Reactions of Fluorinated Organic Radicals in Aqueous Media

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Reactions of Fluorinated Organic Radicals in Aqueous Media

Sebastián Barata-Vallejo[a] and Al Postigo*[a]

Fluorinated radicals in water are shown to enable a useful array of synthetic organic transformations, reflecting these intermediates' distinct behavior in water or aqueous media. The enhanced reactivities of perfluroalkyl radicals in water facilitate their addition reactions to carbon–carbon and carbon–heteroatom multiple bonds. Activated and unactivated unsaturated substrates are equally reactive candidates for radical perfluoroalkylation reactions in aqueous systems. Parallel behavior of perfluorinated radicals in organic solvents and in water is presented, demonstrating the scope of reactions based on fluorinated radicals in aqueous media, as well as the ease of carbocyclic construction.

Introduction

The need for the use of environmentally friendlier or alternative reaction media in order to accomplish radical organic synthetic transformations has encouraged chemists to explore a variety of systems, such as aqueous systems and water alone, or unconventional supports, such as supercritical fluids, ionic liquids and fluorous media.

Recent review articles have emphasized the ease and excellent stereoselectivities observed in organic radical reactions involving carbon- and sulfur-centered radicals[1] and

metal-mediated radical transformations[2] in water and aqueous systems.

The terms "*fluorous media*" and "*aqueous media*" are connected in the sense that both relate to solvent systems in which highly fluorinated compounds and water, respectively, act as reaction media. What is peculiar and significant is that radical reactivities both of perfluoroalkyl (fluorinated) radicals[3,4] and of nonfluorinated radicals are enhanced many fold in aqueous and fluorous media in relation to the corresponding reactivities in standard ordinary organic solvents. Furthermore, synthetic organic radical transformations that are difficult to achieve, or that give low yields, in conventional organic media have been shown to afford products in much better yields in aqueous or fluorous media.

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Al Postigo was born in Argentina and obtained his M.Sc. degree from the University of Buenos Aires, Argentina in 1986. He then worked with Professor Dr. Erra Balsells in the area of organic photochemistry in the Department of Organic Chemistry, Faculty of Science, University of Buenos Aires. He moved to Canada in 1990 and obtained his Ph.D. degree from McMaster University in 1994, under the direction of Professor Dr. William J. Leigh. After postdoctoral positions in Canada, he returned to Argentina and worked with Professor Dr. Roberto Rossi at the University of Córdoba in the area of radical ion reactions. He earned a position of Assistant Professor at that University. In 1999 he became a member of the National Argentinean Research Scientific Council and has remained a member since then. In 2004 he accepted an Associate Professor position at the University of Belgrano, Buenos Aires, in the Faculty of Science and was promoted to Full Professor in 2008. In 2010 he earned a Professor Position at the Department of Organic Chemistry, Faculty of Pharmacy and Biochemistry, University of Buenos Aires. His current interests are in the areas of radical chemistry – both carbon-centered radicals and metallic centered-radicals. In particular he is interested in studying radical reactions of these species in water and unconventional media.

On the other hand, perfluoroalkyl radicals are involved in numerous reactions directed toward the syntheses of perfluoroalkyl-substituted compounds, because radical methodologies circumvent issues associated with drawbacks in polar substitutions with employment of perfluoroalkyl halides.[5]

Perfluoroalkyl-substituted compounds are regarded as important components of fluorophors, for the introduction of fluorous tags into organic substrates,[6] as fluorous media in radical reactions, and in phase-separation techniques.[7] In medicine, fluorocarbons and perfluoroalkyl-substituted alkanes have many applications as, for example, vascular implants,[8] inhalation anesthetics,[9] aerosol propellants,[10] and components in blood substitutes.[11] Biotechnology employs fluorocarbon liquids to transport respiratory gases in cell culture systems.[12] The synthesis of these compounds in organic solvents is achieved through different methods, out of which the addition of perfluoroalkyl radicals to unsaturated bonds represents a convenient choice.

The presence or absence of a hydrogen donor gives rise to either consecutive or halogen-atom-transfer pathways in water. Different radical triggering events can be employed in the initiation of the radical chain mechanisms; these include light-induced homolysis of R_f–I bonds from perfluoroalkyl iodides, thermal decomposition of azo compounds, dioxygen initiation, metal-mediated electron-transfer initiation, and sulfinatodehalogenation reactions based on electron transfer from radical anions produced through the decomposition of sodium dithionate, sodium bisulfite, or sodium sulfite salts.

We therefore describe radical addition, hydrogen abstraction, and substitution reactions of perfluoroalkyl radicals in aqueous media and compare their efficiencies with those of the radical reactions performed in organic solvent systems. Radical perfluoroalkylation addition reactions of carbon-carbon, carbon-nitrogen, carbon-oxygen, and carbon-sulfur multiple bonds are shown to be effectively accomplished in water.

## 1. Perfluoroalkyl Radical Addition Reactions to Carbon–Carbon or Carbon–Heteroatom Bonds in Water

1.1. Halogen-Atom-Transfer Radical Iodoperfluoroalkylation of Alkenes and Alkynes in Aqueous Media

Sulfinatodehalogenation reactions have been well established by Huang and co-workers.[13–17] The use of sodium dithionate, $Na_2S_2O_4$, or sodium sulfite/sodium bisulfite can accomplish radical iodoperfluoroalkylation addition (and substitution) reactions of carbon-carbon unsaturated bonds in aqueous media. The reactions generally proceed at around room temperature and under mild conditions, which facilitates functionalization of a great variety of substrates containing unsaturation.

The mechanisms of these reaction are thought to involve radicals and radical ions as intermediates. Scheme 1 depicts a general mechanism for the iodoperfluoroalkylation of an olefin of the type $RCH=CH_2$ and a perfluoroalkyl iodide (R_fI).
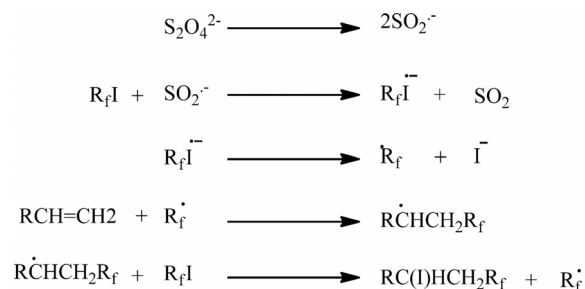
Scheme 1. Mechanism for the sulfinatodehalogenation of olefins in aqueous systems.[18]

A free radical chain involving a single electron transfer (SET) mechanism has been proposed for the addition reaction (Scheme 1).[18] Because sulfur dioxide is generated during the reaction, sodium hydrogen carbonate is often used to regulate the pH. Upon dissociation of $Na_2S_2O_4$, the sulfinic radical anion $SO_2^{·-}$ is produced, and this transfers an electron to R_fI, triggering the dissociative cleavage of the R_f–I bond into $R_f^·$ radicals and iodide anion. These $R_f^·$ radicals add to the carbon-carbon unsaturated bonds of alkenes of the type $RCH=CH_2$ to yield radical adducts [$RCH(^·)CH_2R_f$], and these abstract iodine atoms from R_fI to generate the end products $RC(I)HCH_2R_f$ and $R_f^·$ radicals, which continue the chain reaction (Scheme 1).

