Elemental Fluorine in Organic Chemistry

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There is a gradual realisation that elemental fluorine, for a long time considered too reactive and uncontrollable, can be used in viable syntheses on both the laboratory and industrial scale. This review focuses on recent uses of fluorine for the preparation of perfluorinated and selectively fluorinated molecules as well as for the promotion of other organic transformations.

Keywords: Elemental fluorine, direct fluorination.

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1 Introduction

With a few exceptions, carbon-fluorine bonds are not found in nature and so the enormous range of molecules that have been prepared which contain fluorine are essentially man-made [1]. Of paramount importance, therefore, for the development of organofluorine chemistry, is the invention of simple, effective and highly efficient methods for the introduction of fluorine into organic substrates and many approaches utilising various reagents have been studied and adopted, as detailed in several recent reviews [2–7].

The effect of introducing one or several fluorine atoms into an organic substrate can have a profound effect on the physical, chemical and biological properties of the molecule and this is exemplified by the growing number of pharmaceuticals and plant protection agents that have fluorine atoms incorporated in their structure [8]. More extensively fluorinated compounds, as well as having a distinct and rich chemistry [1, 9, 10], have also found many commercial applications [8].

In this chapter we will focus on the rapidly expanding area concerning the use of elemental fluorine for the preparation of organic compounds containing bonds between fluorine and carbon, oxygen, nitrogen, sulfur or phosphorous. The preparation of perfluorinated compounds by direct fluorination methodology (Section 2) was last reviewed by Lagow [11] in 1979 whilst the preparation of selectively fluorinated compounds, that is substrates containing one or two fluorine atoms, by direct fluorination (Sect. 3), was last comprehensively reviewed by Purrington [12] in 1986, although other articles have since been published [10, 13–19] which are concerned with specific aspects of both of these areas. The present chapter aims to present developments in the use of direct fluorination since these last two major reviews as well as to provide an overview of the more significant mechanistic aspects concerning such processes. A discussion of the processes in which fluorine may be used for the promotion of organic transformations which do not result in the introduction of fluorine into the substrate is also included (Sect. 4).

Elemental fluorine was first prepared in small quantities by Henri Moissan [20, 21] in Paris in 1886 by the electrolysis of a solution of anhydrous hydrogen fluoride which contained a small amount of potassium fluoride. This method remains in use today, as the generation of fluorine is carried out on the industrial scale, largely for use in the nuclear electricity generating industry, by electrolysis of $KF \cdot 2HF$. This electrolyte melts at about 100 °C, allowing the cells to be operated at reasonable temperatures [22]. Several chemical methods for the generation of fluorine have recently been reported [23–26].

Moissan himself carried out the first reactions between neat fluorine and several organic compounds but these usually resulted in extensive decomposition of the substrates and, occasionally, explosions. The high reactivity of fluorine with organic substrates is principally due to the relative weakness of the fluorine-fluorine bond compared to the stronger carbon-fluorine and carbon-hydrogen bonds [11] (Sect. 2.1) and until methods for the efficient dissipation of the substantial heat of reaction were developed, progress concerning the study of direct fluorination reactions was hampered. However, dilution of fluorine by inert gases such as nitrogen or helium, cooling reaction vessels and the use of appropriate solvents, now allows many reactions to be carried out safely and efficiently. It is hoped that the discussion on the following pages demonstrates that fluorine should be considered as the reagent of choice not only for certain fluorination reactions but also for the promotion of other organic transformations.

2 Perfluorination

The preparation of perfluorinated compounds is largely based on the exhaustive fluorination of the corresponding hydrocarbon species and three synthetic procedures have been widely used. Two of these processes, electrochemical fluorination [27] (ECF), successfully used for the preparation of perfluoroacids (3M), and fluorination by high valent metal fluorides [28] such as cobalt trifluoride (itself prepared from cobalt difluoride and fluorine), used for the preparation of perfluorocarbons (Flutec fluids, BNFL), have been reviewed elsewhere. The third major process for the preparation of perfluorinated compounds involves direct fluorination.

Early attempts to moderate the high reactivity of fluorine towards organic substrates led to the development of the vapour-phase "Jet fluorination" apparatus and a catalytic metal-packing process, which both used fluorine diluted with an inert gas such as nitrogen or helium. Much of this initial work is contained in the reviews by Bigelow and Tedder [29, 30]. The introduction of the low temperature gradient LaMar fluorination technique in 1970 gave real impetus to the study of direct perfluorination of organic substrates and the early phases of this work were reviewed by Lagow [11].

2.1 Mechanistic Considerations

Reactions between hydrocarbons and fluorine are highly exothermic since very strong bonds between fluorine and both carbon (BDE C-F, 452-531 kJ mol^{-1}) and hydrogen (BDE, C-H *ca.* 410 kJ mol^{-1}) are formed whilst the dissociation energy of fluorine (BDE, F-F 157.7 kJ mol^{-1}) is very low. Consequently, exhaustive fluorination is generally regarded as being a free radical process [11] (Table 1).

Since fluorine is less than 1% dissociated at room temperature, the concentration of fluorine atoms may not be sufficient to initiate a radical chain process. An alternative initiation step **1b** (Table 1), originally suggested by Miller [31–33], probably occurs but conclusive evidence for this pathway has not been established.

Table 1. Thermodynamic Data for Fluorination of Methane [11]

		ΔH_{25} (kJ mol^{-1})
	Initiation	
1a	$F_2 \longrightarrow 2F^{\cdot}$	157.7
1b	$R\text{-}H + F_2 \longrightarrow R^{\cdot} + HF + F^{\cdot}$	16.3
	Propagation	
2a	$R\text{-}H + F^{\cdot} \longrightarrow R^{\cdot} + HF$	−141.4
2b	$R^{\cdot} + F_2 \longrightarrow R\text{-}F + F^{\cdot}$	−289.1
	Termination	
3a	$R^{\cdot} + F^{\cdot} \longrightarrow R\text{-}F$	−446.8
3b	$R^{\cdot} + R^{\cdot} \longrightarrow R\text{-}R$	−350.6
	Overall Reaction	
4	$R\text{-}H + F_2 \longrightarrow RF + HF$	−430.5

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. For example, early work by Tedder [30, 34], showed that the order of selectivity follows the usual pattern, i. e. tert > sec > prim, but the relative selectivity of fluorine atoms is less than chlorine atoms (Table 2).

Indeed, it has recently been shown by Rozen [13] that tertiary carbon-hydrogen bonds can be selectively replaced by carbon-fluorine bonds when the reaction is carried out in a polar solvent at low temperature, but it was suggested that an electrophilic process involving a carbocationic transition state is occuring in these instances (see 3.1.1.1).

Further fluorination of hydrofluorocarbons becomes increasingly difficult as a perfluorination reaction proceeds, for a number of reasons. The deactivating effect of a fluorine substituent in a hydrocarbon can be seen in the retardation of the rate of fluorination of 1-fluorobutane as compared to *n*-butane (Table 3) and, furthermore, the relative selectivity values obtained upon fluorination of 1-fluorobutane (Table 3) [35] show that fluorination of the CH_2F group is more difficult than both CH_2 and CH_3 groups.

In accordance with these early findings, a recent detailed study of the perfluorination of neopentane by Adcock [36] found the order of hydrogen reactivity to be $CH_3 > CH_2F > CHF_2$ by a comparison of statistical and actual yields of the hydrofluorocarbon products obtained upon polyfluorination. Thus, the hydrogen abstraction step **2a** (Table 1) becomes less favourable as the C-H bond becomes increasingly electron poor and, consequently, less reactive towards highly electrophilic fluorine radicals.

Table 2. Relative Selectivity of Fluorine and Chlorine atoms (− 81 °C, liq. phase) [30, 34]

	$-CH_3$	$-CH_2$	−CH
$F^{\cdot}$	1	1.3	2.5
$Cl^{\cdot}$	1	4.6	10.3

Table 3. Halogenation of 1-Fluorobutane in the Gas Phase [35]

Halogen	Temperature	Relative Selectivities at each Position CH_3-CH_2-CH_2-CH_2F			
		CH_3—	CH_2—	CH_2—	CH_2F—
F	20	1	1.0	0.8	< 0.3
Cl	35	1	3.7	1.6	0.8

This reactivity order also follows the order of steric accessibility of the hydrogen atoms towards radical attack. As a perfluorination reaction proceeds, the carbon skeleton becomes increasingly sterically protected by a sheath of fluorine atoms since the non-bonding electron pairs of fluorine inhibit further attack by incoming fluorine atoms. In cases where the hydrogen atoms are sterically shielded by several very bulky perfluoroalkyl groups, further fluorination is extremely difficult. For instance, both **5** and **6** (Fig. 1) [37, 38] are recovered largely unchanged even after exposure to 100% fluorine over several days.

Fig. 1

However, substitution of sterically shielded hydrogen atoms appears to be possible, in **7** (Fig. 2) for example, but rearrangement of fluoroalkyl radicals (Fig. 2) [38], rather than direct substitution, has been suggested as the fluorination mechanism.

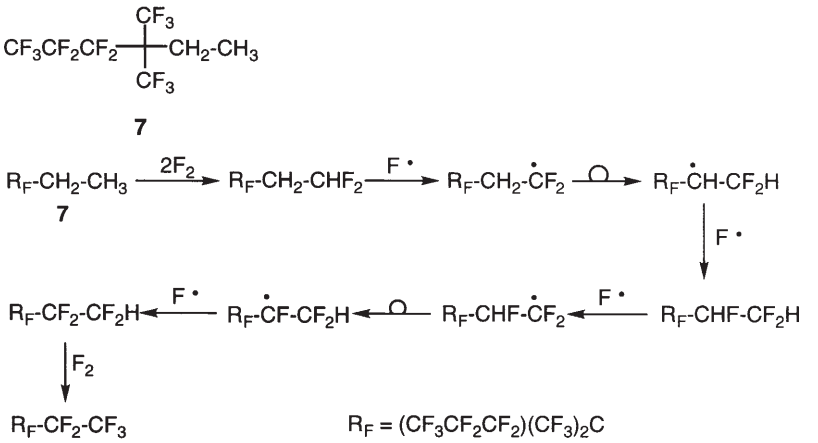


Fig. 2

Furthermore, partially fluorinated substrates are more stable towards the fluorination process since the presence of, for instance, a polyfluoroalkyl group, significantly lowers the oxidation potential of a given hydrocarbon molecule. Consequently, yields of perfluorinated compounds are generally higher when partially fluorinated precursors are used as substrates rather than the corresponding hydrocarbons and methodology for the preparation of perfluoroethers (Fig. 3) [39] and a range of perfluoropolyethers (Fig. 4) [40, 41] has been developed.

