

Aromatic radical perfluoroalkylation reactions

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Abstract: This account intends to cover recent literature on radical perfluoroalkylation reactions of aromatic nuclei in organic and aqueous media. Emphasis will be placed on radical aromatic perfluoroalkylation reactions in water or aqueous media, with the aim of exploring aromatic radical reactivity in a benign environment.

Key words: radical perfluoroalkylation, radicals in aqueous media, aromatic radical perfluoroalkylation.

Résumé : Dans ce travail, on passe en revue la littérature récente sur les réactions de perfluoroalkylation radicalaires de noyaux aromatiques, dans des milieux organiques ou aqueux. On met l'accent sur les réactions de perfluoroalkylation aromatiques dans l'eau ou les milieux aqueux afin d'évaluer la réactivité radicalaire des produits aromatiques dans un environnement bénin.

Mots-clés : perfluoroalkylation radicalaire, radicaux en milieu aqueux, perfluoroalkylation radicalaire aromatique.

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Aromatic perfluoroalkylation reactions in organic conventional media

Introduction

Several important review articles involving radical perfluoroalkylation reactions of aromatic compounds have appeared in the literature in the past.^{1,2} Radical metal-promoted aromatic perfluoroalkylation reactions are rare. Among them, the reactions where the metals employed (e.g., Cu, Zn, Fe)² are not directly involved in the Ar-R_f bond formation step, but are needed to generate the perfluoroalkyl radical from R_fX (X = I, Br), will not be the subject of this review article.

The C₄F₉• and other perfluoroalkyl radicals show a clear-cut electrophilic character in aromatic substitution, as already reported for the addition to alkenes,^{3,4} but the low regio- and chemo-selectivities suggest that the polar effect is not the main factor in determining the high reactivity of perfluoroalkyl radicals toward aromatics (10⁵–10⁶ (mol/L)⁻¹ s⁻¹, two to three orders of magnitude more reactive than alkyl radicals). 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 (the σ-perfluoroalkyl radicals are considered less polarizable and hence less sensitive to polar effects than σ-radicals).⁵ Thus, it is not surprising that electron-rich aromatic nuclei showed the highest reactivity toward R_f radicals.

Aromatic radical perfluoroalkylation triggered by thermal initiators

Minischi and co-workers⁵ used a series of initiation techniques to generate perfluoroalkyl radicals (R_f•) such as (i) benzoyl peroxide; (ii) *t*-BuOOH and Fe(III) salts; (iii) H₂O₂ and acetone; and (iv) H₂O₂, DMSO, and Fe(II) salt. Table 1 summarizes the perfluorobutylation of aromatics employing benzoyl peroxide as the radical initiation technique.

The reaction mechanism according to procedure (i) clearly involves homolytic decomposition of benzoyl peroxide with the formation of phenyl radical; the reaction of this according to eq. [1] appears to be much faster (>10⁸ (mol/L)⁻¹ s⁻¹) than the hydrogen abstraction from the solvent (10⁵ (mol/L)⁻¹ s⁻¹) or the addition to the aromatic ring (10⁵ (mol/L)⁻¹ s⁻¹) because no significant aromatic phenylation was observed.



The radical C₄F₉• adds to the aromatic ring, and the radical adduct is then oxidized in a chain process. The presence of a catalytic amount of Cu(II) salt increases the reaction rate because a redox chain is superimposed to the radical chain (Scheme 1).

