



Tetrahedron report number 627

Perfluoroalkanes

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1. Introduction and scope

Although perfluoroalkanes, saturated systems consisting solely of carbon and fluorine, were first synthesised over 60 years ago¹ and have since been utilised for a variety of industrial applications,^{2–4} it is, arguably, only recently that this class of compound has come to the attention of the wider synthetic organic chemistry community. The recent developments of fluorous biphasic chemistry,⁵ which makes use of the unusual solubility characteristics of perfluoroalkanes, and the realisation that these ‘chemically inert materials’ do, in fact, have an interesting and developing chemistry (carbon–fluorine bond activation⁶) have helped to refocus the efforts of synthetic chemists on the investigation of these systems. It was therefore considered an opportune time to provide an overview of the synthesis and chemistry of perfluoroalkanes in the form of a Tetrahedron report, although, of course, aspects of per-

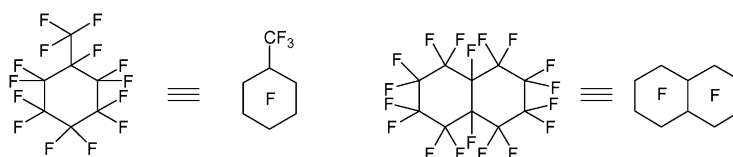
fluoroalkane chemistry have appeared in numerous general books and reviews concerning organofluorine chemistry.^{1,7–10}

This review aims to provide an overview, rather than a comprehensive summary, of the synthesis and reactions of ‘small molecule’ perfluoroalkanes. Perfluoroalkane polymers such as polytetrafluoroethylene and FEP, (a co-polymer of tetrafluoroethylene and hexafluoropropene) have, of course, many industrial uses and the reader is directed to the large commercial and academic literature regarding the synthesis and properties of these systems.¹¹ Similarly, graphite fluoride, $-(CF)_n-$, prepared by the reaction of elemental fluorine with graphite, is covered in detail elsewhere¹² rather than in the present review.

Perfluoroalkanes are systems with an empirical formula C_nF_{2n+2} in which all hydrogen atoms of the corresponding hydrocarbon have been replaced by fluorine. Cyclic perfluoroalkanes (C_nF_{2n}) are usually denoted as shown below where the fluorine in the centre of the ring indicates that all unmarked bonds to carbon are fluorine.

Keywords: perfluoroalkanes; saturated perfluorocarbons; carbon–fluorine bond activation; perfluorination.

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The very strong carbon–fluorine bond, indeed, fluorine forms the strongest single bond to carbon (typical $BDE^\ddagger=452\text{--}531\text{ kJ mol}^{-1}$), imparts some unusual physical properties on perfluoroalkanes.¹³ The compounds are very stable and have atmospheric lifetimes predicted to be >2000 years.¹⁴ Very low intermolecular attractive forces lead to systems with relatively low boiling points and high volatility considering their molecular weight. Perfluorohexane (MW 388), for example, boils at 82.5°C while hexane (MW 84) boils at 69°C , despite having a much higher molecular mass. Perfluoroalkanes are non-polar, non-ozone depleting, colourless, odourless, non-toxic, non-flammable materials that do not require any special handling procedures.

Whilst most typical organic compounds have limited or no solubility in perfluoroalkane fluids, highly fluorinated organic systems are soluble and both these properties have been utilised in the development of fluororous biphasic synthesis (Section 4.2). The factors affecting the partition coefficients of molecules in perfluoroalkane fluids have been assessed by Rabai¹⁵ and, generally, molecules that contain $>60\text{ wt}\%$ of fluorine, several, long perfluoroalkyl groups and a low number of functional groups that are capable of hydrogen bonding are soluble in perfluoroalkanes.

Perhaps surprisingly, perfluoroalkanes can dissolve large quantities of gases.¹⁶ As much as $40\text{ vol}\%$ of oxygen, for example, may be dissolved in perfluorodecalin, giving rise to the now well known oxygen-carrying properties for ‘liquid breathing’ and the long-awaited general development of ‘artificial blood substitutes’.^{17,18}

Since the first syntheses of perfluoroalkanes, many industrial applications have been found for these unusual materials. Perfluoroalkanes have been, and continue to be, used as inert fluids, etchants, cooling agents, for vapour phase soldering, as ultrasound image-enhancing agents, oxygen carriers and to facilitate eye surgery.^{2–4,16}

2. Synthesis of perfluoroalkanes

2.1. Perfluorination of hydrocarbons

Most commonly, the synthesis of saturated perfluoroalkanes consists of the direct replacement of all carbon–hydrogen bonds by carbon–fluorine bonds by transformation of the corresponding hydrocarbon with an appropriate fluorinating agent such as elemental fluorine, cobalt trifluoride or anhydrous hydrogen fluoride in an electrochemical cell. These three methods are very well established and a general

overview of the techniques and principles of each process is now discussed.

2.1.1. Direct fluorination with elemental fluorine. Early experiments by Moissan (see Ref. 1), the first chemist to isolate elemental fluorine, between fluorine and hydrocarbons resulted in very violent reactions and it was some time before a realistic methodology for the transformation of alkanes to perfluoroalkanes, by direct fluorination, was established.

Replacement of hydrogen by fluorine at saturated sites is highly exothermic because of the high bond energies of the bonds being formed ($BDE\text{ C–F}$, $452\text{--}531\text{ kJ mol}^{-1}$ and C–H , ca. 410 kJ mol^{-1}) compared to the weak F–F bond ($BDE\text{ F–F}$ 157.7 kJ mol^{-1}) that is broken. Consequently, perfluorination of hydrocarbon substrates is generally regarded as being a free radical process¹⁹ (Table 1). Unsaturated hydrocarbons may also be transformed to perfluoroalkanes^{20,21} because the total energy released upon fluorine addition to a carbon–carbon double bond (typically, between $251.4\text{--}292.9\text{ kJ mol}^{-1}$) is not sufficient to break carbon–carbon single bonds.

Table 1. Thermodynamic data for the fluorination of methane

Initiation	ΔH_{25} (kJ mol^{-1})
$\text{F}_2 \rightarrow 2\text{F}\cdot$	157.7
<i>Alternative initiation</i>	
$\text{R–H} + \text{F}_2 \rightarrow \text{R}\cdot + \text{HF} + \text{F}\cdot$	16.3
<i>Propagation</i>	
$\text{R–H} + \text{F}\cdot \rightarrow \text{R}\cdot + \text{HF}$	–141.4
$\text{R} + \text{F}_2 \rightarrow \text{R–F} + \text{F}\cdot$	–289.1
<i>Overall reaction</i>	
$\text{R–H} + \text{F}_2 \rightarrow \text{R–F} + \text{HF}$	–430.5

The concentration of fluorine atoms at room temperature may not be sufficient to initiate a free radical chain process (fluorine is $<1\%$ dissociated at ambient temperature) and an alternative initiation step (Table 1) probably occurs,²² although conclusive evidence for this pathway has not been established.

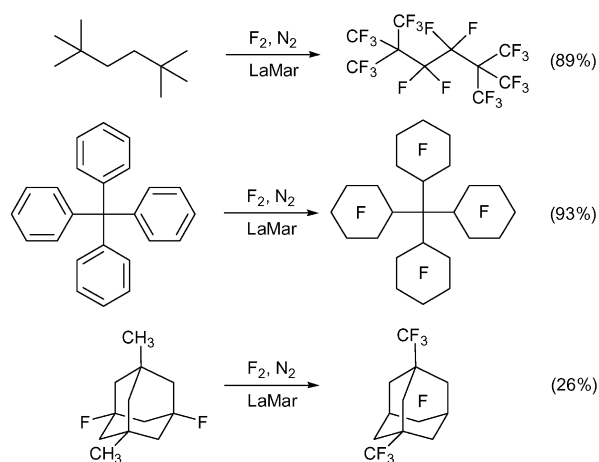
Due to the highly exothermic nature of the process, the replacement of primary, secondary and tertiary hydrogens upon reaction with electrophilic fluorine atoms is not as selective as for other radicals. A detailed study of the perfluorination of neopentane by Adcock²³ under free radical conditions confirmed the order of hydrogen reactivity to be $\text{CH}_3 > \text{CH}_2\text{F} > \text{CHF}_2$. As the C–H bond becomes more electron deficient, due to the presence of neighbouring fluorine atoms, hydrogen abstraction by electrophilic fluorine atoms (propagation, Table 1) becomes less efficient. Since hydrofluorocarbons are less nucleophilic and have a significantly lower oxidation potential, which lowers with increasing fluorine content, than the

[†] Bond dissociation energy.

corresponding hydrocarbons, fluorination becomes increasingly difficult as the perfluorination reaction proceeds. Partially fluorinated substrates are indeed more stable towards the fluorination process and yields of perfluorinated compounds are generally higher when partially fluorinated precursors are used as the substrates rather than the corresponding hydrocarbons because, in these systems, the reactions are more controlled and less substrate degradation occurs.

