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PERFLUOROALKYLATION REACTIONS OF (HETERO)ARENES

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Abstract

Perfluoroalkylation reactions of arenes have not been the subject of intense studies as has been the case for the trifluoromethylation reactions of aromatics. However, the new synthetic methods proposed for achieving homolytic aromatic substitution reactions with perfluoroalkyl moieties have begun to claim a relevant role in functionalization reactions, as revealed by the interesting properties of arenes with large perfluoroalkyl chains. Methods for achieving Ar-R_f bonding reactions can be classified into thermal and photochemical, which can in turn make use of transition metals or be non-metal catalyzed. Reactions are mainly radical in nature. Radical methods for introducing R_f moieties into arenes have resulted as being the most popular and versatile options available to synthetic chemists

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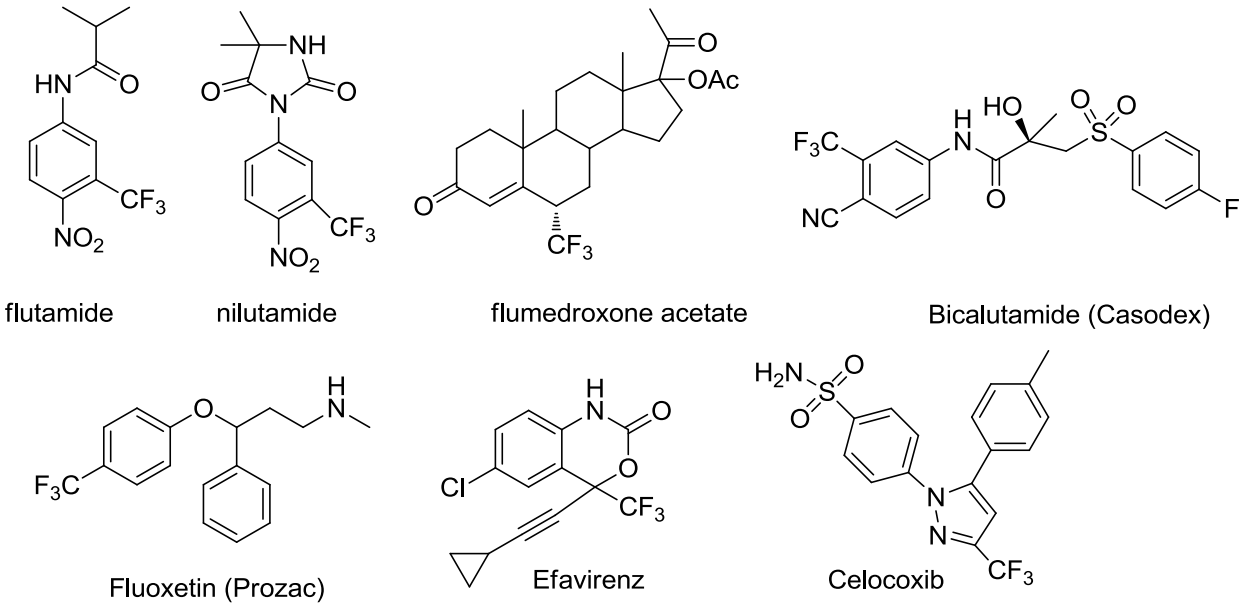
Introduction

Organofluorine compounds are playing an increasingly important role in medicinal chemistry, agriculture chemistry and material science.

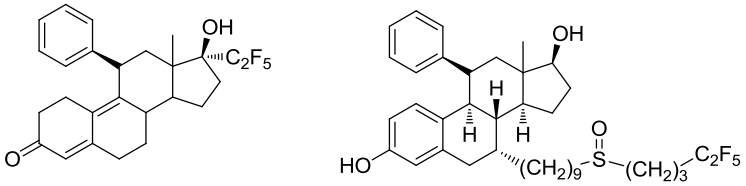
The introduction of a fluoroalkyl moiety into a pharmacophore is often known to increase activity, resistance to oxidation, and lipophilicity/bioavailability.

Many commercial examples do exist of trifluoromethylated drugs[1] with a variety of pharmacological activity, such as androgenic receptors (flutamide, nilutamide, bicalutamide, Scheme 1), estrogen receptors (flumedroxone acetate), antidepressants (fluoxetine), antiarthritics (celocoxib), antiretroviral agents (efavirenz) (Scheme 1) which emphasize the relevant role of the CF_3 group in drugs and drug candidates. Some of these commercial drugs have revenues in the order of the billion dollars.



Scheme 1. Representative commercial drugs bearing the CF_3 group

However, perfluoroalkyl moieties are scarcely found as substituents in pharmacophores.[1b] The pentafluoroethyl group has just begun to be used in drugs. It is found as an alcohol substituent in antiprogestine and at the end of a chain in fulvestrant (Scheme 2). In this latter case, the C_2F_5 group protects the chain from metabolic oxidation, just like the CF_3 group does.



Scheme 2. Examples of drugs and drug candidates bearing perfluoroalkyl moieties

It is expected that future development in perfluoroalkylation[2] strategies bring about the discovery of pharmacophores bearing perfluoroalkyl groups showing a variety of biological activity and increased potency.

One such strategy for the fluoroalkylation of arenes is based on the radical homolytic aromatic substitution reaction (HAS), which has been a well-documented mechanism and has been notoriously employed to accomplish (fluoro)alkyl group substitutions on many (hetero)aromatic nuclei.[3]

Radical homolytic trifluoromethylation reactions of aromatic nuclei have been intensively studied and many recent review articles do exist in this area.[4] However, fewer examples have been documented for HAS perfluoroalkylation.[5-8] C_{Ar-H} perfluoroalkyl-group radical substitution reactions of arenes can be classified into thermal and photoinduced methods. Thermal methods can make use of transition metal-catalysis[9-13] and several perfluoroalkyl sources (Figure 1) or else be non-metal

catalyzed, among which, the use of the Baran reagent[14] or perfluoroalkylsulfinate salts[15] in the presence of organic peroxide[16] or azo initiators[17] (Figure 1) render perfluoroalkyl-substituted arenes efficiently. Also electrophilic perfluoroalkylating reagents in the presence of metals effect C-H bond radical substitutions with R_f groups.[12-18]

Photoinduced methods either through direct homolysis of X-C_nF_{2n+1} bonds[19-20], or by means of photoinduced electron transfer (PET) reactions[21] are capable of generating perfluoroalkyl radicals C_nF_{2n+1} even in aqueous systems[22] (Figure 1). Since the pioneering work of McMillan for the trifluoromethylation reactions of arenes through the use of transition-metal photo-organocatalysts[23], only a few reports on photocatalytic perfluoroalkylations of arenes have been documented.[24]

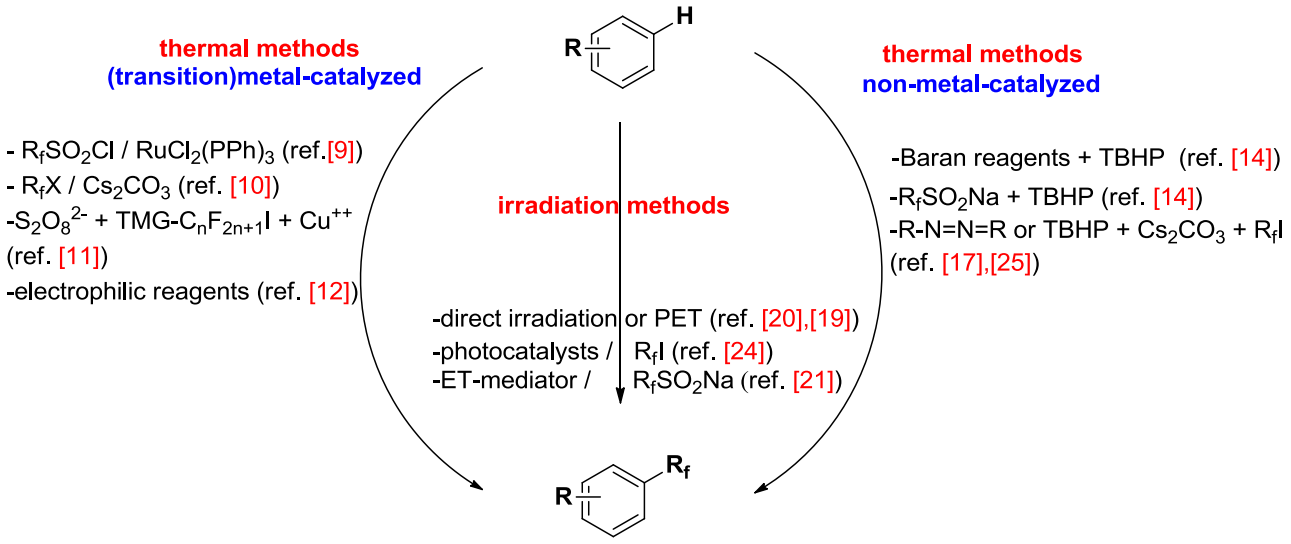


Figure 1. Methods for C-H (HAS) radical perfluoroalkylation of arenes

In the next sections we shall describe methods for the direct perfluoroalkylation (long perfluoroalkyl chain incorporations) of (hetero)arenes under thermal and photoinduced conditions. Those works that have been reviewed, will be properly cited, and new references will be described.

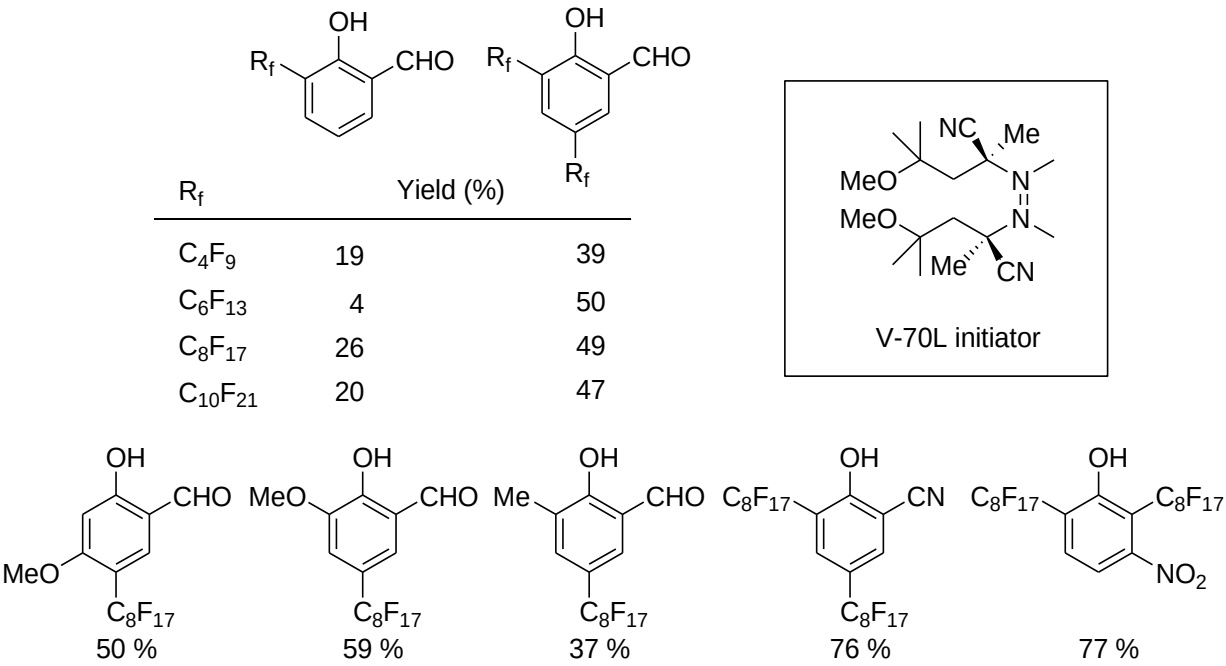
This account excludes the trifluoromethylation strategies for arenes and heteroarenes, as well as the methods for introducing fluorine and trifluoromethylthio substituents into these compounds.

1.-Thermal methods

Early reports on thermal perfluoroalkylation reactions of arenes date back to the 1960´s, and reached the 1980´s, with examples involving the thermolysis or peroxide-promoted thermolysis of perfluoroalkyl iodides[26], and nickel carbonyl- promoted thermolysis of perfluoroacyl chloride in the presence of arenes.[27]

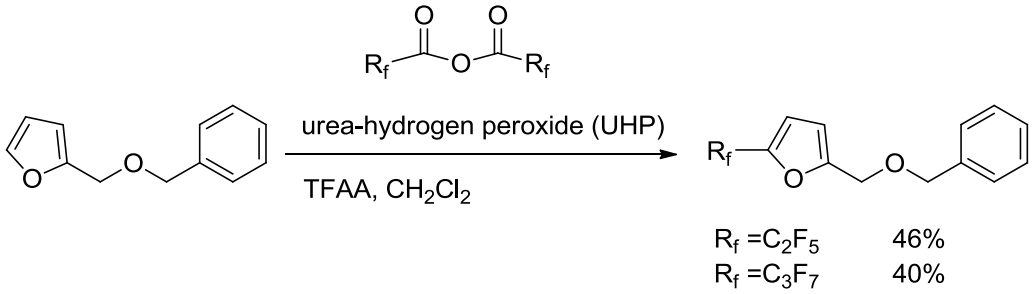
1.1.-Transition metal-free thermal perfluoroalkylation methods

A simple method for direct perfluoroalkylation of phenols under mild conditions has been reported by Matsugi and co-workers.[28] This novel perfluoroalkylation protocol involves the use of a radical initiator V-70L which allows the reaction to be carried out at room temperature in the presence of Cs_2CO_3 as base. The reaction affords regioselectively perfluoroalkylated phenol derivatives in moderate to high yields as depicted in Scheme 3. It is noteworthy that no *O*-perfluoroalkylated products are observed in the reaction mixture. When the reaction was conducted at temperatures higher than 70 °C, the perfluoroalkylation proceeded without the initiator. However, a product mixture rich in di-substituted adducts was obtained.



Scheme 3. Thermal radical perfluoroalkylation of arenes.

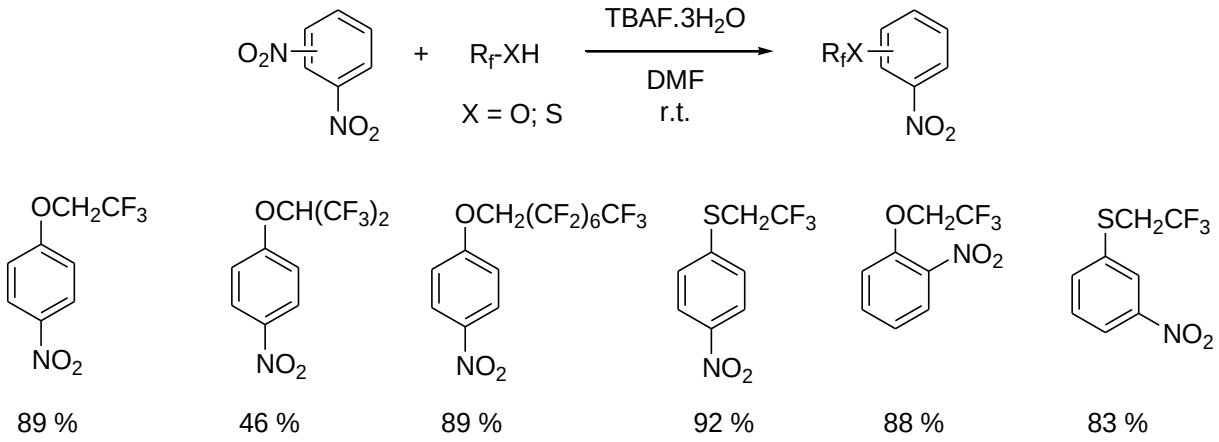
Bräse and collaborators[29] have very recently introduced a metal-free radical perfluoroalkylation method of (hetero)arenes which employs commercially available perfluorocarboxylic anhydrides as source of perfluoroalkyl radicals.[30] The scope of the transformation is illustrated in Scheme 4. The radical initiator in this case is urea-hydrogen peroxide.



