

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

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

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In this work, we present a room- or solar-light-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

Introduction

The aniline moiety is well-represented in pharmaceuticals with a large array of activities. For instance, sulfa drugs are a well-known class of antibacterial agents containing *N*substituted sulfonamide groups at the *para* position of an aniline ring (NH₂ArSO₂NHR). Recently, halogenated derivatives of *N*-substituted-4-aminobenzenesulfonamides, as well as triazine sulfa drug derivatives, have shown remarkable activity towards carbonic anhydrase isozymes^[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 substantially enhanced activity.^[4] Also, largely prescribed anesthetics such as procaine and benzocaine contain aminoaromatic functionalities.

The introduction of a fluoroalkyl moiety into a pharmacophore is often known to increase its 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 as a result of their unwillingness to undergo oxidation.

One general strategy to achieve fluoroalkyl-group substitution is the radical homolytic aromatic substitution reac-

Facultad de Farmacia y Bioquímica, Departamento de Química Orgánica, Junin 954, CP1113 Buenos Aires, Argentina E-mail: apostigo@ffyb.uba.ar http://www.ffyb.uba.ar/

 Supporting information and ORCID(s) from the author(s) for
 this article are available on the WWW under http://dx.doi.org/ 10.1002/ejoc.201501189. 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 onto the reaction intermediates.

tion (HAS).^[6] The HAS reaction with the CF₃ group has been well documented;^[7] however, fewer examples have been reported for HAS perfluoroalkylation.^[8–11] HAS reactions with perfluoroalkyl groups can be performed by two methods: thermal and photoinduced. Thermal methods can make use of transition-metal catalysis^[12–16] and several perfluoroalkyl sources (Figure 1) or else be non-metal-catalyzed: the use of the Baran reagent^[17] or perfluoroalkyl sulfinate salts^[18] in the presence of organic peroxide^[19] or azo initiators^[20] (Figure 1) yield 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]



Figure 1. Methods for C–H (HAS) radical perfluoroal kylation of arenes.

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 sys-

[[]a] Universidad de Buenos Aires,

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tems^[25] (Figure 1). Since the pioneering work of MacMillan in the trifluoromethylation reactions of arenes by using transition-metal organophotocatalysts,^[26] only a few reports on the photocatalytic perfluoroalkylation of arenes have been documented.^[27]

Among the reported synthetic methods described to obtain perfluoroalkyl-substituted anilines by HAS reactions, the Cu^I oxide-^[29] and the zinc-SO₂-mediated methodologies^[30a,30b] 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 PET protocol in the past to effect the HAS reaction on activated aromatic amines to synthesize Ar–R_f, in water or in 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*-C₄F₉I, which affords a radical ion pair (the radical cation of the amine and the radical anion of R_fX), from which C₄F₉ 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] which divert the aromatic-ring R_f group substitution pathways.^[33]

The perfluorobutylation of isonitriles leading to the synthesis of R_f -phenanthridines by employing Cs_2CO_3 according to Scheme 1 has recently been reported.^[28]



Scheme 1. Perfluorobutylation of isonitriles to form 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 organophotocatalysts 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 in the dark, and their reaction with aniline, as summarized in Table 1.

The reactions were carried out in the presence of Cs_2CO_3 , in vessels deoxygenated with Ar, by using 1,4-diox-

ane as solvent at 100 °C, as shown in entry 1, Table 1, to afford a 30% combined yield of 4-perfluorobutylaniline (1) and 2-perfluorobutylanilne (2) at a 1/2 ratio of 70:30. The reaction employing Na₂CO₃ (entry 2, Table 1) does not yield any product. The reaction of aniline and *n*-C₄F₉I carried out in the absence of cesium carbonate in 1,4-dioxane as solvent at 100 °C did not yield a 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 the temperature (entry 11) led to a sluggish substitution of the ring with a perfluorobutyl group and recovery of the 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 , and *n*-C₄F₉I in 1,4-dioxane without deoxygenation (entry 13) also yields the substituted aniline, demonstrating that air does not suppress the radical initiation and/or propagation. Inspection of the crude reaction mixtures (i.e., those from entries 1, 9, and 12, in Table 1, for example) reveals that the methodology compromises substrate integrity, as substantial oligomeric material is formed under the reaction conditions, and the mass balance is not complete (ca. 63%).