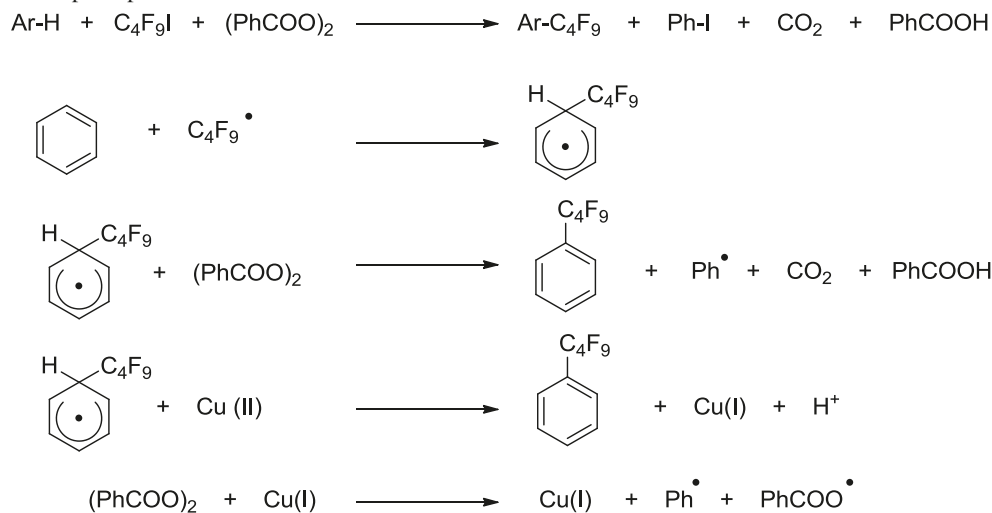
Minischi and co-workers⁵ argue that the solvent is important for the efficiency of the aromatic perfluoroalkylation, because perfluoroalkyl radicals can effectively abstract hydrogen from C–H bonds of the solvent (the rates of abstraction by R_f• are >10³ larger than those of the analogue hydrocarbon radicals).⁶

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Scheme 1. Redox chain superimposed to the radical chain.



Thus, the rate of hydrogen abstraction by $n\text{-C}_7\text{F}_{15}^\bullet$ from THF, whose $\alpha\text{-C-H}$ bond to the oxygen ring is particularly activated by both enthalpic and polar factors toward electrophilic radicals, has been evaluated at $6.1 \times 10^5 \text{ (mol/L)}^{-1} \text{ s}^{-1}$. The authors⁵ expected significantly lower rate constants for hydrogen abstraction from AcOH, DMSO, and MeCOMe by R_f^\bullet , always for enthalpic and polar reasons. The competition of hydrogen abstraction from the used solvents (AcOH, DMSO, and MeCOMe) appears to be negligible with activated aromatic substrates, and the efficiency of aromatic n -perfluoroalkylation is high, as shown by the comparable yields of PhI and $n\text{-C}_4\text{F}_9\text{-Ar}$.¹

However, with deactivated aromatic substrates, such as PhNO_2 or PhCN ,⁵ the conversion of the aromatic compound is significantly lower than the yield, always high, of PhI; in these cases, it would appear that hydrogen abstraction from the solvent by $n\text{-C}_4\text{F}_9^\bullet$ competes with the addition to the deactivated aromatic ring, even if an analysis of the volatile reaction products was not carried out.⁵

Aromatic substitution by procedures (ii)–(iv) is generally cleaner than the previously reported substitutions by thermolysis of R_fI or by homolysis of $(t\text{-BuO})_2$. The main reason is related to the lower efficiency of the rearomatization of the intermediate cyclohexadienyl radical, which, under these conditions, can also undergo disproportionation and dimerization leading to high-boiling derivatives.

The oxidation of cyclohexadienyl radicals by Cu(II) or Fe(III) are, on the contrary, very fast and selective in all cases, and they are always preferable when a catalytic redox chain can be achieved.

No substitution takes place with pyridine in AcOH solution,⁵ whereas nitrobenzene and benzonitrile are attacked by the $\text{C}_4\text{F}_9^\bullet$ radical. The fact that alkyl radicals, generated from alkyl iodides by the same procedures, do not react with homocyclic aromatic substrates suggested that perfluoroalkyl radicals must be much more reactive than alkyl radicals.⁵

On the other hand, protonated pyridine gives good results with alkyl radicals, but is quite unreactive toward $\text{C}_4\text{F}_9^\bullet$ under the same conditions. This would indicate that alkyl and perfluoroalkyl radicals have opposite behavior because

Table 1. Homolytic aromatic radical n -perfluoroalkylation.