Scheme 4. Perfluoroalkylation of heteroarenes employing perfluorocarboxylic anhydrides

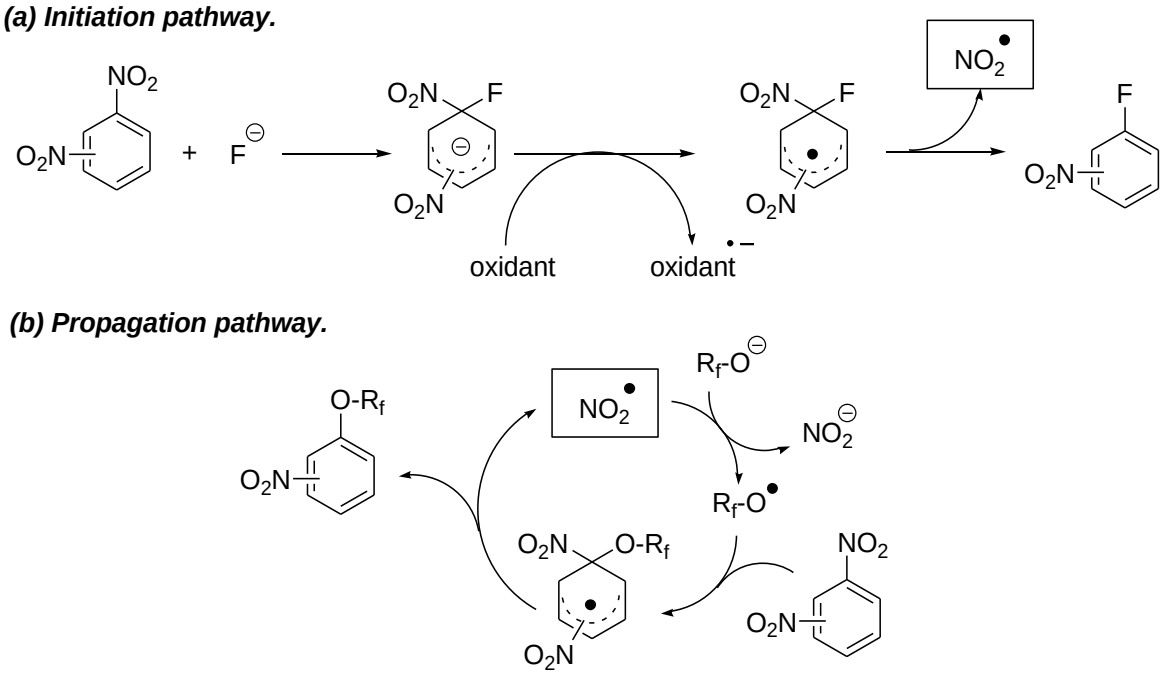
The example in Scheme 4 reflects the preferred regioselectivity of perfluoroalkyl radicals towards the electron-rich furan ring.

Introduction of polyfluoroalkoxy and polyfluoroalkylthio substituents in dinitrobenzene rings can be achieved under mild conditions and short reaction times in DMF as solvent with polyfluoroalcohols and polyfluorothiols in the presence of excess tetrabutylammonium fluoride as a base at room temperature.[31] *Ortho*-, *meta*- and *para*-dinitrobenzenes are used as substrates and the products are obtained in moderate to high yields as shown in Scheme 5 where the displacement of the nitro group by the perfluoroalcohol or perfluoroalkylthiol group takes place efficiently.



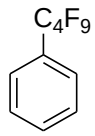
Scheme 5. Perfluoroalkylation of dinitrobenzenes

The reaction mechanism involves a radical chain process that is depicted in Scheme 6. The initiation step is the formation of the *Meisenheimer* complex derived from the dinitrobenzene and fluoride anion that undergoes oxidation by dinitrobenzene or oxygen which is indicated in the Scheme 6 as oxidant. The fast evolution of the resulting *Meisenheimer* radical would give rise to the nitrogen dioxide radical that would enter in the propagation steps of the mechanism. These last steps correspond to a typical radical aromatic substitution.[32]

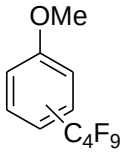


Scheme 6. Proposed mechanism for the perfluoroalkylation of dinitrobenzenes

At the end of the 1990´s, Minisci and co-workers have introduced new and seminal methods of free-radical perfluoroalkylation of aromatic compounds and alkenes with C_4F_9I.[33] These methods can be summarized as follows: (i) benzoyl peroxide in acetic acid refluxing at 116 °C; (ii) *tert*-butanol peroxide in refluxing acetic acid in the presence of Fe(III) salts; (iii) H_2O_2 in refluxing acetone in the presence of catalytic amounts of TFA and; (iv) H_2O_2 in DMSO in the presence of Fe(II) salts at 20 – 30 °C. The perfluoroalkylation reaction of aromatic compounds with electron-donor and electron-withdrawing substituents proceeds in high yields giving the corresponding perfluorobutylated products.[33] Naphthalene, biphenyl and thiophene also afford the perfluoroalkylated products in good yields. Several examples are shown in Scheme 7. The reaction mechanism involved under the aforementioned protocols (i) – (iv) is a homolytic aromatic perfluoroalkylation. The C_4F_9 radical shows a clear-cut electrophilic character in the aromatic substitution but low regio- and chemoselectivities were observed.[33]



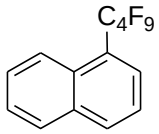
Procedure	Yield (%)
(i)	95
(ii)	96
(iii)	94
(iv)	95



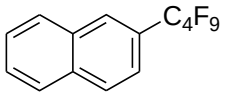
Procedure	Yield (%)		
	o	*m*	*p*
(i)	15	45	40
(ii)	16	43	41
(iii)	16	41	43
(iv)	16	43	41

Substrate	Yield (%)[(a)] *o*	*m*	*p*
Toluene	46	30	24
Chlorobenzene	41	40	19
Benzonitrile	21	52	27
Nitrobenzene	31	37	32

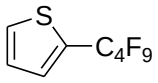
(a) Under protocol (i).



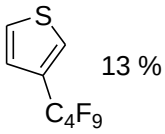
80 %



20 %



86 %

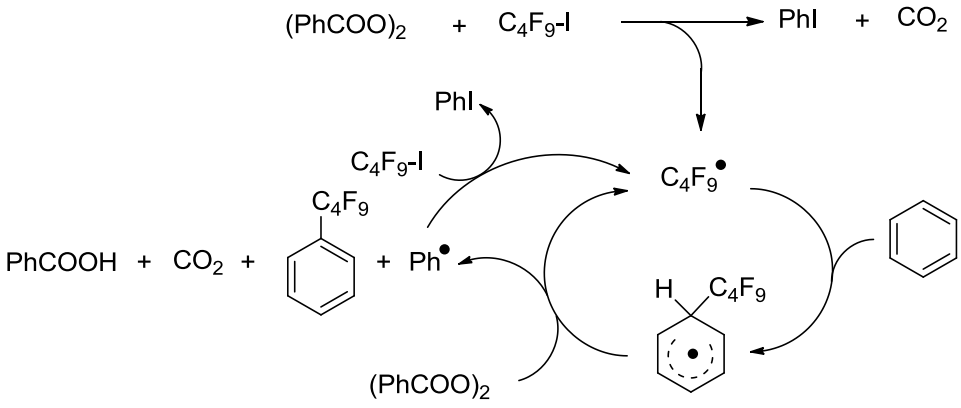


13 %

Scheme 7. Scope of the radical perfluorobutylation reaction of (hetero)arenes by different procedures

The reaction with alkenes, carried out in the presence of catalytic amount of $Cu(OAc)_2$, leads to substitution by a mechanism identical to the aromatic substitution. No usual chain addition of perfluoroalkyl group and iodine atom to the double bond is observed.[33]

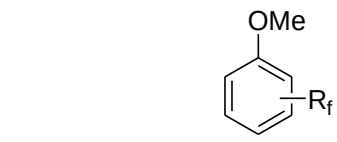
Scheme 8 shows the reaction mechanism of perfluoroalkylation of benzene according to method (i).



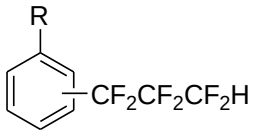
Scheme 8. Mechanism proposed for the radical perfluorobutylation of arenes through dibenzoyl peroxide decomposition

Sulfinatodehalogenation reactions have been intensively used for accomplishing fluoroalkylation reactions of a variety of substrates and many review articles do exist in this area .[34] These reactions consist mainly of spontaneous ET reactions between $Na_2S_2O_4$ (and other sulfinate derivatives) and fluoroalkyl halides (iodides, bromides and chlorides). The reactions have been widely applied, and the method is quite established in the radical chemistry community.

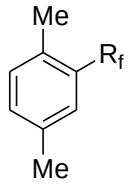
Perfluoroalkyl and polyfluoroalkyl chlorides such as $HCF_2(CF_2)_3Cl$, $HCF_2(CF_2)_5Cl$ and $EtOC(O)CF_2Cl$ react smoothly with electron-rich aromatic compounds with $Na_2S_2O_4$ in DMSO in the presence of $NaHCO_3$ to give fluoroalkylated aromatics in moderate to good yields as shown in Scheme 9.[35] The positions and the electron-donating ability of the substituents have a substantial influence on the structure and yields of the desired products.



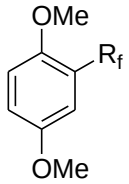
R_f	*o*	*m*	*p*	Yield (%)
$HCF_2(CF_2)_3$	50	35	15	77
$HCF_2(CF_2)_5$	50	40	10	78



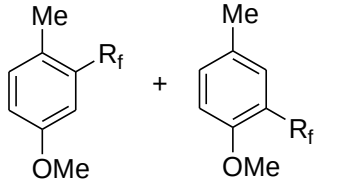
R	*o*	*p*	Yield (%)
NMe_2	21	79	57
Me	40	60	58
OH	70	30	42



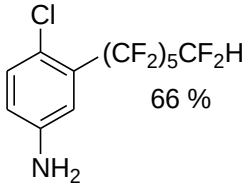
R_f	Yield (%)
$HCF_2(CF_2)_3$	66
$HCF_2(CF_2)_5$	58
$EtOOCCF_2$	45



R_f	Yield (%)
$HCF_2(CF_2)_3$	56
$HCF_2(CF_2)_5$	40

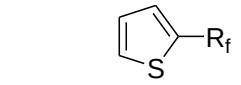


77 % (25:75) $R_f = HCF_2(CF_2)_5$

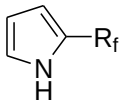


Scheme 9. Perfluoroalkylation of arenes through sulfinatodehalogenation reactions

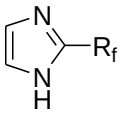
Similarly, treatment of per(poly)fluoroalkyl chlorides with heteroaromatic compounds in the presence of $Na_2S_2O_4$ in DMSO and $NaHCO_3$ as the base afforded the corresponding fluoroalkylated products in moderate to good yields (see Scheme 10).[36]



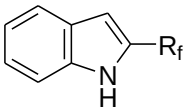
R_f	Yield (%)
$HCF_2(CF_2)_3Cl$	70
$HCF_2(CF_2)_5Cl$	66
$C_8F_{17}Cl$	66



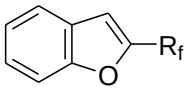
R_f	Yield (%)
$C_6F_{13}Cl$	86
$C_8F_{17}Cl$	84



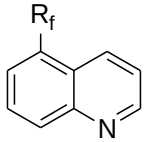
R_f	Yield (%)
$HCF_2(CF_2)_3Cl$	63
$C_6F_{13}Cl$	65
$C_8F_{17}Cl$	67



R_f	Yield (%)
$C_6F_{13}Cl$	71
$C_8F_{17}Cl$	68



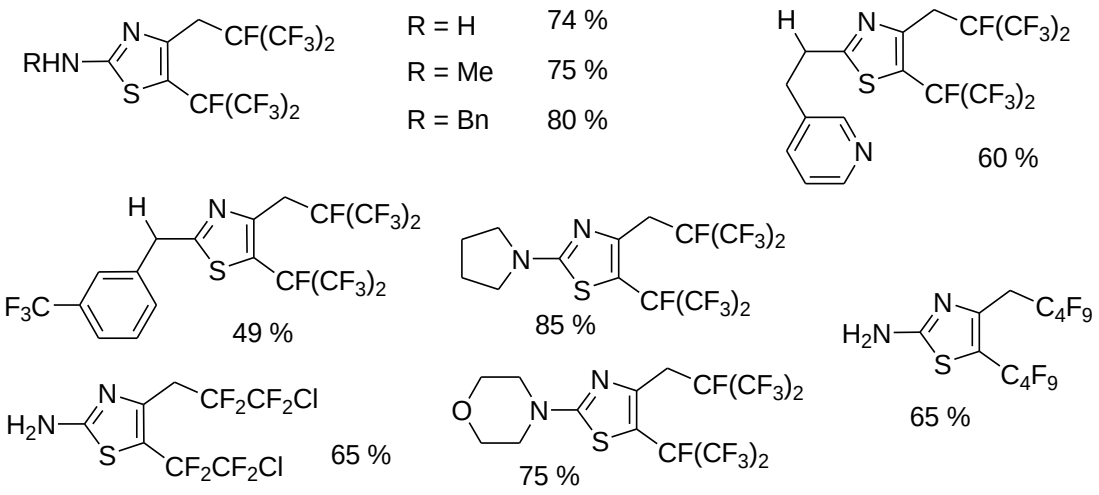
R_f	Yield (%)
$C_6F_{13}Cl$	68
$C_8F_{17}Cl$	65



R_f	Yield (%)
$HCF_2(CF_2)_3Cl$	63
$C_8F_{17}Cl$	55

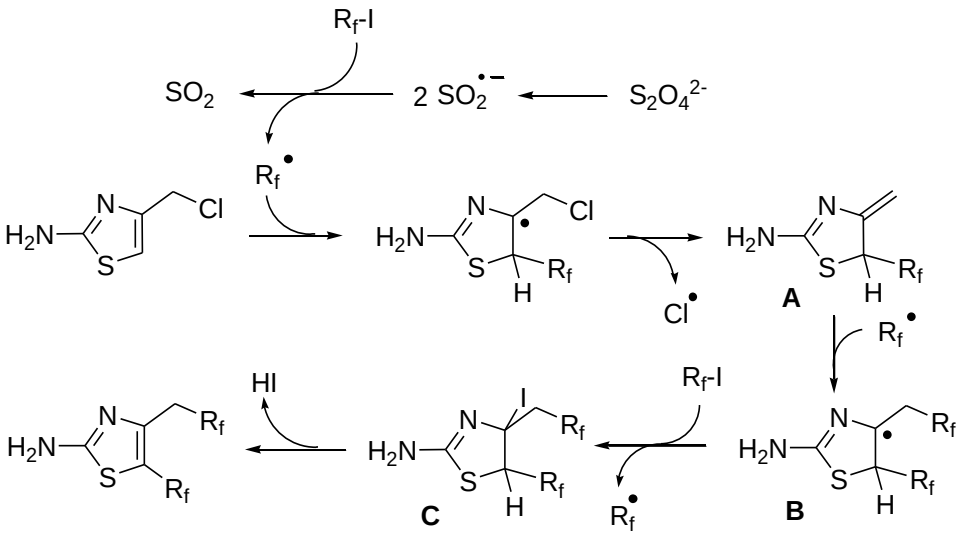
Scheme 10. Perfluoroalkylation of heteroarenes through sulfinatodehalogenation reaction conditions

An efficient and highly selective method for perfluoroalkylation of 2-aminothiazole derivatives with perfluoroalkyl iodides was described by Lu and co-workers.[37] The reaction takes place under very mild conditions by using 3.0 equivalents of $Na_2S_2O_4$ and 4.0 equivalents of $NaHCO_3$ in MeCN/H_2O (4:1) at 5 – 10 °C to afford the polyfluoroalkylated products in good yields as shown in Scheme 11.



