheme 2. Perfluorobutylation of isonitriles and ulterior formation of phenanthridines

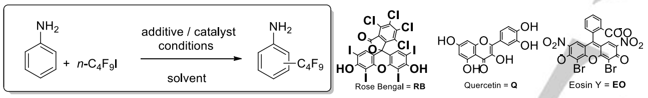
The authors [28] propose that perfluoroalkyl radicals are generated through thermal initiation with Cs_2CO_3, and that a radical anion intermediate is formed along the reaction pathway. We hypothesized that the use of Cs_2CO_3 could be modulated to achieve direct HAS reactions with R_f groups [28b].

We herein report a transition-metal-free and environmentally-benign perfluoroalkylation of aniline derivatives with organic dyes as visible light photoorganocatalysts in the presence of Cs_2CO_3.

Results and Discussion

We commenced our studies by inspecting the role of Cs_2CO_3 [28b] in the radical initiation process for generating C_4F_9 radicals under dark reaction conditions, and their reaction with aniline, summarized in Table 1.

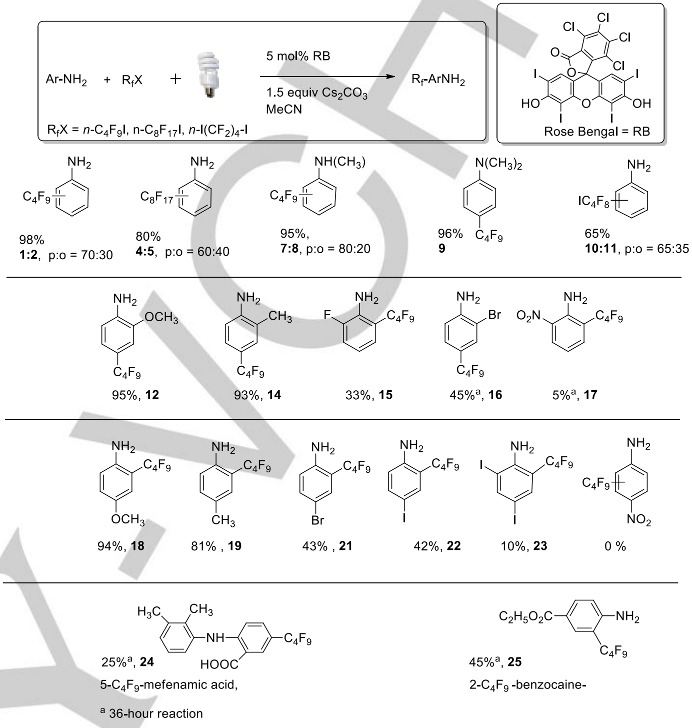
Table 1. Percentage yield of combined 4- and 2- perfluorobutyl-substituted aniline products **1,2,** from 24-hour reaction of aniline (0.2 mmol) with n-C_4F_9I or otherwise noted, an additive salt / catalyst, in a given solvent (3 mL), under Ar-atmosphere and different reaction conditions



#	$[An]:[R_fI]:[additive]$	Additive/ catalyst (0.05 equiv)	T(°C)/ cond.	Solvent system	$\%(1+2)^a$
1	1:3:1.5	Cs_2CO_3 / -	100/dark	1,4-dioxane	30
2	1:3:1.5	Na_2CO_3 / -	100/dark	1,4-dioxane	-
3	1:3:-	- / -	100/dark	1,4-dioxane	-
4	1:3:1.5	CsF/ -	100/dark	1,4-dioxane	< 5
5	1:3:1.5	CsF-Na_2CO_3/ -	100/dark	1,4-dioxane	< 5
6	1:3:1.5	Cs_2CO_3/ -	100/dark	1,4-dioxane:H_2O	-
7	1:3:1.5	Cs_2CO_3/ -	100/dark	THF	< 5
8	1:3:1.5	Cs_2CO_3/ -	100/dark	MeCN	-
9	1:3:3	Cs_2CO_3/ -	100/dark	1,4-dioxane	35
10	1:3:0.75	Cs_2CO_3/ -	100/dark	1,4-dioxane	16
11	1:3:1.5	Cs_2CO_3/ -	60/dark	1,4-dioxane	-
12	1:3:1.5	Cs_2CO_3/ -	100/dark	1,4-dioxane^b	30
13	1:3:1.5	Cs_2CO_3/ -	100/dark	1,4-dioxane^c	20
14	1:3:-	- / **Q**	RT / $h\nu^d$	MeCN	25
15	1:3:-	- / **RB**	RT / $h\nu^d$	MeCN	52
16	1:3:1.5	Cs_2CO_3/ **Q**	RT / $h\nu^d$	MeCN	50
17	**1:3:1.5**	**Cs_2CO_3/ RB**	**RT / $h\nu^d$**	**MeCN**	**98**
18	1:3:1.5	Cs_2CO_3/ **RB**	RT / $h\nu^d$	MeCN^e	81
19	1:3:1.5	Cs_2CO_3/ **EO**	RT / $h\nu^d$	MeCN	62
20	1:3:1.5	Cs_2CO_3/ **RB**	RT / $h\nu^d$	H_2O	< 5
21	1:3:1.5	Cs_2CO_3/ -	RT / $h\nu^d$	MeCN	50
22	1:3:1.5	Cs_2CO_3/ **RB**	RT / $h\nu^d$	MeCN^c	78
23	**1:3:1.5**	**Cs_2CO_3/ RB**	**RT / $h\nu^f$**	**MeCN**	**91**
24	1:3:1.5	Cs_2CO_3/ **RB**	RT /dark	MeCN	-