In order to prevent carbon–carbon bond cleavage during a fluorination reaction, there must be a method of rapidly dissipating the large heat of reaction. Consequently, fluorine is generally diluted with an inert gas such as nitrogen and the reactions are cooled in the initial stages. Sodium fluoride may be added to the reaction medium to act both as a heat transfer agent and as a hydrogen fluoride scavenger.^{24,25} As the perfluorination reaction proceeds and fluorination becomes increasingly difficult, the concentration of fluorine atoms is maximised by lower dilution, higher reaction temperatures and, in some processes, by UV light.

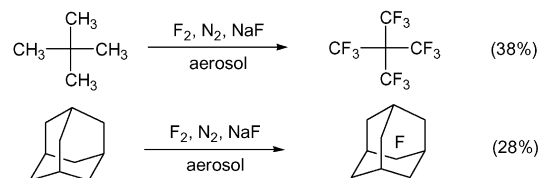
The jet fluorination apparatus and a catalytic metal-packing process were initial techniques that made advances in the development of feasible perfluorination methodology.^{26,27} It was not until the development of the low temperature gradient LaMar technique, however, that any real progress in the study of direct perfluorination of organic substrates was made and the early phases of this work have been reviewed.^{19,28} Essentially, the substrates are condensed at low temperature into a tube packed with copper turnings through which fluorine, initially highly diluted in either helium or nitrogen, is passed. The concentration of fluorine and the reaction temperature are slowly increased over a period of several days to effect perfluorination. Many acyclic, cyclic, polycyclic and cage perfluoroalkanes have been synthesised by this technique and some examples are given below (Scheme 1).^{20,29,30}



Scheme 1.

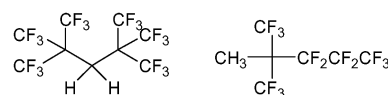
In the continuous flow aerosol fluorination process,²⁴ the substrate is absorbed onto sodium fluoride particles which are then sprayed as aerosols into the fluorination chamber in which the fluorine concentration and the temperature increase along the length of the reaction vessel. A UV photofluorination finishing stage completes the perfluorina-

tion process. Many perfluoroalkanes have been prepared by this technology and two examples are given below (Scheme 2).^{23,31}



Scheme 2.

As a perfluorination reaction proceeds, the carbon skeleton becomes increasingly sterically protected by the growing number of non-bonding electron pairs on fluorine that inhibit further attack by incoming fluorine atoms. In some cases, the hydrogen atoms are so sterically shielded that substitution by fluorine does not occur and, for instance, both substrates shown below are recovered after exposure to 100% fluorine over several days.^{32,33}

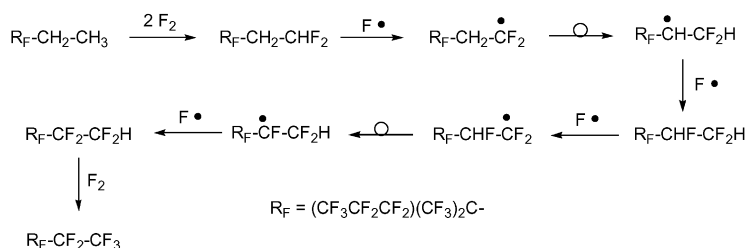


Where substitution of sterically shielded hydrogen atoms appears to be possible, for example, in the case below, radical rearrangement processes rather than direct substitution, are envisaged (Scheme 3).³³

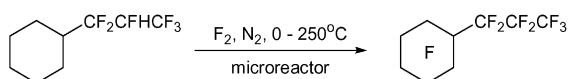
Advances in continuous flow perfluorination technology, making use of microchannels as reaction vessels, provide a very effective methodology for perfluorination. There is a considerable effort worldwide directed towards miniaturisation of a vast array of procedures and reactor design is an especially important area.^{34–36} There are many advantages associated with using continuous flow microreactors for chemical synthesis including high throughput, use of very small quantities of material when appropriate, reduced waste streams, low manufacturing, operation and maintenance costs, low power consumption, increased precision and safety. Miniaturisation may also lead to increased performance of a system due to optimisation of contact between the reagents caused by very rapid mixing in such devices.

In preliminary experiments,³⁷ perfluorination of partially fluorinated alkanes was accomplished in a highly efficient manner when carried out using a nickel microreactor. As an example, perfluorination of the hexafluoropropylcyclohexane derivative, below, was achieved in three stages, each stage consisting of the passage of the substrate in a suitable solvent and an appropriate concentration of fluorine through the microreactor system. The mass recovery is high and the structural integrity of the substrate is maintained (Scheme 4).

In general, therefore, direct fluorination presents an increasingly versatile methodology for the synthesis of a variety of structurally diverse perfluorocarbons because of the lack of rearrangement products observed and, if the



Scheme 3.

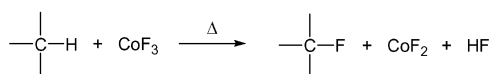


Scheme 4.

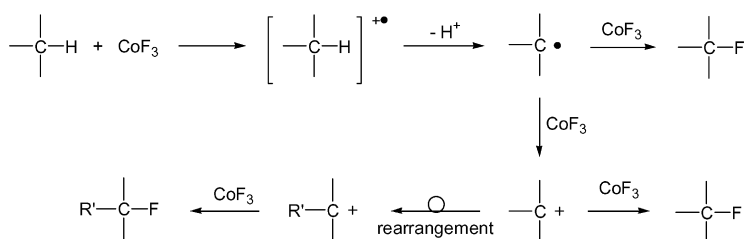
reaction conditions are suitably controlled, the absence of substrate degradation.

2.1.2. Cobalt trifluoride and related reagents. Perfluorination of hydrocarbons by cobalt trifluoride was first achieved over 50 years ago and the development of this methodology has been the focus of much research and industrial effort. The use of cobalt trifluoride has been reviewed extensively^{38–41} for both the perfluorination and polyfluorination of hydrocarbon systems and only a brief overview of this chemistry is given here.

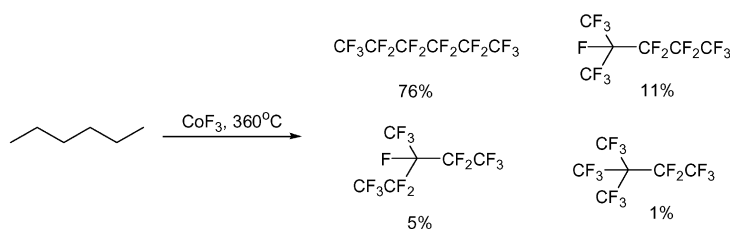
Essentially, the hydrocarbon substrates are passed within a stream of dry nitrogen, over a fluidised bed of cobalt trifluoride heated to at least 300°C to effect perfluorination. Perfluoroalkanes are collected while cobalt trifluoride may be regenerated by heating the cobalt difluoride byproduct with fluorine gas.^{38,42} Perfluorination by cobalt trifluoride is less exothermic than the use of elemental fluorine due to the high lattice energy of cobalt trifluoride compared to the weak fluorine–fluorine bond and so higher temperatures are required compared to the use of fluorine alone (Scheme 5).



Scheme 5.



Scheme 6.



