Volume 4, Issue 5, 2014, 865-872 ISSN 2069-5837

Biointerface Research in Applied Chemistry

www.BiointerfaceResearch.com

Review Article **Open Access Journal**

Received: 23.07.2014 / Revised: 25.09.2014 / Accepted: 10.10.2014 / Published on-line: 15.10.201

Photoinduced perfluorobutylation of organic substrates in aqueous media

Al Postigo [1,*]

[1] Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires. Junín 954 CP1113-Buenos Aires, Argentina

*corresponding author e-mail address: ***apostigo@ffyb.uba.ar***

ABSTRACT

Hydroperfluorobutylation of a series of electron-deficient and electron-rich alkenes through consecutive radical reactions employing perfluorobutyl iodide, n-C4F9I, and (Me3Si)3SiH as chain carrier/hydrogen atom donor is described. The photoinduced Halogen Atom Transfer (HAT) reactions of both olefins and alkynes with n-C4F9I are also shown to be achieved efficiently in aqueous mixtures. On the other hand, aromatic and heteroaromatic substrates can be perfluorobutylated with high efficiency in a photoinduced fashion by means of a Homolytic Aromatic Substitution (SHA) process which involves an Electron Transfer (ET) and a Proton Transfer (PT) step.

1. INTRODUCTION

Perfluoroalkyl compounds have attracted much attention during the past twenty years for their wide applications in different fields of chemistry. In particular, recent advances in fluorous [1] combinatorial technique require convenient methods for selective introduction of fluorous tags containing perfluoroalkyl groups [2] into various organic compounds [3].

The synthesis of these compounds cannot be achieved through classical nucleophilic substitutions on perfluoroalkyl halides, RfX, as these substrates are impeded to react by the SN1 mechanism, on account of the low stability of carbocations, and precluded to undergo SN2 substitutions due to repulsion of the lone electron pairs of the fluorine atoms to the backside attack by the nucleophile [4].

Compounds bearing the perfluoroalkyl moiety Rf-C bond, however, have been synthesized by different routes. One such route involves addition of Rf • radicals to double bonds [5-7]. Perfluoroalkyl iodides and bromides are convenient perfluoroalkyl radical precursors in the presence of radical initiators [8]. As perfluoroalkyl iodides exhibit their absorption in UV and near-UV regions, the photoinitiation based on the homolytic dissociation of the Rf-I bond is also applicable for the iodoperfluoroalkylation of unsaturated compounds and arenes with RfI [9]. Ogawa et al.undertook an iodoperfluoroalkylation of unsaturated carbon-carbon double and triple bonds using benzotrifluoride as solvent [4, 9]. These authors also utilized nonconjugated dienes, conjugated dienes, allenes, vinylcyclopropanes, and isocyanides as radical-acceptor substrates for the radical iodoperfluoroalkylation reactions in benzotrifluoride, affording good yields of the corresponding iodoperfluoroalkylated derivatives.

Another route to the synthesis of compounds with perfluoroalkyl moieties is through the SRN1 mechanism, which involves radicals and radical ions as intermediates [4, 10]. Both aliphatic and aromatic substrates can be made to react with the RfI by the SRN1 mechanism.

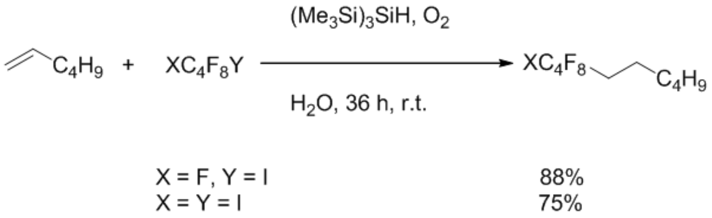
On the other hand, intermolecular radical carbon-carbon bond formation reactions, i.e., consecutive reactions, demand a careful synthetic design to achieve carbon-carbon coupling products in fairly good yields. The key step in these consecutive reactions generally involves the intermolecular addition of R• radicals to a multiple-bonded carbon acceptor. When a hydride chain carrier is involved, care has to be exercised in order to ensure that the effective rate of the radical addition is higher than the rate of H atom transfer.

As for aromatic substrates, the photoinduced methodology for perfluorobuylation will be shown in this study to provide C-H perfluorobutyl bond insertion products.

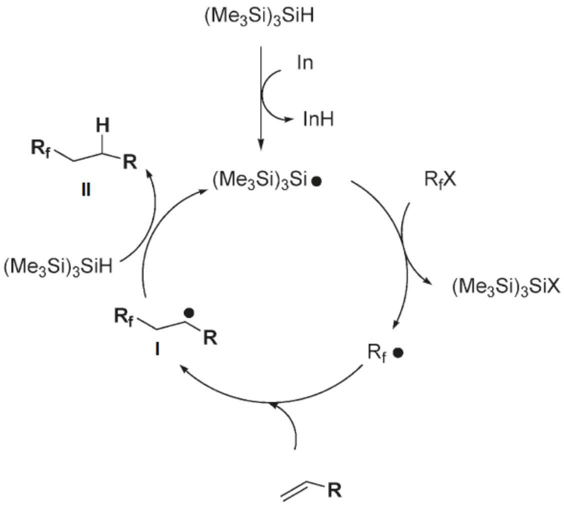
In this account, photoinduced perfluorobutylations of both aliphatic and aromatic substrates are described. In doing so, an array of mechanisms is shown to lead to the desired perfluorobutylated products in fairly good yields.

2. ALIPHATIC SUBSTRATES

The first report on the perfluorobutylation of olefinic substrates in water was published in 2010 [11] illustrating the radical perfluorobutylation of a series of aliphatic substrates which was accomplished in reasonable yields, as shown in Scheme 1. The mechanism of the reaction is depicted in Scheme 2 below. The $(Me_3Si)_3Si$• radical (produced either by dioxygen or thermal decomposition of 1,1´-azobis-cyanocyclohexane, ACCN initiator) in water, abstracts the halogen atom (iodine or bromine) from C_4F_9X. This C_4F_9 • radical reacts faster with the alkene than with the silicon hydride, affording the perfluoroalkylated radical adduct I.

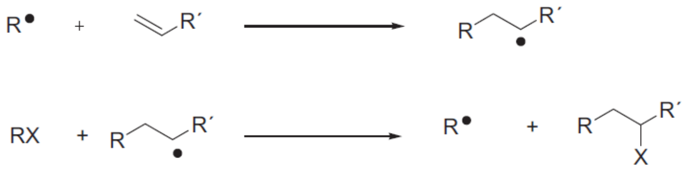


Scheme 1. Perfluorobutylation and iodoperfluorobutylation of 1-hexene.



Scheme 2. Mechanism for the $(Me_3Si)_3SiH$ mediated radical perfluorobutylation of 1-hexene.