a.-yields determined by ^1H and ^{19}F RMN integration (combined 4-C_4F_9, and 2-C_4F_9 yields *para:ortho* = 70:30). **b**.-64-hour reaction. **c**.-without de-oxygenation. **d**.-60 watt fluorescent light bulb. **e**.-18-hour reaction **f.**-15 hour-accumulated sunlight exposure

Table 2. Perfluoroalkylation yields of aniline derivatives by *Rose Bengal* photoredox organocatalysis



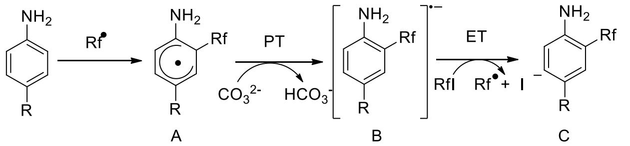
The reaction carried out in the presence of Cs_2CO_3, in Ar-deoxygenated 1,4-dioxane as solvent at 100 °C is reported in entry 1, Table 1, affording 30% yield of combined 4-(perfluorobutyl)-aniline **1**, and 2-(perfluorobutyl)-anilne **2** (**1**:**2** ratio = 70:30). The reaction employing Na_2CO_3 (entry 2, Table 1) does not yield product. The reaction of aniline and n-C_4F_9I carried out in the absence of cesium carbonate, in 1,4-dioxane as solvent at 100° C did not yield substitution product (Table 1, entry 3). Varying the cesium salt (entry 4), the base (entry 5), the solvent (entries 6-8), the stoichiometry (entries 9, 10) or temperature (entry 11) led to a sluggish substitution of the ring with a perfluorobutyl group and recovery of starting material. Prolonging the reaction times (entry 12) of the substitution reaction has little or no effect on the yield of product. The reaction of aniline, Cs_2CO_3, n-C_4F_9I in 1,4-dioxane without de-oxygenation (entry 13) also yields the substituted aniline, purporting that air does not suppress the radical initiation, and / or propagation. Inspection of the crude reaction mixture (*i.e.:* from reaction conditions such as in entries 1,9, and 12, Table 1) reveals that the methodology compromises substrate integrity, as substantial oligomeric material is formed under the reaction conditions, and mass balance is not complete (ca. 63%).