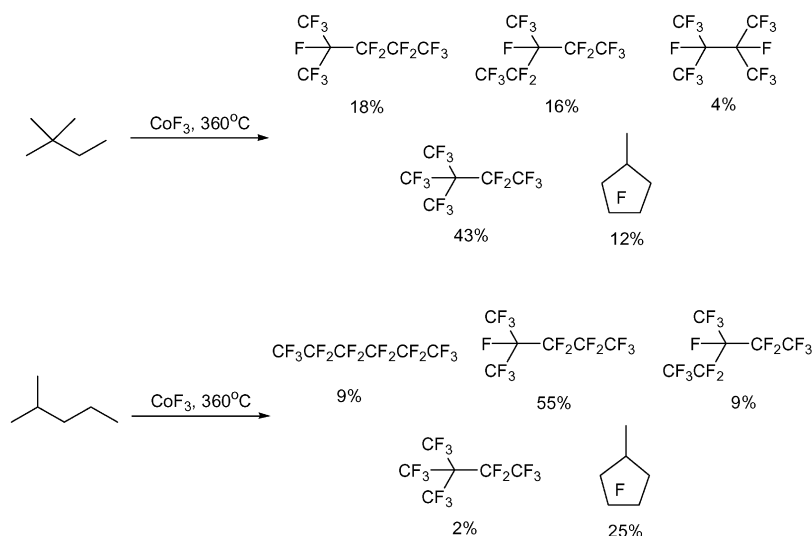
Scheme 7.

Industrially, perfluoroalkanes are synthesised by passing streams of fluorine and the organic substrate simultaneously over a heated, rotating bed of cobalt trifluoride in a continuous process.³ A variety of perfluoroalkanes are currently manufactured by the cobalt trifluoride fluorination methodology and marketed as the Flutec[®] range (F2 Chemicals Ltd, Preston, UK).

Extensive studies indicate that the ease of fluorination is C–H tertiary > C–H secondary > C–H primary and the mechanism of these reactions is generally considered to involve a single electron transfer process as indicated below (Scheme 6).^{43–45}

The presence of carbocation intermediates in the reaction pathway is supported by the isolation of various perfluoroalkanes resulting from initial carbocationic rearrangement processes in the highly acidic reaction medium.⁴⁵ Perfluorination of linear hydrocarbons by cobalt trifluoride, for example, leads to inseparable mixtures of various perfluorinated derivatives, the use of *n*-hexane leading to a mixture of four products (Scheme 7).⁴⁵

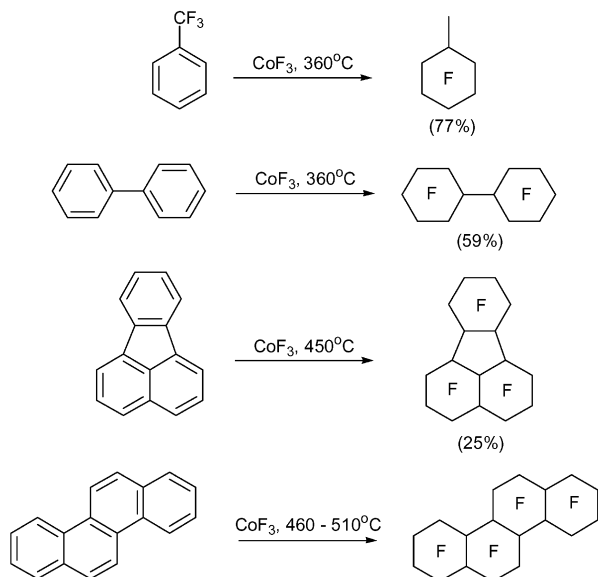
These rearrangements, however, cannot be considered to have reached equilibrium because it would have been expected that perfluoro-2,2-dimethylbutane was the sole product from the fluorination of *n*-hexane if this were true. In addition, if equilibrium is reached, a similar product distribution for the fluorination of all C-6 isomers would be obtained and this is not observed, as shown for the fluorination of various branched C-6 alkanes (Scheme 8).⁴⁵



Scheme 8.

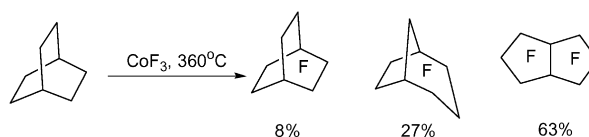
Consequently, the results can be interpreted as involving carbocation intermediates that form and rearrange early in the reaction sequence. The proportion of skeletally rearranged products increases with increasing chain length with, for instance, *n*-octane giving >50% rearranged products upon heating with cobalt trifluoride.⁴⁴ Cobalt trifluoride methodology is not, therefore, realistic for the synthesis of straight chain perfluoroalkanes.

Perfluorination of cyclic alkanes can lead to ring opening, cyclobutane, for example, giving a similar product profile to the fluorination of *n*-butane, or rearrangement. Medium-sized rings such as cyclooctane give many products arising from carbocationic rearrangements early in the reaction sequence.⁴⁶ Perfluorocyclohexane can, however, be prepared in good yield from cyclohexane because, in this case, dehydrogenation to benzene precedes fluorination. Indeed, perfluorination of aromatic substrates has proven to be much more useful for the synthesis of perfluoroalkanes and some representative synthetically useful reactions are given below (Scheme 9).^{47–49}



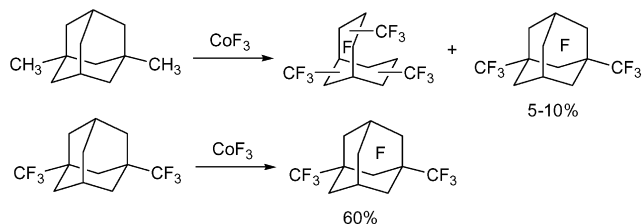
Scheme 9.

Bicyclic hydrocarbons have also been perfluorinated by cobalt trifluoride, although these reactions can be additionally complicated by products arising from carbocation rearrangement processes (Scheme 10).⁵⁰



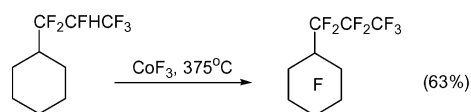
Scheme 10.

Partially fluorinated derivatives are often used to circumvent the skeletal rearrangements found when hydrocarbons are used as the substrates, 1,3-dimethyladamantane giving a range of ring-opened products upon fluorination, whereas 1,3-bis(trifluoromethyl)adamantane gives high yields of the corresponding perfluoroadamantane system (Scheme 11).⁵¹



Scheme 11.

Similarly, various perfluoroalkylated cyclic systems have also been synthesised from polyfluoroalkylated substrates, without the formation of concomitant rearrangement products (Scheme 12).⁵²



Scheme 12.

In these examples, the presence of fluorine atoms in the substrate restricts carbocation formation due to the destabilising effect of fluorine atoms located adjacent to a

positively charged carbon centre. The perfluoroalkyl groups also serve to reduce the oxidation potential of the organic substrate, making the molecules less prone to degradation in the harsh reaction environment. Consequently, if perfluorinated polycyclic derivatives are required, then partially fluorinated substrates should be used.

Other related high valency transition metal fluorides such as potassium tetrafluorocobaltate,⁵³ cerium(IV) fluoride⁵⁴ and manganese(III) fluoride⁵⁵ have been studied as fluorinating reagents for perfluoroalkane synthesis, but these compounds are generally less effective than cobalt trifluoride.

2.1.3. Electrochemical fluorination. Electrochemical fluorination (ECF) is a well-established technique for the synthesis of a variety of functional perfluorocarbon derivatives and this field has been extensively reviewed.^{56–58}

Essentially, electrolysis of an organic substrate, dissolved in anhydrous hydrogen fluoride, at a nickel anode at a voltage lower than that required for the evolution of elemental fluorine, gives the corresponding perfluorinated derivatives. The low solubility and conductivities of hydrocarbons in anhydrous HF makes perfluorination of such substrates more difficult than, for example, ethers and amines, but, nevertheless, perfluoroalkanes can be accessed by ECF methodology, although significant amounts of products arising from rearrangement processes give rise to very complex mixtures from even the simplest of hydrocarbon

substrates.^{59,60} ECF of *n*-heptane is, however, reported to give approximately 70% yield of pure perfluoro-*n*-hexane (Scheme 13).⁴

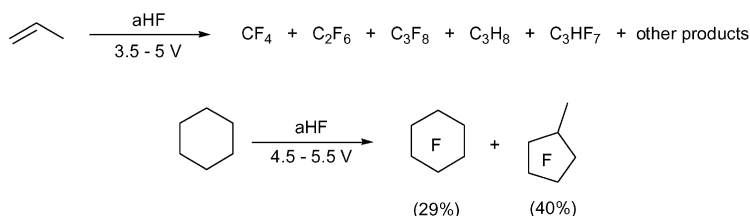
Despite the fact that ECF has been developed by many groups worldwide, the precise mechanism is still under debate and two alternative views are held, these having been discussed at length.⁵⁸ The carbocation mechanism involves oxidation of the organic substrate, followed by trapping of the carbocations formed by fluoride ion (Scheme 14).