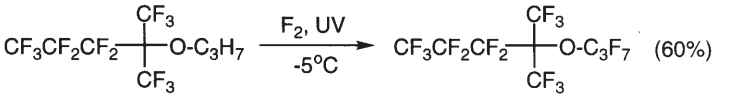


Fig. 3

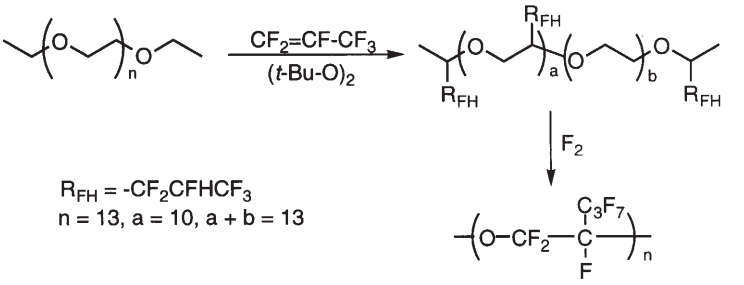


Fig. 4

A consideration of the thermodynamics of fluorination reactions is essential when designing a process for the perfluorination of organic substrates. As is evident from the data (Table 1), a great deal of heat is generated upon substitution of hydrogen by fluorine and a fluorination process must provide a means of rapidly dissipating the large heat of reaction to prevent the weakest bonds in hydrocarbon molecules, the carbon-carbon single bonds (typically between 351 – 368 kJ mol^{-1}), from cleaving. As we have seen, further fluorination of the substrate becomes increasingly difficult as the perfluorination reaction proceeds and so more severe conditions, in which the concentration of fluorine and fluorine radicals is maximised, are required in the later "finishing" stages of perfluorination reactions. Brief descriptions of techniques that have been reported in the literature are given below.

In the LaMar Fluorination process [11] (referred to as LaMar in the following discussion) 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 permit perfluorination. This is a batch process that requires relatively long reaction times to perfluorinate samples of material.

The Aerosol Fluorination process [42] (Aerosol) is operated on the principle that the substrate is absorbed onto the surface of fine sodium fluoride particles in the fluorination apparatus in which the fluorine concentration and the temperature increases along the length of the reaction vessel. A U.V. photofluorination finishing stage completes the perfluorination process which has the advantage that it is a continuous flow method.

The Exfluor–Lagow method [43] involves the slow addition of both the hydrocarbon substrate and an excess of fluorine into a vigorously stirred chlorofluorocarbon or perfluorinated inert solvent. If required, reactions are completed by adding a small quantity of a highly reactive hydrocarbon, such as benzene, which reacts spontaneously with fluorine to produce a very high concentration of fluorine radicals ensuring perfluorination of the substrate.

In the Liquid-Phase Photofluorination [39, 44] process the reactant is injected at a very slow constant rate into an inert fluorocarbon solvent which is saturated by fluorine and under U.V. irradiation. Conditions are chosen to ensure that the concentration of fluorine and fluorine radicals is always much higher than the concentration of the substrate. This method is only suitable for the perfluorination of substrates, such as partially fluorinated ethers (see Section 2.5) and amines (see Section 2.7), that are both soluble in perfluorocarbon solvents and can withstand such vigorous reaction conditions.

Since fluorination of organic substrates results in the generation of hydrogen fluoride and that many substrates are prone to rearrangment or degradation in highly acidic media, a hydrogen fluoride scavenger, such as sodium fluoride, is frequently added to the perfluorination reaction medium [14, 45, 46].

2.2 Hydrocarbons

Many saturated linear, branched [47], cyclic [47, 48] and cage [49, 50] hydrocarbons have been transformed into the corresponding perfluorocarbons by direct fluorination (Figs. 5 and 6).

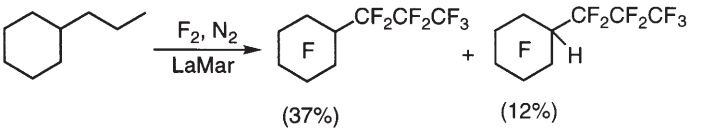


Fig. 5

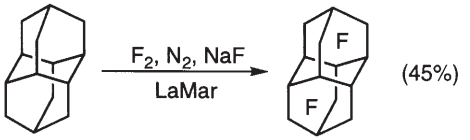


Fig. 6

Fluorination of polyethylene surfaces leads to an increase in the surface energy, some degree of cross-linking and a reduction of the free volume of the polymer. All of these effects impart on the surface of the polymer a barrier that is very impermeable to hydrocarbon solvents. A blow-moulding process, in which a low concentration of fluorine in nitrogen is used as the blow-moulding gas, is used for the production of plastic fuel tanks for the automotive industry (Airopak®, Air Products) [51]. Post-treatment of hydrocarbon surfaces with fluorine is an alternative technology and techniques for the surface fluorination of natural and synthetic rubber have been described [52].

Perfluorination of unsaturated hydrocarbons such as alkenes, allenes (Fig. 7) [53] and aromatics (Fig. 8) [54, 55] is also possible since the total energy released upon fluorine addition to a carbon-carbon double bond (typically between 251.4 – 292.9 kJ mol^{-1}) is not sufficient to break carbon-carbon single bonds.

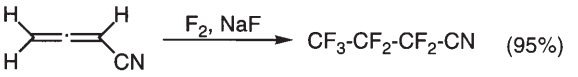


Fig. 7

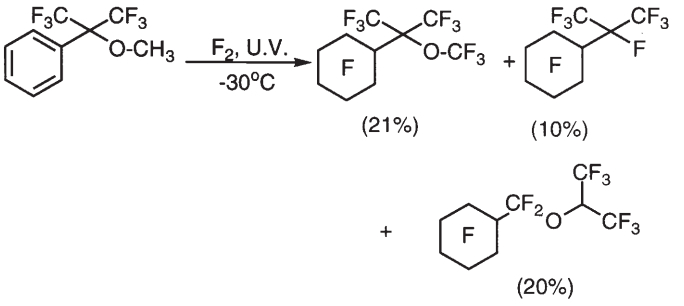


Fig. 8

Mesophase pitch, consisting of a mixture of various aromatic hydrocarbons, reacts with fluorine between 50 – 130 °C to give pitch fluorides [56] with the composition $CF_{1.3}$ to $CF_{1.59}$. These materials have a higher fluorine content than graphite fluoride (see Section 2.7), have very low surface energy and are soluble in some fluorinated solvents.

Addition of fluorine atoms to some perfluoroalkenes results in the production of *tert*-perfluoroalkyl radicals (Fig. 9) [57] which are present in high concentration and are stable to oxygen, acid and base at, and above, room temperature. The stability of these long-lived radicals has been attributed to the large degree of steric shielding of the paramagnetic centre by the highly branched fluorocarbon skeleton.

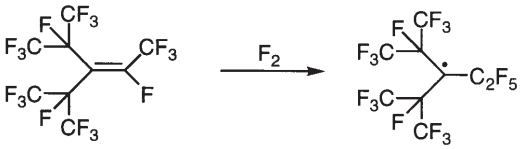


Fig. 9

2.3 Haloalkanes

Detailed studies concerning the perfluorination of haloalkanes by the aerosol fluorination technique have recently been conducted by Adcock and co-workers [14]. Primary alkyl chlorides give the corresponding perfluoroalkylchlorides (Fig. 10) [58] in good yield demonstrating that the carbon-chlorine bond resists the fluorination process. However, secondary alkyl chlorides are susceptible to rearrangement processes (Fig. 11).

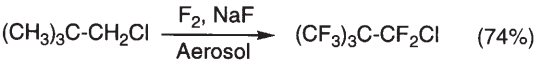


Fig. 10

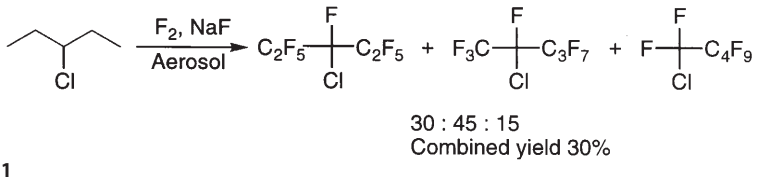


Fig. 11

Perfluorination of 2,2-dichloroadamantane gives **8** and **9** (Fig. 12) and, since, in an analogous reaction, 1,2-dichloroadamantane gives the corresponding perfluoro derivative only, the minor isomer **9** was deduced to have arisen from a 1,3-chlorine shift, the first such rearrangement recorded [59].

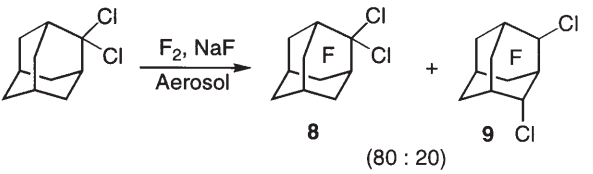


Fig. 12

Perfluorination of tertiary alkyl chlorides gives products arising solely from rearrangement processes (Fig. 13) [60]. Rearrangement of the initially formed radical species **10** by a 1,2-chlorine shift to a more stable tertiary radical **11** in the early stages of the reaction (Fig. 14), accounts for these findings. In other

cases, multiple 1,2-chlorine shifts can lead to a mixture of products [60]. However, 1-chloroadamantane gives only the corresponding perfluoro derivative without any accompanying rearrangement products (Fig. 15) [61]. In this case overlap of the carbon-chlorine -bond orbital with the SOMO of the adjacent paramagnetic centre, which is essential for a 1,2-chlorine shift to occur, is precluded by the geometry of the cage system[59].

Perfluorination of polychlorinated substrates has also been studied and 1,2-chlorine shifts are observed in some cases (Fig. 16) [14, 62].