We then attempted the room-light (60 Watt fluorescent light bulb) photocatalyzed reaction of aniline with n-C_4F_9I in the presence of quercetin (**Q**) as photocatalyst **PC** in MeCN as solvent, obtaining substitution products in 25 % yield (entry 14, Table 1). Encouraged by this result, we used other **PC**s such as Rose Bengal (**RB**) [34] (entry 15, Table 1), and eosine Y (**EO**) (entry 19, Table 1) and obtained good substitution yields with the former (52% yield of combined **1** and **2**). However, when we added Cs_2CO_3 to the photocatalytic reaction of both **Q** (entry 16, Table 1) and **RB** (entry 17, Table 1), the perfluorobutylation yields improved substantially, obtaining quantitative perfluorobutyl-substituted aniline with **RB** as **PC** in the presence of Cs_2CO_3. The illuminated reaction (60 Watt fluorescent light bulb) of aniline and *n*-C_4F_9I in the absence of **PC** and in Ar-de-oxygenated MeCN (entry 21, Table 1) affords 50 % yield of combined substitution products **1** and **2** (*cf.* with entry 1, Table 1) indicating that room light is initiating *n*-C_4F_9• radical production in the presence of Cs_2CO_3, and absence of **PC** (a blank experiment illuminating the reaction mixture of aniline and C_4F_9I in the absence of Cs_2CO_3 and **RB** yields 5% of substitution product). The dye-photocatalyzed reaction without de-oxygenation (entry 22, Table 1) also affords good yields of substitution product (78% yield). We also attempted the reaction under solar exposure and obtained 91% yield of products **1,2** after 15-h of accumulated solar incidence (entry 23, Table 1). We therefore chose **PC RB** in the presence of Cs_2CO_3 in Ar-deoxygenated MeCN as solvent for the model perfluorobutylation reaction of aniline derivatives under a household fluorescent light bulb irradiation. Interestingly, when we inspected the reaction rate profiles of perfluorobutyl-substituted aniline isomers production as a function of irradiation time (Figure 2, Supporting Information), we observed the formation of the di-substituted 2,4-*bis*(perfluorobutyl)-aniline product **3** at the expense of the 2-(perfluorobutyl)-aniline **2** isomer production, purporting that the *p*-isomer (*i.e.:* 4-(perfluorobutyl)-aniline, **1**) is formed first, and disubstitution ensues from the *ortho*-C_4F_9-substituted aniline **2**. A control of the regioselectivity of the photocatalytic reaction (HAS) of aniline was attempted by changing the substrate: C_4F_9I ratio = 3:1. However, the *p:o* isomer ratio remains almost identical (*i.e.:* 70:30). The reaction of aniline with *n*-$C_8F_{17}I$ affords products 4-(perfluorooctyl)-aniline **4** and 2-(perfluorooctyl)-aniline **5** in 80% yield (**4:5** ratio = 60:40, Table 2). The reactions of secondary and tertiary aromatic amines lead to substitution products **7-9** in very good yields (Table 2). Employing another perfluoroalkyl source, such as $I(CF_2)_4I$, we obtained the 4-*(*1,1,2,2,3,3,4,4-octafluoro-4-iodobutyl)aniline derivative **10** and 2-*(*1,1,2,2,3,3,4,4-octafluoro-4-iodobutyl)aniline derivative **11** with retention of the iodine atom, in a 65:35 isomeric ratio (Table 2). No ring-closure product was encountered (*cf.* ref. [34c]). We then proceeded to evaluate the scope of the photocatalytic reaction with different aniline derivatives, bearing electron withdrawing and donating groups in the *ortho* and *para* positions of the aniline ring (Table 2).

For the *2*-substituted anilines with the CH_3O, CH_3, F, Br, and NO_2 groups, major perfluorobutylated products (Table 2, products **12-17**, respectively) arise from homolytic substitution at the *4*-position of the ring with less or none substitution encountered at the *6*-position of the ring (except for F and NO_2, groups where the major substitution occurs at the *6*-position). Di-substitution with C_4F_9 moiety is encountered for 2-anisidine (**13**) (see Supporting information). For the 4-substituted aniline derivatives with CH_3O, CH_3, Br, I, and 2,4-I_2 groups, major perfluoroalkyl-group substitutions take place at the *2*- position (and *6*-position for 2,4-I_2) of the aniline ring (products **18-23**, respectively, Table 2). It is observed from Table 2, that the presence of halides on the aniline moiety does not preclude from a HAS to take place, and the perfluorobutylated products bear the bromine/ iodine atom(s) intact (reactions of 2-bromoaniline, 4-bromoaniline, 4-iodoaniline, and 2,4-diiodo-aniline, affording products **16**, **21**, **22**, and **23**, respectively, Table 2). This is quite interesting, since an orthogonal reactivity is observed for haloarenes, as no *ipso* substitution of the bromine/iodine atom(s) is encountered under photocatalytic conditions. Strong electron-withdrawing groups on anilines such as the 2-nitro group can also render the perfluorobutylated substitution product **17** as well (Table 2), however, the 4-nitro-aniline derivative is unreactive even upon prolonged reaction times (Table 2). Di-C_4F_9-substitution is encountered for *p*-toluidine (product **20**, Supporting Information). Electron rich anilines, substituted with OCH_3, and CH_3 groups render perfluorobutylated aniline derivatives in excellent yields (products **12, 14, 18,** and **19**, 81-95%).