A radical mechanism, involving the generation of either fluorine atoms, fluorine or nickel fluorides that are sufficiently powerful to fluorinate the substrate by a free radical chain process, is the alternative explanation.

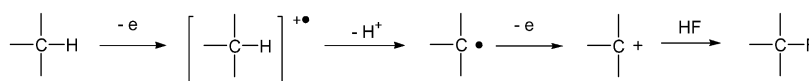
The viewpoint that nickel fluorides, formed at the surface of the anode, may be the fluorinating agents in ECF processes is supported by the fact that nickel tetrafluoride, generated in situ in anhydrous HF, effects the perfluorination of polyfluoroalkanes to the corresponding perfluorinated systems (Scheme 15).⁶¹

2.2. Other synthetic procedures

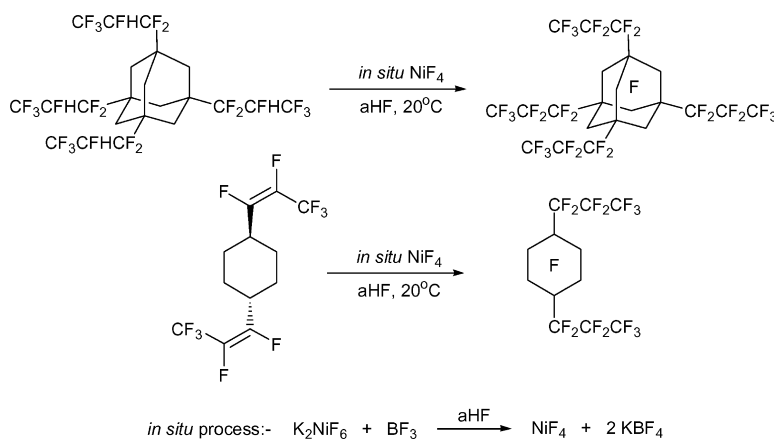
The perfluoroalkane gases, carbon tetrafluoride and hexafluoroethane, may be synthesised by halogen exchange methodology.⁴ Heating carbon tetrachloride with anhydrous hydrogen fluoride over a chromia catalyst furnishes carbon tetrafluoride as the major product, along with various



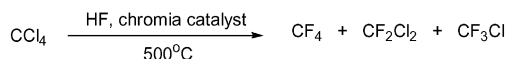
Scheme 13.



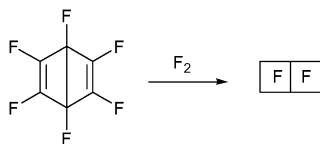
Scheme 14.



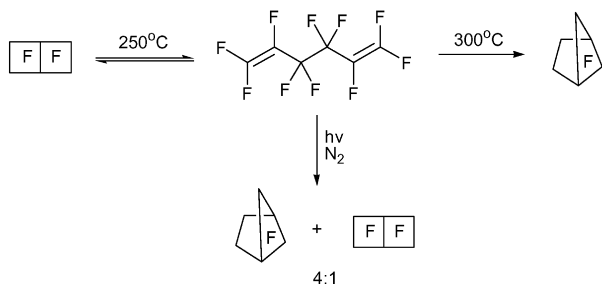
Scheme 15.



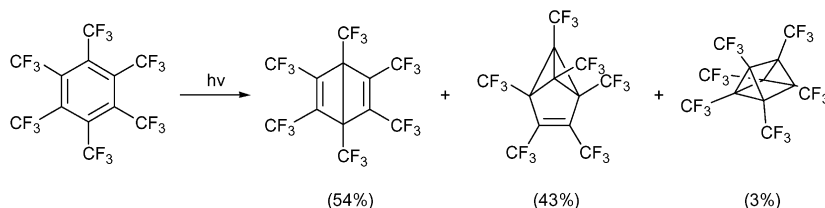
Scheme 16.



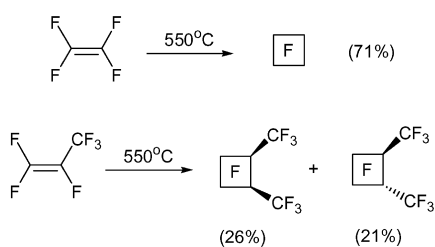
Scheme 17.



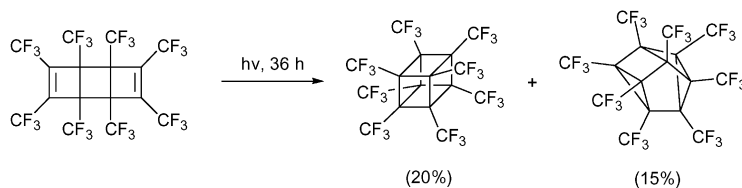
Scheme 18.



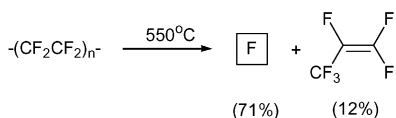
Scheme 19.



Scheme 20.



Scheme 21.



Scheme 22.

chlorofluorocarbons. Higher molecular weight perfluoroalkanes are not synthesised by these processes, due to the instability of the corresponding perchloroalkanes (Scheme 16).

Valence bond isomers of perfluorinated benzenes are unusual starting materials for the synthesis of some highly strained perfluoroalkanes. Perfluoro-Dewar benzene, prepared by the irradiation of hexafluorobenzene,^{62,63} may be isolated and subsequently fluorinated by elemental fluorine to the fully saturated bicyclic system (Scheme 17).⁶⁴

The bicyclic derivative is in equilibrium with the diene which, upon further heating, rearranges to a bridged [1.1.1] system,^{64,65} or a mixture, upon photolysis (Scheme 18).

Hexakis(trifluoromethyl)benzene gives a mixture of three valence bond isomers upon irradiation, with the perfluoroprismene a minor byproduct (Scheme 19).⁶⁶

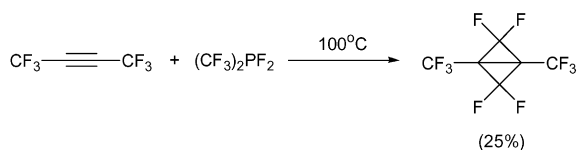
Perfluoroalkenes form cyclic alkanes efficiently upon cyclodimerisation. Tetrafluoroethylene gives perfluorocyclobutane upon heating to high temperature, while hexafluoropropene gives a mixture of *cis* and *trans* 1,2-

bistrifluoromethylcyclobutane derivatives via a [2+2] cycloaddition process (Scheme 20).⁹

Other strained dienes, formed by [2+2] addition reactions, gave perfluorinated cubane and other polycyclic derivatives after photolysis (Scheme 21).⁶⁷

Pyrolysis of polytetrafluoroethylene can give a large mixture of products but, under carefully controlled conditions, useful quantities of perfluorocyclobutane can be obtained (Scheme 22).⁹

Addition of two equivalents of difluorocarbene, generated from bis(trifluoromethyl)phosphorous difluoride, provides moderate yields of a strained bridged system (Scheme 23).⁶⁸

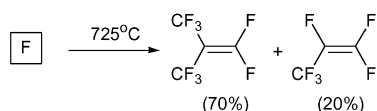


Scheme 23.

3. Chemistry of perfluoroalkanes—carbon–fluorine bond activation

Given the strength of carbon–fluorine bonds in saturated systems and, by definition, the lack of functionality, perfluoroalkanes have, for a long time, generally been perceived to be chemically inert.

Pyrolysis of perfluoroalkanes usually leads to a mixture of products that is not preparatively useful. Perfluorocyclobutane, however, pyrolyses to give good yields of two synthetically versatile perfluoroalkenes (Scheme 24).⁹



Scheme 24.