Scheme 11. Perfluoroalkylation of 2-aminothiazole derivatives through sulfinatodehalogenation reaction conditions

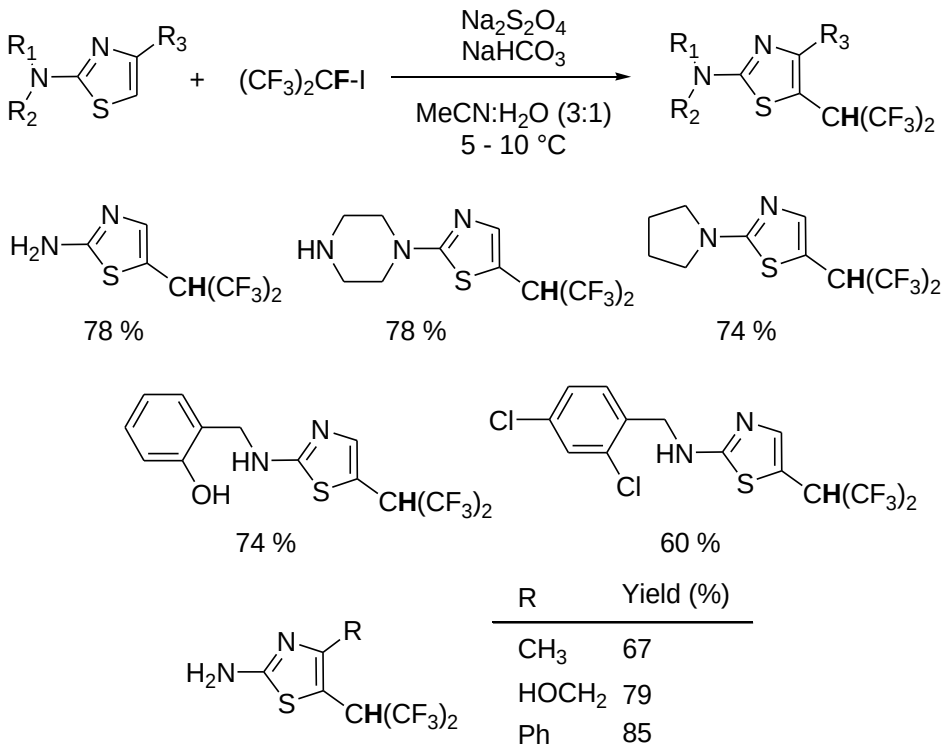
The reaction mechanism of the polyfluoroalkylation of 2-aminothiazole is depicted in Scheme 12. Addition of the perfluoroalkyl radical to 2-amino-4-chloromethylthiazole followed by elimination of chloride radical gives intermediate **A**. Another addition of polyfluoroalkyl radical to intermediate **A** results in intermediate **B** which further reacts with R_fI to give intermediate **C** and regenerate polyfluoroalkyl radical. Elimination of hydrogen iodide under basic conditions affords the desired product. Control experiments showed that the polyfluoroalkylation reaction did not involve a S_N2 type mechanism on the C-Cl bond.



Scheme 12. Proposed mechanism for the perfluoroalkylation of 2-aminothiazole derivatives through sulfinatodehalogenation reaction conditions

Later, the same authors have reported that the reaction of 2-aminothiazole derivatives with C_2F_5I, *n*-C_4F_9I, ClC_4F_8I and $IC_2F_4OC_2F_4SO_2F$ under standard sulfinatodehalogenation reaction conditions ($Na_2S_2O_4$, $NaHCO_3$, MeCN/H_2O (4:1), 5 – 10 °C) proceeded smoothly to render the corresponding 5-polyfluoroalkyl-2-aminothiazoles in good to excellent yields.[38] 4-Aryl-substituted 2-aminothiazoles also react with perfluorobutyl iodides to give the desired products in good yields showing that the substituents chloride, nitro or hydroxyl group on the phenyl ring are compatible under these conditions.

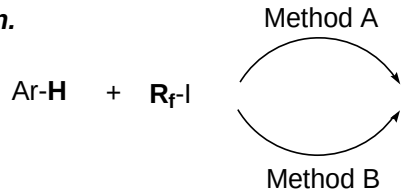
Interestingly, when $(CF_3)_2CFI$ is used under the standard conditions mentioned above, unexpected C – F bond-reduced products instead of the perfluoroalkylated derivatives are isolated. These compounds are obtained in good yields and are shown in Scheme 13.

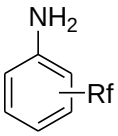


Scheme 13. Fluoroalylation of 2-amino-thiazole employing $(CF_3)_2CFI$

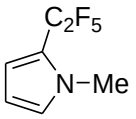
Wakselman and co-workers have reported the perfluoroalkylation of aniline and *N*-methylpirrol with perfluoroakyl iodides induced by sulfur dioxide radical anion precursors.[39] Two alternative methods are proposed, *method A*: Zn°, SO_2, $Na_2S_2O_5$ in DMF at 65 °C; *method B*: $Na_2S_2O_4$, Na_2HPO4 in DMF and H_2O at 80 °C. No selectivity is observed in the perfluoroalkylation of aniline while *N*-methylpirrol was perfluoroalkylated regioselectively in the *2*-position. In both cases, the products are obtained in good yields as shown in Scheme 14.

(a) Product distribution.

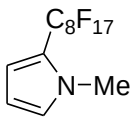




Method	R_f	Yield (%) Regioisomers *ortho*	*para*
B	C_2F_5	21	16
A	C_4F_9	30	30
B	C_8F_{17}	27	27

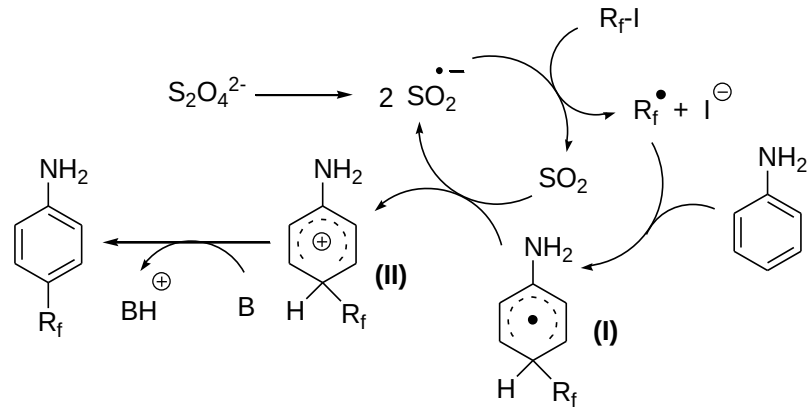


30 %



50 %

(b) Proposed reaction mechanism.

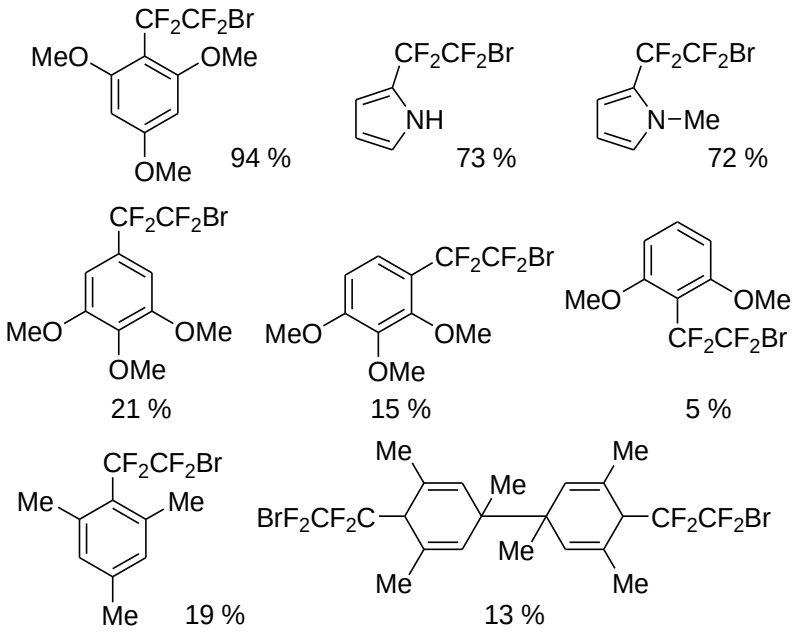


Scheme 14. Perfluoroalkylation of aniline derivatives

This alkylation is interpreted as a radical aromatic substitution. Both methods *A* and *B* provide the SO_2 radical anion that reacts with the perfluoroalkyl iodide through a dissociative single-electron transfer SET affording the perfluoroalkyl radical ($R_f^{\cdot}$). This radical reacts with the (hetero)aromatic compound to render radical intermediate (**I**) which is oxidized by SO_2 radical anion to yield cation intermediate (**II**). The last intermediate reacts with a base ($Na_2S_2O_4$ or $NaHPO_4$) losing a proton and aromatizes to give the perfluoroalkylated products (see Scheme 14).

The perfluoroalkylation reaction of electron-rich (hetero)aromatic compounds with $BrCF_2CF_2Br$ in the $Na_2S_2O_4$, $NaHCO_3$, $MeCN/H_2O$ system proceeds efficiently at room temperature affording the perfluoroalkylated products in moderate to excellent yields (Scheme 15).[40] However,

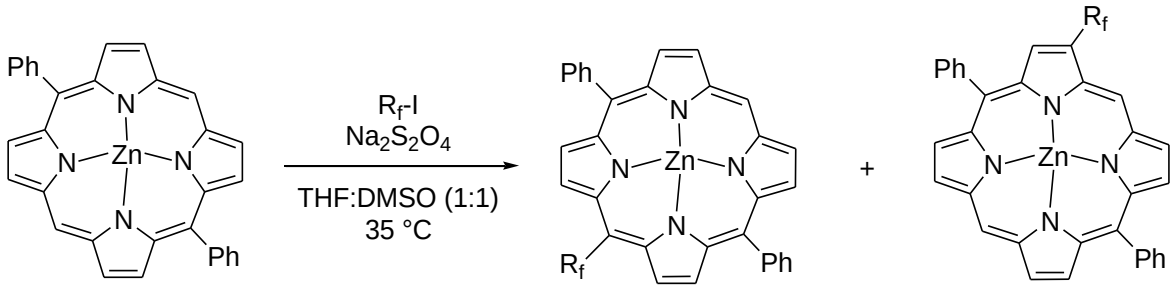
in some cases, no regioselectivity is observed in the product distribution with the exception of pyrrol and *N*-methylpyrrol. The reaction of mesitylene under the same conditions provides a complex mixture from which the perfluoroalkylated product is isolated in 18 % yield together with a dimeric product in 13 %.



Scheme 15. Perfluoroalkylation of electron-rich aromatic compounds

The perfluoroalkykation reaction on porphyrins under sulfinatodehalogenation reaction conditions have been recently reviewed by Xiao and co-workers.[40] For example, treatment of tetra-4-substituted-phenylporphyrins with per(poly)fluoroalkyl iodides in the presence of $Na_2S_2O_4$ and $NaHCO_3$ in a mixture of DMSO and CH_2Cl_2 at room temperature gives the corresponding β-per(poly)fluoroalkyl porphyrin derivatives in low yields.[41] Also, reaction of porphyrins with $X(CF_2)_nI$ (n = 2 – 5; X = Cl or I) under the above experimental conditions promotes the intramolecular cyclization at the *ortho*-position of a neighbouring phenyl moiety as well as an

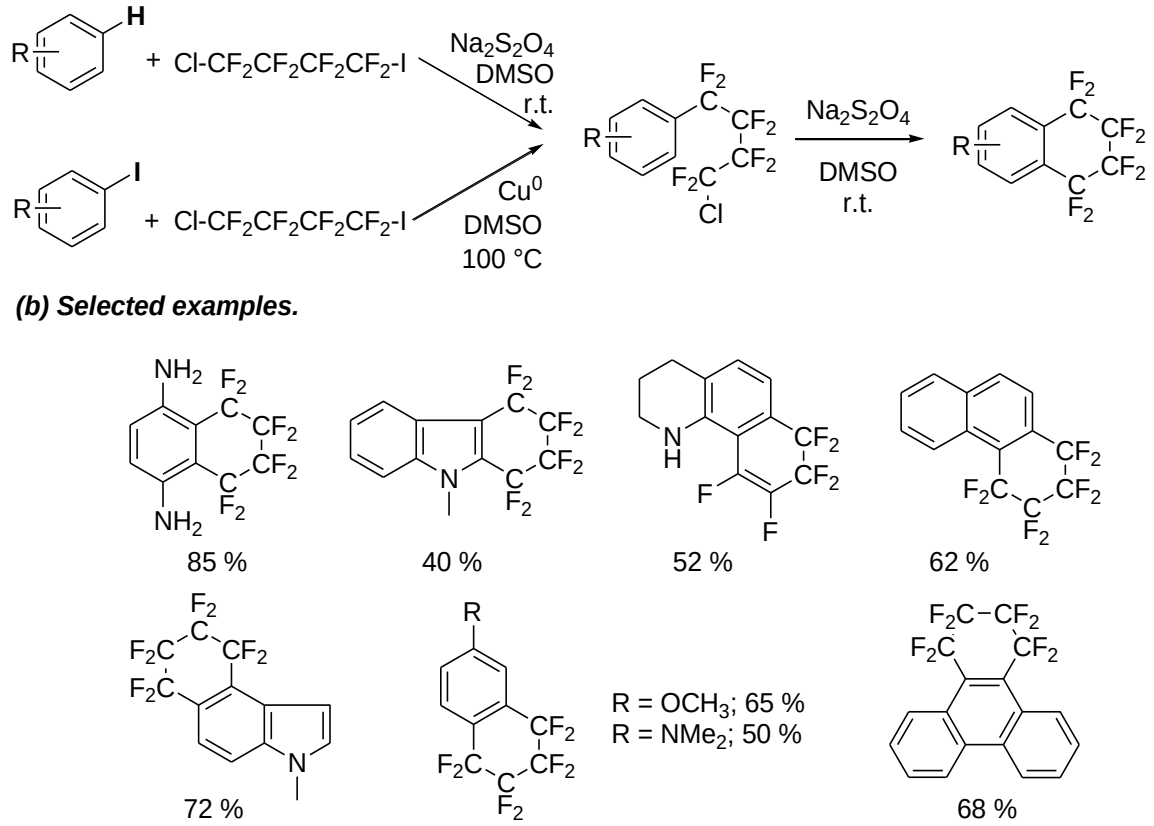
adjacent pyrrolic unit to form five, six, seven- or eight-membered fluorinated porphyrins.[42] Using this method, for zincated 1,15-diphenylporphyrin, both *meso*- and β-fluoroalkylated are obtained in moderate yields as shown in Scheme 16.[43] Also, the free-metal porphyrins react with perfluoroalkyl iodides giving the desired products in moderate yield.



R_f	Yields (%)	
ClC_2F_4	40	10
ClC_4F_8	30	10
C_6F_{13}	40	5
$FSO_2C_2F_4OC_2F_4$	45	9

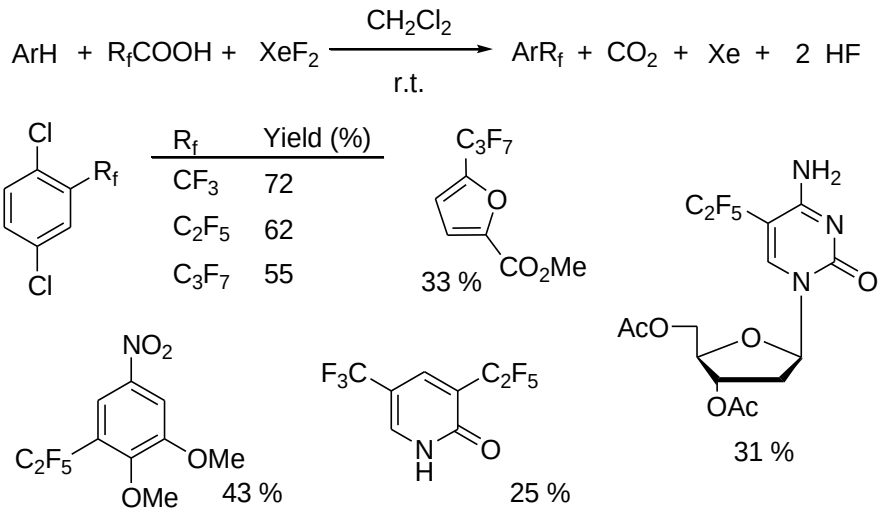
Scheme 16. Perfluoroalkylation of zincated 1,15-diphenylporphyrin

Chen and co-workers have reported an interesting intramolecular perfluoroalkylation reaction of chloroperfluoroalkylarenes with $Na_2S_2O_4$ in DMSO at room temperature in moderate to good yields.[44] The substrates for the intramolecular cyclization reaction are synthetized using two different methodologies: (i) reaction of arenes with 1-chloro-4-iodooctafluorobutane in the presence of $Na_2S_2O_4$ in DMSO and, (ii) copper-catalyzed cross-coupling reaction of aryl iodides with 1-chloro-4-iodooctafluorobutane and, in all cases, the substrates were obtained in good yields (Scheme 17). The intramolecular radical cyclizations are carried out under sulfinatodehalogenation conditions by using $Na_2S_2O_4$ in DMSO at room temperature and the perfluoroalkyl cyclic products are obtained in high yields as sole products with complete conversion of the starting material (Scheme 17).