The perfluorobutylation of mefenamic acid (*i.e.*: 2-((2,3-dimethylphenyl)amino) benzoic acid, an anti-inflammatory drug prescribed world-wide), leads to product **24** in 25% yield (Table 2). The perfluorobutylation of anesthetic benzocaine (*i.e.*: ethyl-4-amino-benzoate) leads to 45% yield of ethyl-4-amino-3-(1,1,2,3,3,4,4,4-octafluoro-2-methylbutyl)benzoate **25**. We attempted a large scale (0.01 mol) reaction of benzocaine, and obtained successfully 30 % yield of **25.** In order to cast some light into the nature of the transition state / intermediate of the photocatalytic reaction, we attempted to measure the ratio of rate constants for the photocatalytic (**RB**) perfluorobutylation of anilines substituted in the *para*-position with substituents of different electronic nature, such as electron withdrawing and electron releasing groups.

Tables 3A & 3B, Supporting Information, depict the competition experiments and the relationship log $k_{p\text{-toluidine}}/k_{ArNH2}$ showing clearly that the substitution reaction is accelerated with electron donating X groups on the aniline ring, implying that a stabilization of the transition state is achieved with electron richer nuclei. The reaction of *N,N*-dimethyl aniline in the presence of 1,4-dinitrobenzene (*p*-DNB, a radical anion scavenger) is not suppressed, observing product **5** in yields as reported in Table 2. The photoreaction of aniline/**RB**/C_4F_9I in the presence of TEMPO does not yield substitution product. Instead, the TEMPO-C_4F_9 adduct is obtained, indicating the intervention of C_4F_9 radicals. The negative result obtained with *p*-DNB does not rule out the intermediacy of a radical anion, as this latter could be very short-lived. A possible mechanism would take into account the C_4F_9• radical attack on an electron-rich position of the aniline derivative, generating a C_4F_9-substituted cyclohexadienyl-type radical **A**, which upon deprotonation by the base (PT, Cs_2CO_3) affords a radical anion of the C_4F_9-substituted product **B**. The fate of this radical anion could be: *i.*-dissociation (in the case of Ar-I •⁻) [35], *ii.*-ET to *n*- I-C_4F_9 (to propagate the chain) and thermoneutral product **C**, *iii.*-ET to the substrate (chain termination), Scheme 3.



Scheme 3. Proton transfer-Electron transfer mechanism for the re-aromatization

However, we observed acceleration of the C_4F_9-substitution reaction rates of anilines bearing electron donating groups (Tables 3A & 3B, Supporting Information), indicating that in addition to the enthalpic factor for the Ar—R_f bond formation (A, Scheme 3), there seems to be a substituent effect on the rates of perfluoroalkyl-substituted anilines formation. An experiment of aniline, **RB,** C_4F_9I in MeCN turning on and off the lamp at different intervals (Figure 3) reveals that the reaction is photocatalytic, and **RB** and light are needed through the entire reaction for substitution product to accumulate.

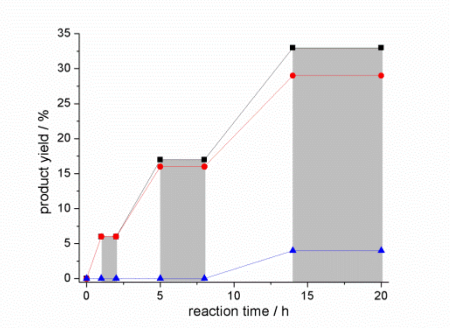


Figure 3. Plot of % product *vs* irradiation time. Lamp is maintained off in areas in shade. (■) % of isomer **1**, (●) % of isomer 2, (▲) % of di-substitution.

A mechanism such as that proposed in Figure 4, where a positively-charged intermediate/transition state develops, would account for these differences in reaction rates. Room-light excitation of **PC RB** leads to **RB*** which transfers an electron to *n*-C_4F_9I, generating C_4F_9• radicals, and the radical cation of $RB^{\cdot+}$ [36] (Figure 4).