The percentage composition of fluorine in organic compounds may be determined by heating the substance with sodium metal, leading to mineralisation. Whilst this technique is for analytical purposes only, its potential for carbon–fluorine activation by metals has been indicated.⁶⁹ Defluorination of perfluoroalkanes to perfluoroaromatic derivatives was established over 40 years ago by Tatlow and co-workers,⁷⁰ representing the development of the first preparatively useful carbon–fluorine bond activation reactions. In recent years, the synthesis of synthetically valuable unsaturated perfluorocarbon derivatives directly from perfluoroalkanes by carbon–fluorine bond activation under milder laboratory conditions has emerged as a developing field of research that has been highlighted and reviewed.^{6,71–76}

The chemistry of perfluoroalkanes relies upon the transfer of electrons, from, for example, sources in the gas phase

(negative ion mass spectrometry), metal surfaces (e.g. iron or other transition metal complexes) or electron-rich organic donors (e.g. thiolates), to the σ^* orbital of a carbon–fluorine bond^{77,78} in the substrate. The radical anions which are formed lose fluorine to begin a cascade process that can lead to further defluorination, or defluorination followed by functionalisation of the newly formed unsaturated fluoro-carbon by nucleophiles present in the reaction medium.

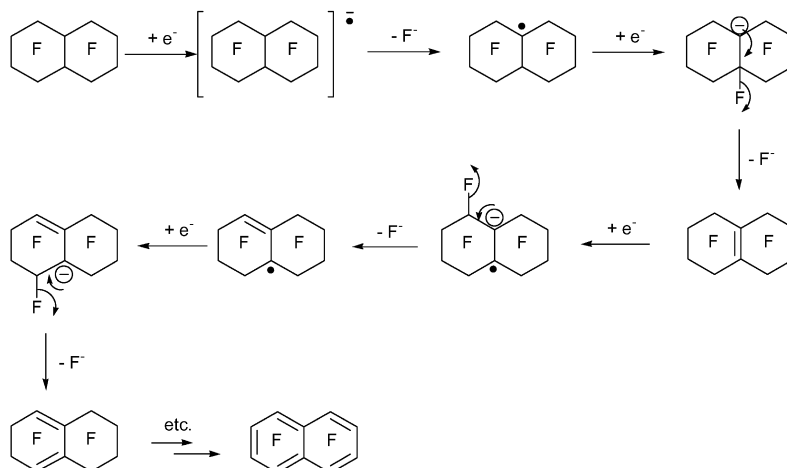
As an example, the defluorination of perfluorodecalin is generally considered to occur by transfer of electrons to the σ^* orbital of the most electron-deficient tertiary carbon–fluorine bond to give a radical anion. Loss of fluoride leads to a tertiary radical that gives a relatively stable tertiary carbanion upon transfer of a further electron from the electron source. Subsequent loss of fluoride gives the tetralin derivative and repeated electron transfer and fluoride ion elimination leads eventually to octafluoronaphthalene (Scheme 25).

Tertiary perfluoroalkyl carbanions have been observed as stable species in solution⁷⁹ and the reaction of zinc, as a source of electrons, with perfluorotetralin has been observed⁸⁰ to yield a variety of dienes and aromatic systems, lending support to the mechanism outlined above.

Electron transfer to tertiary carbon–fluorine bonds occurs preferentially because these bonds are more electron deficient than the secondary carbon–fluorine sites. Consequently, for example, perfluorodecalin is more prone to reaction with electron donors than perfluorocyclohexane and the tertiary carbon–fluorine sites have, therefore, been termed the Achilles heel of these relatively unreactive systems. The perfluoroalkenes and aromatics formed are, of course, highly reactive towards nucleophiles⁷ and defluorination reactions must therefore be carried out in a medium free from nucleophilic species if these products are required.

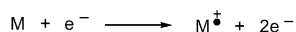
3.1. Negative ion mass spectrometry

Perhaps the most simple source of electrons is the mass spectrometer and it would be expected that the formation of negative ions by the reaction of a perfluoroalkane with electrons would be important in these systems and that such



Scheme 25.

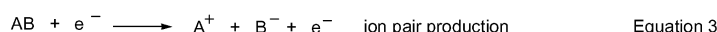
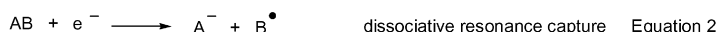
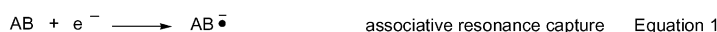
hydrocarbon systems - observation of positive ions in the gas phase



fluorocarbon systems - observation of negative ions in the gas phase



processes for the formation of negative ions in the gas phase



Scheme 26.

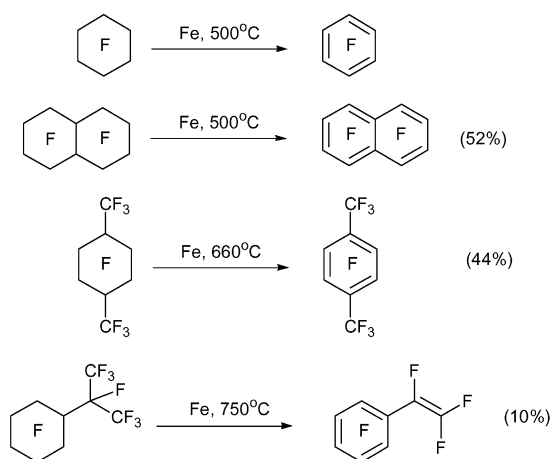
processes could, in principle, be observed by negative ion mass spectrometry. Although this technique is not practically useful, it is mentioned here for completeness.

Three ionisation processes, as shown in Scheme 26, resonance capture (Equation 1), dissociative resonance capture (Equation 2) and ion pair formation (Equation 3) are the possible outcomes of the interaction of an electron with an organic species in the gas phase.⁸¹

Although some negative ion data have been reported for various perfluorocarbons,^{82–84} demonstrating that negative molecular ions may be generated and observed, systematic studies of the negative ion mass spectrometry of highly fluorinated systems remain relatively scarce and no general fragmentation and rearrangement processes have been established, even though perfluorocarbons are often used as reference compounds for calibration purposes.⁸⁵

3.2. Synthesis of perfluorinated unsaturated systems

3.2.1. Defluorination using metals and metal complexes. Defluorination⁷⁴ of cyclic, bicyclic and polycyclic hydrocarbons over hot (500°C) iron or iron oxide, as the source of electrons, is an efficient method for the synthesis of a variety of perfluoroaromatic systems, developed by Tatlow and co-workers (Scheme 27).^{70,86–89}

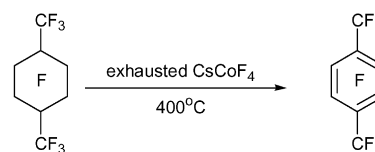


Scheme 27.

Passage of hydrogen gas over the iron surface after the defluorination has occurred regenerates the metal surface

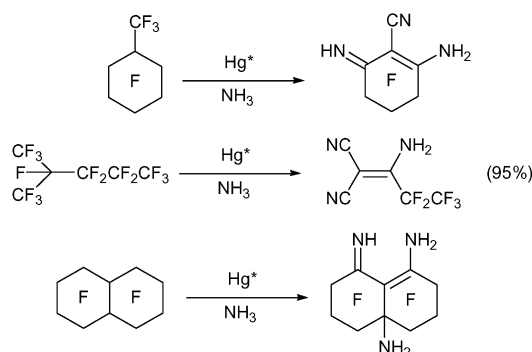
and this continuous flow process has been effectively scaled up for the manufacture of various perfluorinated aromatic derivatives.⁹⁰

Several other high temperature routes to perfluoroaromatics have been reported. Passage of cyclic perfluoroalkanes over exhausted cesium tetrafluorocobaltate permits defluorination to the corresponding aromatic derivative in generally modest yields. The electron-donating species in these reactions must be a cobalt(II) derivative, probably cesium trifluorocobaltate (Scheme 28).⁹¹



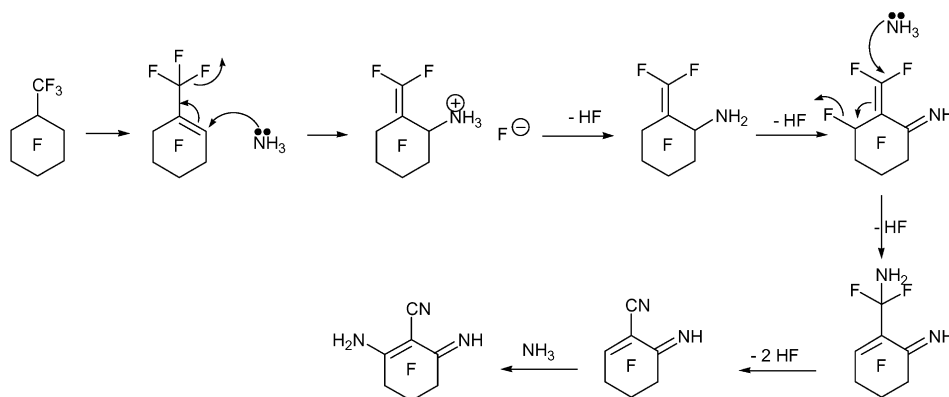
Scheme 28.