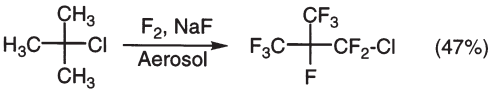


Fig. 13

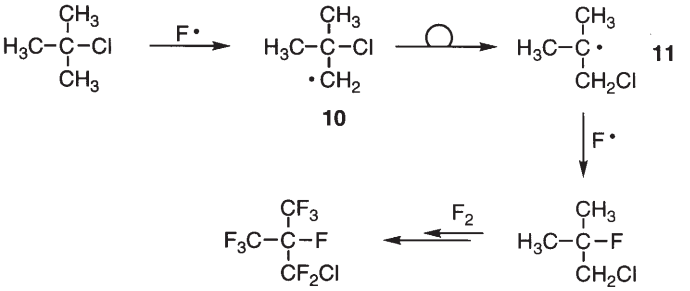


Fig. 14

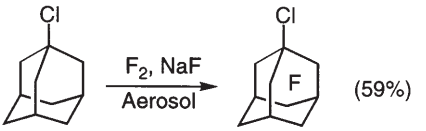


Fig. 15

Fig. 16

Perfluorination of neopentyl bromide, on the other hand, gave a number of products, none of which contained bromine (Fig. 17) [58]. In this case, neopentyl bromide difluoride **12** or tetrafluoride **13** is first formed and these lose BrF_2^- to give carbocationic intermediates **14** and **15**. Familiar carbocationic rearrangements and further fluorination yield the major isolated product, perfluoroisopentane (Fig. 18) [58].

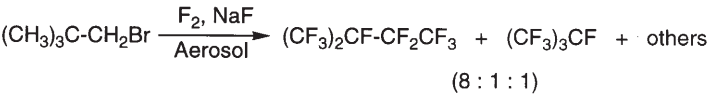


Fig. 17

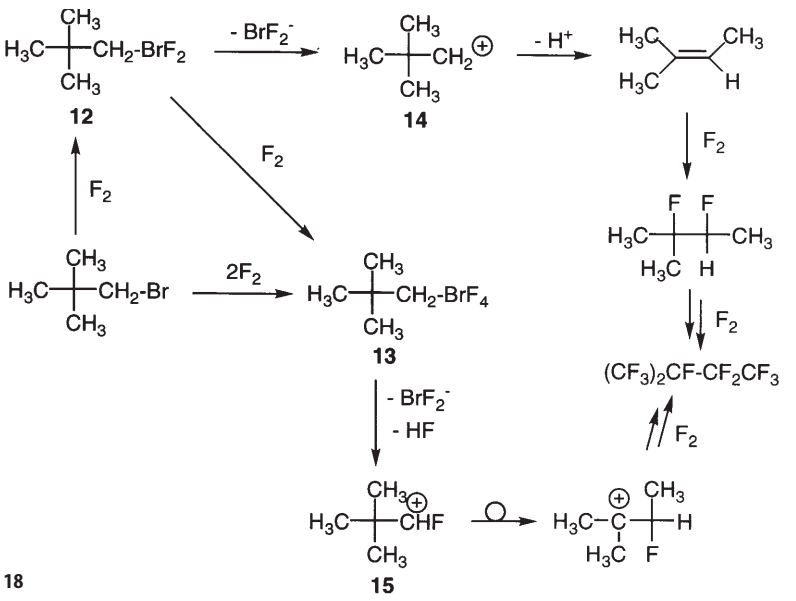


Fig. 18

2.4
Ethers and Polyethers

Many classes of perfluoroethers such as acyclic [63], cyclic [64, 65], glymes [66, 67], highly branched [63], macrocyclic [68–73], orthoformates [74–76] and poly-ethers [15, 77], have been succesfully prepared in high yield by direct fluorination techniques (Figs. 19 and 20). Carbon-oxygen bond cleavage is minimised in these processes by the addition of an HF scavenger, such as sodium fluoride, to the reaction mixture [14, 45, 46].

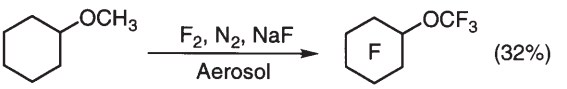


Fig. 19

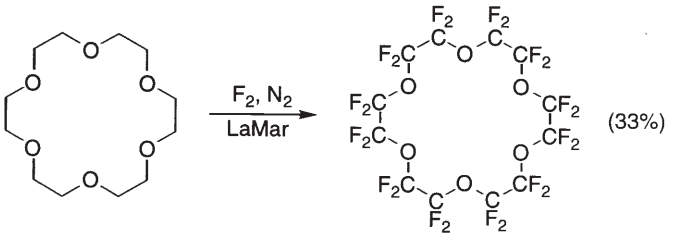


Fig. 20

Carbon-oxygen bond cleavage may occur by β-scission (Fig. 21) but only significantly in cases where relatively stable radicals are the resulting intermediates, such as in the fluorination of *t*-butylmethyl ether (Fig. 22) [78].

Orthocarbonates are particularly susceptible to β-scission, as indicated by the products that are obtained upon fluorination of tetramethylorthocarbonate (Fig. 23) [74].

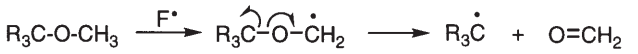


Fig. 21

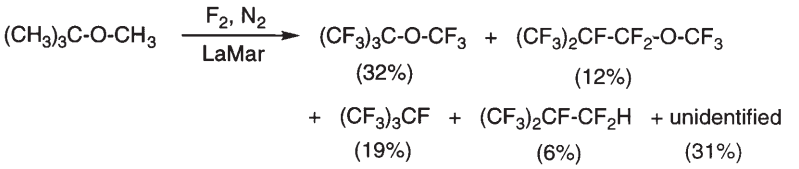


Fig. 22

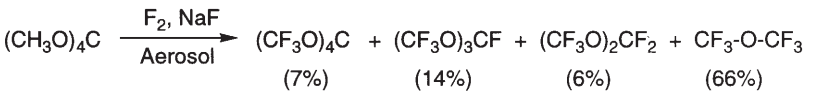


Fig. 23

Perfluorinations of many partially fluorinated ethers have been carried out (Figs. 24–26) [39, 55, 65, 79, 80].

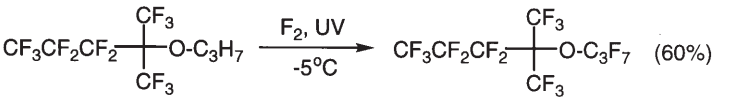


Fig. 24

Fig. 25

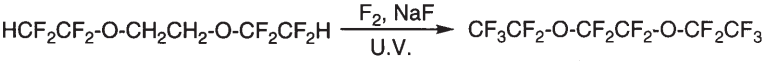
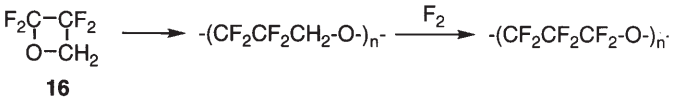


Fig. 26

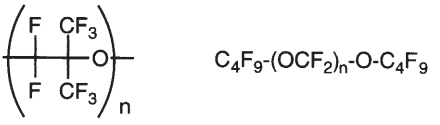
Perfluoropolyethers have found widespread use as high-performance lubricants and several companies manufacture a range of these materials (Krytox®, Du Pont; Fomblin®, Montefluos; Demnum®, Daikin). The Fomblin® fluids and Krytox® require the use of fluorine in the finishing stages [81] whilst Demnum® is synthesised by polymerisation of the fluorooxetane **16** followed by perfluorination using fluorine (Fig. 27) [82].

Many perfluoropolyethers [15, 77, 83] such as **17** [84] and **18** (Fig. 28) [84–86] have been prepared from appropriate polyethers by Lagow and co-workers using the LaMar technique and, indeed, many perfluoroethers are prepared on a commercial scale using direct fluorination technology (Exfluor, 3M) [16].



16

Fig. 27



17 **18**

Fig. 28

2.5 Ketones, Esters and Related Compounds

Acyclic [87, 88], cyclic, cage [89–91] and poly [91, 92]-perfluoroketones have been successfully synthesised by direct perfluorination (Figs. 29 and 30).

Phloroglucinol, which is regarded as the tri-enol form of cyclohexane-1,3,5-trione, gives the hexahydrate of the corresponding perfluoro-trione upon fluorination in formic acid (Fig. 31) [93] (see 3.1.1.2 for a discussion of the fluorination of carbonyl compounds).

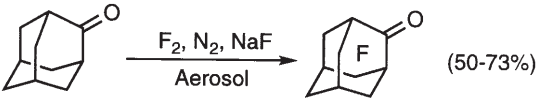


Fig. 29

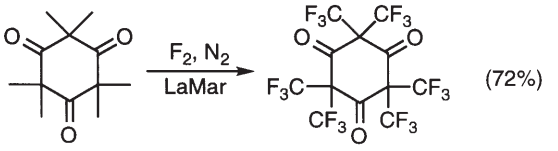


Fig. 30

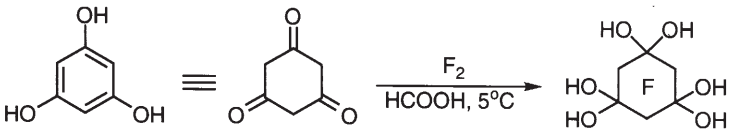


Fig. 31

Highly branched ketones may undergo rearrangement upon fluorination, as for instance pivalone, which gives perfluoroprovalone as the major product (Fig. 32) [94].

Perfluorinations of many related oxygen containing substrates, such as acid halides (Fig. 33) [11], esters (Fig. 34) [14, 95, 96] and polyesters (Fig. 35) [14, 97–99] have been carried out.