Scheme 17. Intramolecular perfluoroalkylation reaction of chloroperfluoroalkylarenes

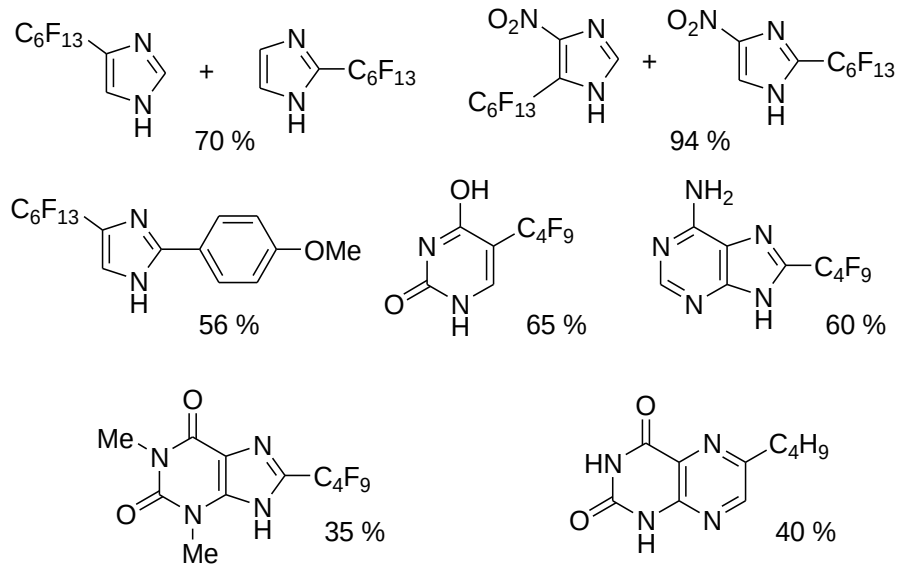
Matsuo and co-workers have reported the direct perfluoroalkylation including the trifluoromethylation of (hetero)arenes with perfluoro carboxylic acids in the presence of xenon difluoride.[45] The perfluoroalkylation reaction proceeds efficiently with electron-poor aromatics and the corresponding perfluoroalkyl (hetero)arenes are obtained in good yields. Unfortunately, when electron-rich arenes are employed as substrates, fluorination predominates over the perfluoroalkylation. The general reaction and some selected examples are depicted in Scheme 18.



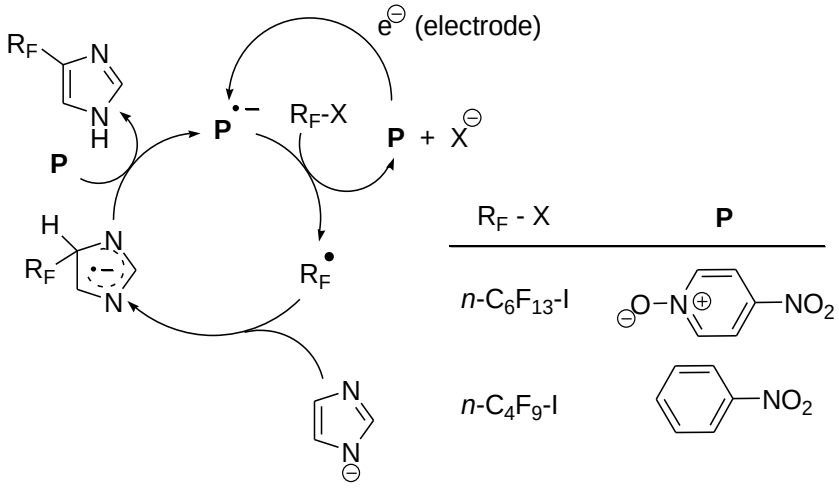
Scheme 18. Perfluoroalkylation of arenes employing XeF_2

Saveant and co-workers have reported the indirect electrochemical reduction, by means of an aromatic anion mediator, of perfluoroalkyl halides in the presence of imidazole, substituted imidazole, purine and pyrimidine anions affording the corresponding C-perfluoroalkylated nitrogen bases by an $S_{RN}1$ mechanism.[46] The redox catalyst mediators used in these experiments are nitrobenzene, terephthalonitrile and 4-nitropyridine-*N*-oxide, depending on the perfluoroalkyl iodide used. Preparative-scale electrolysis of the perfluoroalkylated imidazole, purine and pyrimidine derivatives under the redox catalysis are obtained in moderate to good yields and selected examples are shown in Scheme 19. Also, the same scheme depicts the proposed reaction mechanism where the nucleophiles are the heterocyclic anions.

(a) Selected examples.



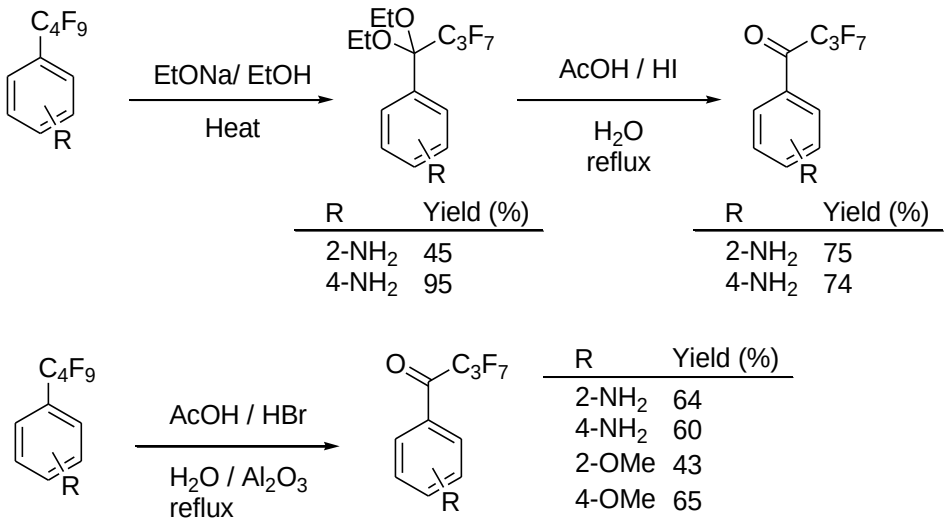
(b) Proposed reaction mechanism.



Scheme 19. Perfluoroalkylation of imidazoles, substituted imidazoles, purines and pyrimidines derivatives

The synthesis of perfluoroalkyl ketones have been studied by Strekowski and co-workers .[47] Direct hydrolysis of *ortho*- and *para*-perfluoroalkyl anilines and anisoles with the system AcOH / HBr / H_2O / Al_2O_3 under reflux affords the desired perfluoroalkyl-substituted aryl ketones in good yields in a one-pot fashion (Scheme 20). Although, *ortho*- and *para*-perfluoroacyl anilines can be

prepared following a two-step methodology by reacting the corresponding perfluoroalkyl anilines with sodium ethoxide followed by hydrolysis of the resultant diethyl acetals with hydroiodic acid.

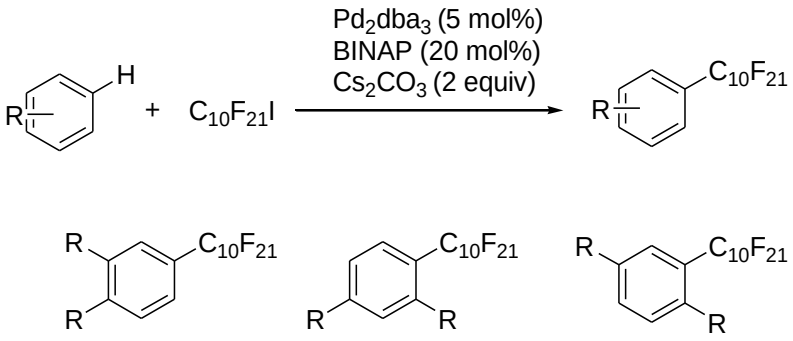


Scheme 20. Synthesis of perfluoroalkyl ketones

1.2.-Transition metal-catalyzed or -activated thermal perfluoroalkylation of arenes

There exist important recent review articles on the metal-catalyzed thermal trifluoromethylation reactions of arenes.[48] However, fewer reports can be found on the metal-catalyzed perfluoroalkylation reactions of (hetero)arenes. In this respect, special mention should be given to copper[49], silver[50], and nickel[51] catalysis of perfluoroalkylation reactions of arenes.

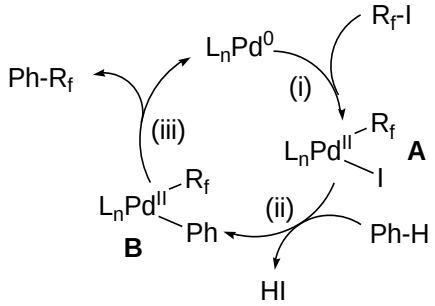
Sanford and collaborators[52] have accomplished the Pd-catalyzed perfluoroalkylation of arenes, employing Pd_2dba_3, BINAP, in the presence of Cs_2CO_3 as base. The scope of the transformation is depicted in Scheme 21.



R			
	Yield (%)		
OMe	76	99	84
Me	79	77	52

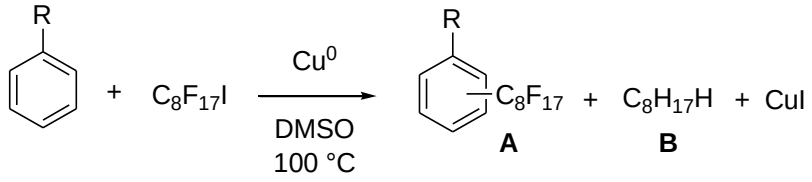
Scheme 21. Scope of the Pd-catalyzed perfluoroalkylation of arenes

The authors[52] propose one potential mechanism for these reactions, similar to that proposed by Fagnou[53] for Pd-catalyzed C-H arylation with aryl iodides. This mechanism would involve: (i) oxidative addition of R_FI to Pd^0 to generate Pd(II) intermediate **A** (Scheme 22), (ii) arene activation at **A** to form the diorgano Pd^{II} species **B**, and (iii) C-C bond-forming reductive elimination to release the product and regenerate the Pd^0 catalyst (Scheme 22). Notably, each step of this catalytic cycle has precedent in the literature for related systems; however, step (iii) is known to be challenging at most phosphine $Pd^{II}(Aryl)(CF_3)$ intermediates.[53]

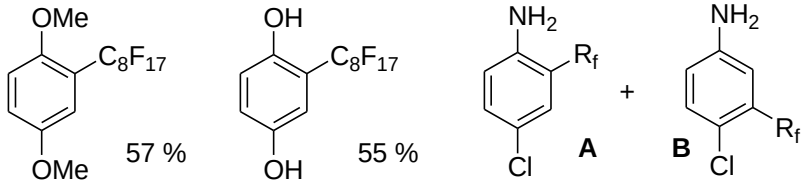


Scheme 22. Potential mechanism for the Pd-catalyzed C-H arylation with perfluoroalkyl iodides

The perfluoroalkylation of various electron-rich and electron-withdrawing substituted benzenes with perfluorooctyl iodide has been reported by Ojima and co-workers.[54] The reaction proceeds readily in the presence of copper bronze in DMSO at 100 °C to afford a mixture of *ortho*, *meta*- and *para*-perfluorooctylarenes and 1-*H*-perfluorooctane in moderate yields as shown in Scheme 23.



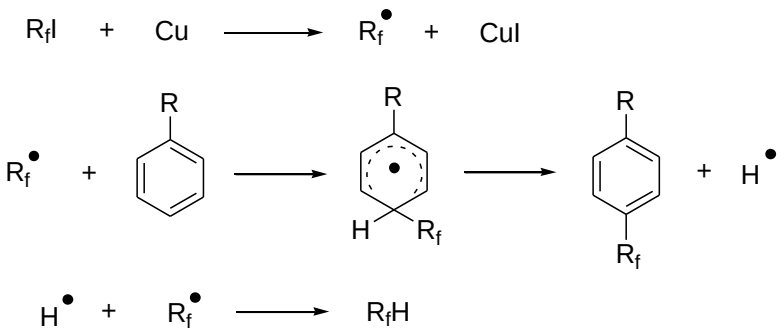
	A	B
R	Yield (%) (*o:m:p*)	Yield (%)
NHCOMe	58 (*12:16:72*)	49
NH_2	58 (*12:16:72*)	44
NMe_2	38 (*39:0:61*)	54
$OCH_2C(O)OMe$	40 (*40:20:40*)	18
OH	38 (*48:0:52*)	19
COOEt	37 (*29:0:71*)	29



R_f-X	Yield (%) (**A**:**B**)
$C_8F_{17}I$	55 (90:10)
$C_8F_{17}Br$	50 (73:23)
C_3F_7I	45 (100:0)

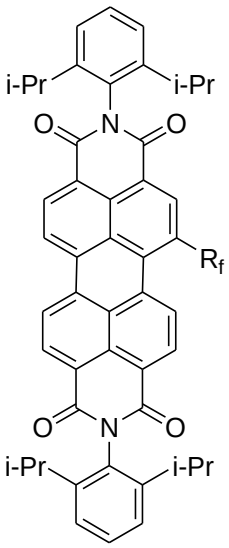
Scheme 23. Cu-mediated perfluoroalkylation of arenes

A possible reaction mechanism is proposed based on the experimental results and can be depicted in Scheme 24.

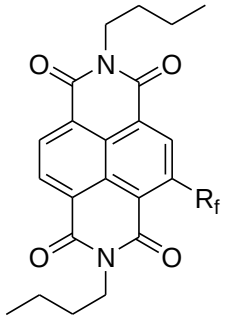


Scheme 24. Proposed mechanism for the perfluoroalkylation of arenes

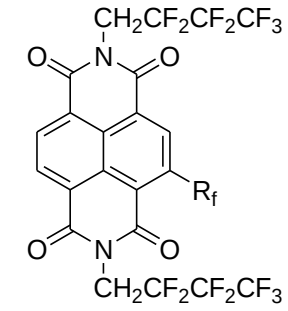
Direct functionalization of electron-withdrawing and electron-rich polycyclic arenes via copper-mediated radical perfluoroalkylation has been achieved in high yields.[55] The reaction takes place in DMSO at 120 °C in the presence of perfluoroalkyl iodides and the product distribution shows a significant regioselectivity, as is depicted in Scheme 25. The authors suggest that the reaction mechanism involved is a homolytic aromatic substitution. The addition of TEMPO to the reaction, a known radical trapping, inhibits the perfluoroalkylation of the polycyclic arenes.