The ground and excited redox states of **RB**, an electron transfer mediator, are important for the formation of the electron deficient perfluorobutyl radical (C_4F_9•), which functions as an oxidant of the substrate and an active species for the formation of perfluorobutylated anilines. The photoinduced downhill electron transfer from the excited state of **RB*** to C_4F_9I (**RB***, excited state singlet energy E_S = 2.17 eV, excited state triplet energy E_T = 1.8 eV [37a,b], in MeCN) is expected to efficiently generate C_4F_9• and $RB^{\cdot+}$ radical cations on the basis of their redox potentials ($E_{RB^{\bullet+}/RB^{*}}$ = -0.68 V *vs* SCE in MeCN [37b], $E_{C4F9I/C4F9\bullet}$ = -1.27 V [37c]), being the ΔG_{ET} for this process = -1.53 eV which suggests a quite favorable spontaneous ET (see Table 4, Supporting Information). The expectation that an electron from C_4F_9I is turned over during the photocatalytic electron-transfer cycle is based solely on the driving force predicted by the redox potentials (*vide supra,* Table 4, Supporting Information). At this stage, no detailed mechanistic data on the two-fold reaction of aniline with C_4F_9• are available, but it is rationally considered that a likely reaction pathway includes the radical addition of C_4F_9• to an electron-rich position of the aniline moiety, generating intermediate **A** (Figure 4) which is followed by oxidation to the Wheland intermediate **B** (rate determining step). This is supported by the acceleration of the substitution reactions of anilines bearing electron donating groups. This proposal (**A** → **B** C_4F_9I oxidation) can propagate the chain. Deprotonation (PT, Figure 4) affords perfluorobutyl substituted aniline derivative. In the case of the **PC** quercetin, **Q**, Markovic and collaborators [38] have found that its radical cation, $Q^{\cdot+}$ **,** will spontaneously be transformed into **Q** in the presence of bases whose HOMO energies are higher than the SOMO energy of $Q^{\cdot+}$ in a given medium, implying that **Q** cannot undergo the ET-PT mechanism which would lead to quercetin radical ($Q^{\cdot}$) and proton H^+. Therefore, it is proposed that in our photocatalysis by **Q** (entries 14,16, Table 1), $Q^{\cdot+}$ accepts an electron from the base (Cs_2CO_3) and therefore forms **Q** thermoneutral (regenerating the **PC**) and carbonate radical anion ($E\ CO_3^{\cdot-}/CO_3^{2-}$ = +1.23 +/-0.15 V [39a]) on the basis of HOMO energy of the carbonate anion. We hypothesize that $RB^{\cdot+}$ [39b] radical cation also accepts an electron from Cs_2CO_3 in an analogous fashion as $Q^{\cdot+}$ to regenerate **RB PC**. The fact that addition of Cs_2CO_3 to the photocatalytic reactions (entries 17 & 18, Table 1) significantly improved the perfluorobutylation yields could support the role of the base as an electron donor adjuvant to regenerate the catalyst. Furthermore, the photoinduced activation observed in the presence of Cs_2CO_3 and absence of **PC** suggests the role of this base as an ET (photo)mediator (entry 21, Table 1). We calculated a value of -0.24 eV for the ΔG_{ET} of this process (ET from CO_3^{2-} to $RB^{\cdot+}$, see Table 4, Supporting Information). Although we have demonstrated that **RB** functions as a photocatalyst (Figure 3) and not merely as an initiator, the fact that step A→B (Figure 4) also generates C_4F_9 radicals must be an indication of this being a rate determinig step. At this point, we are confident that aniline is not acting as an electron donor to the catalyst radical cation, as no product derived from the radical cation of aniline is observed [22]. The UV-vis spectra of C_4F_9I in the presence of Cs_2CO_3 does not show the presence of a CTC complex (Figure 5, Supporting information). Further studies are in progress to assess the electronic nature of the complex (**PC** / Cs_2CO_3 / R_fI), the substrate and the R_fX dependence.

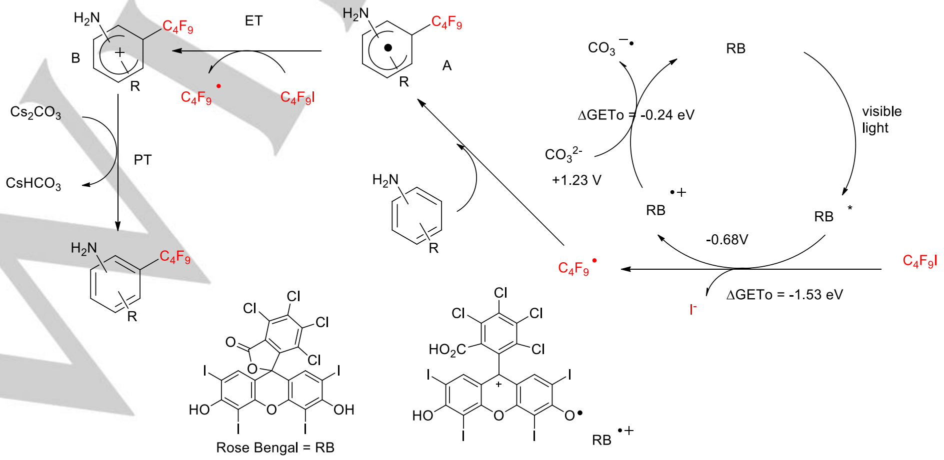


Figure 4. Proposed mechanism for the **RB** photocatalyzed perfluoroalkylation of aniline derivatives