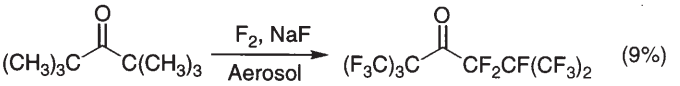


Fig. 32

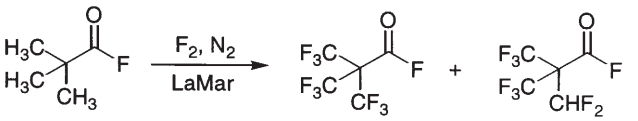


Fig. 33

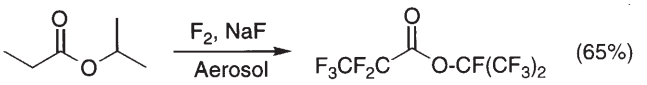


Fig. 34

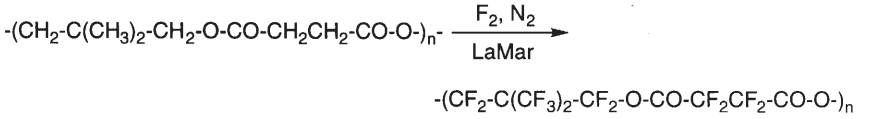


Fig. 35

The preparation of many long-chain perfluorocarboxylic acids and diacids is now carried out on the industrial scale using direct fluorination techniques (Fig. 36) [15, 16, 100].

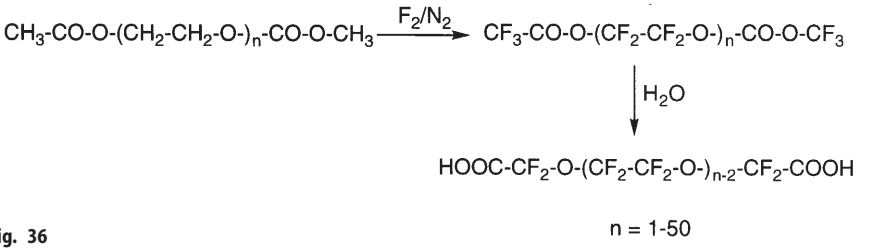


Fig. 36

2.6
Substrates Containing Nitrogen, Sulfur or Phosphorous

Hydrogen atoms bonded to nitrogen, as well as those attached to carbon, are replaced by fluorine upon perfluorination of primary and secondary amines (Fig. 37) [101, 102]. Perfluorinated tertiary amines have also been prepared (Figs. 38 and 39) [78, 103].

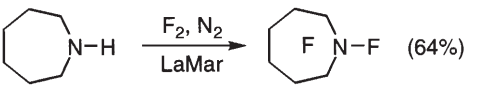


Fig. 37

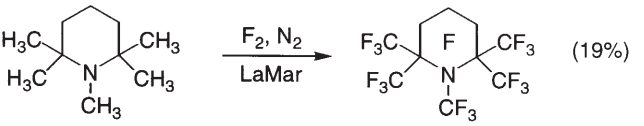


Fig. 38

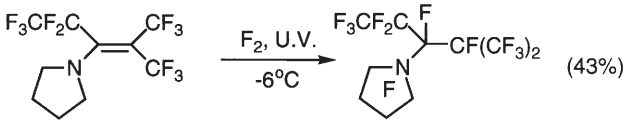


Fig. 39

Sulfur is oxidatively fluorinated up to its highest valence state, six. For instance, alkyl thiols give perfluoroalkyl-sulfurpentafluorides (Fig. 40) [104] and sulfides give perfluorodialkyl-sulfurtetrafluorides (Fig. 41) [105, 106]. Similarly, phosphorous is oxidatively fluorinated up to the pentavalent state (Fig. 42) [107].

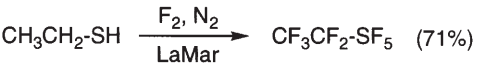


Fig. 40

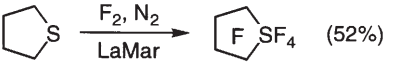


Fig. 41

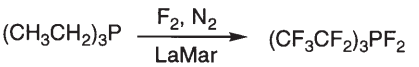


Fig. 42

2.7 Carbon

Fluorinated carbon, CF_x, where x is between 0 and 1.3, is prepared by the direct fluorination of carbon at high temperatures [108]. Many varieties of fluorinated carbon can be prepared depending on the type of carbon used in the process (e.g. graphite, petroleum coke, carbon black, etc.) and the level of fluorination (i.e. the value of x). Fluorinated carbons, such as those manufactured by Allied-Signal (Accufluor®), Central Glass Co. (Cefbon®) and Daikin, are used for the fabrication of cathodes in lithium anode batteries and as solid lubricants [109].

Several groups [110–115] have reported on the direct fluorination of Buckminsterfullerene, C_{60}. Characterisation of highly fluorinated derivatives of C_{60} is very difficult and contradictory results concerning the number of fluorine atoms that can be attached to the sphere without concomitant carbon-carbon bond cleavage have been reported in the literature. The most highly fluorinated $C_{60}F_x$ derivative that has been obtained in reasonable quantities and that has been verified by several complimentary spectroscopic techniques is $C_{60}F_{48}$. In a remarkable reaction, fluorination of C_{60} led to only one isomer of $C_{60}F_{48}$ (two enantiomers) as assigned by ^{19}F-^{19}F COSY NMR (Fig. 43) [116]. Attempts at further fluorination results in carbon-carbon bond cleavage, termed the "cracking of the sphere" [113].

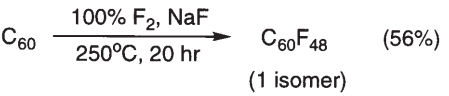


Fig. 43

3
Selective Direct Fluorination

Two approaches to the synthesis of molecules which contain either one or two fluorine atoms or a trifluoromethyl group are the reaction of fluorine with a precursor which then gives the required molecule directly, and the introduction of fluorine into small molecules which are subsequently used as "building blocks" in the synthesis of more complex products [2, 4, 5, 8, 117–120]. Direct reaction between a substrate, or a simple derivative of a substrate, and elemental fluorine has a role to play in both of these approaches. Preparation of fluorinating agents by the reaction of fluorine with various molecules will be discussed but further chemistry of the derived reagents themselves will not be described.

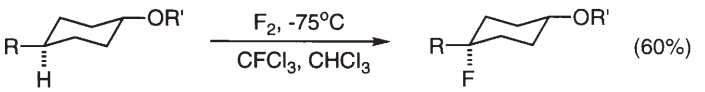
Most successful selective fluorination reactions are carried out under conditions which limit any free radical processes and encourage nucleophilic attack on fluorine either by a one- or two-electron transfer process (see Sect. 3.1.1.3).

3.1
Preparation of Carbon-Fluorine Bonds

3.1.1
Replacement of Hydrogen by Fluorine

3.1.1.1
Alkanes

Elemental fluorine can be used to replace relatively electron rich C-H bonds by C-F. In particular, tertiary hydrogen atoms which are remote from electron withdrawing substituents can be selectively replaced by fluorine and, where there is more than one tertiary hydrogen atom in the substrate, that with the higher electron density is replaced (Fig. 44). In contrast, where there is an electron withdrawing group close to tertiary hydrogen, very little reaction with fluorine takes place and, consequently, when one fluorine atom has been introduced into a molecule further reaction is often inhibited.



R = Me, R' = *p*-O_2N-C_6H_4-CO

Fig. 44

These reactions are carried out in a polar solvent (Solv-H, Fig. 45), such as a 1:1 mixture of fluorotrichloromethane and chloroform, which not only encourages polarisation of the fluorine molecule and makes it more susceptable to nucleophilic attack, but more importantly, acts as an acceptor for the counterion (fluoride ion) in the transition state (Fig. 45). It has been suggested that the

reaction proceeds via a non-classical three-centre two electron carbocation intermediate (Fig. 45) [121] and this mechanism, which accounts for the full retention of configuration observed in these reactions, is supported by recent theoretical studies.

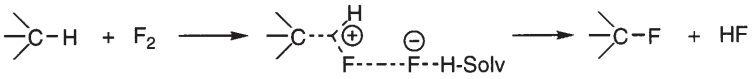


Fig. 45

Many compounds, including fluorinated steroids (Fig. 46) [122], have been prepared by this methodology. These have been compiled by Purrington [12] and the whole area has been reviewed by Rozen, a major contributor to the field [123].

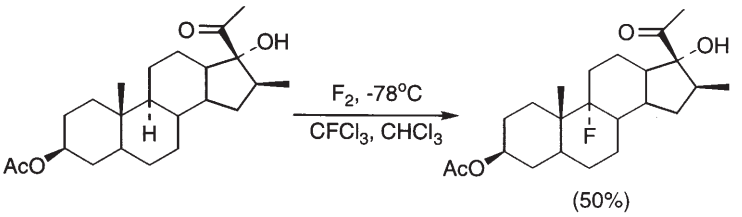


Fig. 46

3.1.1.2 Carbonyl Compounds

Since fluoro-carbonyl compounds are such useful and versatile synthetic intermediates, much effort has been devoted to their preparation [124], but only in a few instances has elemental fluorine been used directly. One of the earliest successful direct fluorinations of a simple carbonyl compound was the fluorination of pyruvic acid derivatives which have a high enol content (R = Aryl, Acyl) (Fig. 47) [125] in the solvent being used (mixtures of $CF_2ClCFCl_2$ and acetonitrile). However, in derivatives where the enol content was low (R = Alkyl), complicated mixtures of products were obtained.

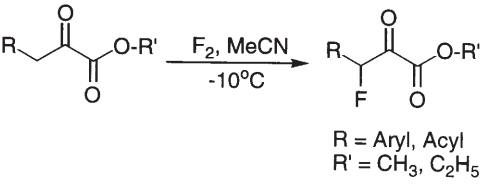


Fig. 47

Recently, it has been shown that β-diketones [126], β-ketoesters (Fig. 48) [126] and *N, N*-dialkyl-β-ketoamides [127] can be fluorinated directly, in high yield, at convenient temperatures (0 ± 10 °C), in polar solvents such as formic acid or acetonitrile. As in the case of the pyruvates, the overall rate of reaction was a

function of the enol content of the substrate. However, even where the enol content at equilibrium was low, high conversions of substrate to product were obtained providing that the rate of enolisation was rapid compared to the time over which the substrate was being exposed to fluorine. Since the monofluorinated compounds, in which R″ is hydrogen (Fig. 48), enolise more slowly than the parent substrate, further fluorination of the monofluorinated compound is correspondingly slow. An exception to this is the case of cyclic β-diketones where, because the monofluorinated compounds exist in their enol forms, the difluorinated product is easily obtained (Fig. 49) [93].