The perfluoroalkylated radical adduct I abstracts hydrogen from the silane, affording the perfluoroalkyl-substituted alkane II, and regenerating the silyl radical, thus propagating the chain [11]. Halogen Atom-transfer (HAT) reactions have been extensively studied and widely used in organic synthesis. The addition of a carbon–halogen bond across a double bond was pioneered by Kharasch [12a] (Scheme 3) and it provides new carbon–carbon and carbon–halogen bonds in a single operation. The choice of the halogen that transfers in the reaction determines the success of atom-transfer additions. More recently, HAT reactions in water have been studied and reviewed [12b].



Scheme 3. Mechanism for the Halogen Atom-Transfer (HAT).

It has been shown that [13] when simple alkenes such as 1a–d are subjected to reaction with 1-iodoperfluorobutane in water under irradiation, iodoperfluorobutyl alkanes 2a–d are obtained in yields ranging from 58 to 84% (Eq. (1)).

Both electron-rich and electron-deficient alkenes react efficiently in water. Organic solvent-soluble alkenes 1b–d as well as water-soluble (allyl alcohol 1a) alkenes react with 1-iodoperfluorobutane in water (Eq. (1), Table 1).

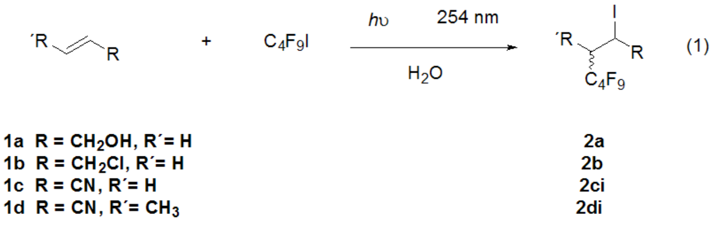
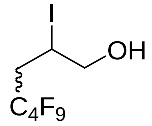
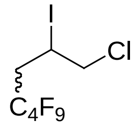
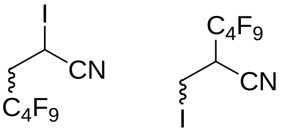
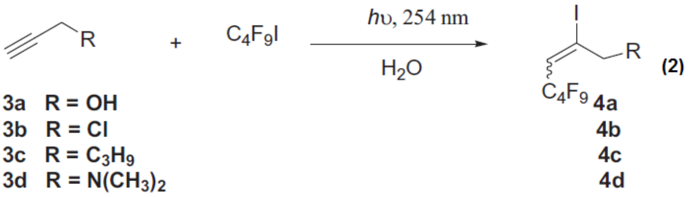


Table 1. Photochemically-induced (254 nm, 60W, 2h) radical perfluorobutylation of alkenes **1a-d** (10 mM) with *n*-C_4F_9I (11 mM) in Ar-deoxygenated water (3 mL) under vigorous stirring at 25 °C.

Entry	Substrate	**Product(s)** (% yield)
1	**Allylic alcohol, 1a**	 **2a** (84)
2	**Allylic chloride, 1b**	 **2b** (75)
3	**Acrylonitrile**, **1c**	 **2ci** + **2cii** (66)
4	**Crotononitrile, 1d**	 2**di** + **2dii** (58)

Acrylonitrile 1c affords two HAT products, i.e.: 2ci and 2cii in an88:12 ratio. Product 2ci prevails in the mixture, as arising from a cyano-substituted, resonance-stabilized secondary alkyl radical adduct.

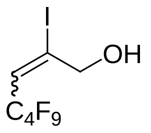
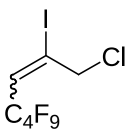
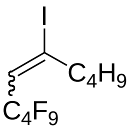
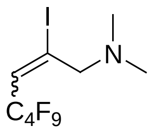
Interestingly, crotononitrile 1d also affords two iodoperfluoroalkylated products, 3,3,4,4,5,5,6,6,6-nonafluoro- 2-(1-iodoethyl)hexanenitrile 2di and 4,4,5,5,6,6,7,7,7-nonafluoro- 2-iodo-3-methylheptanenitrile 2dii in 3 and 97% relative yields, respectively (isolated 58%, Table 1). Clearly, product 2dii is favored over product 2di as the cyano-substituted radical adduct is resonance-stabilized as opposed to the inductively-stabilized alkyl-substituted radical adduct intermediate. When the authors [13] subjected alkynes 3a–d to reaction with 1-iodoperfluorobutane in water under irradiation, iodoperfluorobutyl-substituted alkenes 4a–d (Eq. (2), Table 2) were obtained in yields ranging from 67 to 98%.



The electrophilicity of C_4F_9• radicals are the dominant factor giving rise to their high reactivity. C_4F_9• radicals when added to an alkene form a stronger carbon–carbon bond than alkyl radicals do when added to the same alkene. The greater exothermicity of the C_4F_9• radical addition is expected to lower the activation energy) [14, 15]. It has been observed, in organic solvents, that the rates of addition of C_4F_9• radicals onto alkenes correlate with the alkene IP (which reflects the HOMO energies) [16]. Indeed, the major transition state orbital interaction for the addition of the highly electrophilic C_4F_9 • radical to an alkene is that between the SOMO of the radical and the HOMO of the alkene. Thus, the rates of

C_4F_9• radical addition to electron deficient alkenes are slower than those to electron rich alkenes (as observed in organic solvents) [17].

Table 2. Photochemically-induced (254 nm, 60W, 2h) radical perfluorobutylation of alkynes **3a-d** (12 mM) with n-C_4F_9I (10 mM) in Ar-deoxygenated water (3 mL) under vigorous stirring at 25 ^oC.

Entry	Substrate	Product (%yield)	*E:Z* ratio
1	**Propargyl alcohol**,**3 a**	 **4a** (84)	**70:30**[a]
2	**Propargyl chloride, 3b**	 **4b** (94)	**45:55**[a]
3	**1-hexyne**, **3c**	 **4c** (98)	**93:7**[a]
4	***N,N*-dimethyl propargylamine**, **3d**	 **4d** (67)	**67:33**[a]

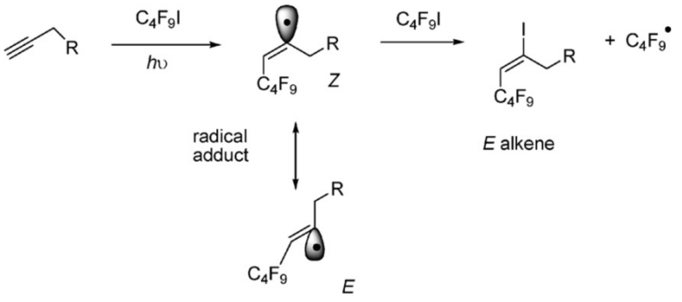
[a] Non-optimized isomer ratio obtained after 2 h- irradiation

From the results obtained by the authors [13], however, it becomes apparent, that in water the reactivity for both electron rich and electron deficient alkenes towards C_4F_9• radical addition could be comparable. This trend has also been found in the consecutive radical perfluoroalkylation addition reaction of alkenes in water mediated by $(Me_3Si)_3SiH$ [18].