We then attempted the reaction of aniline with $n-C_4F_9I$ in the presence of quercetin (Q) as photocatalyst (PC) in MeCN as solvent in room light (60 Watt fluorescent light bulb), obtaining substitution products in 25% yield (entry 14, Table 1). Encouraged by this result, we used other PCs, 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 Cs₂CO₃ to the photocatalytic reaction mixture of Q (entry 16, Table 1) or RB (entry 17, Table 1), the perfluorobutylation yields improved substantially, and perfluorobutyl-substituted anilines were obtained quantitatively with RB as PC in the presence of Cs₂CO₃. The illuminated reaction (60 Watt fluorescent light bulb) of aniline and *n*-C₄F₉I in the absence of PC and in Ar-deoxygenated MeCN (entry 21, Table 1) affords 50% yield of combined substitution products 1 and 2 (cf. with entry 1, Table 1), which indicates that room light initiates $n-C_4F_9$. radical production in the presence of Cs₂CO₃ and in the absence of PC (a blank experiment illuminating the reaction mixture of aniline and C₄F₉I in the absence of Cs₂CO₃ and RB yields 5% of substitution product). The dye-photocatalyzed reaction without deoxygenation (entry 22, Table 1) also affords good yields of substitution product (78%) yield). We also attempted the reaction under exposure to solar light and obtained 91% yield of products 1 and 2 after 15 h of accumulated solar incidence (entry 23, Table 1). We therefore chose PC RB in the presence of Cs₂CO₃ in Ardeoxygenated MeCN as solvent for the model perfluorobutylation reaction of aniline derivatives under irradiation from a household fluorescent light bulb. Interestingly, when we inspected the reaction rate profiles of the production of perfluorobutyl-substituted aniline isomers as a function of irradiation time (Figure S4, Supporting Information), we observed the formation of the disubstituted 2,4-bis(per-



Table 1. Percentage yield of combined 4- and 2-perfluorobutyl-substituted aniline products 1 and 2, from 24-hour reactions of aniline (0.2 mmol) with *n*-C₄F₉I, unless otherwise noted, or an additive salt/catalyst, in a given solvent (3 mL), under an argon atmosphere and different reaction conditions.

		$ \begin{array}{c} NH_2 \\ + n - C_4 F_9 I \end{array} \xrightarrow{ \begin{array}{c} additive / catalyst \\ conditions \end{array}} \\ \begin{array}{c} NH_2 \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$			
Entry	[An]/[R _f I]/[additive]	Additive/catalyst (0.05 equiv.)	T [°C] /cond.	Solvent system	%(1 + 2) ^[a]
1	1:3:1.5	Cs ₂ CO ₃ /–	100/dark	1,4-dioxane	30
2	1:3:1.5	Na ₂ CO 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 ₂ CO ₃ /-	100/dark	1,4-dioxane	< 5
6	1:3:1.5	$Cs_2CO_3/-$	100/dark	1,4-dioxane/H ₂ O	_
7	1:3:1.5	$Cs_2CO_3/-$	100/dark	THF	< 5
8	1:3:1.5	Cs ₂ CO ₃ /-	100/dark	MeCN	_
9	1:3:3	$Cs_2CO_3/-$	100/dark	1,4-dioxane	35
10	1:3:0.75	Cs ₂ CO ₃ /-	100/dark	1,4-dioxane	16
11	1:3:1.5	Cs ₂ CO ₃ /–	60/dark	1,4-dioxane	_
12	1:3:1.5	Cs ₂ CO ₃ /–	100/dark	1,4-dioxane ^[b]	30
13	1:3:1.5	Cs ₂ CO ₃ /-	100/dark	1,4-dioxane ^[c]	20
14	1:3:-	-/Q	r.t./hv ^[d]	MeCN	25
15	1:3:-	-/RB	r.t./hv ^[d]	MeCN	52
16	1:3:1.5	Cs ₂ CO ₃ /Q	r.t./hv ^[d]	MeCN	50
17	1:3:1.5	Cs ₂ CO ₃ /RB	r.t./hv ^[d]	MeCN	98
18	1:3:1.5	Cs_2CO_3/RB	r.t./hv ^[d]	MeCN ^[e]	81
19	1:3:1.5	Cs ₂ CO ₃ /EO	r.t./hv ^[d]	MeCN	62
20	1:3:1.5	Cs_2CO_3/RB	r.t./hv ^[d]	H ₂ O	< 5
21	1:3:1.5	$Cs_2CO_3/-$	r.t./hv ^[d]	MeCN	50
22	1:3:1.5	Cs ₂ CO ₃ /RB	r.t./hv ^[d]	MeCN ^[c]	78
23	1:3:1.5	Cs ₂ CO ₃ /RB	r.t./hv ^[f]	MeCN	91
24	1:3:1.5	Cs ₂ CO ₃ /RB	r.t./dark	MeCN	-