Aromatic substrate	Orientation (%) relative substitution			Yield (%)
Benzene				94.7
Anisole	<i>o</i> (14.7)	<i>m</i> (45.5)	<i>p</i> (39.6)	93.3
Diphenyl ether	<i>o</i> (18.1)	<i>m</i> (24.4)	<i>p</i> (57.5)	90.9
Toluene	<i>o</i> (46.1)	<i>m</i> (30.3)	<i>p</i> (23.3)	90.1
Chlorobenzene	<i>o</i> (41.7)	<i>m</i> (39.6)	<i>p</i> (18.7)	47.1
Benzonitrile	<i>o</i> (20.5)	<i>m</i> (52.2)	<i>p</i> (27.3)	41.4
Nitrobenzene	<i>o</i> (31.1)	<i>m</i> (36.7)	<i>p</i> (32.2)	42.3
Biphenyl	<i>o</i> (25.1)	<i>m + p</i> (74.9)		97.2
Naphthalene	α (80.4)	β (19.6)		99.1
Thiophene	α (86.5)	β (13.1)		97.6

of their opposite polar character (electrophilic and nucleophilic, respectively, for perfluoroalkyl and alkyl radicals).

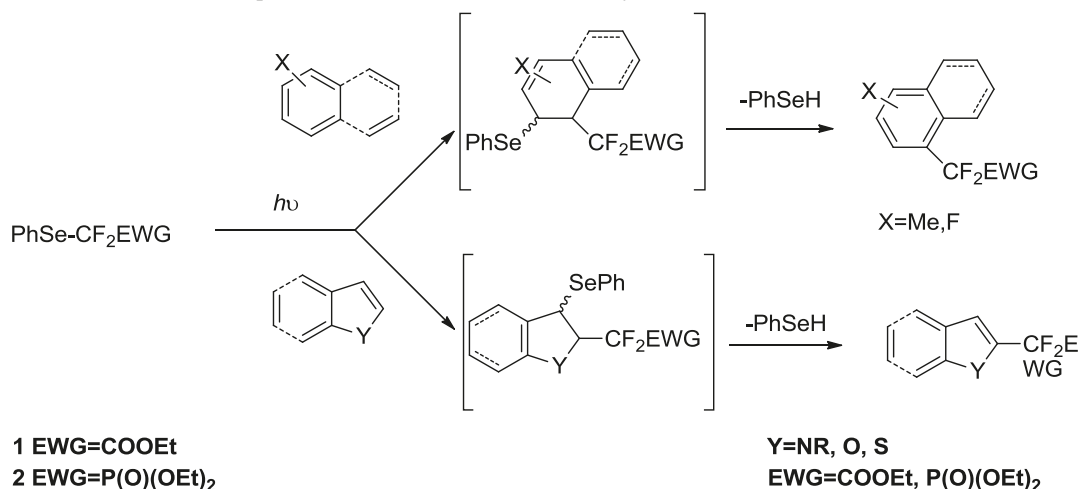
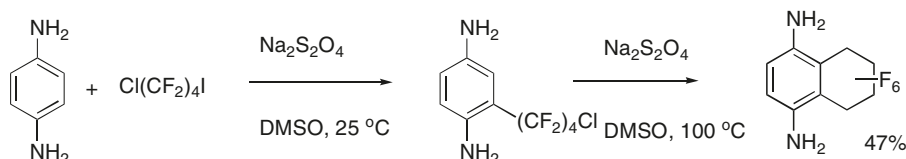
The electrophilic character of $\text{C}_4\text{F}_9^\bullet$ radical is, however, scarcely reflected on the orientation of the substitution.

The ortho, meta, and para positions of toluene, chlorobenzene, anisole, diphenyl ether, benzonitrile, and nitrobenzene are substituted with low selectivity (Table 1), without a macroscopic influence of the polar character of the substituent, the ortho position being, obviously, affected by steric effects (e.g., the isomer distribution in chlorobenzene is characterized by 52% in the ortho position by CF_3^\bullet , but only 14% by the $n\text{-C}_{10}\text{F}_{21}^\bullet$ radical). Substitution of naphthalene, biphenyl, thiophene, and pyrrole is, on the opposite, more selective. It would appear that the orientation is related more to the stabilization of the intermediate radical adducts than to the electron availability of the ring position.⁵

Aromatic radical perfluoroalkylation triggered by photochemical methods

A photochemical method was successfully employed to effect perfluoroalkylation reactions of aromatic and heteroaromatic compounds to provide substitutions with corresponding $\alpha\text{-aryl-}\alpha,\alpha\text{-difluoroacetates}$ and $\alpha\text{-aryl-}\alpha,\alpha\text{-difluoromethylphosphonates}$ in good to moderate yields.⁷

Aromatic and heteroaromatic substitutions with difluoromethyl radicals photogenerated from ethyl α -(phenylseleno)-

Scheme 2. Aromatic and heteroaromatic photo-substitutions with difluoromethyl radicals.**Scheme 3.** Perfluoroalkylation of aromatic amines with Cl(CF₂)₄I in DMSO.**Scheme 4.** Introduction of polyfluoroalkoxy and polyfluoroalkylthio substituents in aromatic rings.