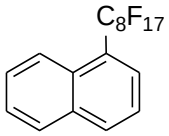
	C_nF_{2n+1}	Yield (%)
a	n = 4	57
b	n = 8	60



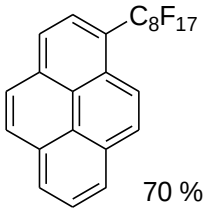
	C_nF_{2n+1}	Yield (%)
a	n = 4	60
b	n = 6	57
b	n = 8	70



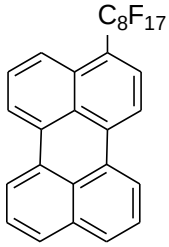
	C_nF_{2n+1}	Yield (%)
a	n = 4	65



75 %



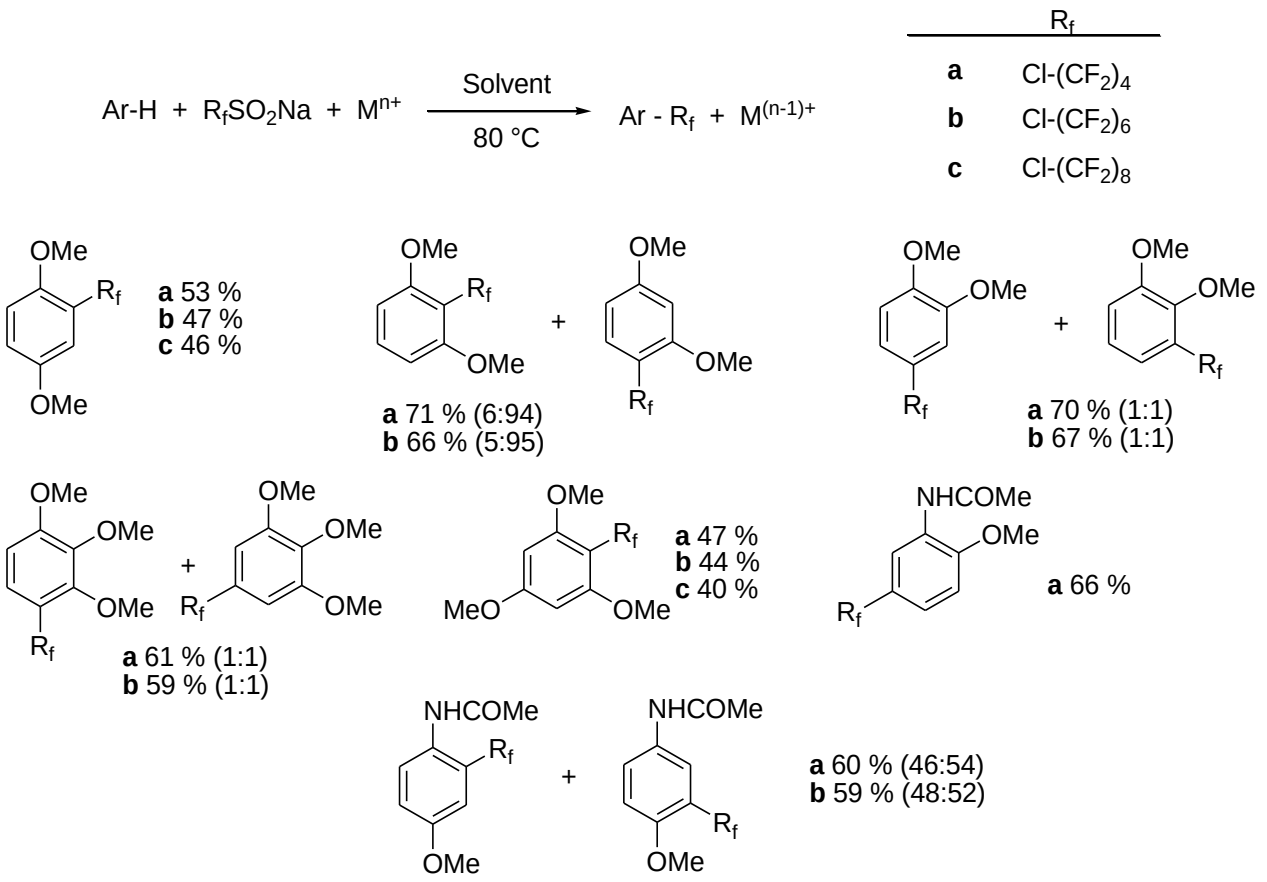
70 %



65 %

Scheme 25. Perfluoroalkylation of polycyclic arenes

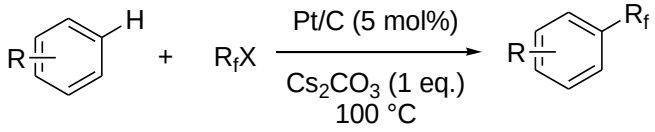
Huang and co-workers have reported the perfluoroalkylation of electron-rich arenes using sodium perfluorosulfinates with single electron oxidizing agents, such as $Mn(OAc)_3.2H_2O$ and $Ce(SO_4)_2$, at 80 °C in MeCN/AcOH/H_2O (5:1:5) solvent mixture.[56] The reaction provides a mixture of *ortho*- and *para*-substituted arenes in moderate to good yields as is depicted in Scheme 26.



Scheme 26. Mn-mediated perfluoroalkylation reaction of electron-rich arenes

Beller and co-workers have very recently developed a simple protocol for the direct C – H perfluoroalkylation of (hetero)arenes with R_fI and R_fBr using a robust supported platinum catalyst as depicted in Scheme 27.[57] The reaction provides perfluoroalkyl-substituted aromatic compounds in good to excellent yields and a noticeable tolerance of a wide range of functionality is observed. Mechanistic insight of the heterogeneous perfluoroalkylation reaction was also carried out in the presence of radical scavengers and it was observed that the reactions are completely halted and radical intermediates are involved. Furthermore, *in situ* EPR measurements of the reaction confirms the participation of such organic radicals. Kinetic isotope effects indicate that the latter C-H bond cleavage is fast while the radical-forming step is the key factor for the desired perfluoroalkylation (see Scheme 27(b)).

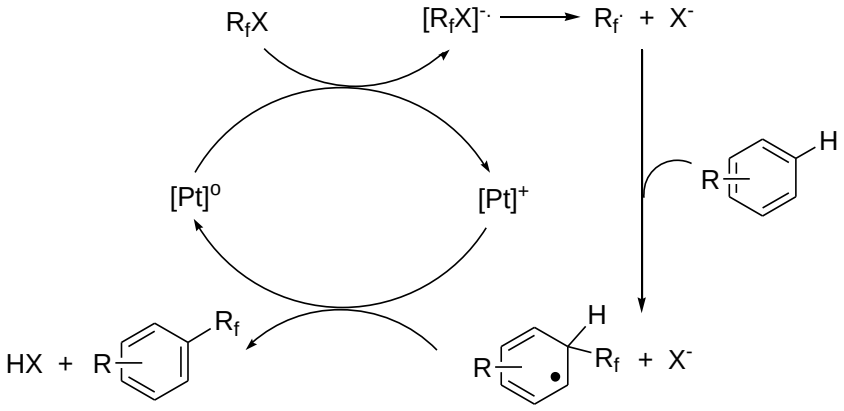
(a) Perfluoroalkylation reaction of (hetero)arenes.



R = H; OMe; F; Br; Cl; Me.

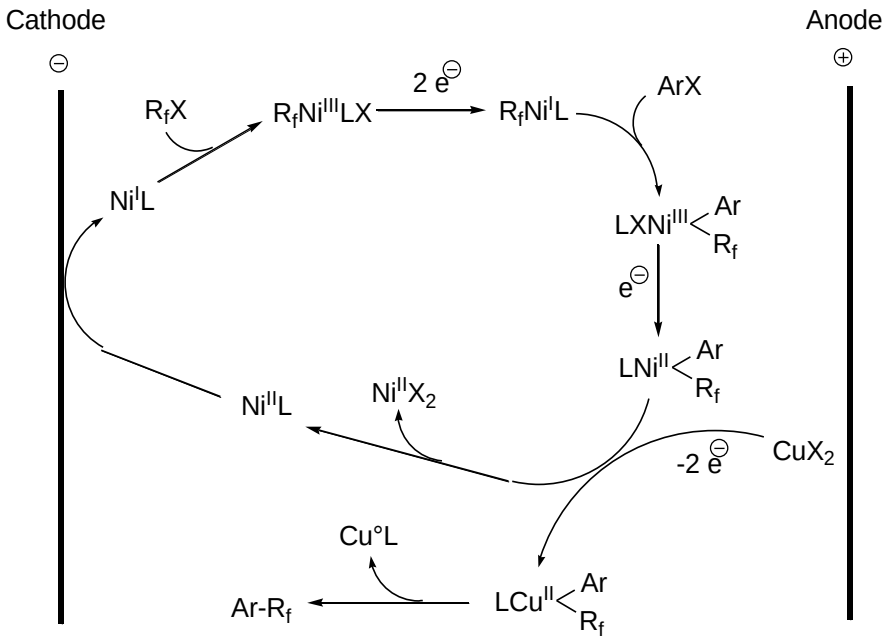
R_fX: $C_{10}F_{21}I$; $C_8F_{17}I$; C_4F_9I; $C_8F_{17}Br$; $C_6F_{13}Br$; CF_3Br.

(b) Proposed reaction mechanism.



Scheme 27. Pt-catalyzed perfluoroalkylation of arenes

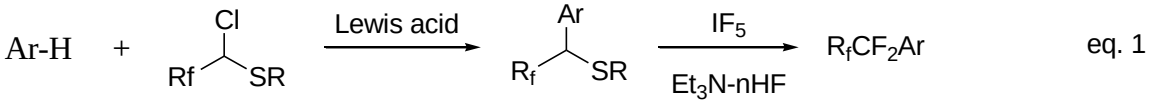
The aromatic perfluoroalkylation with metal complexes have been developed under electrocatalytic conditions by Budnikova and co-workers.[58] Cross-coupling is successful with bromo- and iodobenzene and perfluoroalkyl iodides in the presence of nickel and cobalt complexes (M^IL, L = 2,2'-bipyridine or 4,4'-di-*tert*-butylpyridine) and copper anode. The cross-coupling products are formed in good yields. A key role of transmetalation during the catalytic cycle from R_fMLX to R_fCuLX allows the latter copper complex to react with iodobenzene under conditions of electroreduction providing the desired cross-coupling products. The catalytic cycle of the cross-coupling reaction is depicted in Scheme 28.



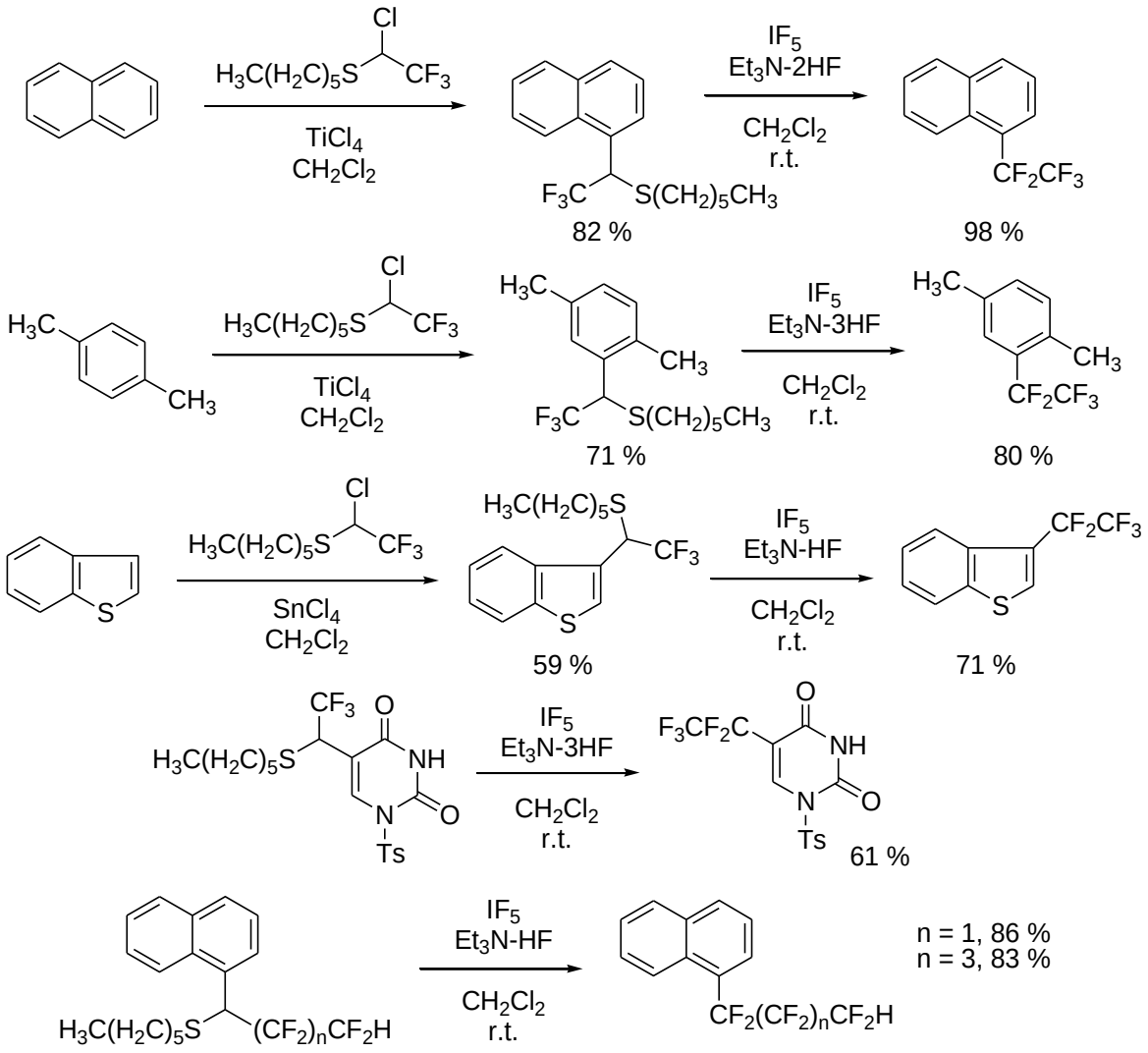
Scheme 28. Perfluoroalkylation with metal complexes under electrocatalytic conditions

Recently, J. F. Soulé and H. Doucet have reported an interesting review dealing with the functionalization of C – H bonds via Pd- or Ru-catalyzed desulfitative coupling of (hetero)aromatic compounds using CF_3SO_2Na as the coupling partner[59], although no perfluoroalkylation was attempted with this desulfitative methodology.

Hara and co-workers have reported an interesting methodology to introduce perfluoroethyl, hexafluoropropyl, and decafluoropropenyl groups to various aromatic compounds by a Friedel-Crafts reaction and subsequent desulfurizing-difluorination of the resulting product.[60] The first step requires the use of Lewis acids such as $TiCl_4$ or $SnCl_4$ while the second step is carried out with IF_5 in the presence of Et_3N and HF in CH_2Cl_2 as described in eq. 1.



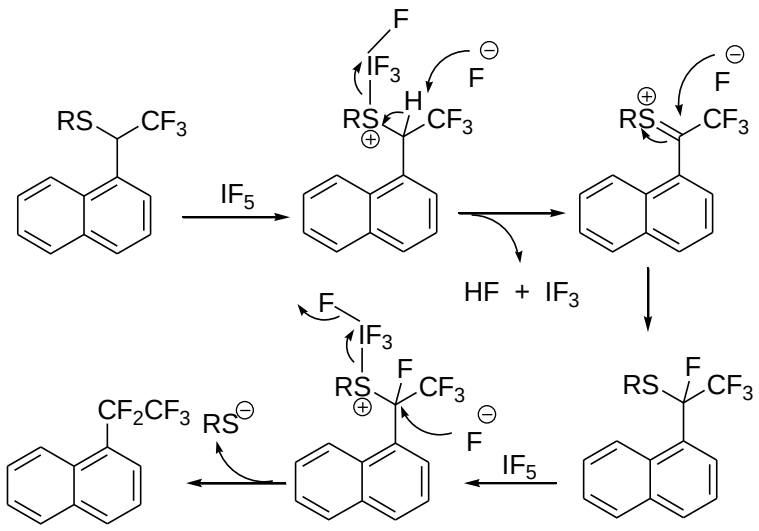
eq. 1



Scheme 29. Lewis acid-mediated perfluoroalkylation of (hetero)arenes in the presence of IF_5

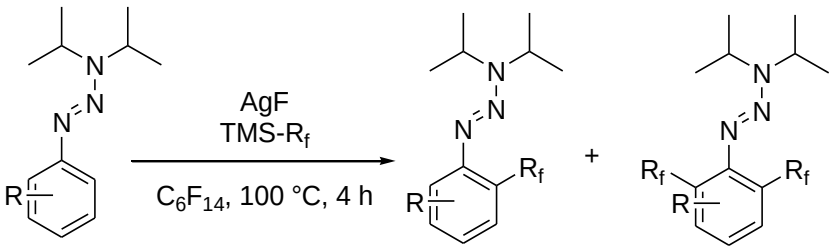
Scheme 29 depicts selected examples that illustrate the perfluoroalkylation reaction.