Terminal olefins are easily haloperfluoroalkylated through initiation with sodium dithionate with a variety of haloperfluoroalkanes or polyhaloalkanes, such as CCl_3Br, CCl_4, CF_2Br_2, CF_2I_2, or $CF_2ClCFCl_2$, as demonstrated by Wu and co-workers.[19]

Wu and co-workers performed additions of ethyl iododifluoroacetate to internal alkenes and cycloalkenes. On further treatment with base, the products underwent ring closure reactions (vide infra).[20] This is quite remarkable, because other radicals such as $(Me_3Si)_3Si^·$ are only known to add to terminal alkene and alkyne substrates in organic solvents[21] and water,[22] and radical additions to internal unsaturated sites display high reversibility. The reactions are depicted in Scheme 2.
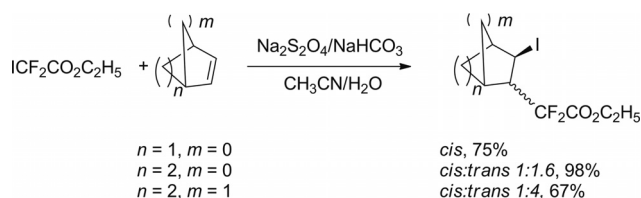
Scheme 2. Reactions of cycloalkenes with ethyl iododifluoroacetate initiated by sodium dithionate.[20]

Sulfinatodehalogenation reactions have also been used to accomplish iodoperfluoroalkylation reaction of alkynes in aqueous media.[23–25] The proposed reaction mechanisms are identical to those for alkenes. Simple alkynes such as
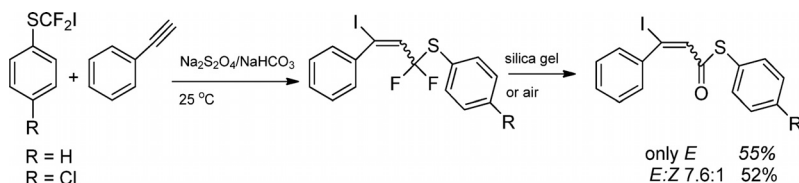
Scheme 3. Sulfinatodehalogenation reaction of an alkyne.[27a]

hex-1-yne,[26] 2-methylbut-3-yn-2-ol,[25] and others afford iodoperfluoroalkylated alkene products in high yields.

An interesting example was recently provided by Wu and co-workers when they attempted reactions between phenyl-acetylenes and (difluoroiodomethyl)sulfanylbenzenes initiated by $Na_2S_2O_4$, as shown in Scheme 3.[27a,28–31]

Moreover, the *trans* selectivity of phenyl-substituted vinyl radicals is well established.[32] Phenyl-substituted vinyl radicals are linear and the β-substituent steers the stereochemical outcome of the reaction (mainly the *E* stereoisomer, as also observed for perfluoroalkyl groups as directing groups).

Very recently, an indium-mediated radical iodoperfluorobutylation of but-3-yn-1-ol in water was achieved with high efficiency [Eq. (1)].[27b]
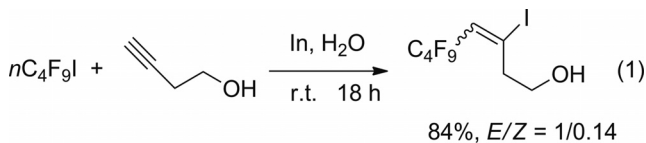

The mechanism [Eq. (1)] involves a spontaneous ET from In metal to R_fI, which triggers dissociation into $R_f^\cdot$ radicals (and iodide ion) that add to the triple bond of but-3-yn-1-ol.

Recently, Postigo and co-workers investigated light-induced halogen-atom-transfer (HAT)/perfluoroalkylation reactions of alkenes and alkynes in water.[3] When the authors subjected alkenes **1a–d** to treatment with 1-iodo-perfluorobutane in water under irradiation conditions, they obtained iodo-perfluorobutyl alkanes **2a–e** in yields ranging from 58 to 84% [Eq. (2)]. Both electron-rich and electron-deficient alkenes react efficiently in water, and both organic-solvent-soluble alkenes **1b–d** and water-soluble alkenes (allyl alcohol **1a**) react with 1-iodoperfluorobutane in water [Eq. (2)].[3]

1a R = CH₂OH, R′= H
1b   CH₂Cl, R′= H
1c   CN, R′= H
1d   CN, R′= CH₃
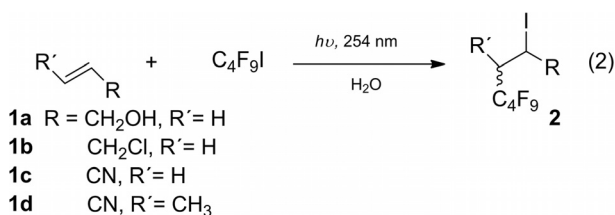
When the authors subjected alkynes **3a–d** to treatment with 1-iodo-perfluorobutane in water under irradiation conditions with vigorous stirring, they obtained iodo-perfluorobutyl-substituted alkenes **4a–d** [Eq. (3)] in yields ranging from 67 to 98%. The stereoselectivities of the obtained iodo-perfluorobutyl-substituted alkenes were in

favor of the *E* isomers. Both organic-solvent-soluble (**3b**, **3c**) and water-soluble (**3a**, **3d**) alkynes reacted efficiently in water.[3]

3a R = OH
3b R = Cl
**3c** R = C₅H₁₁
3d R = N(CH₃)₂
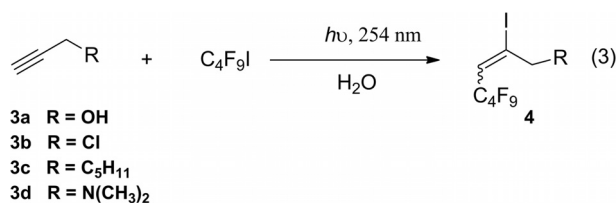
From these results, however, it is apparent that in water, unlike in organic solvents, the reactivities of electron-rich and of electron-deficient alkenes towards $R_f^\cdot$ radical addition could be comparable. This trend has also been found in the consecutive radical perfluoroalkylation addition reactions of alkenes in water mediated by $(Me_3Si)_3SiH$ (vide infra).[4]

In previous reports, the same authors observed that radical hydrosilylation reactions of water-soluble substrates in water took place efficiently with the aid of amphiphilic 2-mercaptoethanol, as chain carrier.[29] This is because silyl radicals, being hydrophobic, need the assistance of amphiphilic thiyl radicals (i.e., $^\cdot SCH_2CH_2OH$) to carry the chain reaction into the aqueous environment, where the water-soluble substrate is dissolved.