Conclusions

In conclusion, we have developed a photocatalytic C_{Ar}-R_f bond formation reaction (HAS) with an inexpensive organic dye, *Rose Bengal*, in the absence of transition metals, through irradiation at ambient temperature with a household fluorescent light bulb (visible light) or solar exposure and readily-available perfluoroalkyl iodides. This method was applied to the synthesis of a variety of perfluoroalkyl-substituted aniline derivatives and work is in progress towards the application of this methodology to other families of organic compounds such as heteroaromatic compounds. As far as we know, this is the first report on a high-yielding, almost quantitative, perfluoroalkylation reaction of aniline derivatives where a photoredox organocatalyst functions as an ET reductant.

Experimental Section

General procedure for the perfluoroalkylation reaction: A mixture of the aniline derivative (0.6 mmol), R_fX (3 equiv), photocatalyst (0.05 equiv), and Cs_2CO_3 (1.5 equiv) in Ar-deoxygenated MeCN (3 mL) is irradiated (24 hrs) with a fluorescent light bulb (60 Watt) under constant stirring. The mixture was extracted with CH_2Cl_2 / H_2O thrice, and the organic layers gathered and dried over anhydrous Na_2SO_4, filtered, reduced under vacuum, separated and purified by column chromatography. Detailed procedures for preparations, purifications, compound characterization, and spectra can be found in Supporting Information.

Acknowledgements

Thanks are given to financial agencies: Concejo Nacional de Investigaciones Científicas y Técnicas (Conicet) and Universidad de Buenos Aires. SBV & AP are research members of Conicet. We also thank Dr. Lucas Fabián from IQUIMEFA-Conicet-FfyB-UBA for acquiring 600 NMR spectra.

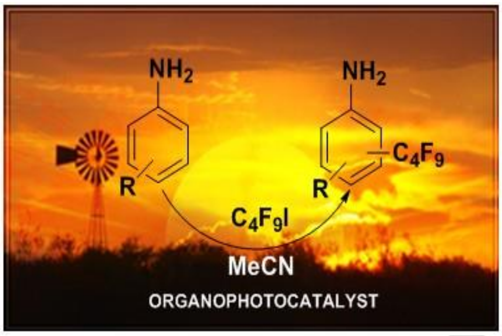
Keywords: radical perfluoroalkylation • organophotocatalyst • photocatalytic perfluoroalkylation •homolytic aromatic substitution • cesium carbonate