Photodefluorination using mercury photosensitisation in the presence of ammonia, leads to a range of nitrogen functionalised products arising from defluorination and subsequent reaction of the fluoroalkenes with ammonia (Scheme 29).⁹²



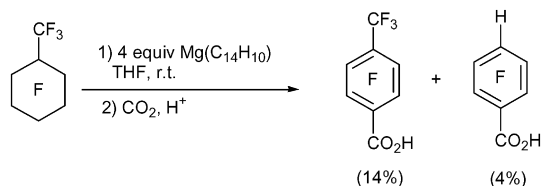
Scheme 29.

Exciplexes $[Hg^*(NH_3)_n, n=1 \text{ or } 2]$ were suggested to be the electron-donating species that give rise to the fluoroalkene that is susceptible to nucleophilic attack. Reaction of the initially formed fluoroalkene in situ with ammonia gives the product by a mechanism, outlined below, following the principles of nucleophilic substitution of perfluoroalkenes (Scheme 30).⁷



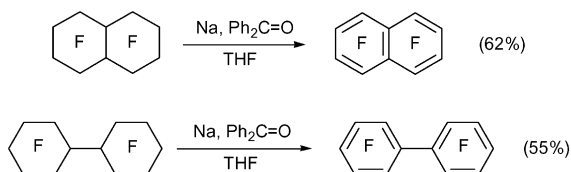
Scheme 30.

Magnesium anthracene, believed to act as a soluble form of magnesium, may defluorinate cyclic perfluoroalkanes to the corresponding aromatic derivatives. Magnesium then inserts into a carbon–fluorine bond to give a Grignard reagent that may be trapped by various electrophiles, in a one-step, low-yield process (Scheme 31).⁹³



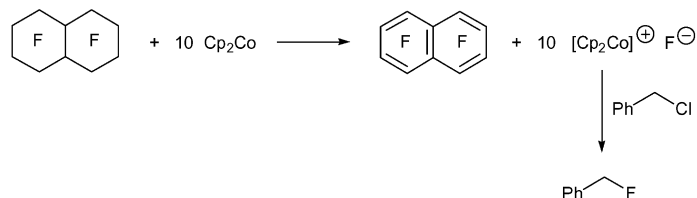
Scheme 31.

The reducing power of sodium metal may be controlled by the addition of benzophenone to generate a radical anion species in solution that may be used as a defluorinating reagent.^{94,95} Linear perfluoroalkanes, however, are mineralised to sodium fluoride, carbon and water, limiting the use of this methodology (Scheme 32).



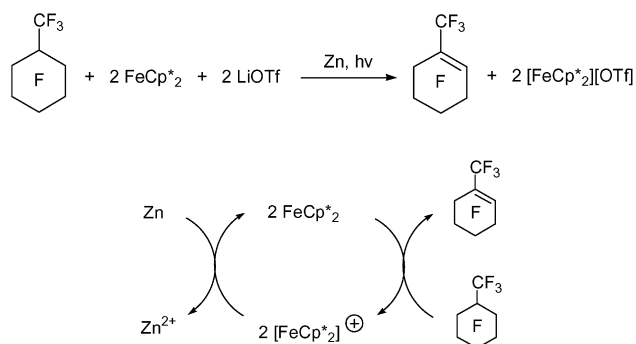
Scheme 32.

Reductive defluorination by transition metal complexes was achieved by treating zirconocene or titanocene species with perfluoroalkanes in the presence of an excess of aluminium metal and mercury(II) chloride in exothermic processes. The catalytic metallocene is considered to transfer electrons from the metal reductants, such as aluminium metal, to the organic substrates (Scheme 33).⁹⁶



Scheme 33.

Perfluoromethylcyclohexane gave the trisubstituted alkene upon reaction of an excess of the photosensitiser, decamethylferrocene, and a fluoride ion acceptor such as lithium triflate.^{97,98} The reaction is autocatalytic by the presence of zinc in the reaction mixture which reduces the ferrocenium salt to decamethylferrocene by the catalytic cycle indicated below (Scheme 34).

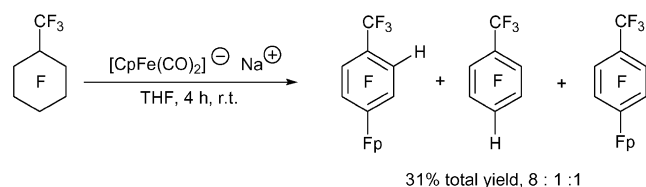


Scheme 34.

Cobaltocenium fluoride is synthesised by the reaction of perfluorodecalin with cobaltocene and this complex can be used as an active source of fluoride ion for a variety of halogen exchange reactions (Scheme 35).⁹⁹

Scheme 35.

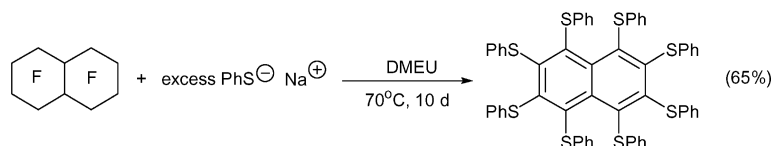
Various iron salts reductively defluorinate cyclic perfluoro-carbons to a mixture of aromatic derivatives in low yield (Scheme 36).¹⁰⁰



Scheme 36.

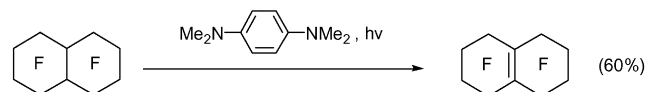
Uranium complexes defluorinate perfluoroalkanes, but no useful organic product could be obtained.¹⁰¹

3.2.2. Defluorination using organic electron donors. In a remarkable reaction, MacNicol and Robertson showed that thiolate salts could transform perfluorodecalin by reductive defluorination followed by nucleophilic substitution of the octafluoronaphthalene intermediate, under very mild conditions (Scheme 37).¹⁰²



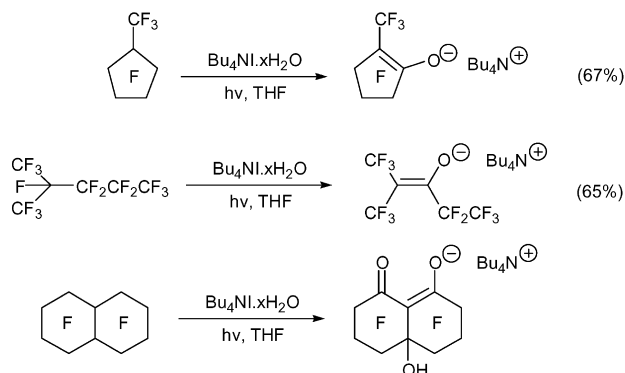
Scheme 37.

Photochemically induced selective defluorination of perfluorodecalin also occurs in the presence of a strong organic electron donor such as an electron-rich diaminobenzene in DMF and hexane.¹⁰³ Electron transfer from the amine leads to a perfluoroalkyl radical anion and subsequent defluorination (Scheme 38).



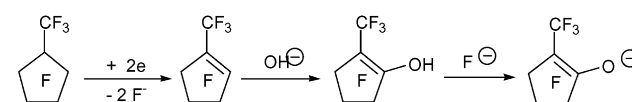
Scheme 38.

3.2.3. Defluorination using other reagents. Irradiation of perfluoroalkanes by a mercury lamp in the presence of hydrated tetramethylammonium iodide gives enolate salts (Scheme 39).¹⁰⁴



Scheme 39.