Interestingly, with $R_f^\cdot$ radicals,[3] both organic-solvent-soluble substrates and water-soluble substrates undergo radical perfluoroalkylation reactions in water without the need for assistance from a chain carrier. This observation could be better interpreted in terms of the distinct reactivity of $R_f^\cdot$ radicals in water rather than in terms of a difference in the hydrophobicities of $R_f^\cdot$ radicals in relation to silyl radicals. Perhaps some distinct amphiphilic character of $R_f^\cdot$ radicals can be invoked in this case.[3]

Huang and co-workers[30] accomplished the synthesis of polyfluoroalkyl imidoyl iodides through sulfinatodehalogenation reactions ($Na_2S_2O_4$/$NaHCO_3$ or Na_2CO_3) between R_fI and *N*-aryl isocyanides directly and under mild conditions, as shown in Scheme 4.

R = *p*-CH₃O R_f = Cl(CF₂)₄   91%
R = *p*-CH₃, R_f = Cl(CF₂)₄   93%
R = *p*-I, R_f = Cl(CF₂)₂   74%
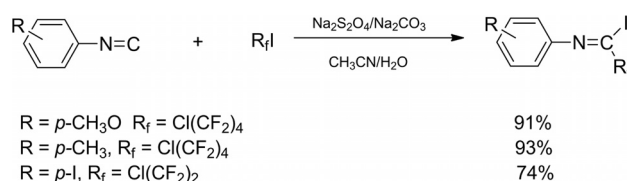
Scheme 4. Synthesis of polyfluoroalkyl imidoyl iodides through sulfinatodehalogenation reactions.[30]

In contrast, Ogawa[31] and co-workers examined the light-induced iodotrifluoromethylation of cyclohexyl isocyanide in benzotrifluoride as solvent and obtained the iodotrifluoromethylated derivative in 68% yield (at –22 °C), as shown in Scheme 5.
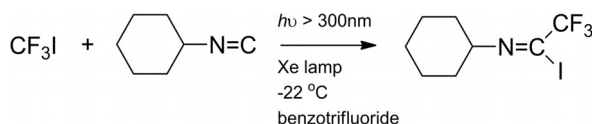
Scheme 5. Radical iodotrifluoromethylation of cyclohexyl isocyanide in benzotrifluoride as solvent.[31]

1.2. Consecutive Radical Perfluoroalkylation Reactions of Alkenes in Water

Conjugated dienoic acids have also been reported to undergo perfluoroalkylation reactions with sodium dithionate in CH_3CN/H_2O mixtures. It has been found that halide-free 1,4 adducts with E configurations are obtained.[23] When (E)-penta-2,4-dienoic acid was treated with R_fI, only the iodide-free 1,4 adduct was obtained, in 57% yield. In the case of sorbic acid (R = CH_3) the yield was 65% (Scheme 6).[23]
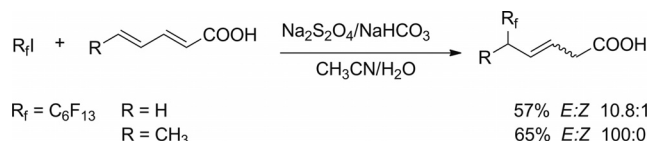
Scheme 6. Reactions between $C_6F_{13}I$ and (E)-penta-2,4-dienoic acid (R = H) or sorbic acid (R = CH_3).[23]

As can be observed from these reactions (Scheme 6), they proceed with very high stereoselectivities in the sense that the E isomers predominate in the product mixture.[23] The authors also propose a single electron transfer (SET) mechanism that can account for the product formation. Thanks to the weaker steric hindrance of the R substituent over the COOH terminus on the dienoic moiety, the radical adds preferentially at the 5-position (Scheme 7).
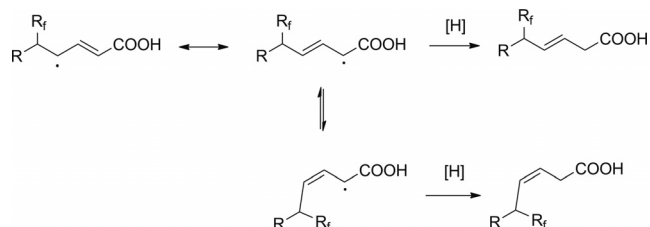
Scheme 7. Proposed mechanism for the perfluoroalkylation of 1,4-dienes.[23]

Although the authors postulate that the *reduction* products arise as a result of the COOH moiety acting as a hydrogen atom donor, this is quite unlikely. H-Donation from other sources such as impurities or co-solvents was not ruled out, nor were deuterium experiments performed.[23]
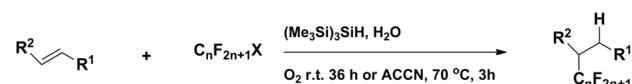
In contrast, light-induced radical iodoperfluoroalkylation of a conjugated diene such as 2,3-dimethylbutadiene in benzotrifluoride (BTF) as solvent afforded a halogen atom-transfer (HAT) product as shown in Scheme 8, together with a minor substitution product (see Section 1.1).[31]
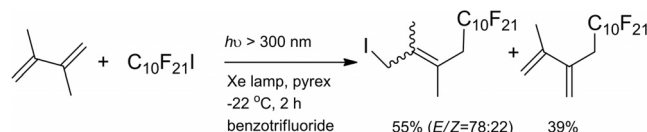
Scheme 8. Radical iodoperfluoroalkylation of 2,3-dimethylbutadiene in benzotrifluoride as solvent.[31]

The obtaining of the HAT product in BTF as solvent could be consistent with the absence of a H-donor source. However, the substitution product obtained in BTF (39%) and its absence in aqueous media supports the assumption of radical addition rates that are faster than substitution rates in water (see Section 2).