[1] G. Compain, A. Martin-Mingot, A. Maresca, S. Thibaudeau, C.T. Supuran, *Bioorg. & Med. Chem*. **2013**, *21*, 1555–1563.
[2] Mariya al-Rashida, S.Hussain, M. Hamayoun, A. Altaf, J. Iqbal, *Bio. Med Res. Int.* Volume **2014**, Article ID 162928, 10 pages.
[3] M.M. Ghorab, F.A. Ragab,H. Heiba, R.K. Arafa, E.M. El-Hossary, *Med. Chem .Res.* **2011**, *20*, 388–400.
[4] T. Heinbockel 1, Ze-Jun Wang, P.L. Jackson-Ayotunde, *Pharmaceuticals* **2014**, *7*, 1069-1090.
[5] M.R. Eno, M.D. Cameron, *Cur. Med. Chem.* **2015**, *22*, 465-489.
[6] S.E. Vaillard, A. Studer, *Radical Arylations*. Encyclopedia of Radicals in Chemistry, Biology and Materials, Wiley, (**2012**), *2*, 1059-1093. Eds. C. Chatgilialoglu & A. Studer.
[7] (a) S. Barata-Vallejo, A. Postigo, *Coord. Chem. Rev*. **2013**, *257*, 3051-3069. (b) B. Zhang, A. Studer, *Org. Biomol. Chem*. **2014,** *12*, 9895-9898. (c) B. Lantaño, M.R. Torviso, S.M. Bonesi, S. Barata-Vallejo, A. Postigo, *Coord. Chem. Rev*. **2015,** *285*, 76-108.
[8] O.A. Tomashenko, V.V. Grushin, *Chem. Rev*. **2011**, *111,* 4475.
[9] Y. Ye, M.S. Sanford, *Synlett* **2012**, *23*, 2005.
[10] T. Liu, Q. Shen, *Eur. J .Org. Chem*. **2012**, *2012*, 6679.
[11] (a) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470 (b) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chemie Int. Ed*. **2013**, *52,* 8214. (c) F. O´Hara, R.D. Baxter, A.G. O´Brien, M.R. Collins, J.A. Dixon, T. Fujiwara, Y. Ishihara, P. S. Baran, *Nature Protocols* **2013**, *8*, 1042.
[12] K. Yuan, J.-F. Soulé, H. Doucet, *ACS-Catalysis* **2015**, *5*, 978-991.
[13] (a) L. He, K. Natte, J. Rabeah, C. Taeschler, H. Neumann, A. Bruckner, M. Beller, *Angew .Chem .Int. Ed*. **2015**, *54*, 4320-4324. (b) R.N. Loy, M.S. Sanford, *Org. Lett.* **2011**, *13*, 2548-2551.
[14] F. Sladojevich, E. McNeill, J. Borgel, S.-L. Zheng, T. Ritter, *Angew. Chemie. Int. Ed.* **2015**, *54*, 1-6.
[15] (a) J. Charpentier, N. Früh, A. Togni, *Chem. Rev*. **2015**, *115*, 650−682. (b) (b) B. Pegot, Y. Macé, C. Urban, P. Diter, J.-C. Blazejewski, E. Magnier, *J. Fluorine Chem.* **2012**, *134*, 156-159.
[16] (a) C. Alonso, E. Martínez de Marigorta, G Rubiales, F. Palacios, *Chem. Rev*. **2015**, *115*, 1847−1935. (b) T. Takagi, T. Kanamori, *J. Fluorine Chem*. **2011**, 427-429.
[17] (a) F. O'Hara , D.G. Blackmond, P.S. Baran, *J. Am. Chem. Soc.*, **2013**, *135* (32), 12122–12134. (b) Y. Fujiwara, J.A. Dixon, F. O'Hara, E.D. Funder, D.D. Dixon, R.A. Rodriguez, R.D. Baxter, B. Herle, N. Sach, M.R. Collins, Y. Ishihara, P.S. Baran, *Nature*, **2012**, *492*, 95-100.
[18] L. Cui, Y. Matusaki, N.Tada, T. Miura, B. Uno, A. Itoh, *Adv. Syn. & Cat.* ***2013***, *355*, 2203-2207.
[19] S. Zhong, A. Hafner, C. Hussal, M. Nieger, S. Bräse, *RSC Adv*. **2015**, *5*, 6255-6258.
[20] M. Matsugi, M. Hasegawa, S. Hasebe, S. Takai, R. Suyama, Y. Wakita, K. Kudo, H. Imamura, T. Hayashi, S. Haga, *Tetrahedron Lett.* **2008**, *49*, 4189-4191.
[21] A. Studer, D. Curran, *Nature Chemistry* **2014**, *6,* 765-773.
[22] S. Barata-Vallejo, M. Martin Flesia, B. Lantaño, J.E. Arguello, A.B. Peñéñory, A. Postigo, *Eur. J. Org. Chem.* **2013**, *2013,* 998-1008.
[23] B. Lantaño, S. Barata-Vallejo, M.R. Torviso, S.M. Bonesi, J.E. Arguello, A. Postigo, *J. Fluorine Chem.* **2014**, *161*, 149-165.
[24] L. Cui, Y. Matusaki, N. Tada, Norihiro, M. Tsuyoshi; B. Bunji, I. Akichika, *Adv. Syn. & Cat.* ***2013***, *355*, 2203-2207.
[25] (a) A. Maroz, R. Hermann, S. Naumov, O. Brede, *J. Phys. Chem. A* **2005**, *109,* 4690 – 4696.