α,α -difluoroacetate (**1**) and diethyl α,α -difluoromethyl-(phenylseleno)phosphonate (**2**) as shown in Scheme 2.

Aromatic radical perfluoroalkylation triggered by sulfinatodehalogenation reactions

Chen and co-workers⁸ achieved the radical perfluoroalkylation reaction of aromatic amines by the substitution of aromatic H for R_f groups in DMSO as solvent, triggered through the decomposition of Na₂S₂O₄, according to Scheme 3 (see the Aromatic radical perfluoroalkylation reactions in aqueous media section for the mechanism of the sulfinatodehalogenation reactions).

A nonradical perfluoroalkylation reaction of activated (ArNH₂) aromatic nuclei has recently been accomplished through Pd catalysis in benzene as solvent.⁹

Aromatic radical perfluoroalkylation triggered by electron-transfer reactions

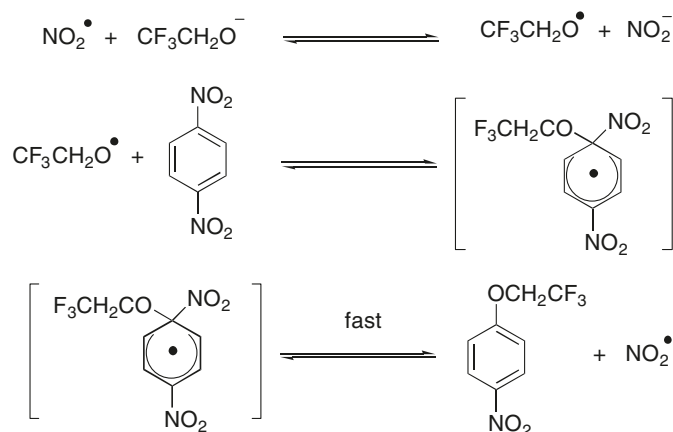
More recently, Yamakawa and co-workers^{2h,10} accomplished the fluorination of aromatic compounds using Fenton reagent in DMSO as solvent. They attempted a series of simple substituted aromatic and heteroaromatic compounds with CF₃I and ethoxycarbonyl difluoromethyl bromide as fluorinating agents.