In another recent report by Postigo and Barata-Vallejo,[4] when hex-1-ene was allowed to react with n-1-iodoperfluorohexane (n-$C_6F_{13}I$) in water, with initiation by $(Me_3Si)_3$-SiH/dioxygen or ACCN [1,1′-azobis(cyanocyclohexane)], 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorododecane (**5a**)[32,33] was obtained in 65–88% yield (Scheme 9). Analogously, oct-1-ene and dec-1-ene, on treatment with n-$C_6F_{13}I$ under the same radical alternate conditions, afforded products **6a**[34] and **7a**[34] in yields ranging from 69 to 74% (Scheme 9).[4]

	R^1	R^2	X	n	% Yield
5a	C_4H_9	H	I, Br	6	
5b	C_4H_9	H	I	4	
5d	C_4H_9	H	Br	8	62–88
5e	C_4H_9	H	I, Br	10	
6a	C_6H_{13}	H	I	6	59–77
7a	C_8H_{17}	H	I	6	48–74
8a	C_6H_5	H	I	6	77–81
9a	p-CH_3-C_6H_4	H	I	6	46–66
10a	CN	H	Br, I	6	
10d	CN	H	Br	8	44–77
10e	CN	H	Br	10	
11a	CHO	CH_3	Br, I	6	
11d	CHO	CH_3	Br	8	55–62
11e	CHO	CH_3	Br	10	
12a	CO_2CH_3	H	Br, I	6	
12d	CO_2CH_3	H	Br	8	43–75
12e	CO_2CH_3	H	Br	10	
13a	$COCH_3$	H	Br, I	6	
13d	$COCH_3$	H	Br	8	66–76
13e	$COCH_3$	H	Br	10	

Scheme 9. Intermolecular radical carbon–carbon bond formation in water. Reactions between different alkenes and n-1-haloperfluoroalkanes initiated by $(Me_3Si)_3SiH/dioxygen$ or ACCN.[4]

Styrene and p-methylstyrene, when treated with n-$C_6F_{13}I$ in water with initiation by $(Me_3Si)_3SiH/dioxygen$ or ACCN, gave products **8a**[35] and **9a**[36] in 46–85% yields (Scheme 9). Alkenes with electron-withdrawing groups, such as acrylo-

nitrile, crotonaldehyde, methyl acrylate, and methyl vinyl ketone, also reacted with n-C_6F_{13}I under the same radical conditions to afford the corresponding perfluoroalkylated products **10a**,[37,38] **11a**, **12a**, and **13a**[39,40] in good yields (Scheme 9).[4]

As well as the use of n-C_6F_{13}I as perfluoroalkylating reagent, the authors investigated the perfluoroalkylation reactions of electron-rich hex-1-ene with an array of perfluoroalkyl halides (C_nF_{2n+1}X, with n = 4, 8, 10, X = Br, I) in water under the same radical conditions (ACCN or dioxygen) to obtain products **5b**[41] (n = 4), **5d**[34] (n = 8), and **5e**[34] (n = 10) in yields ranging from 62–88% (Scheme 9) when X = I. With X = Br the yields were much lower.[4] This might reflect stronger BDEs of R_f–Br bonds than of R_f–I bonds.[4]

Acrylonitrile, on treatment with the C_nF_{2n+1}Br series (n = 6, 8, and 10), afforded the perfluoroalkylated-substituted propiononitriles **10a**,[39] **10d**,[42] and **10e**[39] in yields ranging from 44–77% when the reactions were initiated with ACCN. Crotonaldehyde, on treatment with n-C_6F_{13}Br, n-C_8F_{17}Br, and n-$C_{10}F_{21}$Br under the reaction conditions (ACCN), gave the perfluoroalkylated-substituted butyraldehydes **11a**, **11d**, and **11e** in 62, 60, and 55% yields, respectively (Scheme 9).[4]

On treatment with the C_nF_{2n+1}Br series (n = 6, 8, and 10), methyl acrylate afforded the perfluoroalkylated-substituted methyl propionates **12a**, **12d**,[43] and **12e** in yields ranging from 43–75% (Scheme 9), whereas vinyl methyl ketone, on treatment with n-C_6F_{13}Br, n-C_8F_{17}Br, and n-$C_{10}F_{21}$Br in water under ACCN/(Me_3Si)_3SiH thermal initiation conditions, afforded the 5-perfluoroalkylated-substituted butan-2-ones **13a**,[39,44] **13d**[45,39] and **13e**[29,39] in 67, 70, and 66% yields, respectively (Scheme 9).[4]

These sets of experiments might indicate that the lower yields obtained with the bromo-substituted perfluoroalkanes and alkenes in water under dioxygen initiation conditions, in relation to those obtained under ACCN initiation conditions, could be attributable to slower initiation in the former case rather than a retardation in the propagation step due to differences in the BDEs of R_f–I and R_f–Br bonds; however, some involvement of the BDEs of R_f–I and R_f–Br should also be considered.[4]

It was observed that the yields of products **5a**–**13a** under ACCN initiation conditions were much better than those under dioxygen initiation conditions (Scheme 9).

The authors also subjected electron-rich diallyl ether – 3-(allyloxy)prop-1-ene – to the radical perfluoroalkylation reaction conditions with n-C_6F_{13}I in water (ACCN initiation) and obtained the perfluoroalkylated tetrahydrofuran derivative **14a**[38] in 68% yield and in a *cis/trans* ratio of about 80:20 [Eq. (4)]. The *exo* cyclization of the *hex-6-enyl*
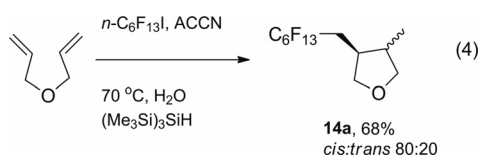
radical is a useful probe for elucidation of the radical mechanism of the reaction in water, as has also been observed for the cyclization of a 1-allyloxy-2-iodobenzene derivative in water.[46,47]

It can be deduced that all water-insoluble materials (substrates and reagents) suspended in the aqueous medium can interact as a result of the vigorous stirring, which creates an efficient vortex and dispersion.[4,48]

From these results, however, it becomes apparent that in water the reactivities of both electron-rich and electron-deficient alkenes towards R_f radical addition could be comparable (cf. substrates **5a**–**7a** and **10a**–**13a** in Scheme 9). In order to clarify this subtle aspect of the reactions in water, the authors undertook a set of experiments designed to compare the ratios of $(k_H/k_{add})_{hex-1-ene}$ and $(k_H/k_{add})_{acrylonitrile}$ for the addition reactions of n-C_6F_{13}I to the electron-rich hex-1-ene and the electron-deficient acrylonitrile, respectively, where k_H is the rate constant for H-abstraction from the silane [(Me_3Si)_3SiH] by the R_f radical and k_{add} is the rate constant for addition of R_f radical to the alkene. These ratios of rate constants are obtained by plotting [n-C_6F_{13}H]/[**5a**] versus [(Me_3Si)_3SiH]/[hex-1-ene] and [n-C_6F_{13}H]/[**10a**] versus [(Me_3Si)_3SiH]/[acrylonitrile], respectively, with thermal initiation of the reactions with use of incremental amounts of (Me_3Si)_3SiH and maintenance of constant alkene and n-C_6F_{13}I concentrations. Slopes for the two plots equal to 1.55 ± 0.09 (r^2 = 0.998) and 1.88 ± 0.19 (r^2 = 0.989) were obtained for $(k_H/k_{add})_{hex-1-ene}$ and $(k_H/k_{add})_{acrylonitrile}$, respectively. This seems to indicate that the reactivities of electron-rich and electron-deficient alkenes towards R_f radicals in water are leveled off. This well-known observed difference in the reactivities of electron-rich and electron-poor substrates towards R_f radicals in aqueous and organic solvents is of note, in view of the electrophilic character of R_f radicals.