Iodide ion acts as the electron donor and the negatively charged enolate ion precludes further nucleophilic attack by water present in the system. The enolate derivatives have been used for a variety of subsequent transformations (Scheme 40).

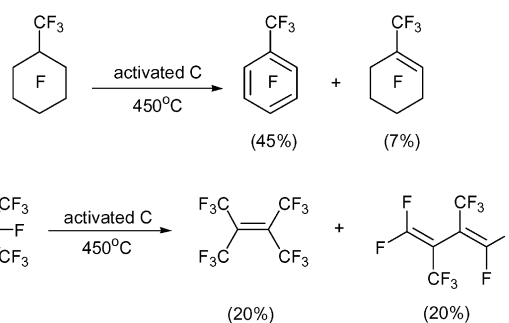


Scheme 40.

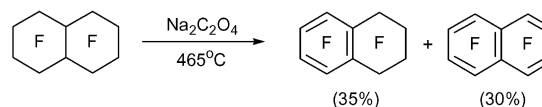
High surface area activated carbon can be used to effect the high temperature defluorination of, for example, perfluoromethylcyclohexane to perfluorotoluene, although the mechanism for this transformation is unclear (Scheme 41).^{105,106}

Aromatisation of perfluorodecalin also occurs upon heating at 465°C with sodium oxalate (Scheme 42).^{107–109}

The decomposition of sodium oxalate at such high

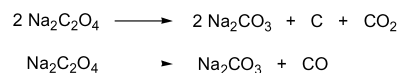


Scheme 41.



Scheme 42.

temperatures occurs by two pathways, leading the authors to conclude that carbon, generated in the reaction chamber, is essential for the reduction of sodium oxalate and the consequent defluorination of the perfluoroalkane substrate (Scheme 43).



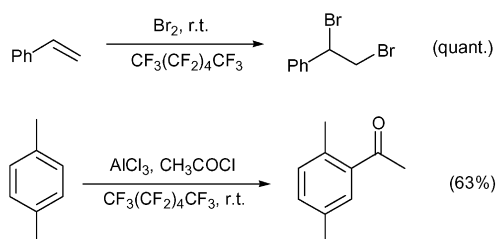
Scheme 43.

Although, therefore, this process is similar to the defluorination reactions involving carbon, described above, differing product profiles are obtained.

4. Applications in organic synthesis

4.1. As inert reaction media

The interest in developing more environmentally benign chemical processes has prompted the search for novel effective reaction media that are non-ozone depleting, do not produce toxic byproducts and can be easily recovered and recycled. The developing uses of ionic liquids¹¹⁰ and supercritical carbon dioxide¹¹¹ as reaction media are directed towards these goals.¹¹² In this context, perfluoroalkane fluids have been investigated as inert, recyclable reaction media because of the easy separation of the perfluoroalkane, due to the very low solubility of organic materials in the perfluoroalkane solvents and, therefore, the ready recycling of these systems. Reactions such as esterifications, transesterifications and polymerisations,¹¹³ flash photolysis,¹¹⁴ bromination,¹¹⁵ hydroboration,¹¹⁶ and Friedel–Crafts acylations¹¹⁷ have been carried out successfully in inert perfluoroalkane media and the solvent efficiently recycled, as shown below (Scheme 44).



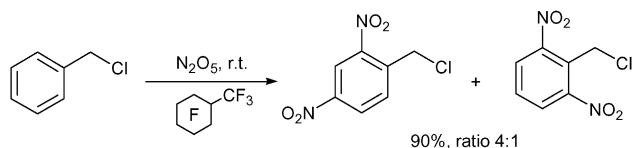
Scheme 44.

Of particular utility is the high solubility of gases in perfluoroalkanes that has led to the development of efficient gas/liquid reaction processes. Oxidations^{118,119} and epoxidations,¹²⁰ for example, can be performed in perfluoroalkane media very effectively due to the relatively high solubility of oxygen in these systems (Scheme 45).



Scheme 45.

Nitration and polynitration of various aromatic systems using gaseous dinitrogen pentoxide, a more environmentally friendly substitute for mixed acid nitration systems, may also be carried out in perfluoroalkane media (Scheme 46).^{121,122}



Scheme 46.

In many reactions, solvents are simply used to enable mixing of the substrates and to provide a heat transfer. In such reactions, much of the solvent may be replaced by perfluoroalkane media, which may perform both of these

tasks without impairing the performance of the reaction. A range of halogen exchange processes have been performed in which most, or all, of the sulpholane, the medium conventionally used, is replaced by perfluoroalkane fluid. After completion of the reactions, the products were recovered from the reduced quantity of sulpholane in the usual manner and the perfluoroalkane was recycled (Scheme 47).¹²³

In some cases, the products obtained using sulpholane/perfluoroalkane media were different from those found when using sulpholane alone. Hexachlorodiene, for example, gave hexafluorobut-2-yne as the major product rather than heptafluorobut-2-ene, which is the product obtained in exclusively sulpholane solvents (Scheme 48).¹²³

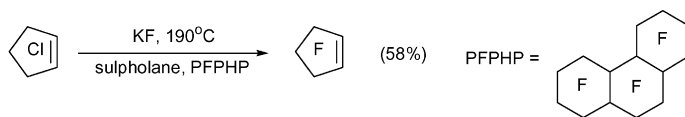
Reaction of fluoride ion with the perchlorinated butadiene leads to an intermediate carbanion which abstracts a proton from the solvent if sufficient sulpholane is present. In a perfluoroalkane-rich reaction medium, however, elimination of fluoride to give the alkyne occurs preferentially.

4.2. Fluorous biphasic synthesis

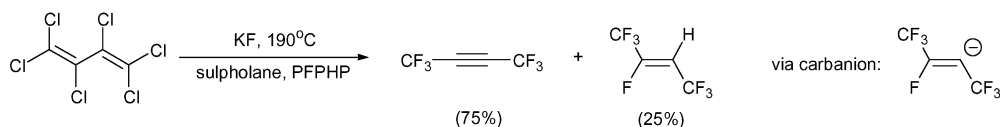
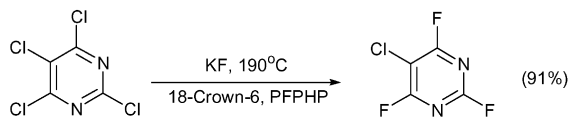
Fluorous biphasic chemistry, introduced by Horvath and Rabai⁵ and now a growing field of research, relies upon the fact that perfluorocarbon fluids and hydrocarbon solvents are immiscible at room temperature but completely miscible when warmed. Moreover, upon cooling, perfluorocarbons and organic solvents completely phase separate. Molecules can be rendered preferentially soluble in perfluorocarbon fluids by the incorporation of, for example, large perfluoroalkyl groups in their structure and a growing number of fluorous-phase reagents and catalysts have been reported. The last eight years has witnessed a growing interest in fluorous biphasic chemistry and the area has been regularly reviewed at length^{5,124–136} whilst a recent *Tetrahedron Symposium-in-Print*¹³⁷ provides the state of the art in this research field to which the reader is directed for more details. Consequently, only brief notes concerning the general strategy of fluorous biphasic chemistry in which perfluoroalkanes have a significant role are given here and only representative examples from the very recent literature are used to illustrate the points made.

The general strategies for fluorous biphasic catalysis and synthesis are outlined below. For fluorous phase catalysis, generally, a fluorous soluble catalyst is dissolved in a perfluoroalkane fluid and heated with a solution of the substrate dissolved in a conventional organic solvent. Upon cooling, the fluorous-labelled catalyst partitions into the fluorocarbon fluid while excess substrate and product remains in the organic phase, enabling simple separation of the expensive, recyclable catalyst from the organic products (Scheme 49).

Hydroformylation of alkenes, for example, gives the corresponding terminal aldehydes upon reaction with an appropriate rhodium catalyst and fluorous-soluble ligand system.^{138,139} In the example shown below, oct-1-ene is soluble in the perfluoroalkane solvent but the aldehyde phase separates from the reaction mixture when formed, enabling simple separation and purification (Scheme 50).