The hexylsulfanyl derivatives react with IF_5 through a fluoro-Pummerer rearrangement to provide the perfluoroalkyl derivative as shown in Scheme 30.



Scheme 30. Perfluoroalkylation of arenes

Bräse and co-workers have recently reported a robust method for perfluoroalkylation and ethoxycarbonyldifluoromethylation of functionalized aromatic triazenes.[61] Using AgF and different fluorinated trimethylsilyl-substituted species under solvent-free (neat) conditions, provides the preparation of various *ortho*-fluorinated triazenes in good yields and regioselectivity via C-H substitution processes (Scheme 31). Further transformations on the triazene moiety make these reactions interesting for the synthesis of fluorinated building blocks.



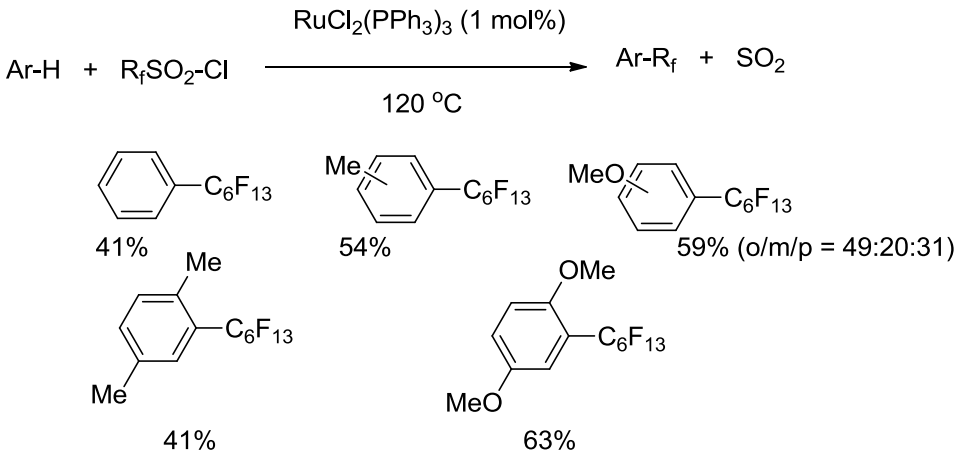
R_f	R	Yield (%)	
C_2F_5	4-I	62	17
	4-Br	53	10
	4-Cl	42	12
	4-F	64	traces
	4-COOEt	45	11
	2-Me	69	
	2-CN	69	
	2-I	43	
C_3F_7	4-I	50	19
	4-Br	54	13
	4-Cl	62	8
	4-F	49	7
	4-COOEt	43	18
	2-Me	70	
	2-CN	70	
	2-I	41	
CF_2COOEt	4-I	8	28
	4-Br	36	32
	4-Cl	24	29
	4-F	26	36
	4-COOEt	20	28
	2-CN	18	13

Scheme 31. Perfluoroalkylation of aromatic triazines

A series of (hetero)arenes are perfluoroalkylated in good yields when the coupling partners are CF_3SO_2Cl or $C_6F_{17}SO_2Cl$ under $RuCl_2(PPh_3)_2$ catalysis (*vide infra*).

With respect to ruthenium(II) catalysis[5], Kamigata and coworkers pioneered the use of readily available perfluoroalkylsulfonyl chlorides in a direct desulfitative cross-coupling reaction through a C−H bond activation of simples arenes for fluorinated molecule synthesis (Scheme 32) .[3]

$RuCl_2(PPh_3)_3$ catalyst promotes the perfluoroalkylation of simples arenes with trifluoromethanesulfonyl chloride or tridecafluorohexane-1- sulfonyl chloride. It is important to note that the reaction proceeds smoothly for such aromatic compounds possessing electron-donating groups, like toluene, anisole, *p*-xylene, 1,4-dimethoxybenzene, whereas chlorobenzene, bromobenzene, and ethyl terephthalate proved to be unsuitable substrates for this reaction.

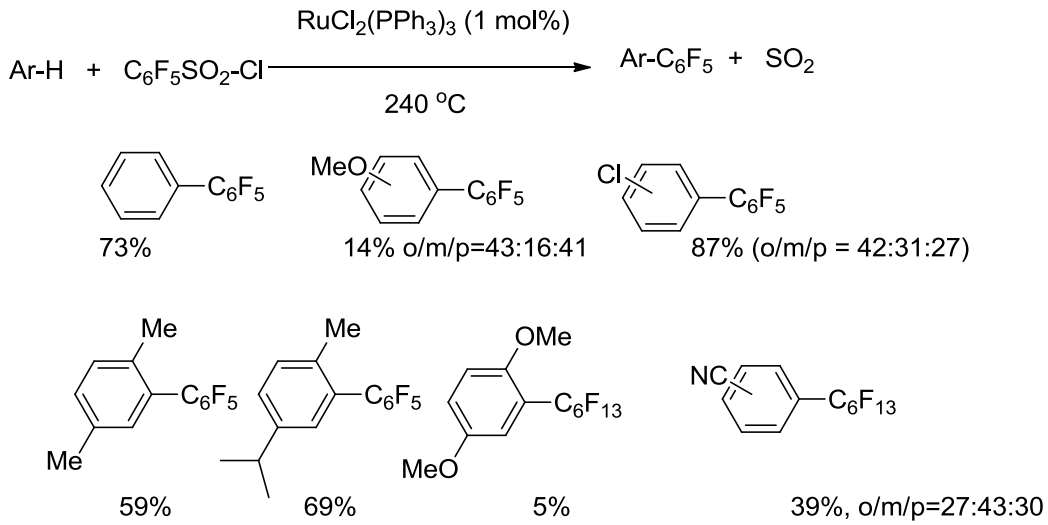


Scheme 32. Ru-catalyzed perfluorobutylation of arenes

Kamigata and co-workers extended the scope of the above-mentioned reaction using pentafluorobenzenesulfonyl chloride as the coupling partner. The corresponding products were obtained in moderate to good yields but the protocol suffers from harsh reaction conditions (*i.e.*, 240 °C)[62] (Scheme 33).[4] In contrast to the perfluoroalkylsulfonyl chlorides, which react preferentially with electron-rich arenes (Scheme 32), pentafluorobenzenesulfonyl chloride allows the formation of desired biaryls in good yields with electron-deficient arenes. The reaction proceeds in solvent-free conditions, but at a very high temperature (*i.e.*, 240 °C).

The proposed mechanism involves a redox-transfer reaction between pentafluorobenzenesulfonyl chloride and the Ru(II) catalyst to afford the radical anion **A**, which could be cleaved homolytically to give the pentafluorobenzenesulfonyl radical **B** and Ru(III)−Cl

(Figure 2). The pentafluorophenyl radical **C**, formed from the radical **B** by extrusion of sulfur dioxide, adds to the aromatic nucleus to give the cyclohexadienyl radical **D**.



Scheme 33. Scope of the Ru-catalyzed perfluoroarylation of arenes

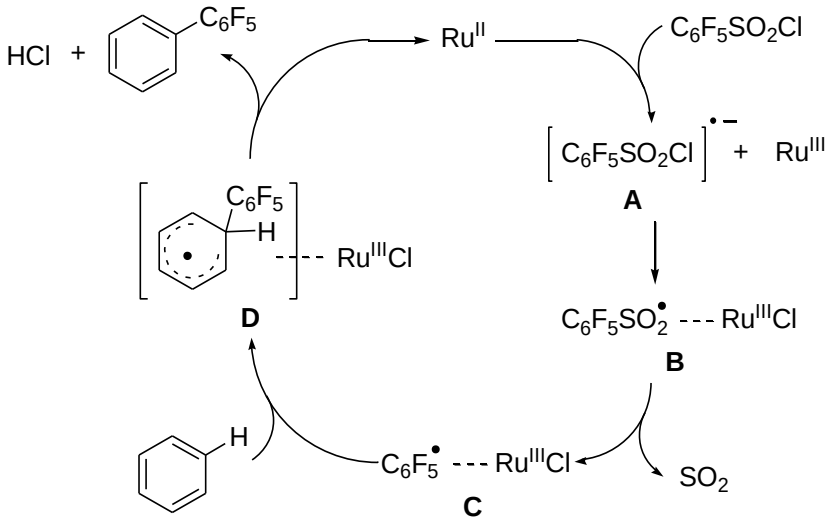


Figure 2. Proposed mechanism for the Ru-catalyzed perfluoroarylation of arenes

The subsequent hydrogen atom abstraction by a Ru(III)−Cl species from the radical **D** affords the desired arylated product and hydrogen chloride, and the ruthenium(II) catalyst is

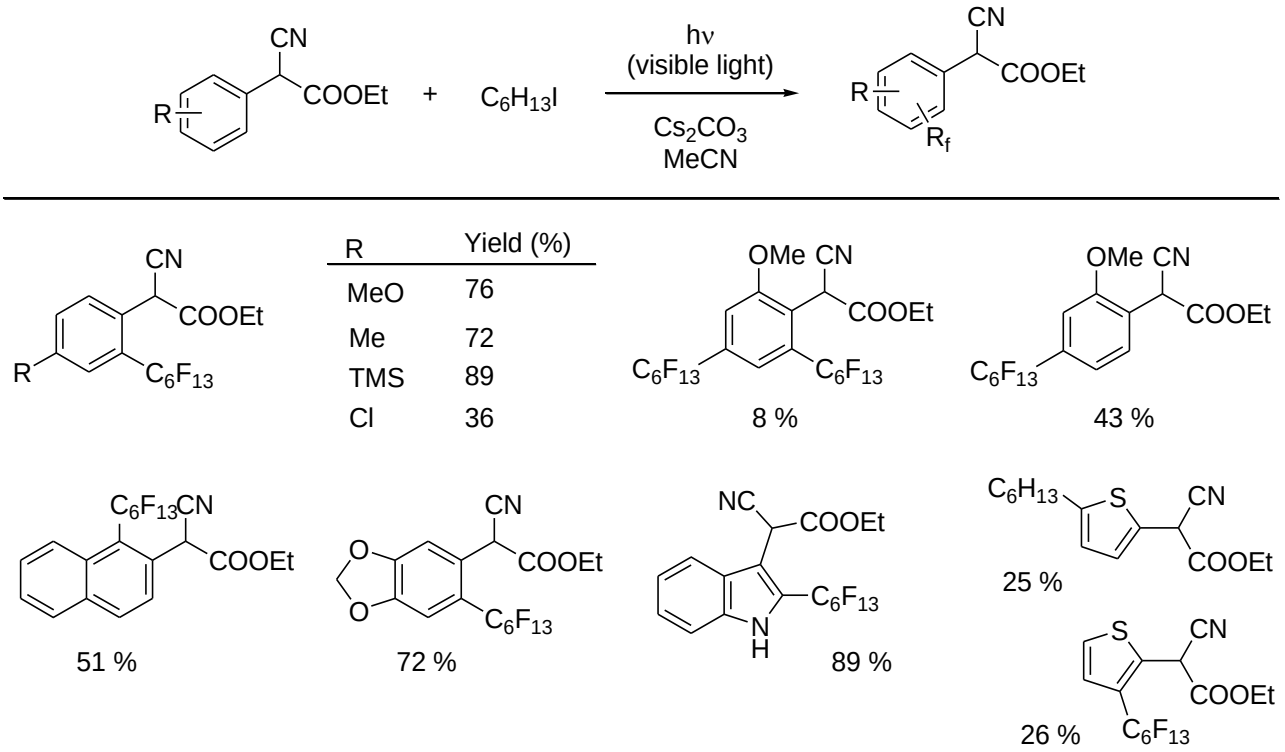
regenerated. The radicals **B**, **C**, and **D** are considered to be confined in the coordination sphere of the ruthenium complex.

2.-Photoinduced methods for perfluoroalkylation of arenes

2.1.-Transition metal-free photoorganocatalyzed perfluoroalkylation reaction of arenes

Nakamura and colleagues[63] have introduced a photoinduced method to generate R_f radicals from short-wavelength photolysis (185 nm) of perfluoroazooctane and make them react with arenes yielding perfluorooctyl-substituted arenes in reasonable good yields.

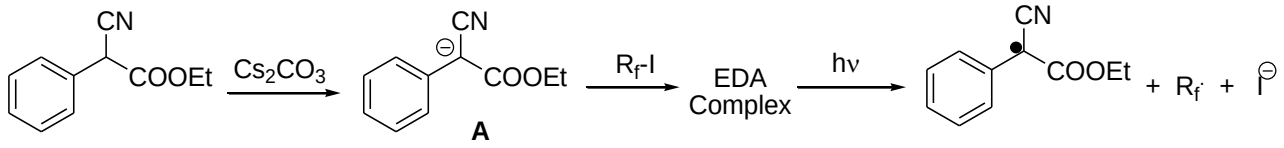
A metal-free photochemical perfluoroalkylation reaction of α-cyanoarylacetates has been developed by Melchiorre and co-workers.[64] The reaction occurs at ambient temperature, under visible-light irradiation and is driven by the photochemical activity of electron donor-acceptor (EDA) complexes. These EDA complexes are formed *in situ* by the interaction of transiently generated enolates, which is formed due to the presence of a base, and perfluoroalkyl iodides. *Para*-substituted arylacetates are selectively perfluoroalkylated at the *ortho* position in high chemical yields while *ortho*- or *meta*-substitution patterns result in perfluoroalkylation with moderate regioselectively. However, the *para* isomers are formed preferentially. The reaction also occurs with heteroaryl moieties. Several examples are shown in Scheme 34. In general, electron-withdrawing substituents attached to the aryl moiety reduced the efficiency of the photochemical reaction.



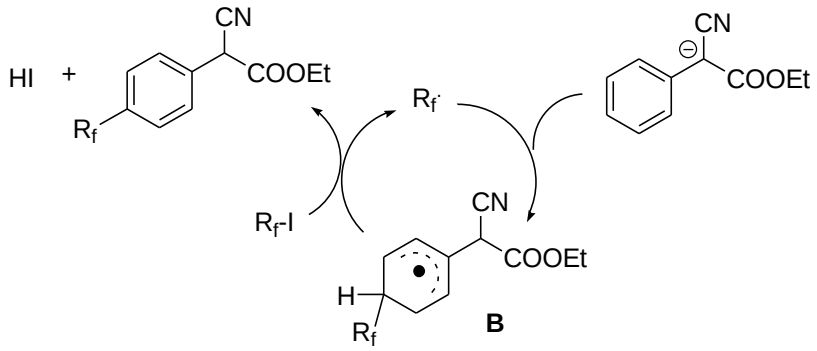
Scheme 34. Photoinduced perfluorobutylation of arenes

The reaction mechanism of the photochemical reaction is depicted in Scheme 35.

(a) Initiation via EDA Complex.