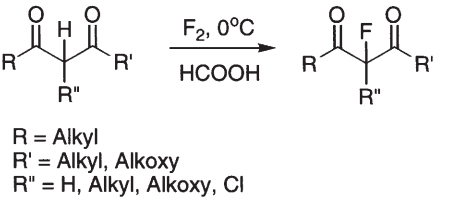


Fig. 48

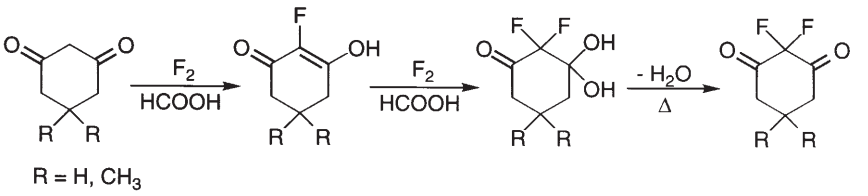


Fig. 49

Diketones react more rapidly with fluorine than the corresponding keto-esters, and dialkyl malonates do not react at all under these conditions. However, if dialkyl malonates are first converted into their sodium salts, reaction with fluorine gives the corresponding fluoro-compound (Fig. 50) [128].

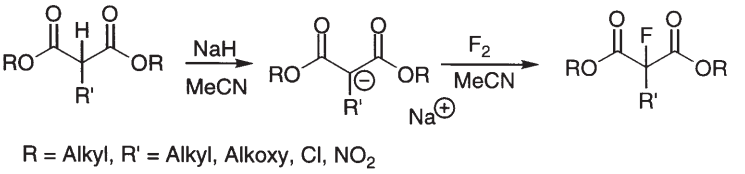


Fig. 50

Attempts to use fluorine in the preparation of simple α-fluoro-carbonyl compounds were not successful initially. Even when derivatives of carbonyl compounds such as enol acetates were treated with fluorine, a complicated mixture of products was obtained from which none of the desired α-fluoro

compounds could be isolated [129]; and when the trimethylsilyl enol ether of cyclohexanone was treated with fluorine in dichloromethane, cyclohexanone was recovered [130]. However, by treating the trimethylsilyl derivatives of aldehydes, ketones, carboxylic acids, esters, *N,N*-dimethylamides, malonates, β-diketones and β-ketoesters with fluorine and using fluorotrichloromethane as the solvent at –78 °C, Purrington obtained moderate to good yields of the corresponding α-fluoro-carbonyl compounds (Fig. 51 and 52) [131 – 133]. The most frequently observed by-products were the corresponding α,α-difluorinated compounds, which can be accounted for by an addition-elimination sequence (Fig. 53) [134].

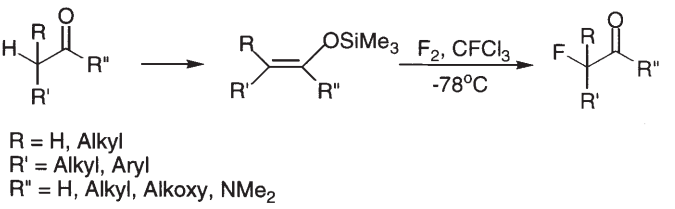


Fig. 51

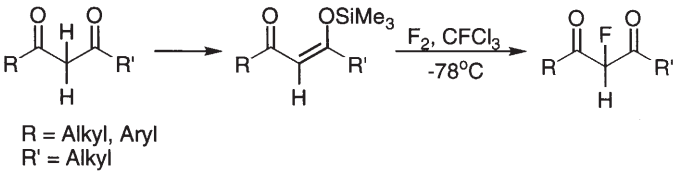


Fig. 52

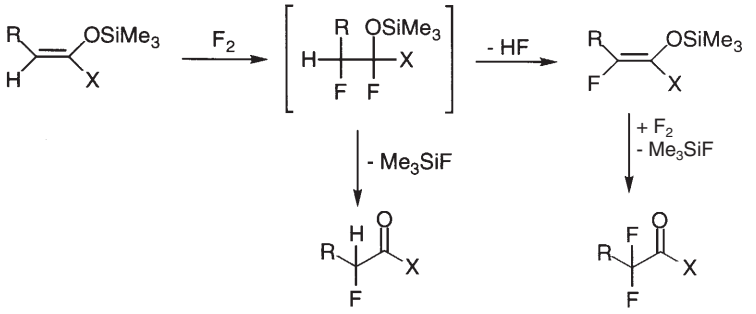


Fig. 53

Under similar conditions, the enol acetate and the trimethylsilyl ether of estrone were fluorinated to give the corresponding α-fluoro carbonyl compound (Fig. 54) [135].

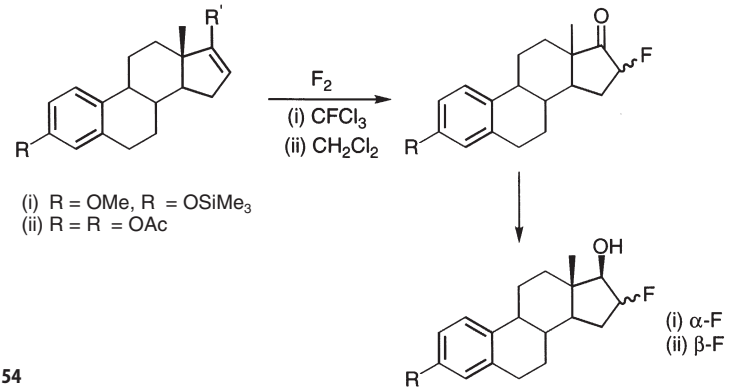


Fig. 54

3.1.1.3 Benzenoid Compounds

Several studies on the direct fluorination of aromatic compounds have been carried out and, although the reaction conditions were not the same in each case, there are several generalisations that can be made [136–143].

In principle, two mechanisms involving either one or two-electron transfer from the aromatic substrate to fluorine may occur and, in practice, the mechanism of fluorination of any given aromatic molecule probably lies between these two extremes. The distinction between electron transfer (Path A, Fig. 55) and S_N2-type processes (Path B, Fig. 55) in reactions between various electrophilic fluorinating agents and nucleophiles has been addressed by Differding [144, 145] but these principles can also be applied to reactions involving elemental fluorine.

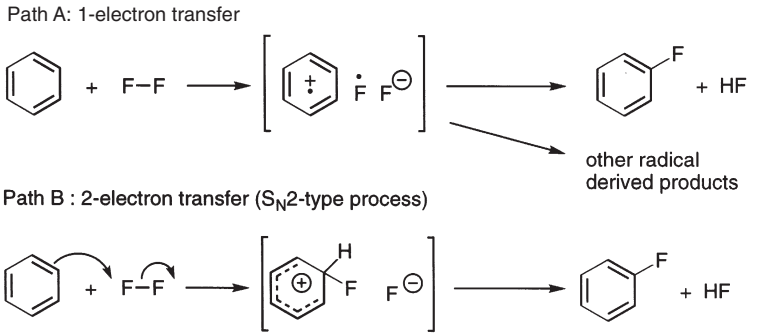


Fig. 55

Fluorination of toluene gives a mixture of *ortho*- and *para*-fluorotoluene, as expected for an electrophilic process (B), but the partial rate factors (Table 4) [139] show a very high *ortho*:*para* ratio indicating that radical processes (A) must also be involved. Furthermore, fluorination of the methyl group, giving benzyl fluoride, also occurs in increasing yield as the reaction temperature is raised.

Table 4. Partial Rate Factors for Fluorination of Ph-X by Fluorine in $CFCl_3$ at –78 °C [139]

X	ortho	meta	para
CH_3	8.5	1.55	8.2
NO_2	0.005	0.041	0.011
CF_3	0.014	0.058	0.036

The fluorination of other activated aromatic compounds, such as anisole and phenol, undergo monofluorination mainly in the *ortho* and *para* positions, whereas the fluorination of deactivated aromatics, such as nitrobenzene, trifluoromethylbenzene and benzoic acid, give predominantly the corresponding *meta* fluoro-derivatives which is consistent with a typical electrophilic substitution process. Also, fluoro-, chloro- and bromo-benzenes are deactivated with respect to benzene itself but are fluorinated preferentially in the *ortho* and *para* positions [139]. At higher temperatures, polychlorobenzenes undergo substitution and addition of fluorine to give chlorofluorocyclohexanes [136].

The nature of the solvent has a major effect on the rate (extent) of reaction. Recently, polar and acidic solvents have been used as reaction media to promote the electrophilic fluorination pathway (B) in which the interaction between fluorine and the acid is envisaged (Fig. 56) [146, 147].

The acidity and dielectric constant of the reaction media can have a profound effect on the fluorination process. Studies concerning the fluorination of a model substrate, 4-fluorobenzoic acid, in a variety of solvents showed that conversion of the substrate to 3,4-difluorobenzoic acid (Table 5) rose as the acidity of the solvent increased, due to the increased interaction between fluorine and the reaction medium (Fig. 56) [147].

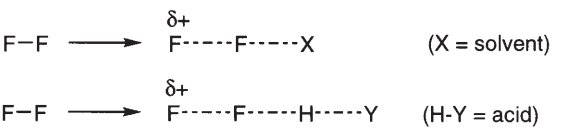


Fig. 56

Table 5. Fluorination of 4-Fluorobenzoic Acid in Various Solvents [147]

Solvent	Conversion to 3,4-Difluorobenzoic Acid (%)
CF_2Cl-$CFCl_2$	0
CF_3-CH_2OH	10
CH_3-COOH	25
CH_3-CN	53
CF_3-COOH	56
H-COOH	65
conc. H_2SO_4	84

Hence, in highly acidic media, fluorine may act as a very powerful and selective electrophile and, by this method, 2,4-difluorobenzoic acid, which is highly deactivated towards electrophilic attack, can be fluorinated in concentrated sulphuric acid to such an extent that 2,3,4,5-tetrafluoro- and even small amounts of pentafluoro-benzoic acid are produced [146, 147].

Direct fluorination, therefore, is not particularly effective for the preparation of mono-fluorinated aromatic compounds from monosubstituted precursors since, in these cases, electrophilic fluorination gives mixtures of isomeric products. However, when there are two or more groups in the aromatic substrate which activate the same carbon atom towards electrophilic attack, as in the case of 4-fluorobenzoic acid (Table 5), then direct fluorination is an efficient method for the preparation of fluoroaromatic compounds (Fig. 57) [148].