1.3. Intramolecular Cyclization Reactions of Perfluoroalkyl Radicals in Water

The radical cyclization of 1-[(E)-but-2-enyloxy]-2-iodobenzene in water, affording 3-ethyl-2,3-dihydrobenzofuran in 85% yield with employment of (Me_3Si)_3SiH and an azo initiator, has been reported.[47] In this same account, 6-bromo-3,3,4,4,5,5,6,6-octafluorohex-1-ene[49] [**15**, Eq. (5)] was subjected to treatment with (Me_3Si)_3SiH and dioxygen in water to afford the *exo-trig* cyclization product 1,1,2,2,3,3,4,4-octafluoro-5-methylcyclopentane (**16**) in 76% yield (isolated).[2]

$$\text{15} \xrightarrow[\text{H}_2\text{O}/ (Me_3Si)_3SiH]{O_2 \text{ (r.t.), 24 h}} \text{16} \tag{5}$$
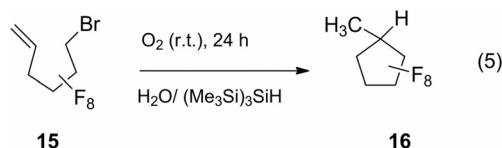
Although measurement of the rate constant for cyclization in the heterogeneous water system is difficult to achieve, only the *exo* cyclization product was found. The six-membered ring cyclized product (*endo* cyclization) has

$$\xrightarrow[\substack{70\ ^\circ C,\ H_2O \\ (Me_3Si)_3SiH}]{n\text{-}C_6F_{13}I,\ ACCN} \quad \textbf{14a}, 68\% \quad cis:trans\ 80:20 \tag{4}$$

not been observed in water (nor in organic solvents) under the reaction conditions reported. No uncyclized reduced product is observed either.[2]

Analogously, cyclization of 5-bromo-1,1,2,3,3,4,4,5,5-nonafluoropent-1-ene [**17**, Eq. (6)] triggered by $(Me_3Si)_3$-SiH/dioxygen in water leads to nonafluorocyclopentane, the *exo-trig* cyclization product, in 68% yield (isolated). No reduced product could be isolated from the reaction mixture. When carried out in $[D_6]$benzene the reaction did not afford cyclization product.[2]
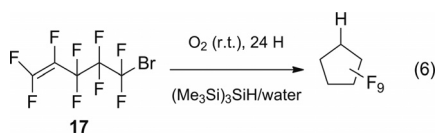
1.4. Intermolecular Cyclization Reactions of Perfluoroalkyl Radicals in Water

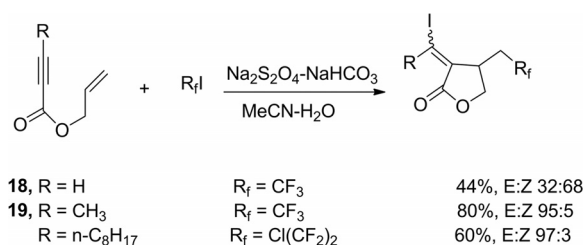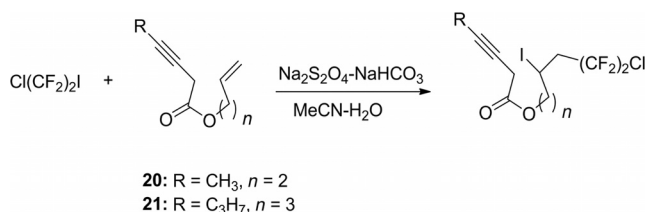Sulfinatodehalogenation reactions have also been used to accomplish intermolecular cyclization reactions of perfluoroalkyl radicals in water. Some of these reactions were reviewed as early as 1995 by Lu and co-workers.[50] A facile synthesis of perfluoroalkylated 3-iodoalkylidene-2(3*H*)-dihydrofuranone was achieved by making use of the preferential addition of perfluoroalkyl radicals generated from ET reactions of R_fI with $Na_2S_2O_4$ to electron-rich π bonds (Scheme 10).

Scheme 10. Synthesis of perfluoroalkylated 3-iodoalkylidene-2(3*H*)-dihydrofuranones through sulfinatodehalogenation reactions.[50]

When homoallyl but-2-ynoate (**20**) and bishomoallyl hex-2-ynoate (**21**) were subjected to the same reaction conditions as above, both gave simple addition products and no cyclization products were detected (Scheme 11).

Scheme 11. Sulfinatodehalogenation reactions of homoallyl but-2-ynoate (**20**) and bishomoallyl hex-2-ynoate (**21**).[50]

The difficulty in forming six- and seven-membered rings is understood in terms of the *hept-6-enyl* and *oct-7-enyl* radicals cyclizing at rather low rates relative to *hex-5-enyl* radicals.[51a]

On the other hand, when allyl but-2-enoate (**22**) was subjected to the same reaction conditions, no ring closure product was obtained (Scheme 12).[50]
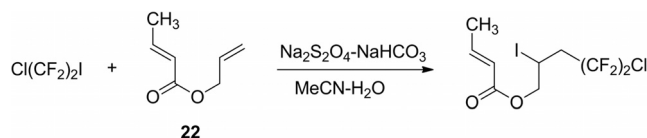
Scheme 12. Sulfinatodehalogenation reaction of allyl but-2-enoate (**22**).[50]

The difference between allyl alk-2-ynoates **18** and **19** and allyl alk-2-enoate **22** is that the triple bond in the alkyne could provide two orthogonal π bonds for the possible cyclization. Whereas **23** must adopt an unfavorable conformation to accomplish the overlap of the radical SOMO and the π-orbital of the double bond, **24** was easily able to achieve an arrangement for cyclization without disturbing the stabilizing conjugation between the triple bond and the carbonyl group (Figure 1).[50]
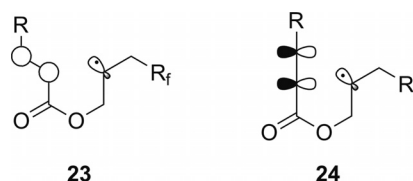
Figure 1. Preferential intramolecular cyclization of radicals onto triple bonds versus double bonds.