The authors [13] suspected that kinetic solvent effects (KSE) are somewhat responsible for this leveling of reactivity (vide infra). Perhaps, some amphiphilic character of C_4F_9• radicals could be invoked to account for these indirect kinetic solvent effects. In previous reports, the authors [11] have observed that the radical hydrosilylation reactions in water of water-soluble substrates took place efficiently with the aid of amphiphilic 2-mercaptoethanol, as chain carrier [19]. This is because silyl radicals being hydrophobic need the assistance of amphiphilic thiyl radicals (i.e.• SCH_2CH_2OH) to carry on the chain reaction in the aqueous environment, where the water-soluble substrate is dissolved.

Interestingly, both organic solvent-soluble substrates and water-soluble substrates undergo radical pefluoroalkylation reactions in water without the assistance of a chain carrier. This observation could be better interpreted in light of the distinct reactivity of C_4F_9• radicals in water rather than to a difference in hydrophobicity of C_4F_9• radicals in comparison to silyl radicals. Perhaps, some distinct amphiphilic character of C_4F_9 radicals could be invoked in this case.

Ogawa and collaborators have shown that the perfluoroalkylated radical adduct formed upon addition of C_4F_9• radicals to alkenes or alkynes is followed by addition of an iodine atom to afford the iodoperfluoroalkylated compound. For a chain reaction to take place, it is likely that a mechanism such as that illustrated in Scheme 2 takes place. The radical adduct (in this case an alkenyl-substituted adduct) abstracts iodine atom from n-C_4F_9I, rendering the end addition product (i.e.4a–e) and C_4F_9 radical, which carries on the chain reaction. The Eend-alkene is favored over the Zisomer, as accounted in Scheme 2, and Table 2. The radical adduct formed upon addition of C_4F_9• radical onto the alkyne, which can equilibrate between the Eand Zstereoisomers, will abstract iodine atom from the less hindered/congested radical adduct in the Zconfiguration than the Econfiguration, rendering the Ealkene end product (Scheme 4).



Scheme 4. Proposed mechanism for the perfluorobutyl-substituted *E* alkenes in water.

The prevalence of the Z stereoisomer from propargyl chloride 3b radical addition reaction, i.e. product 4b, is due to a post-isomerization process of the initially formed 4b (E) isomer, as confirmed by analyzing aliquots at shorter photolysis times, where the mixture is enriched in the E-isomer.

3. AROMATIC SUBSTRATES

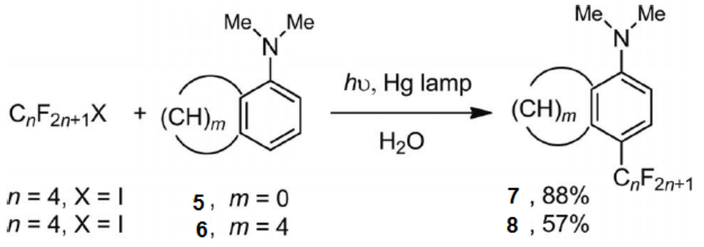
A recent report on the perfluorobutylation of electron-rich aromatic compounds has uncovered the convenience of the photoinduced methodology to produce C_4F_9 • radicals from iodoperfluoroalkanes [20] that are able to effect aromatic H substitution reactions. These processes entail radical homolytic aromatic substitution pathways.

When the authors [20] subjected a heterogeneous mixture of N,N-dimethylaniline 5 or N,N-dimethyl-1-naphthyl amine 6 and n-C_4F9_I to a photoinduced reaction [21], they obtained the nonafluorobutyl para substitution product 7 and the 4-positionsubstitution product 8, respectively, in yields ranging from 57 to 88% (yields based on starting n-C_4F_9I concentration), according to Scheme 5. The product yields increase upon increasing the concentration of the substrates. Thus the best product yields are obtained when the substrate:n-C_4F_9I ratio is ca. 5:1.

The authors [20] also undertook the photoreaction of 6 and n-C_4F_9I in Ar-deoxygenated water with filtered 350-nm fluorescent lamps, and obtained a similar substitution yield of 8, demonstrating that the lower emission wavelengths of the medium pressure Hg lamp (i.e. 313 nm) do not influence the product yields or distribution.

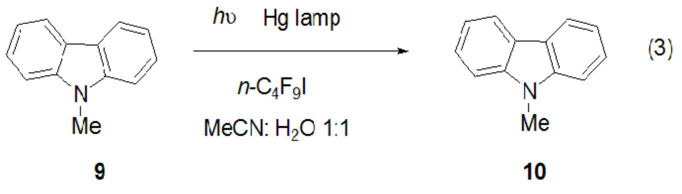
In order to cast some light into the reactive excited state manifold of substrate 5 (or 6), product studies of the photoinduced electron transfer (PET) reaction in 5 (or 6)were carried out [20] (at irradiation wavelength λ = 310 nm), in the presence of n-C_4F_9I and 4- methoxyacetophenone (MAP, 15 mmol), a well- known triplet energy sensitizer (ETriplet = 310 KJ mol-1). Under these reaction conditions, no substitution product 7 (or 8 from substrate 6) was encountered (i.e. E Triplet (6) = 226 KJ mol-1 [21c]). This would seem to imply that the singlet excited state manifold isresponsible for the aromatic substitution product in water, and that sensitized population of the triplet state of the amine does not lead to an aromatic substitution reaction.

The n-C_4F_9• radical shows a clear-cut electrophilic character in the aromatic substitution, as already reported for the addition to alkenes [11, 22, 23], but the low regio- and chemoselectivities in organic solvents suggest that the polar effect is not the main factor in determining the high reactivity of perfluoroalkyl radicals toward aromatics [23]. The enthalpic factor, related to the involved bond energies, appears to be the major cause of the increased reactivity. The polar effect is considered as related more to the polarizability than to the polarity of a radical [24].



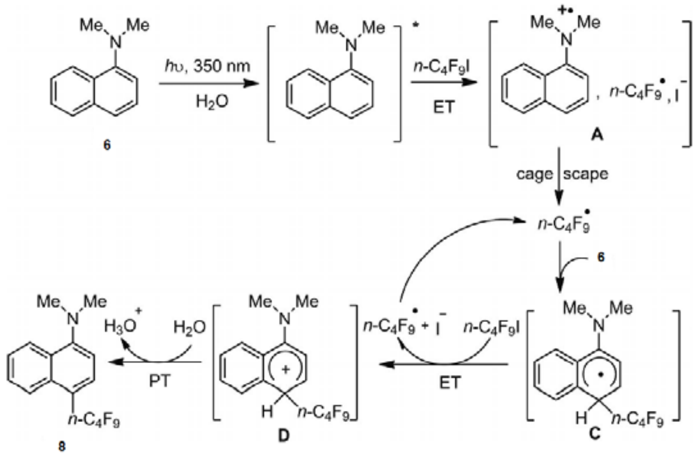
Scheme 5. Perfluorobutylation of aromatic amines.