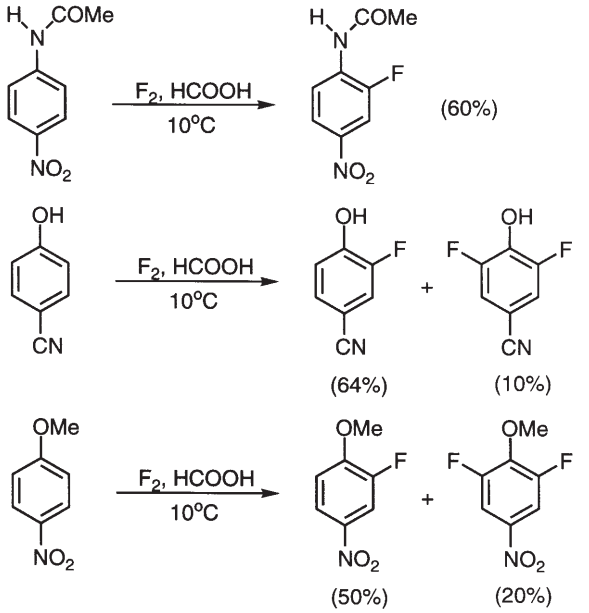


Fig. 57

3.1.1.4 Heterocyclic aromatic compounds

Despite continued interest in the halogenation of heteroaromatic systems [149–151], there are still relatively few reports concerning the direct fluorination of heterocycles compared to publications that describe analogous chlorination and bromination reactions.

Fluorine reacts with N-methylpyrrole and thiophene to give mixtures of mono-fluorinated isomers, consistent with an electrophilic fluorination process (Fig. 58) [152, 153], whilst furan gives a mixture of products largely resulting from addition of fluorine to the ring. The conversions of the reactions reported

were kept deliberately low in order to minimise substrate degradation and are, therefore, not preparatively useful.

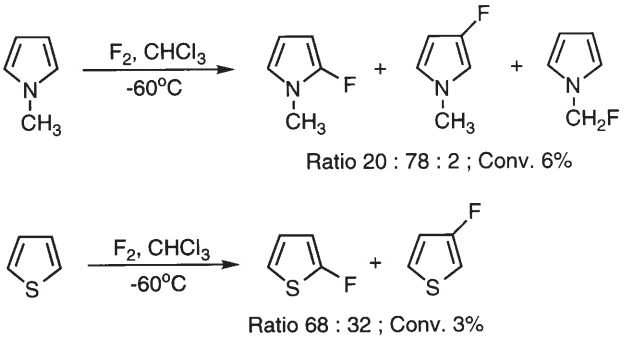


Fig. 58

Meinert demonstrated that fluorination of pyridine at low temperatures gives the ionic salt *N*-fluoropyridinium fluoride, a compound that was reported to be explosive at 0 °C (Fig. 59) [154]. However, direct fluorination of variously substituted pyridines is possible and good yields of the corresponding 2-fluoropyridines (Figs. 60 and 61) [155] are obtained, offering an attractive alternative to the usual halogen-exchange and Balz–Schiemann routes to these products. These reactions probably proceed via *N*-fluoropyridinium salts (Fig. 62) which are activated towards nucleophilic attack.

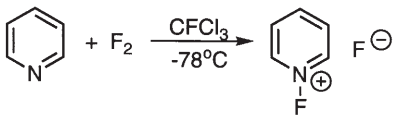


Fig. 59

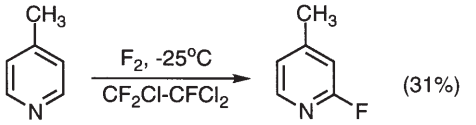


Fig. 60

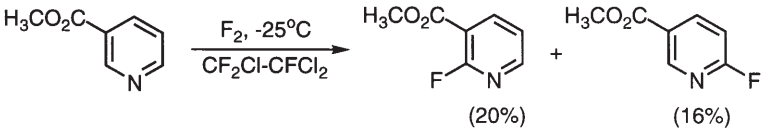


Fig. 61

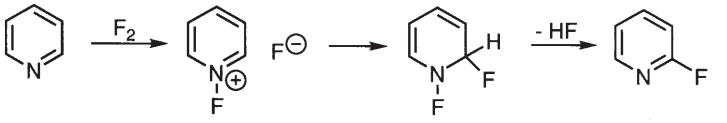


Fig. 62

Reaction of 2-chloropyridine gives 2-chloro-6-fluoropyridine as the major product which arises from the preferential substitution of hydrogen over chlorine and would be unexpected on the basis of the nucleophilic substitution mechanism described above. The product obtained was suggested, therefore, to arise from the addition of fluorine to the most electron rich carbon-nitrogen double bond, followed by elimination of HF [155].

5-Fluorouracil has been used for some time for cancer treatment. Its preparation using fluorine is operated commercially (P.C.R. Inc) and has been the focus of numerous studies [12, 150] in the past. In a more recent study, the products obtained upon fluorination of uracil, usually carried out in acetic acid solvent, indicate that the reactions proceed via an addition-elimination process involving radical cation intermediates (Fig. 63) [156].

Direct fluorination of nucleosides has been achieved (Fig. 64) [157] and fluoroguanine derivatives have recently been prepared (Fig. 65) [158].

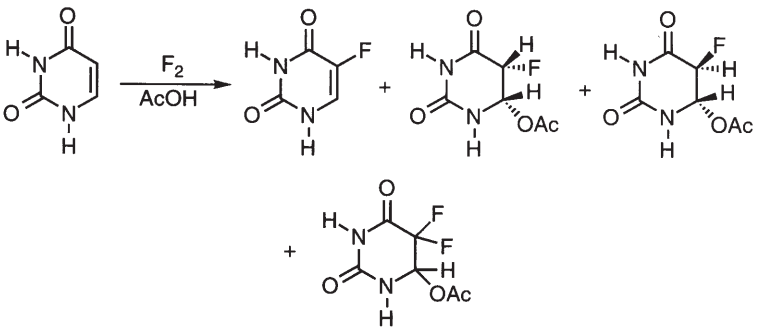


Fig. 63

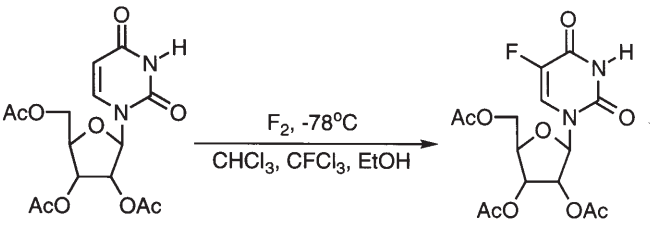


Fig. 64

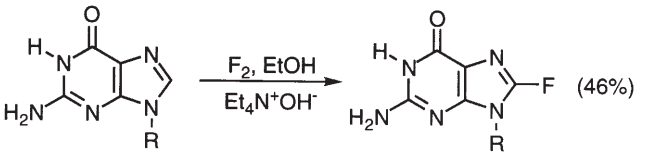


Fig. 65

Reactions of various aza-heterocycles with fluorine/iodine mixtures gave good yields of the corresponding heterocycles selectively fluorinated at positions *ortho* to the ring nitrogen (Fig. 66) [159]. Reaction of fluorine and iodine is assumed to result in the *in situ* generation of sources of both iodonium and fluoride ion, and a mechanism similar to that described above (Fig. 62), in this case proceeding via an *N*-iodopyridinium fluoride, is envisaged.

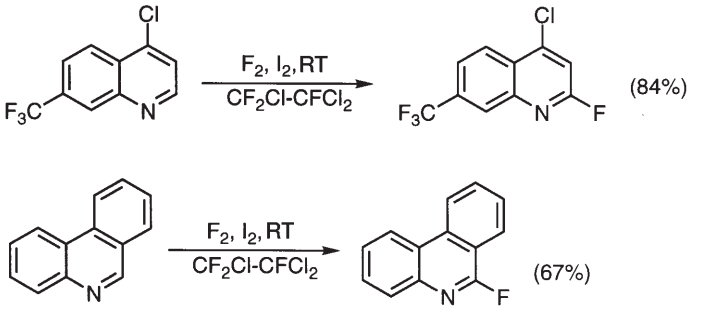


Fig. 66

3.1.2
Fluorodesulfurization Reactions

The conversion of carbon-sulfur bonds to carbon-fluorine bonds using fluorine was first achieved in reactions with thiols in highly acidic HF/HBF_4 solution (Fig. 67) [160]. It was suggested that fluorine oxidises the thiol to the dipositive species, R-SF_3^{2+}, which could be cleaved by HF to give the alkyl fluoride. The existence of the leaving group, SF_3^+, had already been observed in HF, lending support to this rationale.

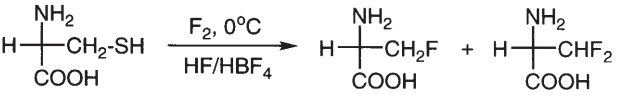


Fig. 67

Fluorine/iodine mixtures, which can be regarded as sources of both iodonium and fluoride ion, have been used to prepare glycosyl fluorides from the corresponding thioglycosides and *gem*-difluorides from some diaryl-1,3-dithiolanes (Fig. 68) [161, 162]. Activation of the carbon-sulfur bond towards nucleophilic attack by fluoride ion is achieved by complexation of the thiophilic iodonium species with the sulfur atoms.

Carbon-sulfur double bonds have been transformed to CF_2 groups in the preparation of difluoroformals from thionocarbonates (Fig. 69) [163, 164].

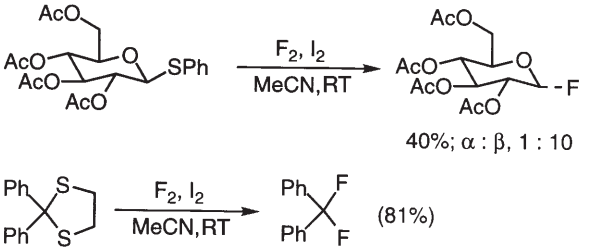


Fig. 68

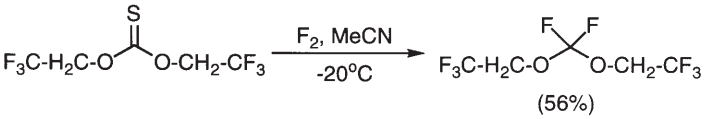


Fig. 69

3.1.3
Fluorodemetallisation

Fluorine can be introduced into alkanes indirectly by treating either lithium or Grignard reagents with fluorine (Fig. 70) [165] at –60 °C in hydrocarbon ether solvents. The lithium reagents reacted more rapidly than the corresponding Grignard reagents, and primary or secondary alkyl compounds were more reactive than tertiary.