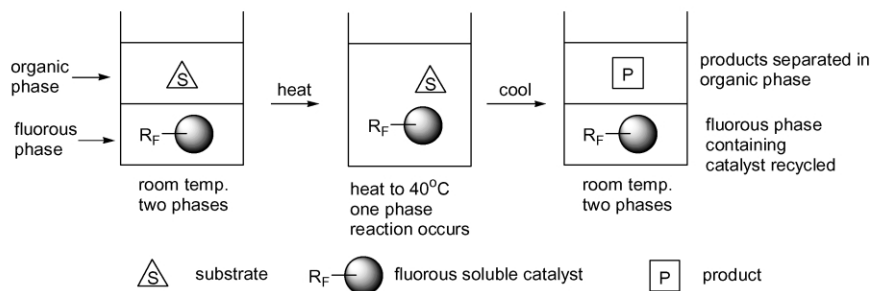


Scheme 47.

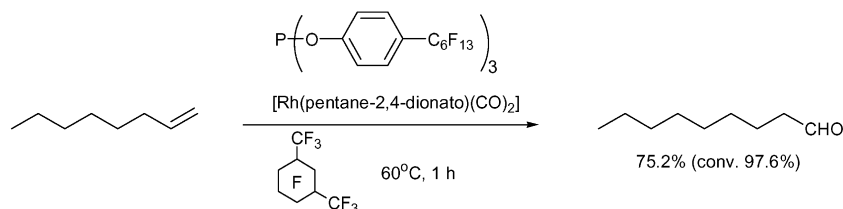


Scheme 48.

Fluorous phase catalysis



Scheme 49.

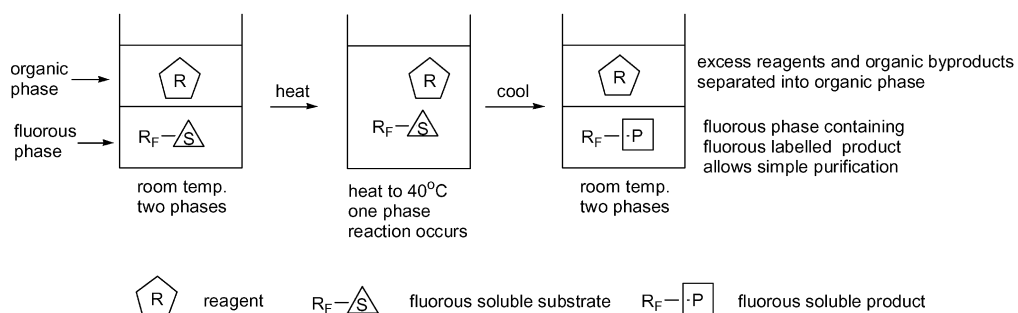


Scheme 50.

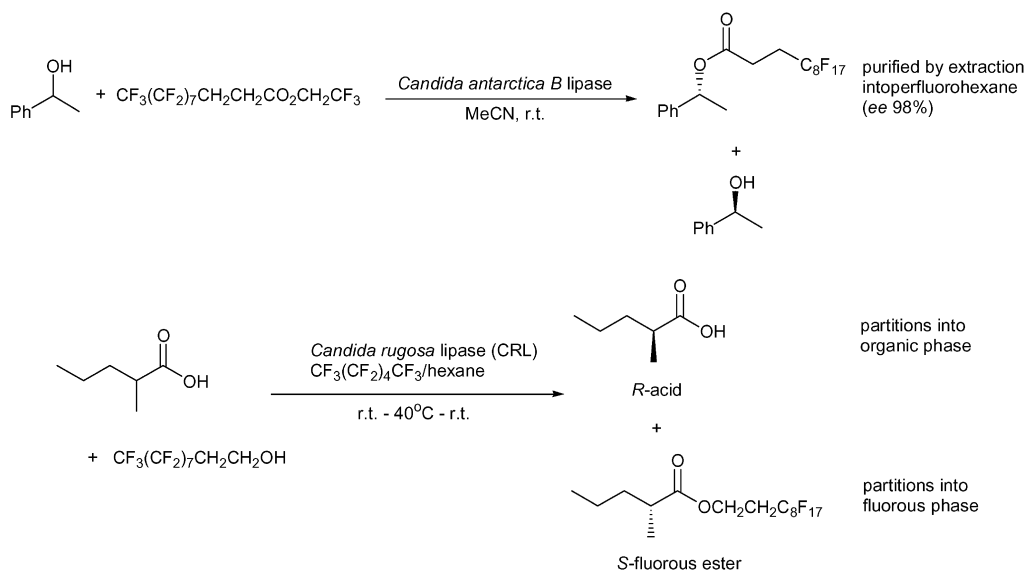
Fluorous phase synthesis adopts similar ideas, as indicated schematically below. Here, an organic substrate is rendered soluble in a perfluoroalkane fluid by attachment of a long perfluoroalkyl group at a point in the molecular structure from where it can be removed at a later stage of the synthesis, if required. Excess reactant can be used to drive

each reaction stage to completion and the pure fluorous-labelled derivative is easily obtained in the fluorous solution after phase separation. Cleavage of the product from the fluorous label generates the desired product and the fluorous label, which can, ideally, be recycled. At each stage, the perfluorocarbon fluid can also be recycled (Scheme 51).

Fluorous phase synthesis



Scheme 51.



Scheme 52.

Fluorous biphas technology has recently been applied to lipase-catalysed esterification and trans esterification processes, enabling the separation and isolation of pure enantiomers from racemic mixtures of chiral alcohols,^{140, 141} esters and carboxylic acids (Scheme 52).¹⁴²

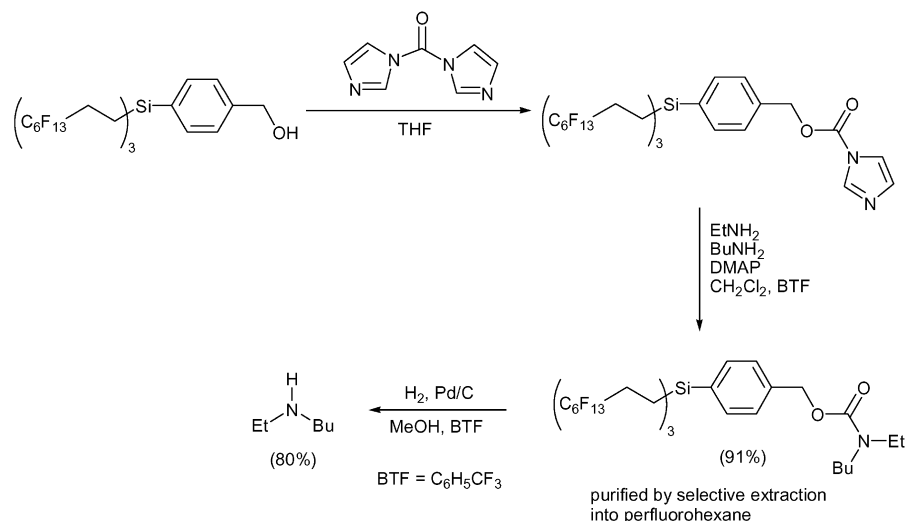
A fluorous soluble benzyloxycarbonyl protecting group has been used for the synthesis and ready purification of various secondary amines. The protected amines were purified by liquid–liquid extraction into perfluorohexane and readily purified before hydrogenolysis to the free amines (Scheme 53).¹⁴³

The high cost and global warming potential of perfluoroalkanes probably precludes their use for liquid–liquid separations in anything but laboratory-scale processes. Consequently, new solid–liquid phase extraction techniques, using fluorocarbon-coated silica gel rather than perfluoroalkanes, are now becoming the favoured method-

ology for the separation of fluorous reagents and catalysts from organic systems.^{135,144–146}

5. Summary

The continuing advances in perfluorination technology now allows the synthesis of a greater variety of perfluoroalkanes, for which a chemistry, involving carbon–fluorine bond activation by a variety of electron donors, is emerging. Of course, the preparation of multi functional perfluoro-alkenes and aromatic systems in two steps from commodity hydrocarbon feedstocks via perfluoroalkanes is also a very useful and effective example of carbon–hydrogen bond activation, a topic that has received considerable worldwide interest.^{147,148} Perfluoroalkanes have, additionally, over the years, been adapted for use for many commercial and synthetic laboratory applications and these continue to grow.



Scheme 53.

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Biographical sketch

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