The photoreaction of N-methylcarbazole 9 with n-C4F9I in MeCN:water led to substitution product 10, in fairly good yields, according to Eq.3 below. As far as the authors were concerned [25], the carbazole ring had only been trifluoromethylated before through Pd-catalysis with triethylsilyltrifluoromethane (TSTM) in organic solvents [24].



Interestingly, this substitution of the carbazole ring takes place solely at the 3- position, a position commonly activated in classical electrophilic aromatic substitution reactions.

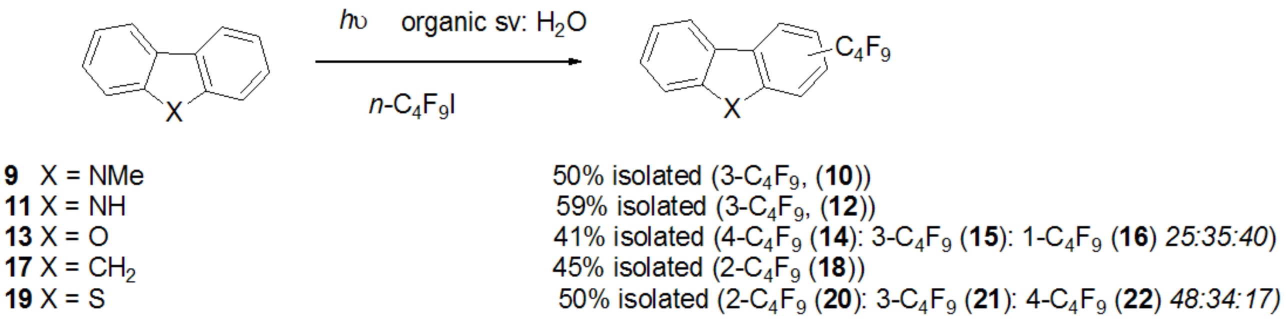
The authors [25] thus postulated a PET mechanism where, upon light absorption by substrates 5 or 6, the corresponding radical cation (5+•or 6+•) together with the n-C_4F_9• and iodide anion are formed in the solvent cage by an ET (Scheme 6, for substrate 6). This is the initiation step. Upon cage-scape of 6+•(or 5+•) and n-C_4F_9•, the radical n-C_4F_9• adds to the 4-position of 6 (and the paraposition of 5) to render an aromatic substituted cyclohexadienyl radical intermediate C (in the case of 6). Cyclohexadienyl radical intermediate C donates an electron (ET) to n-C_4F_9I, to generate the oxidized cation intermediate D (a σ-adduct which is stabilized by resonance effect from the N atom, i.e. Wheland intermediate) and n-C_4F_9• + I-. This n-C_4F_9• triggers a chain sequence. Upon proton loss (PT), adduct D generates the substitution product 6. n-C_4F_9• radicals enter the substitution cycle as depicted in Scheme 6. It is observed that this is a chain PET mechanism, where n-C_4F_9• behaves as a radical chain carrier.



Scheme 6. Proposed reaction mechanism for the photoinduced ET (PET) perfluorobutylation substitution of aromatic amines in water.

On the other hand, when the authors [26] subjected an Ar-deoxygenated mixture of 9H-carbazole 11 andn-C_4F_9I in MeCN:H_2O mixture to 350-nm irradiation with an unfiltered medium pressure Hg lamp (MPL), they obtained 3-(perfluorobutyl)-9H-carbazole 12, in 10% yield (Scheme 7). However, when an Ar-deoxygenated mixture of 9H-carbazole 11 andn-C_4F_9I in MeCN:H_2O is irradiated with 254-nm lamps, under vigorous stirring, they obtained 3-(perfluorobutyl)-9H-carbazole 12 in 59% isolated yield. The dissimilar substitution yields for substrates 9 and 11 with the C_4F_9 moieties is intriguing, since it has been postulated [27]that in aqueous mixtures, the NH and OH functionalities are not good hydrogen donors in radical transformations due to their hydrogen-bonding stabilization in the aqueous environment, thus rendering substitution of the arene ring feasible. Interestingly, substitution at the 3-position of the carbazole (and 9-methylcarbazole) ring is typical of a classical aromatic electrophilic substitution pattern. In previous studies [25], the authors were able to discriminate the substitution pathways arising from either an initial ET initiation within the excited aromatic moiety and C_4F_9-I, or a substitution route from direct homolysis of the F_9C_4-I bond and ulterior homolytic aromatic ring substitution with C_4F_9• radicals

In order to optimize reaction conditions, the authors [26] varied substrate and *n*-C_4F_9I concentrations with the purpose of maximizing product yields. This was accomplished by plotting graphs of % substitution product versus *n*-C_4F_9I or substrate concentration, at 254-nm irradiation (not shown), and the best results were obtained as shown in column 3, Table 3.



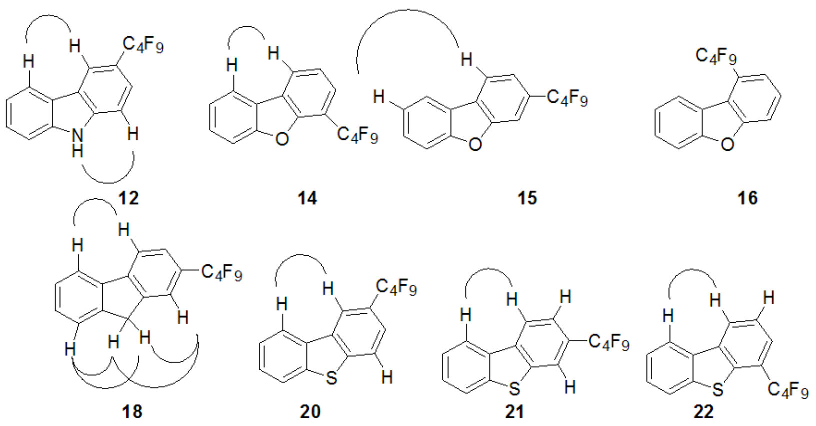
Scheme 7. Photoinduced perfluoroalkylation of dibenzo(hetero)arenes in aqueous mixtures.

Table 3. Optimized reaction conditions tested in the Homolytic Aromatic Substitution ($S_{Ar}H$) reaction of arenes with perfluoroalkyl halides in heterogeneous media under vigorous stirring.