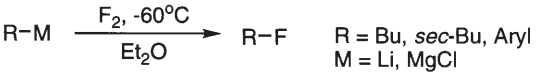


Fig. 70

Fluoroaromatic compounds can also be prepared by treating certain metal derivatives of aromatic compounds with fluorine (Fig. 71). Thus, when trialkyl silicon, germanium or tin derivatives of aromatic compounds were treated with fluorine at a variety of temperatures, the main reaction was the replacement of the metallic residue by fluorine. Higher yields (up to 70 %) were obtained when the metal was tin rather than silicon, presumably due to the C-Sn bond being weaker than the C-Si bond, and when the solvent was $CFCl_3$, $CHCl_3$ or CCl_4 rather than CH_2Cl_2. Furthermore, electron withdrawing groups in the *para* position caused a reduction in the yield (Fig. 71) [166–169].

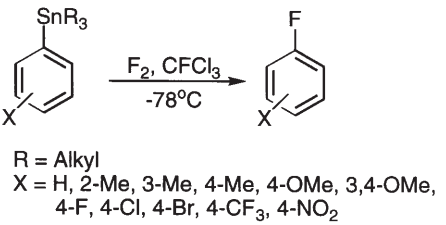


Fig. 71

3.1.4
Addition of Elemental Fluorine to Carbon-Carbon Double Bonds

Merritt et al. [124, 170–174] carried out some of the earliest additions of fluorine to carbon-carbon double bonds. The fluorination of *cis* and *trans* propenyl benzene in a nonpolar solvent at low temperature gave predominantly *erythro* and *threo* difluorides respectively. More recently, Rozen [175] carried out similar reactions, but used a more polar solvent (trichlorofluoro methane, chloroform and ethanol) and a very low concentration of fluorine. Thus, in the fluorination of *cis* and *trans* 3-hexene-1-ol acetate (Fig. 72), *syn* addition occured to give exclusively the *erythro* and *threo* difluoro compounds respectively. Corresponding results were obtained in the addition of fluorine to other alkenes, including cyclic alkenes and cyclic enones.

Unlike the addition of other halogens to double bonds, where *trans* addition occurs, Rozen suggested that the *syn* addition of fluorine procedes by way of a tight ion pair which collapses before any rotation about the C-C bond takes place (Fig. 73) [175].

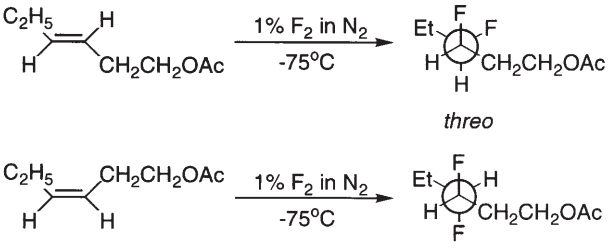


Fig. 72

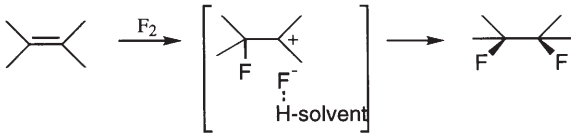


Fig. 73

In the fluorination of alkenes with a terminal double bond, a significant amount of trifluoro compound was produced. This is believed to occur by the loss of H^+ from the cationic intermediate followed by addition of fluorine to the resulting double bond (Fig. 74).

As well as having theoretical interest, this reaction has been used as a key step in the synthesis of more complex enantiomerically pure fluorine containing compounds. For example, fluorine has been added to i) 5,6-unsubstituted and 6-substituted 1,3-dioxin-4-ones (Fig. 75) [176, 177], ii) cholest-4-en-3-one (which gave the adduct and two monofluoro-compounds) (Fig. 76) [178], iii) bicyclo [2.2.1] hept-2-ene derivatives (Fig. 77) [179, 180], iv) 2-azabicyclo [2.2.1]

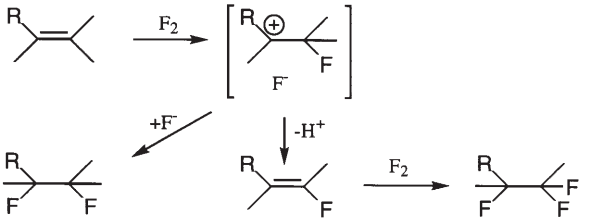


Fig. 74

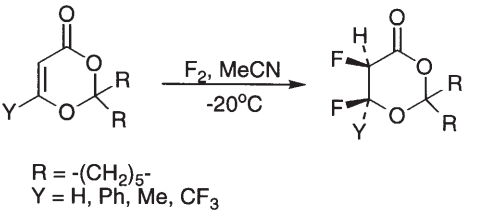


Fig. 75

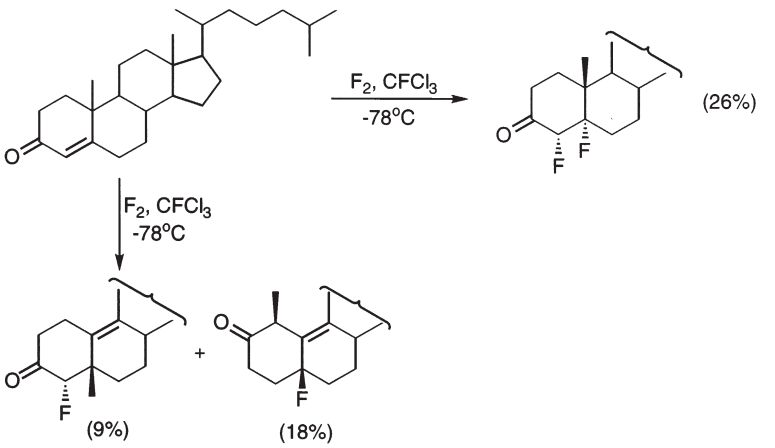


Fig. 76

hept-5-en-3-one and related compounds (Fig. 78) [179, 180], v) azlactones (Fig. 79) [181], and vi) carbocyclic and heterocyclic β-chloro enones (Fig. 80) [182].

Reaction between fluorine and maleic anhydride in a mixture of chloroform and fluorotrichloromethane with sodium fluoride gave a significant amount of chlorinated products indicating that radical processes were operating. Even at – 25 °C, significant reaction took place by a radical mechanism and at about 0 °C this was the main process [183].

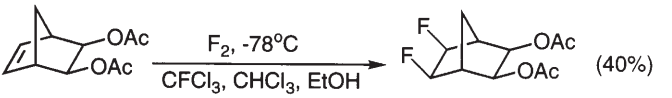


Fig. 77

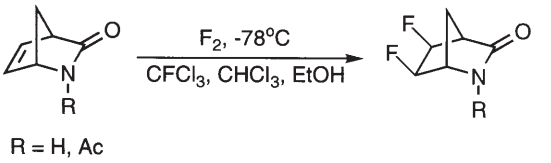


Fig. 78

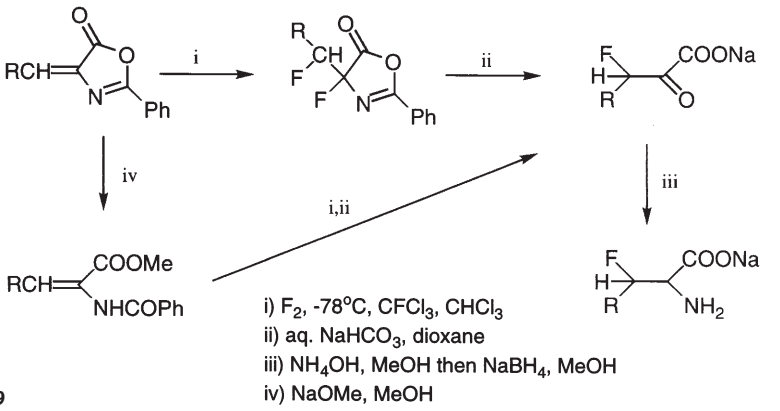


Fig. 79

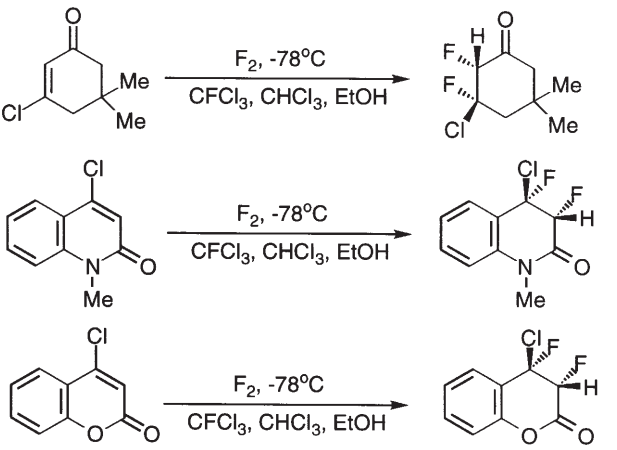


Fig. 80

3.2
Preparation of Oxygen-Fluorine Bonds.

3.2.1
Perfluoroalkyl, Acyl and Perfluoroacyl Hypofluorites

Trifluoromethyl hypofluorite was first made by Cady by passing methanol [184] or carbon monoxide [185, 186] with fluorine over silver difluoride at elevated temperatures. Later, trifluoromethyl hypofluorite and higher perfluoroalkyl hypofluorites were prepared by treating the appropriate carbonyl compound with fluorine in the presence of dry caesium fluoride at sub-zero temperatures (Fig. 81) [187–189].

More recently, Rozen found that treating suspensions of sodium or potassium perfluorocarboxylates with fluorine in an inert solvent, such as trichlorofluoromethane, afforded "oxidising solutions" which proved to be mixtures of hypofluorites (Fig. 82) [190–192].