The main problem in cyclizations of radicals of types **23** and **24** is the low populations of the reactive rotamers. The orbitals can only interact if the radicals are in the higher-energy *cis* configurations (see **23** and **24**; vide infra in Scheme 14 for alkynamides). For the propiolates the *E/Z* rotamer ratio is more favorable for cyclization (populations of the *E* isomers are higher, due to weaker steric interaction with the smaller triple bonds than with the double bonds in the acrylates). An explanation is provided by the Ueno–Stork approach through the acetals.[51b]

The same authors also attempted perfluoroalkylation of *N*-allyl-alk-2-ynamides (Scheme 13).[50]
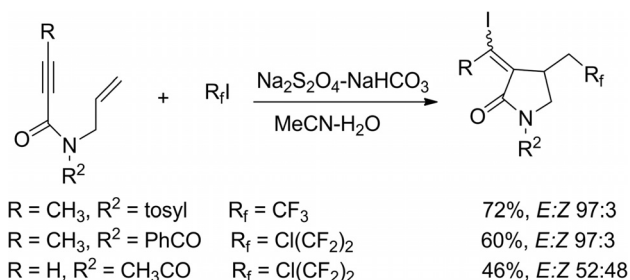
Scheme 13. Perfluoroalkylations of *N*-allyl-alk-2-ynamides initiated by sodium dithionate/sodium hydrogen carbonate.[50]

When the substituents on the nitrogen atoms of the *N*-allyl-alk-2-ynamides were small, such as H, CH_3, or C_3H_7, ring opening products were obtained as well. This can be explained in terms of *trans* rotamers such as those shown in Scheme 14, with radical centers far away from the triple bonds being incapable of cyclization.[50]
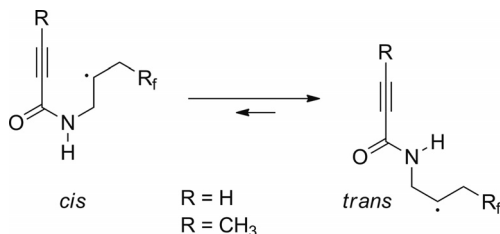
Scheme 14. Rotamers (*cis* and *trans*) of *N*-allyl-alk-2-ynamides.[51a]

Huang and co-workers attempted the sulfinatodehalogenation reaction between diallyl ether and CF_2Br_2 in CH_3CN/H_2O, obtaining the ring-closed product in good yield.[24]

The synthesis of perfluoroalkyl-substituted γ-lactones under sulfinatodehalogenation reaction conditions has also been accomplished (Scheme 15).[52]

$R^1 = R^2 = R^3 = R^4 = H$	81 %
$R^1 = R^2 = CH_3$, $R^3 = R^4 = H$	86 %
$R^1 = R^2 = H$, $R^3 = R^4 = CH_3$	85 %
$R^1 = n$Bu, $R^2 = R^3 = R^4 = H$	70 %
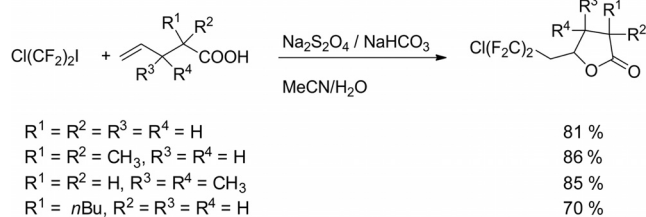
Scheme 15. Synthesis of perfluoroalkyl-substituted γ-lactones.[52]

Wu and co-workers[53] performed the synthesis of fluoro-alkyl δ-lactones from polyfluoroalkyl iodides and hex-5-en-oic acids under sulfinatodehalogenation reactions (Scheme 16).

Shi and Huang attempted sulfinatodehalogenation reactions between *gem*-aryl-disubstituted methylenecyclopropanes (MCPs) and perfluoroiodoalkanes (Scheme 17).[54]

A plausible mechanism for the formation of products **25**–**27** is illustrated in Scheme 18.

Sodium dithionate generates the corresponding perfluoroalkyl radical species ($R_f^·$) by a single-electron-transfer (SET) process as shown initially in Scheme 1. This $R_f^·$ radical adds to the double bond of the MCP to give radical

$R_f = C_2F_5$ R = H, Et, Bu	88%, E:Z 3:1	10%
$R_f = C_6F_{13}$ R = H, Et, Bu	60%, E:Z 5.5:1	35%
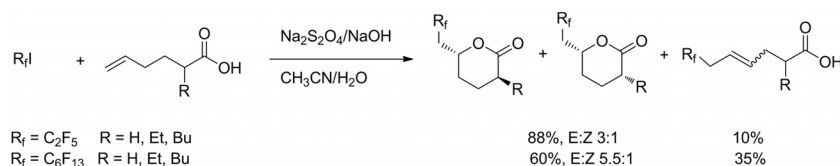
Scheme 16. Synthesis of fluoroalkyl δ-lactones from polyfluoroalkyl iodides and hex-5-enoic acids.[53]

R = H
R = CH_3
R = MeO

25: 38%, **26**: 12%, **27**: 6%
25: 41%, **26**: 10%, **27**: 6%
25: 56%, **26**: 24%, **27**: 6%

Scheme 17. Sulfinatodehalogenation reactions between *gem*-aryl-disubstituted methylenecyclopropanes (MCPs) and perfluoroiodoalkanes.[54]
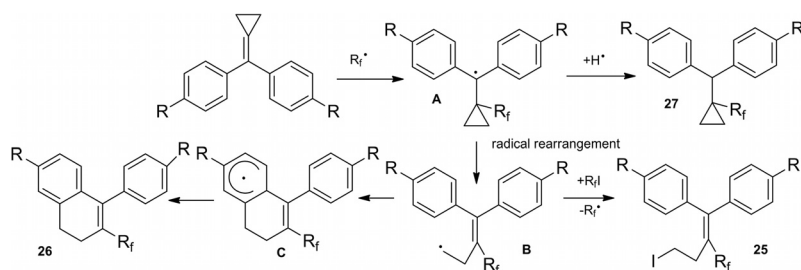
Scheme 18. Plausible mechanism for the $Na_2S_2O_4$-mediated radical reactions between methylenecyclopropenes (MCPs) and polyfluoro-iodoalkanes.[54]

intermediate **A**, due to its electrophilic nature, and this is transformed into the subsequent radical intermediate **B** through the well-known cyclopropyl radical rearrangement (Scheme 18). The radical intermediate **B** reacts with another molecule of R_fI through an iodine atom transfer to produce **25** and to regenerate the $R_f^·$ radical species (Scheme 18). On the other hand, the radical intermediate **B** can also generate the radical intermediate **C** through an intramolecular homolytic aromatic substitution (S_H) reaction, from which product **26** (Scheme 18) is formed and a hydrogen radical (H·) is generated. The recombination of radical intermediate **A** with a hydrogen radical (H·) affords product **27** (Scheme 18).

