

Photoinduced perfluorobutylation of organic substrates in aqueous media

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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 fluoros [1] combinatorial technique require convenient methods for selective introduction of fluoros 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 S_N1 mechanism, on account of the low stability of carbocations, and precluded to undergo S_N2 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,

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 (Me₃Si)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 C₄F₉X. This C₄F₉• radical reacts faster with the alkene than with

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.

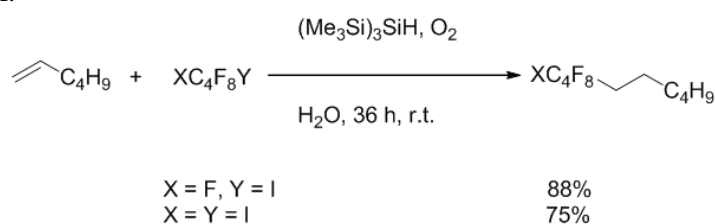
Another route to the synthesis of compounds with perfluoroalkyl moieties is through the SRN1 mechanism, which involves radicals and radical ions as intermediates [4, 10]. Both aliphatic and aromatic substrates can be made to react with the RfI by the SRN1 mechanism.

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.

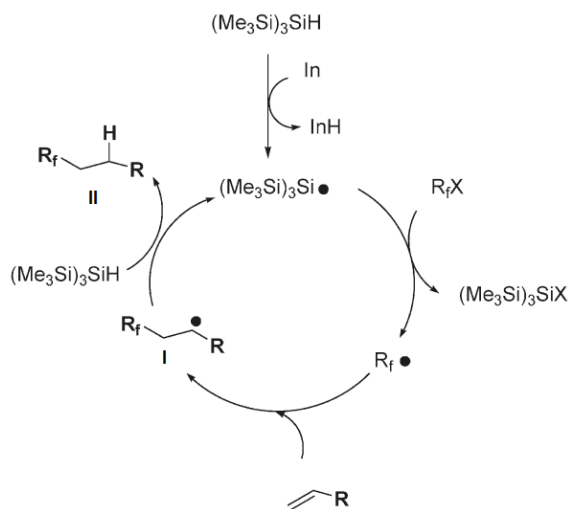
As for aromatic substrates, the photoinduced methodology for perfluorobutylation will be shown in this study to provide C-H perfluorobutyl bond insertion products.

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.

the silicon hydride, affording the perfluoroalkylated radical adduct I.

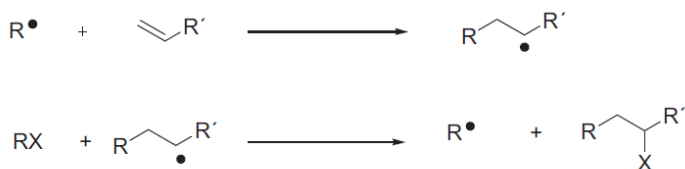


Scheme 1. Perfluorobutylation and iodoperfluorobutylation of 1-hexene.



Scheme 2. Mechanism for the $(\text{Me}_3\text{Si})_3\text{SiH}$ 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).

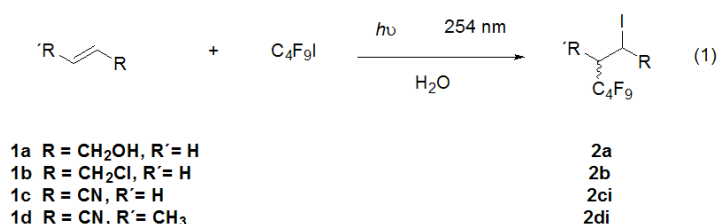


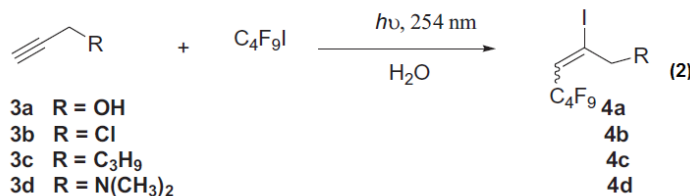
Table 1. Photochemically-induced (254 nm, 60W, 2h) radical perfluorobutylation of alkenes **1a–d** (10 mM) with

$n\text{-C}_4\text{F}_9\text{I}$ (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	 2di + 2dii (58)

Acrylonitrile **1c** affords two HAT products, i.e.: **2ci** and **2cii** in an 88:12 ratio. Product **2ci** prevails in the mixture, as arising from a cyano-substituted, resonance-stabilized secondary alkyl radical adduct.