Entry	**Synthetic method**	**Substrates** (mmol)	**Solvent system,** (mL) [a]	**Product** (% yield)	$A_{substrate}:A_{RfX}$ [b] pH$_{initial}$/pH$_{final}$ [c]
1	**MPL**[d]	**11** (1), ***n*-C_4F_9I** (0.2)	**MeCN:H_2O** 1:1, (30)	**12** (10) [e]	*1:0.1*[b] 5/3 [c]
2	**λ 254 nm**	**11** (0.06), ***n*-C_4F_9I** (4.5)	**MeCN:H_2O** 1:1, (4)	**12** (59) [e]	*1:1*[b] 5.5/3 [c]
3	**MPL**[d]	**9** (1), ***n*-C_4F_9I** (0.2)	**MeCN:H_2O** 1:1, (30)	**10** (50) [e]	*1:0.1*[b] 5/3 [c]
4	**λ 254 nm**	**13** (0.3), ***n*-C_4F_9I** (2.4)	**MeCN:H_2O** 1:1, (4)	(41) [e,f] **14** (33) [g] **15** (42) [g] **16** (25) [g]	*2.3:1* [b] 5.5/3 [c]
5	**λ 254 nm**	**13** (0.3), ***n*-C_4F_9I** (2.4)	**DCM:H_2O** 1:1, (4)	(45) [e] **14** (25) [g] **15** (35) [g] **16** (40) [g]	*2.3:1* [b] 5.5/3 [c]
6	**λ 254 nm**	**17** (0.3), ***n*-C_4F_9I** (2.3)	**MeCN:H_2O** 3:1, (4)	**18** (45) [e]	*7.8:1* [b] 5.5/3 [c]
7	**λ 254 nm**	**19** (0.3), ***n*-C_4F_9I** (2.3)	**MeCN:H_2O** 3:1 (4)	(50) [e] **20** (48) [g] **21** (34) [g] **22** (17) [g] **23** (< 1) [g]	*7.1:1* [b] 5.5/3 [c]

---

[a] Ar-deoxygenated solutions; [b] Absorbance ratio at the irradiation wavelength (254 nm or 365 nm) in pure organic solvent; [c] pH registered at the beginning of the reaction/pH registered at the end of the reaction; [d] Medium pressure Hg lamp, unfiltered; [e] isolated product yield; [f] yield in the presence of $Na_2S_2O_3$; [g] relative regioisomer yield.



Scheme 8. NOESY spectra analyses for compounds **12, 14-16, 18** and **20-22**.

When reaction conditions are such that the absorption of substrates prevails at 254-nm irradiation wavelength, very low yields of substitution products are obtained. By increasing the amounts of *n*-C_4F_9I in the reaction mixtures, a steady increase in substitution product yields is obtained, purporting that the reaction is initiated through homolysis of F_9C_4—I bond leading to $C_4F_9^{\bullet}$ radicals. The optimized concentration ratios of substrate:*n*-C_4F_9I found were those shown in column 3, Table 3 (*i.e.* the highest substitution product yields are obtained when *n*-C_4F_9I are in excess with respect to the substrate).

Direct trifluoromethylation of carbazole at the *1*-position has been accomplished by Catellani and collaborators through a Pd-catalyzed non-radical process [28]. Neither a direct trifluoromethylation of the carbazole nucleus (**11**) has ever been reported at the *2*-, *3*-, or *4*-positions of the ring, nora protocol for the direct trifluoromethylation of **9** at the *1*-, *2*-, *3*-, or *4*-positions of the ring has been reported. Indirect methods for obtaining 3-trifluoromethylcarbazole through a Suzuki-Miyaura reaction from a biphenyl derivative [29a] or through a Pd-catalyzed arylation of anilines [29b] have been reported earlier.

Analogously, when dibenzo[*b,d*]furan **13** (Scheme 7) is made to react at 254-nm in a MeCN:H_2O/$Na_2S_2O_3$ [30] mixture in the presence of *n*-C_4F_9I, it affords the mono C_4F_9-substitution products at the *4*- (product **14**), *3*- (product **15**), and *1*- (product **16**) positions of the dibenzofuran ring, in 41% isolated overall yield (Table 3, entry 4 and Scheme 7) [26]. Regioisomers **14, 15**,and **16** are obtained in a relative ratio of 33:42:25, respectively. When the reaction of **13** and *n*-C_4F_9I is carried out in a CH_2Cl_2:H_2O mixture (1:1) under 254-nm irradiation instead, products **14**, **15**, and **16** are obtained in 25:35:40 relative yields, as indicated in Table 3, entry 5 [26]. Under these reaction conditions, the overall monosubstitution yield of substrate **13** is 45%. These products were characterized as individual isomers by employing standard spectroscopic methods. The authors [26] state that the chromatographic separation of regioisomers **14-16** is challenging. Neither column chromatography nor preparative TLC systems employing ordinary eluant mixtures accomplished separation of the isomers. When a perfluoroalkylated solvent mixture (a fluorous phase) was employed instead as eluant, (*i.e.* 1-trifluoromethyl-perfluorodecaline:isooctane, 1:1), regioisomer **14** was separated as an individual isomer by preparative TLC techniques. To unambiguously characterize products **14-16**, the authors [26] undertook multidimensional and NOESY NMR experiments, and the correlations shown in Scheme 8 were observed. Compound **14** (Scheme 8) shows NOE correlations between protons H*1* and H*9*. Compound **15** shows H*1*-H*8* NOE correlation, whereas compound **16** does not show NOE correlations (Scheme 8). Substitution at the *2*-position of the dibenzofuran ring with the C_4F_9 moiety, under the above reaction conditions, was obtained in very low relative yield (< 1%), and the product could not be fully characterized [26]. The synthesis of *2*-, *3*-, and *4*-CF_3-substituted dibenzofurans by non-radical methods has been reported in the literature [31-33].

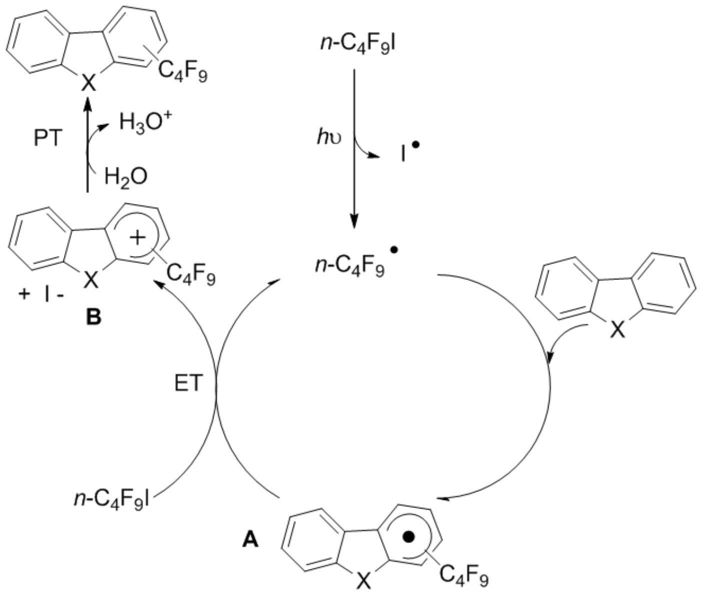
Trifluoromethylation of dibenzofuran at the *4*-position has very recently been achieved with CF_3SO_2Na (Langlois reagent) in the presence of copper catalysts and *t*-BuOOH by Sanford and colleagues [34]. The authors employed aryl-boronic acids as starting materials. The method relies on transition metal catalysis, selective radical reactions, and properly-substituted dibenzofuran rings. Indirect methods for obtaining 3-trifluoromethyl-substituted dibenzofuran either through biphenyl ether Ni-cross-coupling reactions [35a] or through Pd-catalyzed biphenyl coupling processes [35b] have also recently been reported. The methodology presented by the present authors in [26] seems to provide three main C_4F_9-substituted regioisomers of dibenzofuran, whose mixture can be enriched in regioisomer **15** or **16** depending on the solvent system, and where the *4*-positional regioisomer (*i.e.* **14**) could be separated with a fluorous phase eluant.