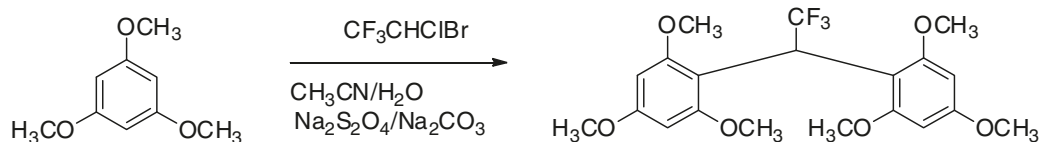
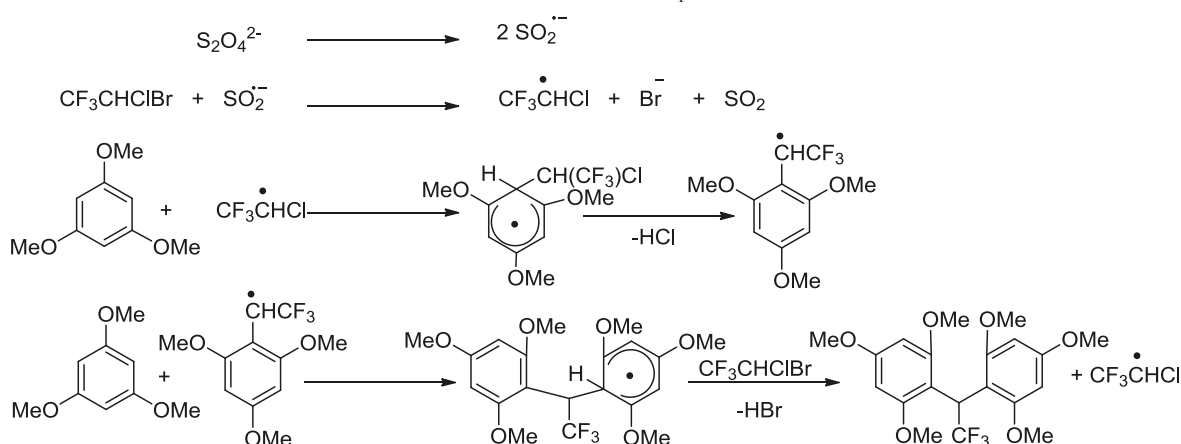
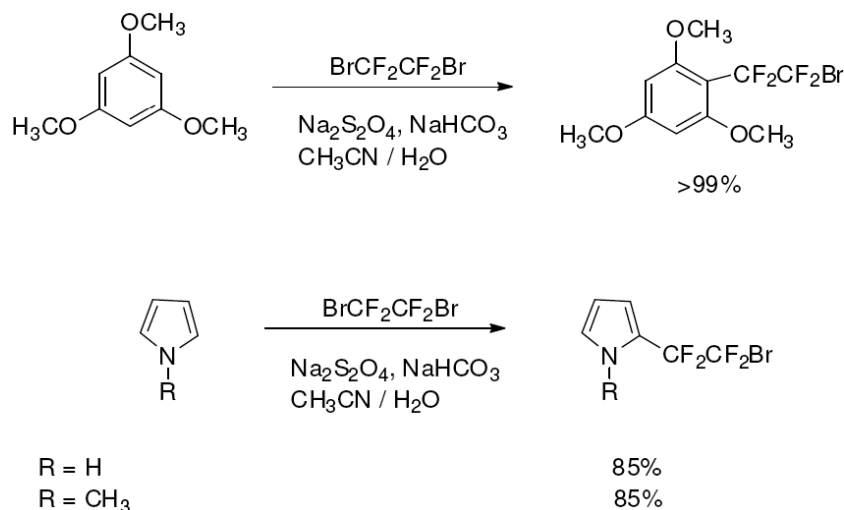
Introduction of polyfluoroalkoxy and polyfluoroalkylthio substituents in aromatic rings can be achieved with mild conditions and short times through the reaction of concentrated

Table 2. Introduction of polyfluoroalkoxy and polyfluoroalkylthio substituents in aromatic rings.

Entry	Substrate	Nucleophile	Product yield (%)	Rxn. time (h)
1	<i>p</i> -DNB	CF ₃ CH ₂ OH	98	1
2	<i>p</i> -DNB	(CF ₃) ₂ CHOH	30	21
3	<i>p</i> -DNB	CF ₃ (CF ₂) ₆ CH ₂ OH	89	2
4	<i>p</i> -DNB	CF ₃ CH ₂ SH	92	2
5	<i>o</i> -DNB	CF ₃ CH ₂ OH	76	1.5
6	<i>m</i> -DNB	CF ₃ CH ₂ OH	70	3
7	<i>m</i> -DNB	CF ₃ (CF ₂) ₆ CH ₂ OH	—	24
8	<i>m</i> -DNB	CF ₃ CH ₂ SH	34	5

Note: DNB, dinitrobenzene.

Scheme 5. Radical propagation mechanism for the substitution of *p*-dinitrobenzene (DNB).

Scheme 6. Synthesis of trifluoromethyl-bis(2,4,6-trimethoxyphenyl)methane by sulfinate dehalogenation reaction.¹⁹**Scheme 7.** Mechanism for the aromatic radical substitution reaction of H for R_f .¹⁹**Scheme 8.** Radical aromatic substitution reactions of 1,3,5-trimethoxybenzene and pyrroles with $\text{BrCF}_2\text{CF}_2\text{Br}$ under sulfinate dehalogenation reaction conditions.²⁰

solutions of dinitrobenzenes in DMF with polyfluoroalcohols and polyfluoroethiols in moderate excess in the presence of excess tetrabutylammonium fluoride as a base.¹¹ Terejo et al.¹¹ postulated an operable fast radical chain mechanism. This mechanism is elicited from the oxidation of a Meisenheimer complex and proceeds through a radical aromatic substitution with the polyfluoroalkoxy or the polyfluoroalkylthio radicals as key intermediates. At low concentrations, entrainment can be achieved with the superoxide anion (Scheme 4).