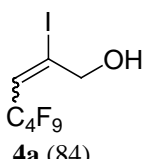
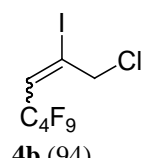
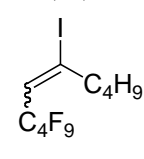
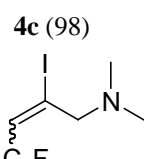
Interestingly, crotononitrile **1d** also affords two iodoperfluoroalkylated products, 3,3,4,4,5,5,6,6,6-nonafluoro-2-(1-iodoethyl)hexanenitrile **2di** and 4,4,5,5,6,6,7,7,7-nonafluoro-2-iodo-3-methylheptanenitrile **2dii** in 3 and 97% relative yields, respectively (isolated 58%, Table 1). Clearly, 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 $\text{C}_4\text{F}_9\cdot$ radicals are the dominant factor giving rise to their high reactivity. $\text{C}_4\text{F}_9\cdot$ 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 $\text{C}_4\text{F}_9\cdot$ radical addition is expected to lower the activation energy) [14, 15]. It has been observed, in organic solvents, that the rates of addition of $\text{C}_4\text{F}_9\cdot$ 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 $\text{C}_4\text{F}_9\cdot$ radical to an alkene is that between the SOMO of the radical and the HOMO of the alkene. Thus, the rates of

$C_4F_9\bullet$ 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 °C.

Entry	Substrate	Product (% yield)	E:Z ratio
1	Propargyl alcohol, 3a	 4a (84)	70:30 ^a
2	Propargyl chloride, 3b	 4b (94)	45:55 ^a
3	1-hexyne, 3c	 4c (98)	93:7 ^a
4	<i>N,N</i> -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 $C_4F_9\bullet$ 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 $C_4F_9\bullet$ 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-

3. AROMATIC SUBSTRATES

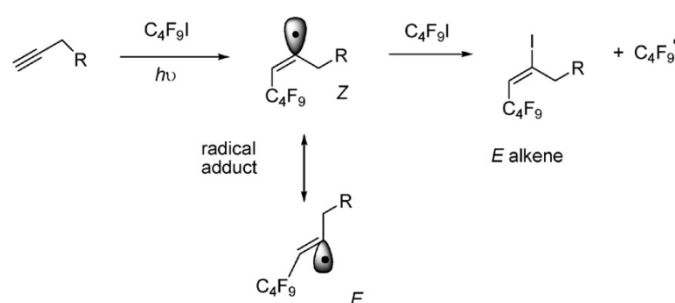
A recent report on the perfluorobutylation of electron-rich aromatic compounds has uncovered the convenience of the photoinduced methodology to produce $C_4F_9\bullet$ radicals from iodoperfluoroalkanes [20] that are able to effect aromatic H substitution reactions. These processes entail radical homolytic 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 $n-C_4F_9I$ to a photoinduced reaction [21], they obtained the nonafluorobutyl para substitution product **7** and the 4-positionsubstitution product **8**, respectively, in yields ranging from

mercaptoethanol, as chain carrier [19]. This is because silyl radicals being hydrophobic need the assistance of amphiphilic thiyl radicals (i.e. $\bullet SCH_2CH_2OH$) 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 perfluoroalkylation reactions in water without the assistance of a chain carrier. This observation could be better interpreted in light of the distinct reactivity of $C_4F_9\bullet$ radicals in water rather than to a difference in hydrophobicity of $C_4F_9\bullet$ radicals in comparison to silyl radicals. Perhaps, some distinct amphiphilic character of $C_4F_9\bullet$ radicals could be invoked in this case.

Ogawa and collaborators have shown that the perfluoroalkylated radical adduct formed upon addition of $C_4F_9\bullet$ 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 $C_4F_9\bullet$ radical, which carries on the chain reaction. The E-end-alkene is favored over the Z isomer, as accounted in Scheme 2, and Table 2. The radical adduct formed upon addition of $C_4F_9\bullet$ radical onto the alkyne, which can equilibrate between the E and Z stereoisomers, will abstract iodine atom from the less hindered/congested radical adduct in the Z configuration than the E configuration, rendering the E alkene end product (Scheme 4).