The dibenzoarene *fluorene***17** (9*H*-fluorene), upon reactionwith *n*-C_4F_9I in MeCN:H_2O/$Na_2S_2O_3$ under 254-nm irradiation (quartz vessel, 4 h), has been reported to afford 2-(perfluorobutyl)-9*H*-fluorene **18** in 45% yield as the sole product (Table 3, entry 6) [26]. Fluorenes, substituted at the *2* and *3*-positions with the trifluoromethyl group have been synthesized by a Pd-catalyzed process before [31]. Identification of product **18** was accomplished by standard spectroscopic techniques. NOESY correlations of proton H*1* with protons at the *9*-position as well as correlations between H*8* with protons at the *9*-position of the fluorene ring have been observed for product **18** (Scheme 8) [26]. Also, a correlation between H*4* and H*5* was observed in NOE-experiments. Fluorene, as substrate, has never been trifluormethylated or perfluoroalkylated by a direct method before [31]. The methodology of the authors [26] exclusively affords the regioisomer substituted at the *2*-position, as opposed to that of Chang and collaborators [31a].

Dibenzo[*b,d*]thiophene **19**, under the same reaction conditions [26], affords a mixture of three main regioisomers, substituted at the *2*- (product **20**, Scheme 7), *3*- (product **21**, Scheme 7), and *4*- (product **22**, Scheme 7) positions. The overall substitution isolated yield of products **20-22** was rather low (10%). Some sulfur-containing polymeric material was observed in the crude reaction mixture. However, when the reaction was carried out in the absence of $Na_2S_2O_3$, the yield of products **20-22** increases substantially (50%, Table 3, entry 7), and intractable material was not observed. Isomers **20-22** were obtained in a relative ratio of 48:34:17. Isomers **20-22** were separated by preparative TLC techniques, by employing a mixture of isooctane:chloroform, 2:1. Compounds **20-22** showed NOE correlations between H*1*-H*9* (Scheme 8). *2*-, and *4*-CF_3-substituted dibenzothiophenes have been reported in the literature before [31, 32], and have been previously synthesized by a Cu- mediated *ipso* substitution of the respective *2*-, and *4*-iodo-dibenzothiophene precursors [28, 33]. By using the methodology of the authors in [26], a *3*-substituted fluoroalkyl-dibenzothiophene regioisomer (**21**) could be obtained. The synthesis of *3*-C_4F_9-substituted regioisomers through a direct C-H substitution method has never been reported in the literature before.

A minor isomer, accounting for less than 1% of the total yield of the mixture could be distinguished by the ^1H NMR spectrum of the chromatographed reaction mixture, which seems to correspond to another C_4F_9-regioisomer [26]. Through a combination of 2D-NMR techniques, full spectral characterization of this isomer was possible in the mixture, and the identity of the compound was assigned as 1-(perfluorobutyl)-dibenzo[*b*,*d*]thiophene **23**. It is to be pointed out that dibenzoheteroarenes have never been perfluoroalkylated directly by a substitution reaction, let alone by a homolytic substitution process.

Addition of di-*tert*butyl nitroxide (DTBN, 2% equiv), a well-known radical scavenger, to either 254-nm or 350-nm irradiation in MeCN:H_2O mixtures, provoked a retardation of the reactions, purporting the presence of radicals as intermediates [26]. Addition of *p*-dinitrobenzene(*p*-DNB), a known radical anion scavenger, did not affect the yields of the perfluoroalkyl group substitutions of the dibenzoarenes and dibenzoheteroarenes. The photoreactions carried out under basic conditions (pH ~ 10) did not show an increase in product yields. This would seem to imply that radical anions are not intermediates in these reactions. When 4-nitrodibenzofuran was allowed to react with n-C_4F_9I in MeCN:H_2O mixtures either under 254-nm or 350-nm irradiation conditions, no substitution products were observed [26]. At 254-nm irradiation, where most of the light is absorbed by n-C_4F_9I (see Table 3, column 6, footnote *b*), homolysis of F_9C_4-I bond produces $C_4F_9^{\bullet}$ radicals that add to the dibenzo(hetero)arene as shown in Scheme 9 below, to yield the radical adduct intermediate **A**. The radical adduct **A** undergoes an oxidation reaction coupled with an ET to n-C_4F_9I (to afford cation intermediate **B**, Wheland intermediate, oxidation triggered through the favourable Gibbs energy) and then the proton transfer (PT) steps to yield the substitution products in averaged good yields.



Scheme 9. Proposed mechanism for the perfluorobutylation of dibenzoheteroarenes in aqueous mixtures.

This proposed mechanism [26] is analogous to that shown in Scheme 6.

4. CONCLUSIONS

Perfluorobutylation reactions of a series of alkenes and alkynes can be accomplished efficiently in water or organic solvent-water mixtures either through consecutive radical reactions or photoinduced HAT processes. Photoinduced CAr-H perfluorbutylation reactions of aromatic and heteroaromatic compounds can be achieved through a sequence of ET-PT steps in good yields.

5. REFERENCES

[1] (a) Zhang, W., Fluorous Technologies for Solution-phase High-throughput Organic Synthesis, *Tetrahedron*, *59*, 4475-4489, **2003**. (b) Curran, D. P., Fluorous Techniques for Combinatorial and Parallel Synthesis, *Pharm. News*, *9*, 179-188, **2002**. (c) Villard, A.-L., Warrington, B. H., Ladlow, M. A., Fluorous-Tagged, Acid-Labile Protecting Group for the Synthesis of Carboxamides and Sulfonamides, *J. Comb. Chem*., *6*, 611-622, **2004**. (d) Zhang, W., Luo, Z., Chen, C. H.-T., Curran, D. P., Solution-Phase Preparation of a 560-Compound Library of Individual Pure Mappicine Analogues by Fluorous Mixture Synthesis, *J. Am. Chem. Soc.*, *124*, 10443-10450, **2002**. (e) Lindsley, C. W., Zhao, Z., Newton, R. C., Leister, W. H., Strauss, K. A., Construction of Functionalized Tricyclic Dihydropyrazino-quinazolinedioneChemotypes *via* an Ugi/N-acyliminium Ion Cyclization Cascade, *Tetrahedron Lett*., *43*, 4467-4470, **2002**. (f) Lindsley, C. W., Zhao, Z., Leister, W. H., Strauss, K. A., Fluorous-tethered Amine Bases for Organic and Parallel Synthesis: Scope and Limitations, *Tetrahedron Lett.*, *43*, 6319-6323, **2002**.