When 3,3,4,4-hexa-1,5-diene (**28**) is allowed to react with $(Me_3Si)_3SiH$/dioxygen and C_2F_5I in water, product **29** is obtained in 61 % yield, based on C_2F_5I [Eq. (7)].[55]

(7)

2. Hydrogen Abstraction Reactions of Perfluoroalkyl Radicals

Dolbier et al.[56] found perfluorinated radicals to be much more reactive than their hydrocarbon counterparts in addition reactions with normal, electron-rich alkenes such as hex-1-ene (40000 times more reactive) in organic solvents, and also found H transfer from $(Me_3Si)_3SiH$ to a perfluoro-*n*-alkyl radical such as n-$C_7F_{15}CH_2CH(·)C_4H_9$ [**30**, Eq. (8)] to be 110 times more rapid than to the analogous hydrocarbon radicals.[57]

The authors thus determined that k_{add} [Eq. (8)] has a value of 7.9×10^6 $M^{-1}s^{-1}$ in [D_6]benzene at 298 K and that the value of k_H is about 50×10^6 $M^{-1}s^{-1}$ in [D_6]benzene at 303 K.

According to what was observed and measured by Dolbier et al.,[56] in [D_6]benzene the ratio of products [**32**]/[**31**] [Eq. (8)] should equal the ratio of the rate constants for addition (of perfluorinated heptyl radical to hex-1-ene) and for H abstraction from $(Me_3Si)_3SiH$ multiplied by the ratio of concentrations of alkene and silane.

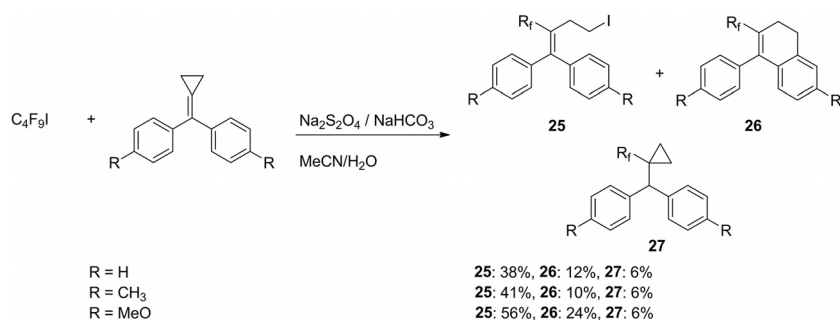The ratio of rate constants $(k_H/k_{add})_{hex-1-ene}$ obtained in benzotrifluoride as solvent[16] for the reaction between n-$C_7F_{15}I$ and hex-1-ene with $(Me_3Si)_3SiH$ as the hydrogen donor [Eq. (8)] is 6.32, whereas that same ratio of rate constants for the reaction between n-$C_6F_{13}I$ and hex-1-ene in water is 1.55 (vide supra).[4] The unavailability of rate constants for $R_f^·$ radical addition onto double bonds in *water* makes comparisons difficult, but results from the same authors seem to imply that the rate for hydrogen donation from $(Me_3Si)_3SiH$ to the $R_f^·$ radical relative to the addition reaction is four times *slower* in *water* than in benzotrifluoride as solvent [i.e.: $(k_H/k_{add})_{water}/(k_H/k_{add})_{benzotrifluoride} = 0.25$]. Indeed, it is likely that water does influence the H-transfer step from the silane to the C-radical. This is well established and important for phenols, but not known for silanes. In the phenol series, H-bonding between the phenol and the solvent leads to stabilization and consequently to less efficient H-transfer.[58] H-bonding from the silane to water might have a similar effect, because the authors report on slower H-transfer relative rates in water. It can also be hypothesized that in view of the known hypervalency of silicon, coordination of a water molecule might diminish the hydrogen atom donation of the silicon hydride.

The authors[4] also showed that on plotting [n-$C_6F_{13}H$]/[**5a**] versus [$(Me_3Si)_3SiH$]/[hex-1-ene] (Scheme 9) a straight line, the slope of which represents $(k_H/k_{add})_{hex-1-ene}$, is obtained (with a value of 1.55 ± 0.09, $r^2 = 0.998$). The intercept of this plot shows, remarkably, no deviation from the ideal value of zero, implying that the only source of n-$C_6F_{13}^·$ radical reduction (i.e., n-$C_6F_{13}H$) is the silane, and not the solvent or the alkene.[59]

3. Aromatic Radical Substitutions of Perfluoroalkyl Radicals

Unlike radical perfluoroalkylation addition reactions of unsaturated compounds, fluoroalkyl radical substitution on aromatic ring systems has received little attention.

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 (Scheme 19) and 1-bromo-1-chloro-2,2,2-trifluoroethane was treated under sulfinatodehalogenation reaction conditions ($Na_2S_2O_4$/$NaHCO_3$ in CH_3CN/H_2O), a radical substitution of H by R_f was achieved.[60]

The authors[60] postulate a radical mechanism such as that depicted in Scheme 20.

(8)
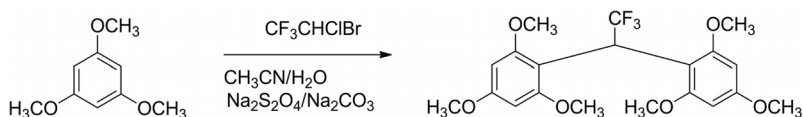
Scheme 19. Synthesis of trifluoromethyl-bis(2,4,6-trimethoxyphenyl)methane through a sulfinatodehalogenation reaction.[60]
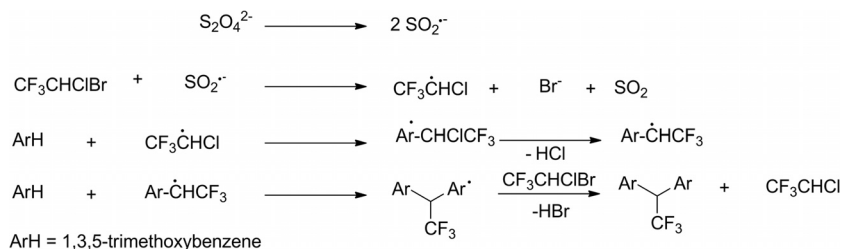
Scheme 20. Mechanism for the aromatic radical substitution reaction of H by R_f.[60]

In another report by the same leading author,[61] aromatic substitutions of trimethoxybenzenes and pyrroles with $BrCF_2CF_2Br$ were attempted (Scheme 21).
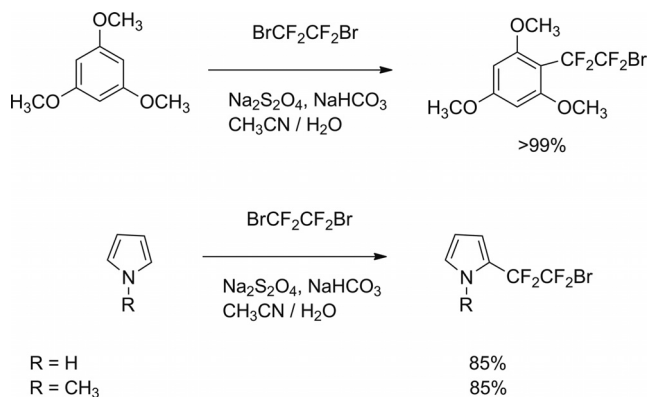
Scheme 21. Radical aromatic substitution reactions of 1,3,5-trimethoxybenzene and pyrroles with $BrCF_2CF_2Br$ under sulfinatodehalogenation reaction conditions.[61]