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

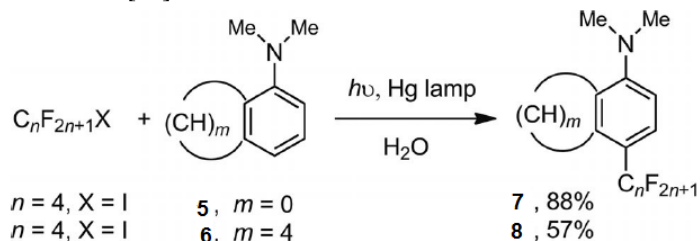
The prevalence of the *Z* stereoisomer from propargyl chloride **3b** radical addition reaction, i.e. product **4b**, is due to a post-isomerization process of the initially formed **4b** (*E*) isomer, as confirmed by analyzing aliquots at shorter photolysis times, where the mixture is enriched in the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

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.

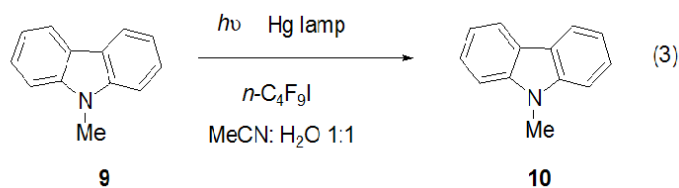
In order to cast some light into the reactive excited state manifold of substrate 5 (or 6), product studies of the photoinduced electron transfer (PET) reaction in 5 (or 6) were carried out [20] (at irradiation wavelength $\lambda = 310$ nm), in the presence of $n\text{-C}_4\text{F}_9\text{I}$ and 4-methoxyacetophenone (MAP, 15 mmol), a well-known triplet energy sensitizer ($E_{\text{Triplet}} = 310$ KJ mol⁻¹). Under these reaction conditions, no substitution product 7 (or 8 from substrate 6) was encountered (i.e. $E_{\text{Triplet}}(6) = 226$ KJ mol⁻¹ [21c]). This would seem to imply that the singlet excited state manifold is responsible 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 $n\text{-C}_4\text{F}_9\bullet$ 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.

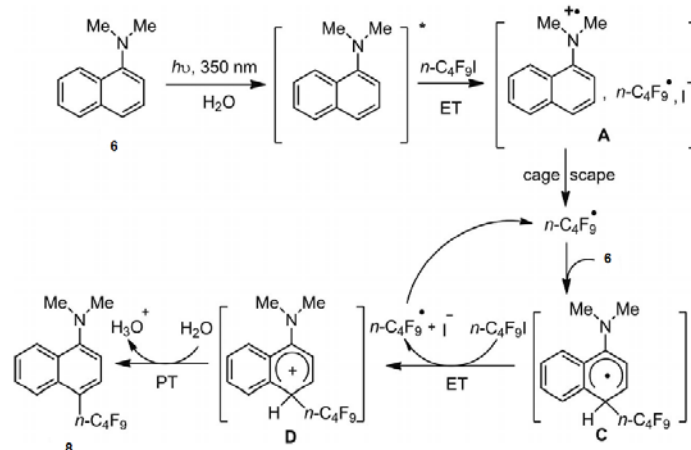
The photoreaction of N-methylcarbazole 9 with $n\text{-C}_4\text{F}_9\text{I}$ in MeCN:water led to substitution product 10, in fairly good yields, according to Eq.3 below. As far as the authors were concerned [25], the carbazole ring had only been trifluoromethylated before through Pd-catalysis with 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.