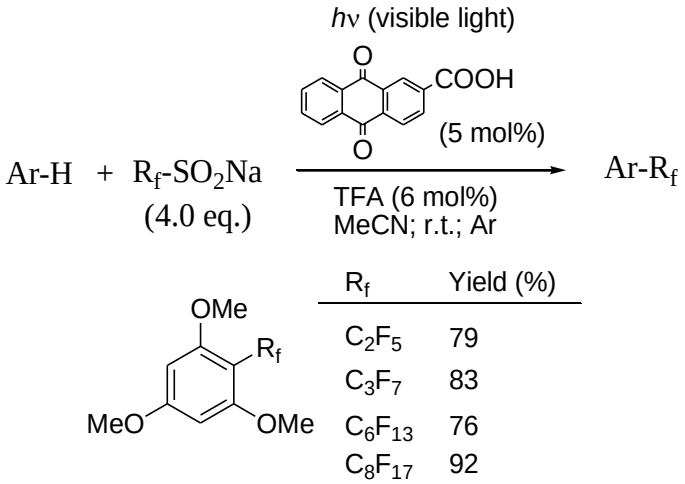
(b) Propagation pathway.



Scheme 35. Reaction mechanism of the photochemical perfluorobutylation of α-cyanoarylacetates

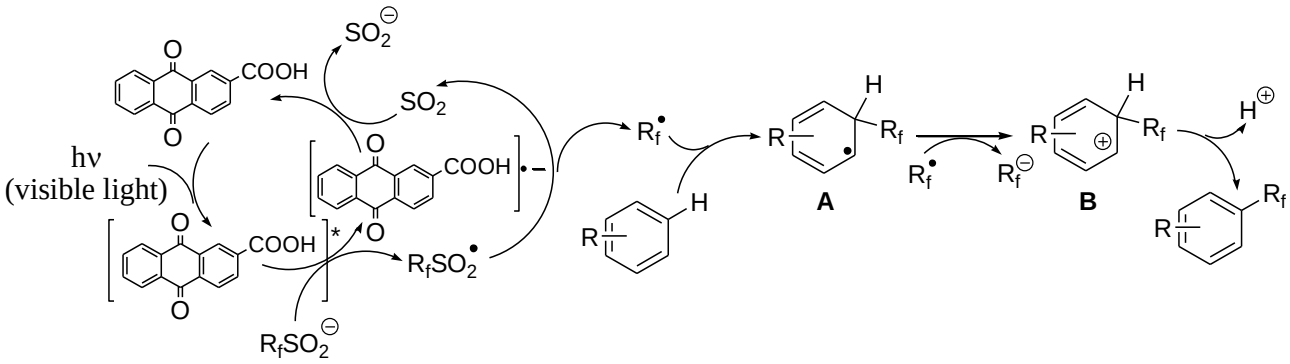
A quantum yield of 3.8 measured at 400 nm suggests a radical chain mechanism as the main reaction pathway. Excitation of the EDA complex with visible-light provides the perfluoroalkyl radical ($R_f^{\cdot}$) that reacts with the enolate **A** to give cyclohexenyl radical **B**. The last step of the propagation pathway involves a single electron transfer to perfluoroalkyliodide follow by deprotonation to give the desired products.

Itoh and co-workers have reported an interesting photoinduced C – H perfluoroalkylation of (hetero)arenes using sodium perfluoroalkylsulfinates as the $R_f^{\cdot}$ source and anthraquinone-2-carboxylic acid as the catalytic photosensitizer (Scheme 36).[65] This metal-free photo redox reaction proceeds under visible light irradiation and in the presence of TFA. However, it is still uncertain why TFA accelerates the reaction rate. Electron-rich arenes give the corresponding products in good yields and some substituted heteroarenes are also obtained in good yields while electron-poor arenes, e.g. nitrobenzene, do not react at all.



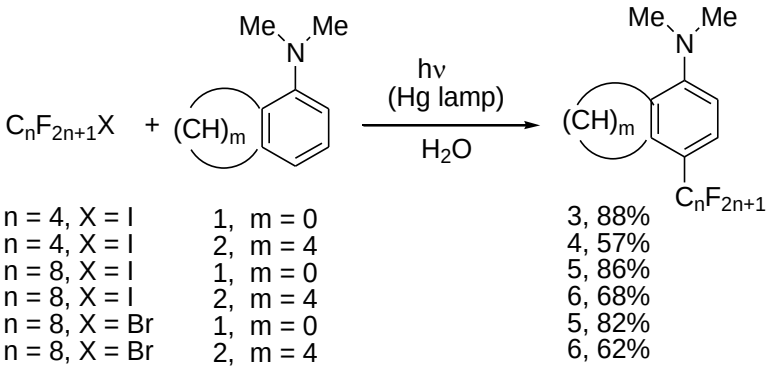
Scheme 36. Photoredox-organocatalyzed perfluoroalkylation of arenes

A plausible reaction mechanism of the perfluoroalkylation of (hetero)arenes is depicted in Scheme 37. The photoredox cycle provides the perfluoroalkyl radical that reacts efficiently with the (hetero)arenes to give intermediate **A**. Oxidation of intermediate **A** to cation **B** through an electron transfer by R_f radical followed by deprotonation to give the corresponding perfluoroalkylarene. However, the authors state that the latter reaction may be considered as a hydrogen abstraction of intermediate **B** by R_f radical and this dichotomy could not be ruled out by the authors.



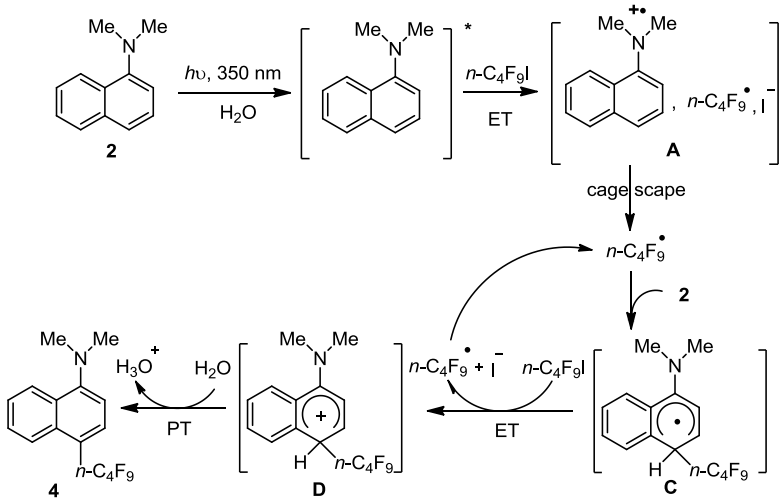
Scheme 37. Photoredox cyclo for the anthraquinone-2-carboxylic acid-catalyzed perfluoroalkylation of arenes

Postigo and collaborators have accomplished the HAS reaction of *N*,*N*-dialkyl aryl amines with perfluoroalkyl moieties through a Photoinduced Electron Transfer (PET) reaction.[66] The photoinduced electron transfer (PET) substitution reaction of electron rich aromatic nuclei with perfluoroalkyl R_f groups is carried out *in water* or aqueous mixtures to afford the substitution products resulting from replacement of aromatic H´s with the R_f moiety in good yields (57-88%). A radical mechanism superimposed with a redox process is proposed to account for product formation. The scope of the reaction is depicted in Scheme 38.[66]



Scheme 38. Scope of the PET perfluoroalkylation of *N*,*N*-disubstituted aromatic amines

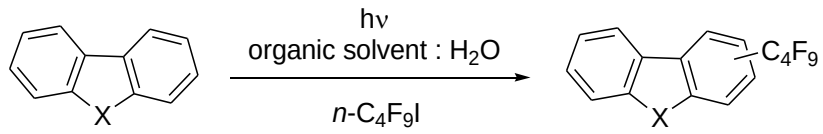
Evidence for the radical cation species (as an initiation event) generated from electron-rich arenes in the presence of perfluoroalkyl halides is provided by the UV-*vis* transient spectra obtained by Nanosecond Laser Flash Photolysis techniques.[66] The mechanism of the reaction is illustrated in Scheme 39.



Scheme 39. Proposed mechanism for the PET perfluoroalkylation of *N*,*N*-disubstituted aromatic amines

The authors[66] postulate a photoinduced electron transfer (PET) mechanism, where upon light absorption by substrates **1** or **2**, the corresponding cation ($1^{+\bullet}$ or $2^{+\bullet}$) together with *n*-$C_4F_9^{\bullet}$ and iodide anion, are formed in the solvent cage by an ET process (Scheme 39, for substrate **2**). This constitutes the initiation step. Upon cage-scape of $\mathbf{2}^{+\bullet}$ (or $\mathbf{1}^{+\bullet}$) and *n*-$C_4F_9^{\bullet}$, the radical *n*-$C_4F_9^{\bullet}$ adds to the *para*-position of **2** (and the *para* position of **1**) to afford an aromatic substituted cyclohexadienyl radical intermediate **C** (in the case of **2**). 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-$C_4F_9^{\bullet}$ + I^-. This latter n-$C_4F_9^{\bullet}$ radical triggers a chain sequence. Upon proton loss (PT), adduct **D** generates the substitution product **4**. *n*-C_4F_9• radicals enter the substitution cycle depicted in Scheme 7. It is observed that this is a *chain* PET mechanism, where *n*-C_4F_9• behaves as a radical chain carrier.[66]

The same authors also attempted the photoinduced perfluorobutylation of (di)benzo(hetero)arenes in reasonable good yields, according to Scheme 40.[67]

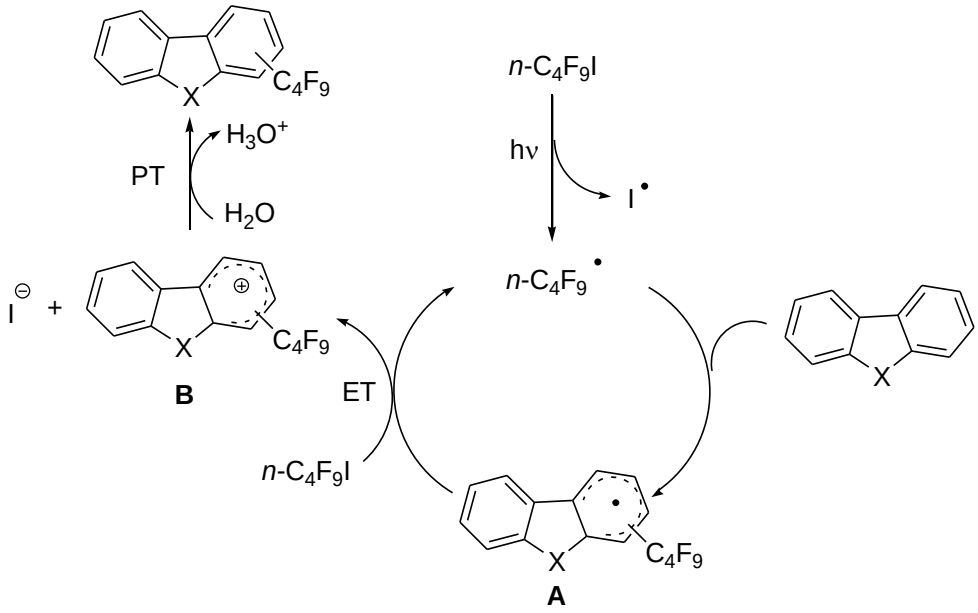


1 X = NH	59% isolated (3-C_4F_9, (**6**))
2 X = NMe	50% isolated (3-C_4F_9, (**7**))
3 X = O	41 % isolated (4-C_4F_9 (**8**) : 3-C_4F_9 (**9**) : 1-C_4F_9 (**10**) *25:35:40*)
4 X = CH_2	45% isolated (2-C_4F_9 (**11**))
5 X = S	50% isolated (2-C_4F_9 (**12**) : 3-C_4F_9 (**13**) : 4-C_4F_9 (**14**) *48:34:17*)

Scheme 40. Photoinduced perfluorobutylation of (di)benzo(hetero)arenes

The postulated mechanism is depicted in Scheme 41. At 254 nm irradiation, where most of the light is absorbed by *n*-C_4F_9I, homolysis of F_9C_4-I bond produces perfluorobutyl radicals that add to the (di)benzo(hetero)arene to yield the radical adduct intermediate **A**. The radical adduct **A**

undergoes a sequence of ET to *n*-C_4F_9I to afford cation intermediate **B** (Wheland intermediate, oxidation triggered through the favorable Gibbs energy) and then proton transfer (PT) steps to yield the substitution products in averaged good yields.[67]

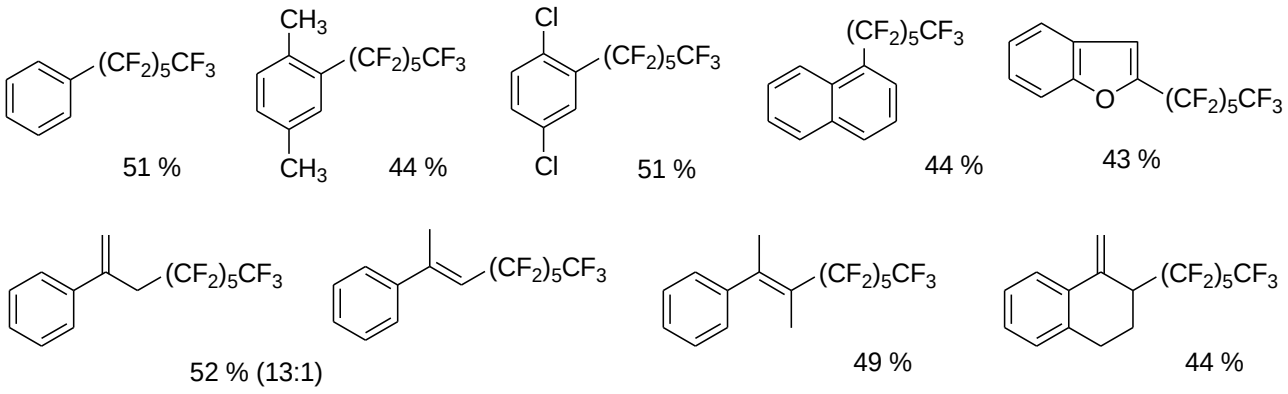


Scheme 41. Proposed mechanism for the perfluorobutylation of dibenzoheteroarenes in aqueous mixtures

2.2.-Transition metal photocatalyzed perfluoroalkylation of arenes

Perfluoroalkylation of (hetero)arenes and β-methylstyrene has been reported by Yoshida and co-workers under titanium oxide photocatalysis.[68] The photoreaction of (hetero)arenes proceeds smoothly when is carried out in a mixed solvent system of MeCN/MeOH (9:1) in the presence of $NaBF_4$ as an additive giving the corresponding products in moderate yields (see Scheme 42). Furthermore, a high molar ratio of arene to perfluoroalkyl iodide is used. In all the cases studied the

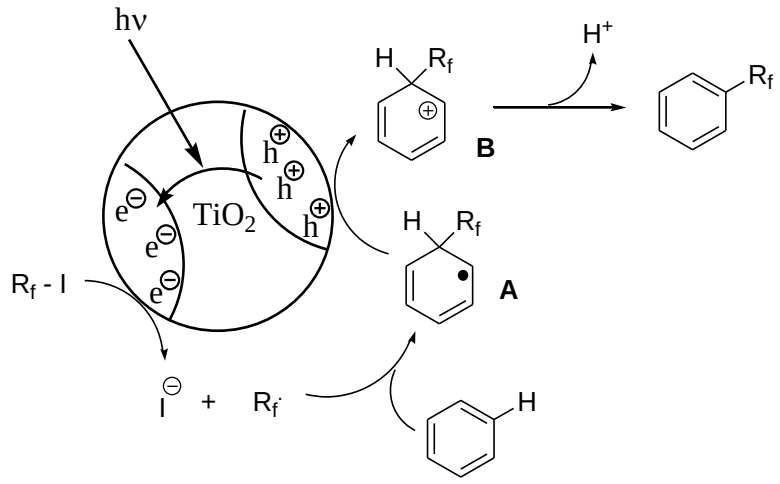
photoreaction is efficient while for the case of 1,4-dichlorobenzene the yield of the product is poor. This behavior has been attributed to the electrophilicity of the perfluoroalkyl radical formed during the photoreaction.