More recently, Lu and co-workers[62] have accomplished the polyfluoroalkylation of 2-aminothiazoles (Scheme 22). Treatment of 2-aminothiazole with C_4F_9I under sulfinatodehalogenation reaction conditions gave the substitution product in 80% yield with total selectivity for the 5-position of 2-aminothiazole (Scheme 22). A number of N-substituted 2-aminothiazoles also reacted with R_fI and R_fBr with yields ranging from 58 to 90%.[62]
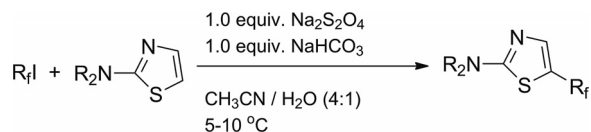
Scheme 22. Radical perfluoroalkylation of 2-aminothiazole derivatives.[62]

Interestingly, when $(CF_3)_2CFI$ was used under the same conditions, unexpected C–F bond reduced products were obtained in place of the perfluoroalkylated derivatives (Scheme 23).
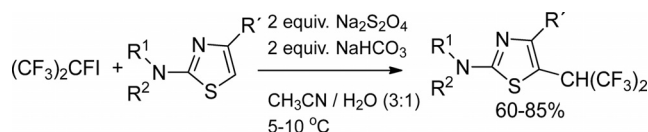
Scheme 23. Radical perfluoroalkylation substitution reactions between 2-aminothiazole derivatives and $(CF_3)_2CFI$ under sulfinatodehalogenation reaction conditions.[62]

The proposed mechanism for the reduced products is depicted in Scheme 24.
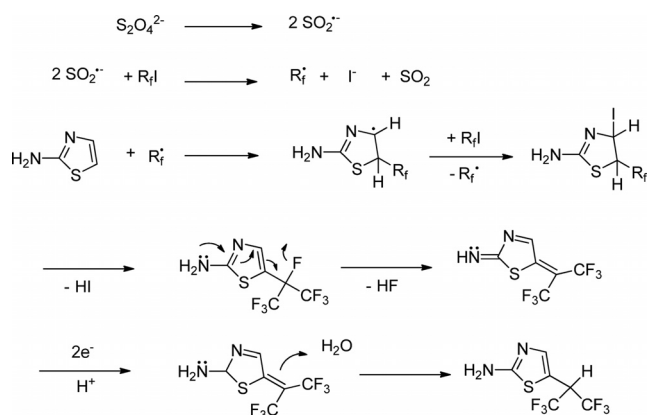
Scheme 24. Proposed mechanism for reduced products from 2-aminothiazoles and $(CF_3)_2CFI$.[62]

Although defluorination of polyfluoroalkyl-substituted arenes followed by nucleophilic attack by water has been well documented,[63] very few reductive defluorinations of polyfluoroalkyl-substituted arenes under mild conditions have previously been reported, and no other such reaction in an aqueous medium has been documented.

4. Radical Perfluoroalkylation of Ammonium Enolates

Cahard and co-workers[64] investigated the radical trifluoromethylation of cyclic and acyclic 1,3-dicarbonyl com-

pounds (β-keto esters and 1,3-diketones) with CF_3I, diiso-propylethylamine (DIEA) as the base, $Na_2S_2O_4$ as the radical initiator, and CH_3CN/H_2O as the solvent. Cyclic β-keto esters **33a–d** reacted with CF_3 radical generated from $Na_2S_2O_4$ and CF_3I to give the corresponding products **34a–d** in high isolated yields (Table 1). When benzyl 2-oxocyclopentanecarboxylate was used as a cyclic substrate with no aromatic fused ring, the trifluoromethylation occurred in only 28% yield. Replacement of the ester moiety with a keto group, as in 1,3-diketone **33e**, afforded the trifluoromethylated compound **34e** in 80% yield.

Table 1. Radical trifluoromethylation of β-dicarbonyl compounds.[64]

Substrate	n	R	Product	Yield [%], isolated prod.
33a	1	OMe	**34a**	84
33b	2	OMe	**34b**	86
33c	1	OBn	**34c**	84
33d	1	O-menthyl	**34d**	94
33e	2	Me	**34e**	80

The acyclic ammonium enolates generated from **33f–h** produced the trifluoromethylated products **34f–h** (Scheme 25) in moderate yields in the presence of the phase-transfer catalyst nBuNI and K_2CO_3.[64]

Scheme 25. Radical trifluoromethylation of acyclic 1,3-dicarbonyl compounds.[64]

A mechanism for the radical trifluoromethylation of 1,3-dicarbonyl compounds was proposed by the same authors.[64] The sulfinic radical anion $SO_2^{\cdot-}$, existing in equi-librium with dithionate anion $S_2O_4^{2-}$, generates the highly electrophilic trifluoromethyl radical from CF_3I by a SET mechanism. The CF_3 radical adds to the enolate **A** to afford the anion radical intermediate **B**, which reacts with another molecule of CF_3I to give trifluoromethylated anion **C**. After elimination of halogen atom, the trifluoromethylated product **D** is formed (Figure 2).[64]

The capture of the CF_3 radical with sulfinic anion radical to give the trifluoromethanesulfinate (*triflinate*) is not usually observed in trifluoromethylation of 1,3-dicarbonyl compounds. A control experiment demonstrated that CF_3I does not react with sodium dithionate alone; however, the addition of a nitrogen base enabled the formation of ammonium trifluoromethanesulfinates (Scheme 26). The nitrogen base therefore activates CF_3I.

Scheme 26. Synthesis of ammonium trifluoromethanesulfinates.

Conclusions

The advantages of performing radical addition and substitution perfluoroalkylation reactions with fluorinated radicals and organic substrates in water and aqueous media are well-known as a result of their efficiency, selectivity, easy-to-separate products, and handling in environmentally-benign reaction media. The enhanced reactivities of perfluoroalkyl radicals in water facilitate their addition reactions to carbon-carbon and carbon-heteroatom multiple bonds. The aim of this account is to show that radical perfluoroalkylation reactions of unsaturated compounds can effectively be achieved in water or aqueous media, with ease in separation and reductions in environmental impact and costs.

Acknowledgments

Figure 2. Proposed mechanism for the formation of 2-trifluoromethyl-substituted 1,3-dicarbonyl compounds by radical trifluoromethylation.[64]

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