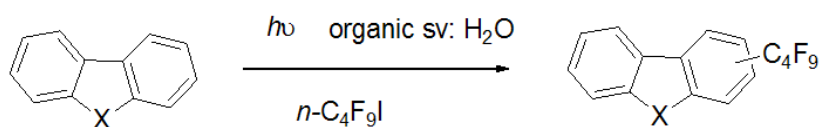
The authors [25] thus postulated a PET mechanism where, upon light absorption by substrates 5 or 6, the corresponding radical cation ($5^{+\bullet}$ or $6^{+\bullet}$) together with the $n\text{-C}_4\text{F}_9\bullet$ and iodide anion are formed in the solvent cage by an ET (Scheme 6, for substrate 6). This is the initiation step. Upon cage-escape of $6^{+\bullet}$ (or $5^{+\bullet}$) and $n\text{-C}_4\text{F}_9\bullet$, the radical $n\text{-C}_4\text{F}_9\bullet$ 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 $n\text{-C}_4\text{F}_9\text{I}$, 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 $n\text{-C}_4\text{F}_9\bullet + \text{I}^-$. This $n\text{-C}_4\text{F}_9\bullet$ triggers a chain sequence. Upon proton loss (PT), adduct D generates the substitution product 6. $n\text{-C}_4\text{F}_9\bullet$ radicals enter the substitution cycle as depicted in Scheme 6. It is observed that this is a chain PET mechanism, where $n\text{-C}_4\text{F}_9\bullet$ 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 and $n\text{-C}_4\text{F}_9\text{I}$ in MeCN:H₂O 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 and $n\text{-C}_4\text{F}_9\text{I}$ in MeCN:H₂O 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 $\text{C}_4\text{F}_9\text{-I}$, or a substitution route from direct homolysis of the $\text{F}_9\text{C}_4\text{-I}$ bond and ulterior homolytic aromatic ring substitution with $\text{C}_4\text{F}_9\bullet$ radicals. In order to optimize reaction conditions, the authors [26] varied substrate and $n\text{-C}_4\text{F}_9\text{I}$ concentrations with the purpose of maximizing product yields. This was accomplished by plotting graphs of % substitution product versus $n\text{-C}_4\text{F}_9\text{I}$ or substrate concentration, at 254-nm irradiation (not shown), and the best results were obtained as shown in column 3, Table 3.



- 9** X = NMe
11 X = NH
13 X = O
17 X = CH₂
19 X = S

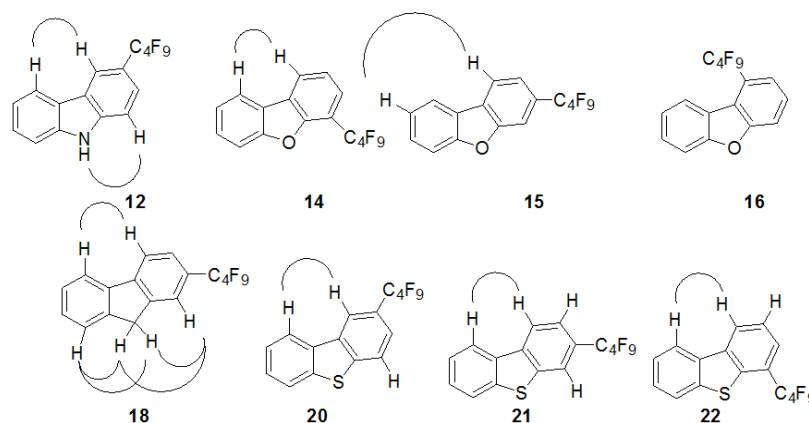
- 50% isolated (3-C₄F₉, (**10**))
 59% isolated (3-C₄F₉, (**12**))
 41% isolated (4-C₄F₉ (**14**): 3-C₄F₉ (**15**): 1-C₄F₉ (**16**) 25:35:40)
 45% isolated (2-C₄F₉ (**18**))
 50% isolated (2-C₄F₉ (**20**): 3-C₄F₉ (**21**): 4-C₄F₉ (**22**) 48:34:17)