[a] Yields determined by ¹H and ¹⁹F NMR integration (combined $4-C_4F_9$, and $2-C_4F_9$ yields *paralortho* = 70:30). [b] 64-hour reaction. [c] Without deoxygenation. [d] 60 Watt fluorescent light bulb. [e] 18-hour reaction. [f] 15-hour accumulated sunlight exposure.

fluorobutyl)aniline product 3 at the expense of the production of the 2-perfluorobutylaniline (2) isomer, demonstrating that the *p*-isomer [i.e., 4-perfluorobutylaniline (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/C₄F₉I ratio to 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-perfluorooctylaniline 4 and 2-perfluorooctylaniline 5 in 80% yield (4/5 = 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(CF₂)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 electron-donating groups at the ortho and para positions of the aniline ring (Table 2).

For the 2-substituted anilines with the CH₃O, CH₃, F, Br, and NO₂ groups, major perfluorobutylated products (Table 2, products 12, 14, 15, 16, and 17, respectively) arise from homolytic substitution at the 4-position of the ring with less or no substitution encountered at the 6-position of the ring (except for F and NO₂ groups, where the major substitution occurs at the 6-position). Disubstitution with the C_4F_9 moiety is encountered for 2-anisidine (13) (see Supporting Information). For the 4-substituted aniline derivatives with CH₃O, CH₃, Br, I, and 2,4-I₂ groups, major perfluoroalkyl-group substitutions take place at the 2- and 6-positions for $2,4-I_2$ of the aniline ring (products 18, 19, 21, 22, and 23, respectively, Table 2). It is observed in Table 2 that the presence of halides on the aniline moiety does not preclude the occurrence of a HAS reaction, and

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



the perfluorobutylated products keep 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 (Table 2); however, the 4-nitro-aniline derivative is unreactive even after prolonged reaction times (Table 2). Di- C_4F_9 -substitution is encountered for *p*-toluidine (product 20, Supporting Information). Electron-rich anilines, substituted with OCH₃ and CH₃ 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 successfully obtained 30% yield of **25**. In order to cast some light onto the nature of the transition state or intermediate of the photocatalytic reaction, we attempted to measure the ratio of rate constants for the photocatalytic (RB) perfluorobutylation of anilines substituted at the *para*-position with substituents of different electronic nature, such as electron-withdrawing and electron-releasing groups.

Tables S3A and S3B in the Supporting Information depict the competition experiments and the relationship $\log k_{p-\text{toluidine}}/k_{\text{ArNH}_2}$, showing clearly that the substitution reaction is accelerated by electron-donating X groups on the aniline ring, which implies that a stabilization of the

transition state is achieved with more electron-rich nuclei. The reaction of N,N-dimethylaniline in the presence of 1,4dinitrobenzene (p-DNB, a radical anion scavenger) is not suppressed, observing product 5 in yields as reported in Table 2. The photoreaction of aniline/RB/C₄F₉I in the presence of TEMPO does not yield the substitution product. Instead, the TEMPO-C₄F₉ adduct is obtained, indicating the intervention of C₄F₉ 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 at an electron-rich position of the aniline derivative, generating a C₄F₉-substituted cyclohexadienyl-type radical A, which upon deprotonation by the base (PT, Cs₂CO₃) affords a radical anion of the C_4F_9 -substituted product **B**. The fate of this radical anion could be: (1) dissociation (in the case of Ar–I[–]),^[35] (2) electron transfer (ET) to n-I–C₄F₉ (to propagate the chain) and thermoneutral product C, or (3) ET to the substrate (chain termination), as shown in Scheme 2.



Scheme 2. Proton-transfer/electron-transfer (PT/ET) mechanism for the re-aromatization.

However, we observed acceleration of the C_4F_9 -substitution reaction rates of anilines bearing electron-donating groups (Tables S3A and S3B, Supporting Information), which indicates that, in addition to the enthalpy factor for the formation of Ar-R_f bonds (A, Scheme 2), there seems to be a substituent effect on the rates of formation of per-



fluoroalkyl-substituted anilines. A reaction of aniline, RB, and C_4F_9I in MeCN monitored by turning the lamp on and off at different intervals (Figure 2) reveals that the reaction is photocatalytic, and RB and light are needed through the entire reaction for the substitution product to accumulate.