Scheme 42. Scope of the Ti-photocatalyzed reaction of arenes

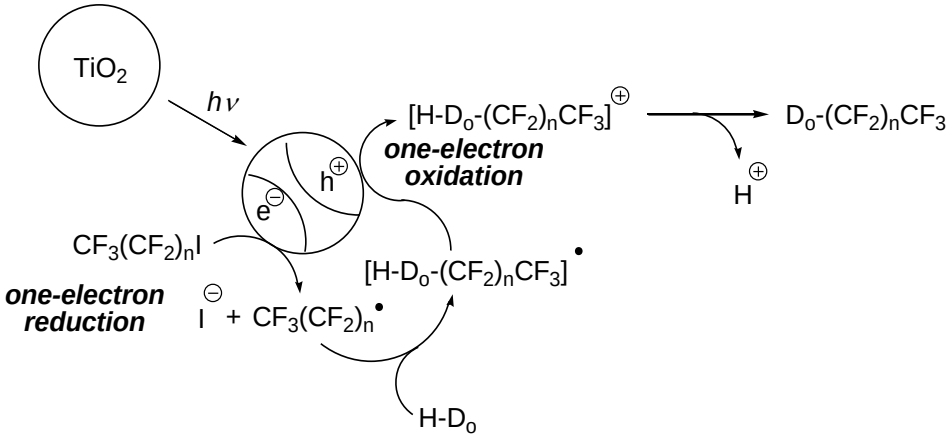
This practical photocatalytic perfluoroalkylation also applies to β-methylstyrene, 2-phenyl-2-butene and 3,4-dihydro-1-methylnaphthalene. The corresponding products are obtained in moderate yields (see Scheme 43).

Photoirradiation of TiO_2 excites electrons from the valence band to the conduction band, leaving holes in the valence band. This behavior confers to TiO_2 catalyst the ability to reduce the perfluoroalkyl iodide and to oxidize intermediate **A** to the cation intermediate **B** on the surface of the catalyst. The reaction mechanism for arenes is depicted in Scheme 43.



Scheme 43. Proposed TiO_2-photocatalyzed perfluoroalkylation of arenes

The resulting radical reacts with an organic molecule to provide a new radical species, which is successively oxidized to the corresponding cationic intermediate as shown in Scheme 44.



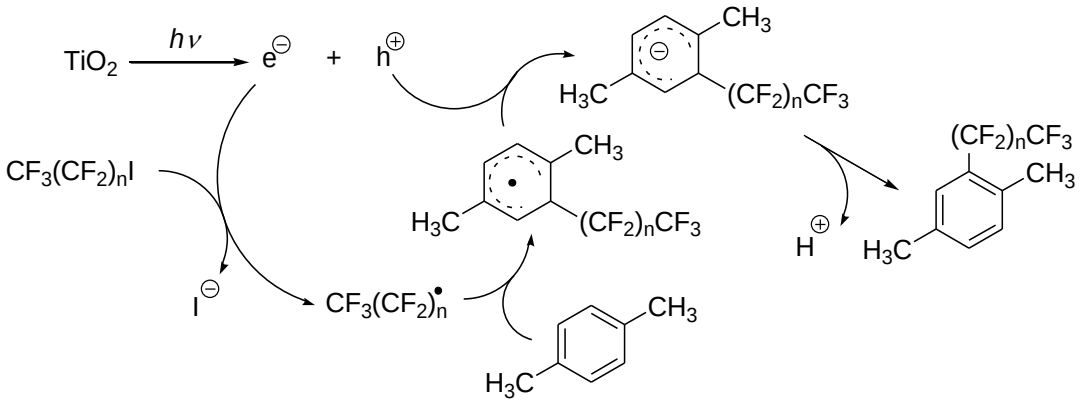
Scheme 44. Generation of perfluoroalkyl radicals by TiO_2-photocatalyzed one electron reduction of perfluoroalkyliodides

The TiO_2-photocatalytic aromatic perfluoroalkylations of *p*-xylene, benzene and 1,4-dichlorobenzene with perfluoroalkyl iodide have been examined in a mixed solvent system of CH_3CN/CH_3OH in the presence of $NaBF_4$. The reactivity of these arenes in the production of

perfluorohexylated arenes is consistent with the electrophilicity of the perfluoroalkyl radical. This methodology has been applied to the practical preparation of perfluoroalkylated arenes such as *p*-xylene, naphthalene and benzofuran, and these arenes were obtained in moderate isolated yields. The reactivity of perfluoroalkyl radical with naphthalene is much higher than even that with electron-rich benzenes such as toluene or anisole.[69] The authors do not provide an explanation for this observation.

Similarly, perfluoroalkylation of benzofuran proceeds effectively for the reaction of the perfluoroalkyl iodide with 2 mmol of benzofuran. In these reactions, the desired perfluoroalkylated products are easily separated from the starting arenes. Thus, TiO_2-photocatalitic reactions of perfluoroalkyl iodides with electron-rich aromatic compounds are proposed as a practical method for introducing perfluoroalkyl groups to the aromatic ring.[70]

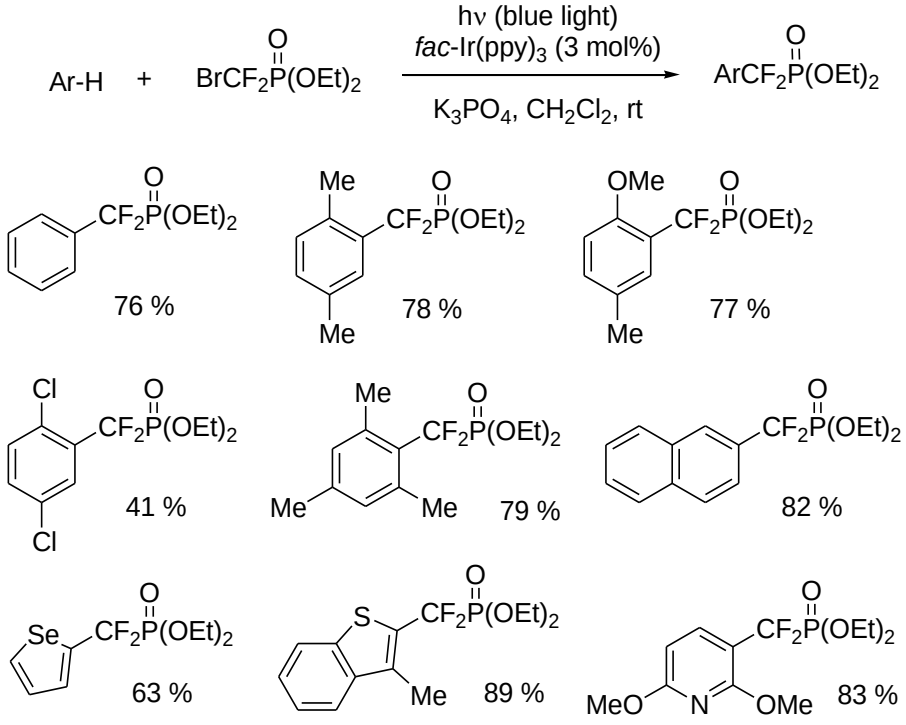
For *p*-xylene, the mechanism is depicted in Scheme 45.



Scheme 45. TiO_2-photocatalytic aromatic perfluoroalkylations of *p*-xylene.

One of the most potent strategies involves the use of photoredox catalysis to generate electrophilic radicals.[17-24] Hereby, polypyridyl organometallic complexes, such as $[Ru(bpy)_3Cl_2]$, are activated by visible light and have proven to be mild and more sustainable alternatives for traditional photochemistry utilizing UV energy.[25,71-73]

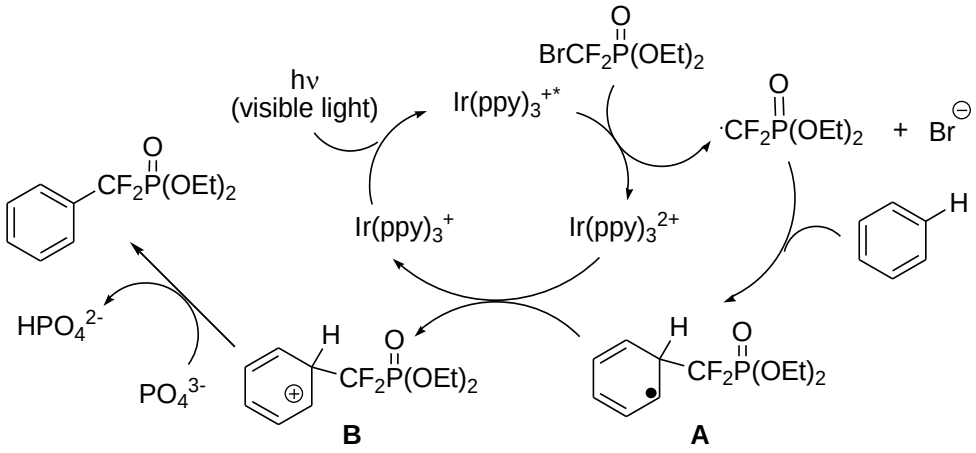
Photosensitized direct C – H difluoromethylenephosphonation of (hetero)arenes has been reported by Liu and co-workers.[74] Selective irradiation of the photosensitizer *fac*-Ir(ppy)$_3$ with blue light, photocatalyzes the reaction providing the corresponding products in good to excellent yields as is shown in Scheme 46. The photoreaction proceeds efficiently with an array of arenes bearing electron-donating and electron-withdrawing substituents, naphthalene and a variety of heterocyclic compounds at room temperature in the presence of diethyl bromodifluoromethyl phosphonate as the precursor of difluoromethylphosphonate radical and K_2HPO_4 as the base.



Scheme 46. Direct C – H difluoromethylenephosphonation of (hetero)arenes

The reaction involves an exothermic dissociative photoinduced electron transfer from the excited Ir(ppy)$_3$ to diethyl bromodifluoromethyl phosphonate depicted in Scheme 47. The difluoromethyl phosphonate radical formed reacts efficiently with the arene to produce a radical intermediate **A** that oxidizes to a cationic intermediate **B** through an electron transfer process with the photocatalyst. Finally, the base takes the proton from intermediate **B** and re-aromatizes to give

the desired product. The addition of an electron transfer scavenger such as 1,4-dinitrobenzene and radical scavengers such as BHT and TEMPO fully suppresses the photochemical reaction and no target product is formed. Kinetic isotope effects are found to be 1.0 indicating that the C – H bond fission of intermediate **B** is not rate-determining in the photoredox catalytic cycle.

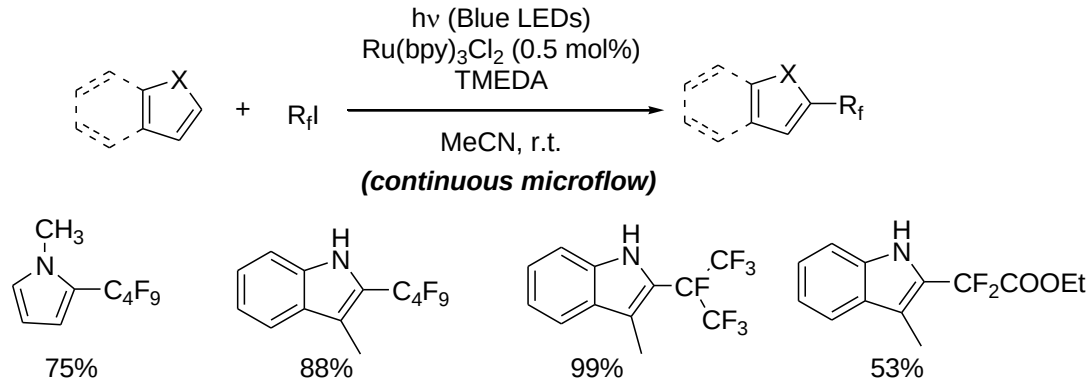


Scheme 47. Mechanism proposed for the direct C – H difluoromethylenephosphonation of (hetero)arenes

Due to their high surface-to-volume ratios, microreactors offer the advantage of an increased control over different process parameters (e.g., heat and mass-transfer, gas-liquid characteristics, residence time control), which leads to a safer handling of hazardous compounds.[75-79] As a consequence of the relatively high extinction coefficient of photoredox catalysts, a considerable amount of light is absorbed within the first few hundreds of micrometers of the light path, which makes the use of microreactor technology vital for successful scale-up by a numbering- up strategy .[80-85] A series of experiments have recently been conducted by Noeel and collaborators[86] to evaluate the scope of the continuous-microflow trifluoromethylation method. Next, the authors[86] have extended their focus by developing a continuous flow method for the photocatalytic perfluoroalkylation of heteroarenes using perfluoroalkyl iodides (RCF_2I). Perfluoroalkylation offers, besides the profound effects of the presence of fluorine substituents for pharmaceuticals and

materials, a straightforward pathway to introduce other functional groups such as esters, ethers or other halogens.

With the optimal conditions in hand, the authors have evaluated the method by perfluoroalkylating a selection of five-membered heteroarenes with different perfluoro-1-iodoalkanes (Scheme 48). The construction of perfluoroalkylated *N*-methylpyrrole and a number of indole analogues is easily achieved within several minutes (t_R=10 min) and delivers the target compound in good yields (53–88%). In addition, 3-methylindole also reacts with perfluoro-2-iodopropane and ethyl 2-bromo-difluoroacetate, providing the corresponding products in good yield (99% and 72%).



Scheme 48. Perfluoroalkylation of heterorenes

3.-Conclusions

Perfluoroalkylation reactions of arenes have not been as profusely studied as has been the case for the trifluoromethylation reactions of aromatics. The interesting properties of arenes with large perfluoroalkyl chains, such as the enhanced lipophilicity, resistance to oxidation, the increased fluorescent properties of perfluoroalkyl-substituted arenes (which make them excellent candidates as fluorescent tags) and in the case of pharmacophores, the extended bioavailability, have awoken a

surge of activity for studying new synthetic methods to achieve homolytic aromatic substitution reactions with perfluoroalkyl moieties..

Long chain perfluoroalkylating sources are mainly electrophilic or radical in nature, as evidenced by the lack in nucleophilic perfluoroalkylating reagents[87] . Electrophilic perfluoroalkylating reagents, however, which are synthetically challenging and expensive, have not been fully developed, and only very scarce examples have been documented. However, the high stability of the perfluoroalkyl radical, manifested by the high degree of pyramidalization of the radical structure, compensates electron repulsion between the lone electron and the fluorine electron clouds to a minimum. Therefore, radical methods for introducing R_f moieties into arenes can be regarded as the most versatile and resourceful options accessible to the synthetic chemist. Work should be directed into researching methods for environmentally benign techniques such as photoorganocatalysis with readily available organic dyes, in the presence of commercial perfluoroalkyl sources such as perfluoroalkyl chlorides, bromides and iodides in green solvents.

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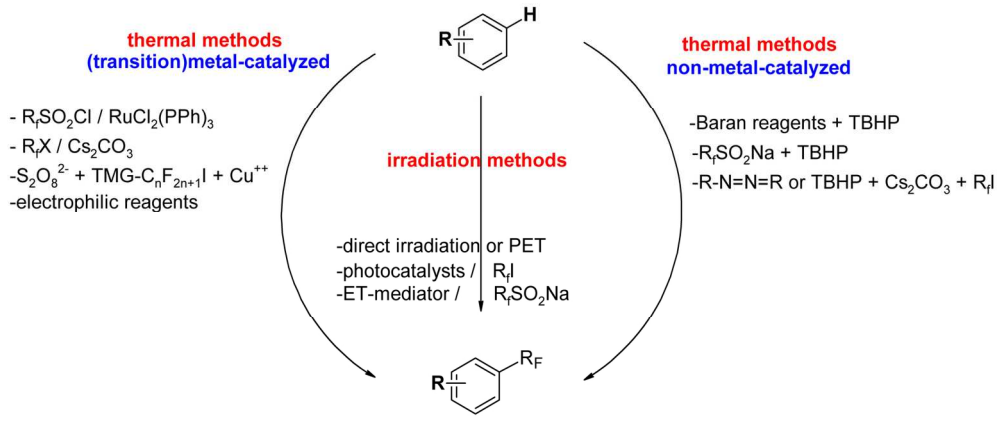

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