[2] Gladysz, J. A., Emnet, C., Rabai, J. **2004**, In The Handbook of Fluorous Chemistry, J. A. Gladysz, D. P. Curran and I. T. Horvath (Eds.), Wiley-VCH: Weinheim, Germany, 56-112.

[3] Park, G., Ko, K.-S., Zakharova, A., Pohl, N. L., Mono- vs. Di-fluorous-tagged Glucosamines for Iterative Oligosaccharide Synthesis, *J. Fluorine Chem.*, *129*, 978-982, **2008**.

[4] Vaillard, S., Postigo, A., Rossi, R. A., Novel Perfluoroalkyl-Diphenylphosphine Compounds. Syntheses and Reaction Mechanisms, *Organometallics*, *23*, 3003-3007, **2004**.

[5] Bravo, A., Bjorvski, H.-R., Fontana, F., Liguori, L., Mele, A., Minischi, F., New Methods of Free-Radical Perfluoroalkylation of Aromatics and Alkenes. Absolute Rate Constants and Partial Rate Factors for the Homolytic Aromatic Substitution by *n*-Perfluorobutyl Radical, *J. Org. Chem.*, *62*, 7128-7136, **1997**.

[6] (a) Brace, N. O., Syntheses with Perfluoroalkyl Iodides. A review: Part III., *J. Fluorine Chem.*, *108*, 147-175, **2001**. (b) Brace, N. O., Syntheses with Perfluoroalkyl Radicals from Perfluoroalkyl Iodides. A Rapid Survey of Synthetic Possibilities with Emphasis on Practical Applications. Part One: Alkenes, Alkynes and Allylic Compounds, *J. Fluorine Chem*., *93*, 1-25, **1999**. (c) Brace, N. O., Syntheses with Perfluoroalkyl Iodides. Part II. Addition to Non-conjugated Alkadienes; Cyclization of 1,6-Heptadiene, and of 4-substituted 1,6-heptadienoic Compounds: Bis-allyl Ether, Ethyl Diallylmalonate, *N,N′*-Diallylamine and N-substituted Diallylamines; and Additions to Homologous Exo-andEendocyclicAlkenes, and to Bicyclic Alkenes, *J. Fluorine Chem*., *96*, 101-127, **1999**

[7] Cahard, D., Ma, J.-A., Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions, *Chem. Rev.*, *104*, 6119-6146, **2006**.

[8] Baasner, B., Hagemann, H., Tatlow, J. C., Houben-Weyl Organo-Fluorine Compounds; Thieme: Stuttgart, Germany, 1-56, **2000**

[9] Tsuchii, K., Imura, M., Kamada, N., Hirao, T., Ogawa, A., An Efficient Photoinduced Iodoperfluoroalkylation of Carbon-Carbon Unsaturated Compounds with Perfluoroalkyl Iodide, *J. Org. Chem.*, *69*, 6658-6665, **2004**.

[10] (a) Rossi, R. A., Postigo, A., Recent Advances on Radical Nucleophilic Substitution Reactions, *Curr. Org. Chem.*, *7*, 747-769, **2003**.

(b) Rossi, R. A., Pierini, A. B., Peñéñory, A. B., Nucleophilic Substitution Reactions by Electron Transfer, *Chem. Rev., 103*, 71-168, **2003**.

[11] Barata-Vallejo, S., Postigo, A., $(Me_3Si)_3SiH$-Mediated Intermolecular Radical Perfluoroalkylation Reactions of Olefins in Water, *J.Org. Chem., 75*, 6141-6148, **2010**.

[12] (a) Kharasch, M. S., Mayo, F. R., The Peroxide Effect in the Addition of Reagents to Unsaturated Compounds. I. The Addition of Hydrogen Bromide to Allyl Bromide, *J. Am. Chem. Soc. 55*, 2468-2496, **1933**. (b) Postigo, A., Synthetically Useful Carbon–carbon and Carbon–sulphur Bond Construction Mediated by Carbon- and Sulphur-centred Radicals in Water and Aqueous Media, *RSC Adv. 1*, 14-32, **2011**.

[13] Slodowicz , M., Barata-Vallejo, S., Vázquez, A., Sbarbati Nudelman, N., Postigo, A., Light-induced Iodoperfluoroalkylation Reactions of Carbon–carbon Multiple Bonds in Water, *J. Fluorine Chem., 135*, 137-143, **2012**.

[14] (a) Scaiano, J. C., Stewart, L. C., Phenyl Radical Kinetics, *J. Am. Chem. Soc.,105*, 3609-3614, **1983**. (b) Johnston, L. J., Scaiano, J. C., Ingold, K. U., Kinetics of Cyclopropyl Radical Reactions. 1. Absolute Rate Constants for Some Addition and Abstraction Reactions, *J. Am. Chem. Soc., 106*, 4877-4881, **1984**.

[15] Lemal, D. M., Perspective on Fluorocarbon Chemistry, *J. Org. Chem., 69*, 1-11, **2004**.

[16] Ueda, Y., Kanai, M., Uneyama, K. Perfluoralkyl-chalcogenation of Alkynes, *Bull. Chem. Soc. Jpn*., *67*, 2273-2277, **1994**.

[17] Dolbier, W. R. Jr., Structure, Reactivity and Chemistry of Fluoroalkyl Radicals, *Chem. Rev., 96*, 1557-1584, **1996**.

[18] Barata-Vallejo, S., Sbarbati Nudelman, N., Postigo, A., Organic Synthesis in Water Mediated By Silyl Radicals, *Curr. Org. Chem., 15*, 1826-1842, **2011**.

[19] (a) Postigo, A., Kopsov, S., Ferreri, C., Chatgilialoglu, C., Radical Reactions in Aqueous Medium Using $(Me_3Si)_3SiH$, *Org. Lett., 9*, 5159-5162, **2007**. (b) Postigo, A., Ferreri, C., Navacchia, M. L., Chatgilialoglu, C., The Radical-Based Reduction with $(TMS)_3SiH$ 'On Water', *Synlett, 18*, 2854-2856, **2005**.

[20] Barata-Vallejo, S., Martín Flesia, M., Lantaño, B., Arguello, J. E., Peñéñory, A. B., Postigo, A., Heterogeneous Photoinduced Homolytic Aromatic Substitution of Electron-Rich Arenes with Perfluoroalkyl Groups in Water and Aqueous Media – A Radical-Ion Reaction, *Eur. J. Org. Chem., 2013*, 998-1008, **2013**.

[21] (a) Cuquerella, M. C., Boscá, F., Miranda, M. A., Photonucleophilic Aromatic Substitution of 6-Fluoroquinolones in Basic Media: Triplet Quenching by Hydroxide Anion, *J. Org. Chem., 69*, 7256-7261, **2004**. (b) Kiyota, T., Yamaji, M., Shizuka, A. Hydrogen-Bonding-Induced Electron Transfer from Triplet *N,N*-Dialkyl-1-naphthylamines to Benzophenone via Triplet Exciplexes, *J. Phys. Chem., 100*, 672-679, **1996**. (c) Yamaji, M. , Kiyota, T., Shizuka, H., Solvent Dependence of Interactions Between Triplet Benzophenone and *N,N*-Dimethylaminonaphthalene Studied by Laser Flash Photolysis, *Chem. Phys. Lett., 226*, 199-205, **1994**.