The series of substituted products obtained under these conditions are illustrated in Table 2.

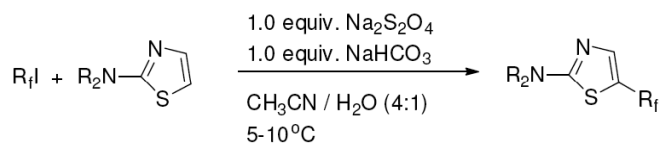
In Scheme 5, the proposed propagation mechanism is described, accounting for product formation.

Indeed, the mechanism corresponds to a typical radical aromatic substitution.¹² It is known that superoxide anion is a good oxidant for relatively acidic protic substrates to the

corresponding radical through a process that includes dismutation.^{13,14}

Terejo et al.¹¹ managed to generate the trifluoroethanol radical alternatively by the action of superoxide anion on trifluoroethanol ($pK_a = 23.6$ in DMSO).¹⁵ The fast reaction between *p*-DNB and trifluoroethanol could be triggered by the addition of a catalytic amount of KO_2 (and an equimolecular amount of 18-crown-6 ether to achieve its solubilization in DMF). This represents a good example of entrainment, and considering the superoxide anion has no outer sphere electron-transfer oxidant properties,¹³ this result strongly supports the operation of the trifluoroethoxy radical as an intermediate.

Scheme 9. Radical perfluoroalkylation of 2-aminothiazole derivatives.²¹



Aromatic radical perfluoroalkylation reactions in aqueous media

As opposed to radical perfluoroalkylation addition reactions of unsaturated compounds,^{16,17} fluoroalkyl radical substitution on the aromatic ring has received little attention. Furthermore, aromatic radical perfluoroalkylation in aqueous mixtures is restricted to a few examples of sulfinate dehalogenation reactions.

Recently, Barata-Vallejo and Postigo¹⁸ summarized radical perfluoroalkylation reactions in aqueous media. In particular, activated aromatic nuclei, such as 1,3,5-trimethoxybenzene were employed in perfluoroalkyl substitution radical reactions in aqueous media. When a mixture of 1,3,5-trimethoxybenzene and 1-chloro-1-bromo-2,2,2-trifluoroethane was treated under sulfinate dehalogenation reaction conditions ($\text{Na}_2\text{S}_2\text{O}_4/\text{NaHCO}_3$ in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$), a radical substitution reaction of H for R_f was achieved, as shown in Scheme 6.¹⁹

Dmowski et al.¹⁹ postulated a radical mechanism such as that depicted in Scheme 7.

In another report by Dmowski et al.,²⁰ the aromatic substitution of trimethoxybenzenes and pyrroles with $\text{BrCF}_2\text{CF}_2\text{Br}$ was attempted as shown in Scheme 8.

More recently, Lu and co-workers²¹ accomplished the polyfluoroalkylation of 2-aminothiazoles, as shown in Scheme 9. Reactions of 2-aminothiazole with $n\text{-C}_4\text{F}_9\text{I}$ under sulfinate dehalogenation reaction conditions gave the substitution product in 80% yield with total selectivity at the 5-position of 2-aminothiazole (Scheme 9). A number of N-substituted 2-aminothiazoles also reacted with R_fI and R_fBr in yields ranging from 58% to 90%.²¹

While defluorination of polyfluoroalkyl-substituted arenes followed by nucleophilic attack from water has been well documented,²² very few reductive defluorinations of polyfluoroalkyl-substituted arenes under mild conditions have been previously reported, and no other such reaction has been documented in aqueous media.

Conclusions

It becomes apparent that aromatic radical perfluoroalkylation reactions progress in good yields under different reaction and medium conditions. The types of reactions explored encompass simple aromatic radical substitutions triggered by the thermal decomposition of thermal initiators, photochemical initiation, metal-entrainment reactions, sulfinate dehalogenation reactions, and electron-transfer initiation. Remarkably, some of these initiations can be carried out in aqueous media, lowering the environmental impact of aromatic radical homolytic and ipso substitutions.

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