[26] D.A. Nagib, D.W.C. MacMillan, *Nature* **2011**, *480*, 224-228.
[27] (a) M. Iizuka, M. Yoshida, *J. Fluorine Chem*. **2009**, *130*, 926-932. (b) N.J.W. Straathof, D.J.G.P. van Osch, A. Schouten, X. Wang, J.C. Schouten, V. Hessel, T. Noeel, *J. Flow Chem*. **2014**, *4*, 12-17. (c) N.J.W. Straathof, H.P.L. Gemoets, X. Wang, J.C. Schouten, V. Hessel, T. Noeel, *Chem. Sus. Chem*. **2014**, *7*, 1612-1617. (d) J-B. Xia, C. Zhu, C. Chen, *J.Am.Chem.Soc*. **2013**, *135*, 17494-175001.
[28] (a) B. Zhang, A. Studer, *Org. Lett*. **2014**, *16(15*), 3990-3993. (b) M. Nappi; G. Bergonzini; P. Melchiorre, *Angew. Chemie, Int. Ed.*, **2014,** *53*, 4921,
[29] (a) M. Moreno-Mañas, R.P.S. Villarroya, *Synlett* **1999,** *1999,* 1996-1998. (b) T. Fuchikami, I. Ojima, *J. Fluorine Chem*. **1983**, *22*, 541-556. (c) B.R. Langlois, E. Laurent, N. Roidot, *TetrahedronLett.* **1991**, *32*, 7525-7528.
[30] (a) C. Wakselma, M. Tordeux, *J. Chem. Soc. Chem. Comm*. **I987**, 1701-1703. (b) M. Tordeux, B. Langlois, C. Wakselman, *J. Chem. Soc., Perkin Trans. 1:* Organic and Bio-Organic Chemistry , **1990**, *8* ,2293-9. (c) W.-Y. Huang, W.-P. Ma, W. Wang. *Chin. J. Chem*. **1990**, *8*, 175.
[31] M. Jonsson, D.D.M. Wayner, J. Lusztyk, *J. Phys. Chem*. **1996**, *100*, 17539 – 17543.
[32] (a) A. Yu, Y. Liu, Z.Li, J-P. Cheng, *J. Phys. Chem. A* **2007**, *111*, 9978 - 9987. (b) F.G. Bordwell, X-M. Zhang, J-P. Cheng, *J. Org. Chem*. **1993**, *58*, 6410 - 6416.
[33] (a) N. Karakostas, S. Naumov, O. Brede, *J. Phys. Chem. A* **2009**, *113*, 14087 – 14094. (b) C-C. Zeng, J.Y. Becker, *J. Org. Chem*. **2004**, *69*, 1053 - 1069. (c) S. Fukuzumi, J. Yuasa, N. Satoh, T. Suenobu, *J. Am. Chem. Soc.* **2004**, *126*, 7585 - 7594. (d) S. Dileesh, K.R. Gopidas, *Chem. Phys. Lett*. **2000**, *330*, 397 - 402.
[34] (a) C. Lambert, T. Sarna, T.G. Truscott, *J. Chem. Soc. Faraday Trans*. **1990**, 86, 3879-3882. (b) R.A. Thorson, G.R. Woller, Z.L. Driscoll, B.E. Geiger, C. A. Moss, A.L. Schlapper, E.D. Speetzen, E. Bosch, M. Erdélyi, N.P. Bowling, *Eur. J. Org. Chem.* **2015**, 1685–1695. (c) H.P. Cao, J.C. Xiao, *J.Fluorine Chem*. **2006**, *127*, 1079.
[35] (a) H. Yi, A. Jutand, A. Lei, *Chem. Comm*. **2015**, *51(3),* 545-548. (b) A.B. Pierini, J.S. Duca, *J. Chem. Soc. Perkin Trans 2*, **1995**, *9*, 1821-1828.
[36] (a) Armstrong, D. A.; Waltz, W. L.; Rauk, A. *Can. J. Chem. 84*(12),1614-1619. (b) H. Liu, W. Feng, C.W. Kee, Y. Zhao, D. Leow, Y. Pan, C.-H. Tan, *Green Chem*. **2010**, *12*, 953-956.
[37] (a) C. Lambert, I.E. Kochevar, *Photochem.& Photobiol.* **1997**, *66*, 15-25. (b) D. Burget, J.P. Fouassier, *J. Chem. Soc. Faraday Trans.* **1998**, *94*, 1849-1854. (c) C.P. Andrieux, L.G. Clis, M. Medebielle, P. Pinson, J.M. Saveant, *J. Am. Chem. Soc*. **1990**, *112*, 3509-3520.
[38] Z. Markovic, D. Amic, D. Milenkovic, J.M. Dimitri-Markovic, S. Markovic. *Phys. Chem. Chem. Phys*. **2013**, *15*, 7370-7378.

Entry for the Table of Contents

SHORT COMMUNICATION

We have developed a photocatalytic C_{Ar}-R_f bond formation reaction (HAS) with an inexpensive organic dye, *Rose Bengal*, in the absence of transition metals, through irradiation at ambient temperature with visible light and readily-available perfluoroalkyl halides. This method was applied to the synthesis of a variety of perfluoroalkyl-substituted aniline derivatives.



*Sebastián Barata-Vallejo, Damian E. Yerien, and Al Postigo**

Page No. – Page No.

Benign Perfluoroalkylation of Aniline Derivatives through Photoredox Organocatalysis under Visible Light Irradiation