[22] Rong, X. X., Pan, H.-Q., Dolbier, W. R. Jr., Reactivity of Fluorinated Alkyl Radicals in Solution. Some Absolute Rates of Hydrogen-Atom Abstraction and Cyclization, *J. Am. Chem. Soc., 116*, 4521-4522, **1994**.

[23] (a) Davis, C. R., Burton, D. J., Yang, Z.-Y., Titanium-catalyzed Addition of Perfluoroalkyl Iodides to Alkenes, *J. Fluorine Chem., 70*, 135-140, **1995**. (b) Le, T. D., Arlauskas, R. A., Weers, J. G., Characterization of the Lipophilicity of Fluorocarbon Derivatives Containing Halogens or Hydrocarbon Blocks Original, *J. Fluorine Chem., 78*, 155-163, **1996**. (c) Huang, X.-T., Chen, Q.-Y., Synthesis of Fluorinated Acetylenes, *J. Org. Chem., 66*, 4651-4656, **2001** (d) Scannell, M. P., Fenick, D. J., Yeh, S.-R., Falvery, D. E., Model Studies of DNA Photorepair: Reduction Potentials of Thymine and Cytosine Cyclobutane Dimers Measured by Fluorescence Quenching, *J. Am. Chem. Soc., 119*, 1971-1977, **1997**.

[24] Cho, E. J., Senecal, T. D., Kinsel, T., Zhang, Y., Watson, D. A., Buchwald, S. L., The Palladium-Catalyzed Trifluoromethylation of Aryl Chlorides, *Science, 328*, 1679-1681, **2010**.

[25] Postigo, A., Homolytic Aromatic Radical Perfluoroalkyl-Group Substitution of Arenes in Water, *Trends in Photochem.&Photobiol., 14*, 93-110, **2012**

[26] Lantaño, B., Barata-Vallejo, S., Torviso, M. R., Bonesi, S. M.; Arguello, J. E., Postigo, A., Direct C—HPerfluoroalkylation of Dibenzoarenes and Dibenzoheteroarenes in Aqueous Media, *J.Fluorine Chem., 161*, 149-165, **2014**.

[27] (a) Litwinienko, G., Beckwith, A. L. J., Ingold, K. U., The Frequently Overlooked Importance of Solvent in Free Radical Syntheses, *Chem. Soc. Rev., 40*, 2157-2163, **2011**. (b) Foti, M. C., Amorati, R., Pedulli, G. F., Daquino, C., Pratt, D. A., Ingold, K. U., Influence of "Remote" Intramolecular Hydrogen Bonds on the Stabilities of Phenoxyl Radicals and Benzyl Cations, *J. Org. Chem., 75*, 4434-4440, **2010**. (c) Litwinienko, G., Di Labio, G. A., Mulder, P., Korth, H.-G., Ingold, K. U., Intramolecular and Intermolecular Hydrogen Bond Formation by Some Ortho-Substituted Phenols: Some Surprising Results from an Experimental and Theoretical Investigation, *J. Phys. Chem. A., 113*, 6275-6288, **2009**.

[28] (a) Della, N., Ca, S., Catellani, G. M. A., Direct Palladium-Catalyzed Route to Selectively Substituted Carbazoles through Sequential C C and C N Bond Formation: Synthesis of Carbazomycin A, *Adv. Synth. Catalysis, 350*, 2179-2182, **2008**. (b) Schümperli, M. T., Hammond, C., Hermans, I., Reactivity of α-amino-peroxyl Radicals and Consequences for Amine Oxidation Chemistry, *Phys. Chem. Chem. Phys., 14*, 11002-11007, **2012**.

[29] (a) Kitamura, Y., Yoshikawa, S., Furuta, T., Kan, T., One-Pot Synthesis of Carbazole via Tandem Suzuki-Miyaura and Amination Reaction, *Synlett, 3*, 377-380, **2008**. (b) Watanabe, T., Ueda, S., Inuki, S., Oishi, S., Fujii, N., Ohno, H., One-pot Synthesis of Carbazoles by Palladium-Catalyzed *N*-arylation and Oxidative Coupling, *Chem. Comm., 43*, 4516-4518, **2007**.

[30] Wiehn, M. S., Vinogradova, E. V., Togni, A., Electrophilic Trifluoromethylation of Arenes and N-Heteroarenes Using Hypervalent Iodine Reagents, *J. Fluorine Chem., 131*, 951-957, **2011**

[31] (a) Huang, S. J., Kim, H. J., Chang, S., Highly Efficient and Versatile Synthesis of Polyarylfluorenes *via* Pd-Catalyzed C─H Bond Activation, *Org. Lett., 11*, 4588-4591, **2009**. (b) Zhang, C.-P., Cai, J., Zhou, C.-B., Wang, X.-P., Zheng, X., Gu, Y.-C., Xiao, J.-C., Copper-mediated Trifluoromethylation of Arylboronic Acids by Trifluoromethyl Sulfonium Salts, *Chem. Comm., 47*, 9516-9518, **2011**.

[32] Nervig, C. S., Waller, P. J., Kalyani, D., Palladium-Catalyzed Intramolecular C–H Arylation of Arenes Using Tosylates and Mesylates as Electrophiles, *Org. Lett., 14*, 4838-4841, **2012**.

[33] Lockner, J. W., Dixon, D. D., Risgaard, R., Baran, P. S., Practical Radical Cyclizations with Arylboronic Acids and Trifluoroborates, *Org. Lett., 13*, 5628-5631, **2011**.

[34]Ye, Y., Kunzi, S. A., Sanford, M. S., Practical Method for the Cu-Mediated Trifluoromethylation of Arylboronic Acids with CF_3 Radicals Derived from $NaSO_2CF_3$ and tert-Butyl Hydroperoxide (TBHP), *Org. Lett., 14*, 4979-4981, **2012**.

[35] (a) Wang, J., Ferguson, D. M., Kalyani, D., Nickel-catalyzed Intramolecular C–H Arylation Using Aryl pivalates as Electrophiles, *Tetrahedron, 69*, 5780-5790, **2013**. (b) Xiao, B., Gong, T.-J., Liu, Z.-J., Liu, J.-H., Luo, D.-F., Xu, J., Liu, L., Synthesis of Dibenzofurans via Palladium-Catalyzed Phenol-Directed C–H Activation/C–O Cyclization, *J. Am. Chem. Soc., 133*, 9250-9253, **2011**.

6. ACKNOWLEDGEMENTS

The author wishes to acknowledge Conicet, AgenciaNacional de PromociónCientífica y Técnica, and Universidad de Buenos Aires for financial support.