Figure 2. Plot of % product vs. irradiation time. The lamp is kept off for the shaded areas. (\blacksquare) % of isomer 1, (\blacklozenge) % of isomer 2, (\blacktriangle) % of disubstitution.

A mechanism such as that proposed in Figure 3, where a positively charged intermediate/transition state develops, would account for these differences in reaction rates. Roomlight excitation of PC RB leads to RB*, which transfers an electron to n-C₄F₉I, generating C₄F₉⁻ radicals and the radical cation of RB^{+[36]} (Figure 3).

The ground and excited redox states of RB, an electrontransfer mediator, are important for the formation of the electron-deficient perfluorobutyl radical (C_4F_9) , which



Figure 3. Proposed mechanism for the RB-photocatalyzed perfluoroalkylation of aniline derivatives.

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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_8 = 2.17 eV, excited state triplet energy $E_{\rm T}$ = 1.8 eV,^[37a,37b] in MeCN) is expected to efficiently generate the C_4F_9 and RB^{.+} radical cations on the basis of their redox potentials $(E_{\text{RB}^+/\text{RB}^*} = -0.68 \text{ V vs. SCE in MeCN},^{[37b]} E_{\text{C}_4\text{F}_9\text{I}/\text{C}_4\text{F}_9} = -1.27 \text{ V}^{[37c]}$, the ΔG_{ET} for this process is -1.53 eV, which suggests a quite favorable spontaneous ET (see Table S4, Supporting Information). The expectation that an electron from $C_4 F_9 I$ is turned over during the photocatalytic electron-transfer cycle is based solely on the driving force predicted by the redox potentials (vide supra, Table S4, Supporting Information). At this stage, no detailed mechanistic data on the twofold reaction of aniline with C₄F₉ are available, but it is rationally considered that a likely reaction pathway includes the radical addition of C₄F₉⁻ to an electron-rich position of the aniline moiety, generating intermediate A (Figure 3), 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 $(A \rightarrow B C_4 F_9 I \text{ oxidation})$ can propagate the chain. Deprotonation (PT, Figure 3) affords the perfluorobutyl-substituted aniline derivative. Markovic and collaborators^[38] have found that the radical cation of the PC quercetin, Q⁺⁺, will spontaneously be transformed into Q in the presence of bases whose HOMO energies are higher than the SOMO energy of Q⁺⁺ in a given medium, implying that Q cannot undergo the ET/PT mechanism which would lead to the quercetin radical (Q^{\cdot}) and a proton (H⁺). Therefore, it is proposed that, in our photocatalysis by Q (entries 14, 16, Table 1), Q⁺⁺ accepts an electron from the base (Cs₂CO₃) and therefore forms thermoneutral Q (regenerating the PC) and carbonate radical anion ($E_{CO_3-/CO_3^{2-}} = +1.23$ +/-0.15 V^[36a]) on the basis of the HOMO energy of the carbonate anion. We hypothesize that the RB^{+[36b]} radical cation also accepts an electron from Cs₂CO₃ in a fashion analogous to that of Q^{'+} to regenerate RB PC. The fact that addition of Cs₂CO₃ to the photocatalytic reactions (entries 17 and 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 Cs₂CO₃ and in the absence of PC suggests the role of this base as an ET (photo)mediator (entry 21, Table 1). Although we have demonstrated that RB functions as a photocatalyst (Figure 2) and not merely as an initiator, the fact that step A \rightarrow B (Figure 3) also generates C₄F₉ radicals must be an indication that this step is a rate-determining 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 spectrum of C₄F₉I in the presence of Cs₂CO₃ does not show the presence of a charge-transfer complex (Figure S5, Supporting information). Further studies are in progress to assess the electronic nature of the

complex (PC/Cs₂CO₃/R_fI), the substrate, and the R_fX dependence.

Conclusions

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 under exposure to solar light and with use of 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 in which 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), $R_f X$ (3 equiv.), photocatalyst (0.05 equiv.), and Cs_2CO_3 (1.5 equiv.) in Ar-deoxygenated MeCN (3 mL) was irradiated (24 h) 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 were gathered and dried with 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 the Supporting Information.

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