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)	$A_{\text{substrate}}:A_{\text{RfX}}$ ^b pH _{initial} /pH _{final} ^c
1	MPL ^d	11 (1), <i>n</i> -C ₄ F ₉ I (0.2)	MeCN:H ₂ O 1:1, (30)	12 (10) ^e	1:0.1 ^b 5/3 ^c
2	λ 254 nm	11 (0.06), <i>n</i> -C ₄ F ₉ I (4.5)	MeCN:H ₂ O 1:1, (4)	12 (59) ^e	1:1 ^b 5.5/3 ^c
3	MPL ^d	9 (1), <i>n</i> -C ₄ F ₉ I (0.2)	MeCN:H ₂ O 1:1, (30)	10 (50) ^e	1:0.1 ^b 5/3 ^c
4	λ 254 nm	13 (0.3), <i>n</i> -C ₄ F ₉ I (2.4)	MeCN:H ₂ O 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), <i>n</i> -C ₄ F ₉ I (2.4)	DCM:H ₂ O 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), <i>n</i> -C ₄ F ₉ I (2.3)	MeCN:H ₂ O 3:1, (4)	18 (45) ^e	7.8:1 ^b 5.5/3 ^c
7	λ 254 nm	19 (0.3), <i>n</i> -C ₄ F ₉ I (2.3)	MeCN:H ₂ O 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 Na₂S₂O₃; ^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*-C₄F₉I in the reaction mixtures, a steady increase in substitution product yields is obtained, purporting that the reaction is initiated through homolysis of F₉C₄—I bond leading to C₄F₉• radicals. The optimized concentration ratios of substrate:*n*-C₄F₉I found were those shown in column 3, Table 3 (*i.e.* the highest substitution product yields are obtained when *n*-C₄F₉I 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, nor a 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:H₂O/Na₂S₂O₃ [30] mixture in the presence of *n*-C₄F₉I, it affords the mono C₄F₉-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*-C₄F₉I is carried out in a CH₂Cl₂:H₂O 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 fluororous 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 H1 and H9. Compound **15** shows H1-H8 NOE correlation, whereas compound **16** does not show NOE correlations (Scheme 8). Substitution at the 2-position of the dibenzofuran ring with the C₄F₉ 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-CF₃-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 CF₃SO₂Na (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 C₄F₉-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 fluororous phase eluant.

The dibenzoarene fluorene **17** (9*H*-fluorene), upon reaction with *n*-C₄F₉I in MeCN:H₂O/Na₂S₂O₃ 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 H1 with protons at the 9-position as well as correlations between H8 with protons at the 9-position of the fluorene ring have been observed for product **18** (Scheme 8) [26]. Also, a correlation between H4 and H5 was observed in NOE-experiments. Fluorene, as substrate, has never been trifluoromethylated 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].

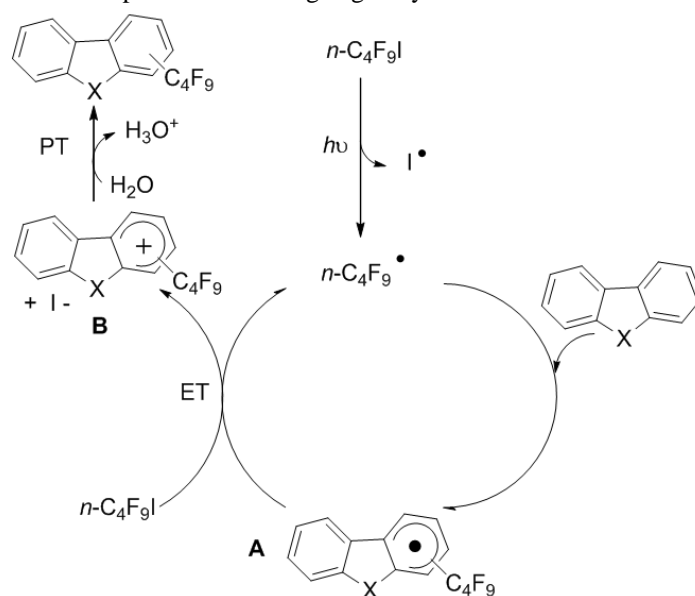
Dibenzo[*b,d*]thiophene **19**, under the same reaction conditions [26], affords a mixture of three main regioisomers, substituted at the 2- (product **20**, Scheme 7), 3- (product **21**, Scheme 7), and 4- (product **22**, Scheme 7) positions. The overall substitution isolated yield of products **20-22** 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 Na₂S₂O₃, 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 H1-H9 (Scheme 8). 2-, and 4-CF₃-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-C₄F₉-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 C₄F₉-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:H₂O 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*-C₄F₉I in MeCN:H₂O 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*-C₄F₉I (see Table 3, column 6, footnote *b*), homolysis of F₉C₄-I bond produces C₄F₉• 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*-C₄F₉I (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

perfluorobutylation reactions of aromatic and heteroaromatic compounds can be achieved through a sequence of ET-PT steps in good yields.

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