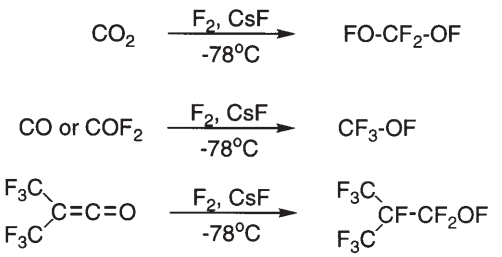


Fig. 81

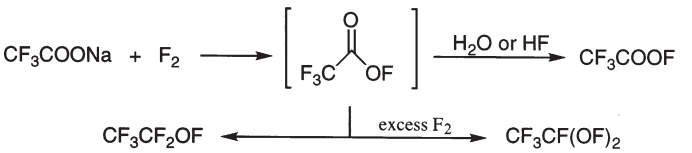


Fig. 82

Anhydrous conditions favoured perfluoroalkyl hypofluorite formation whereas the presence of water led to the formation of perfluoroacyl hypofluorites [190–192]. Acetyl hypofluorite could be prepared in a similar manner[193] and this methodology was also successful for the preparation of higher homologues, provided there was at least one electron withdrawing group on the α carbon and that long aliphatic chains were not present [194]. The reagents were generally synthesised by passing fluorine through a suspension of a sodium acetate/acetic acid mixture, but it was later found that passing fluorine through a column

packed with sodium acetate/acetic acid [195] also gave a good yield of the desired hypofluorite.

Of the hypofluorites mentioned above, only the chemistry of the trifluoromethyl, trifluoroacetyl and acetyl compounds has been explored seriously. These compounds have been used as sources of electrophilic fluorine and details of this chemistry can be found in reviews which have appeared over the years and in the primary literature to which they refer [6, 12, 13, 18, 123, 196–199].

3.2.2
Alkyl Hypofluorites

When fluorine is passed through a mixture of methanol in acetonitrile at –45 °C or propionitrile at –75 °C a solution of methyl hypofluorite, stabilised by the solvent, is produced [200]. While methyl hypofluorite can be isolated, its chemistry has been investigated by treating various substrates with freshly prepared solutions rather than with isolated material. Unlike the hypofluorites which have been discussed so far, methyl hypofluorite behaves as a synthon for the rare methoxylium species, "MeO^+", and adds to various alkenes electrophilically in accordance with Markovnikov's Rule [201]. In the reaction between methyl hypofluorite and indene, almost exclusive *trans* addition occurred.

tert-Butyl hypofluorite has been prepared in a similar manner but attempts to prepare other hypofluorites having an α-hydrogen failed, although evidence for the formation of the deuterated hypofluorites, CH_3CD_2OF and CD_3CD_2OF has been obtained [202].

Hypofluorous acid decomposes very rapidly above –100 °C but, by passing fluorine through aqueous acetonitrile, a complex of HOF with acetonitrile is formed which is stable for several hours at room temperature. The chemistry of this interesting reagent has been reviewed recently [6, 19, 199].

3.3
Preparation of Nitrogen-Fluorine Bonds

One of the most active areas of research in fluorine chemistry over the last ten years has been the development of the N-F electrophilic fluorinating reagents. These compounds fall into two categories, namely, neutral molecules and salts, and the reader is referred to recent reviews and papers which describe in detail their preparation and chemistry [7, 18, 197, 203–211].

Early N-F electrophilic fluorinating reagents weren't particularly active, they decomposed below room temperature and were hygroscopic. More recently, reagents have been developed that are stable, safe, convenient to handle, offer a range of fluorinating powers, and some of these are available commercially [7] (e.g. Selectfluor®, Air Products). The general method for increasing the fluorinating power has been to reduce electron density on the nitrogen and thereby increase the susceptibility of the fluorine to nucleophilic attack. In the case of the neutral N-F reagents, electron density on the nitrogen is most frequently

reduced by the presence of adjacent carbonyl or sulfonyl groups, with the sulphonyl group generally yielding the more stable reagents. Stability of the N-F salts can also be enhanced by having counter-anions which have extremely low nucleophilicity and low basicity e.g. BF_4^-, OTf^-, while the "fluorinating power" can be controlled by the nature of groups adjacent to the nitrogen. General methods for the preparation of these reagents are outlined in Table 6 [page 34] and examples of the main structural types are given in Table 7 [page 35].

4
Fluorine as a Reagent for the Synthesis of Non-Fluorinated Compounds

In this section we will discuss the use of elemental fluorine for the promotion of organic transformations that do not result in the introduction of fluorine into the substrate. As we described above (Sect. 3), fluorine may be used to prepare many extremely useful reagents which may be employed as, for example, oxidising and oxygen transfer agents. The use of O-F compounds, such as acetyl hypofluorite and the HOF.MeCN complex, in functionalisation processes has been indicated above (Sect. 3.2), and this area has been discussed in detail in an excellent account by Rozen [19].

In this section we will focus on the use of fluorine for the promotion of organic transformations where elemental fluorine is used in single-step procedures. Transformations which are carried out in two-stages where the preparation of the fluorine containing reagent is followed by the addition of the substrate, are not included. Although, in many cases, *in situ* generated intermediates are probably the reacting species, we feel that the increased convenience of carrying out reactions in one stage is far more amenable to large scale synthesis.

4.1
Organic Transformations Promoted by Fluorine

Although fluorine is an extremely powerful oxidant, controlled oxidation of secondary alcohols to the corresponding ketones can be achieved by passing fluorine through a solution of the substrate in dry acetonitrile (Fig. 83) [226]. Similarly, oxidation of secondary 1,2-diols gives α-hydroxy-ketones, rather than products arising from carbon-carbon bond cleavage, as usually occurs upon oxidation of such substrates by more conventional methods. However, oxidation of primary alcohols gives complex mixtures of products including aldehydes and higher molecular weight material. It is difficult to establish whether the reaction proceeds either via an ionic or a radical process (Fig. 84).

Sulfoxides are oxidised to sulfones, with concomitant α-fluorination, upon reaction with fluorine in aqueous acetonitrile (Fig. 85) [227].

Carboxamidation of heteroaromatic compounds, promoted by fluorine, provides a convenient alternative to the well-known Chichibabin amination reaction (Fig. 86) [228]. The mechanism of this reaction was suggested to proceed via a carbene intermediate (Fig 87).

Table 6. Preparation of N-F Electrophilic Fluorinating Agents

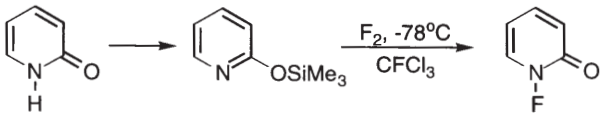
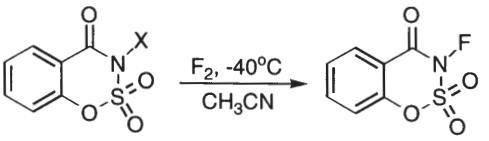
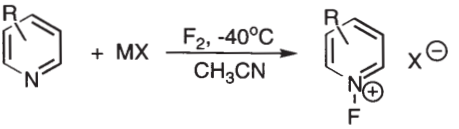
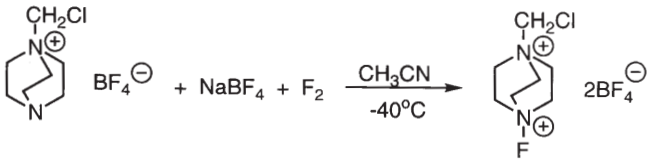
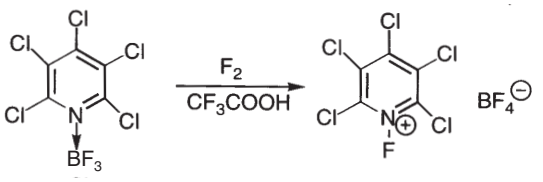
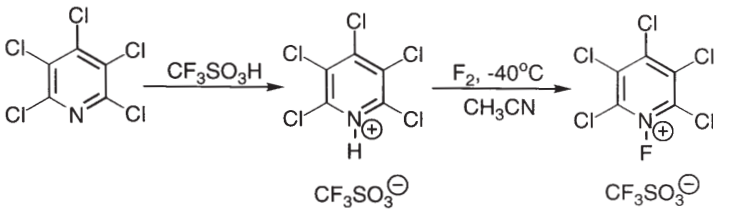
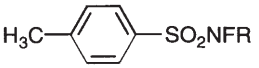
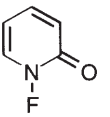
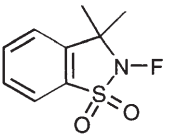
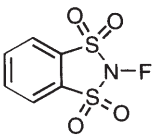
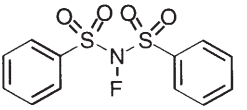
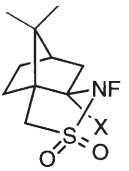
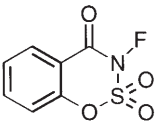
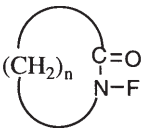
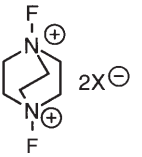
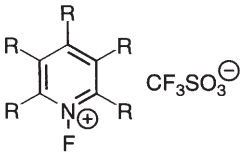
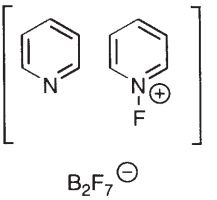
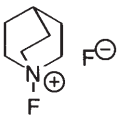
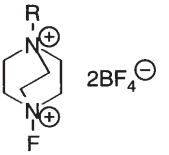
Reaction	Ref.
	[212]
 X = H, Na, K	[213]
 X = TfO, BF_4, PF_6, SbF_6, ClO_4 M = Na, K	[204]
 (89%)	[214]
	[204]
	[204]

Table 7. N-F Electrophilic Fluorinating Reagents; Main Structural Types

	[215]		[212]
$(R_F\text{-}SO_2)_2N\text{-}F$	[216, 217]		[218]
	[219]		[220]
 X= H, Me	[221]		[213]
	[222]		[223]
	[203, 204]		[210, 224]
	[225]		[209, 214]

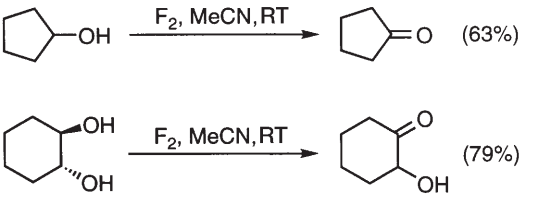


Fig. 83

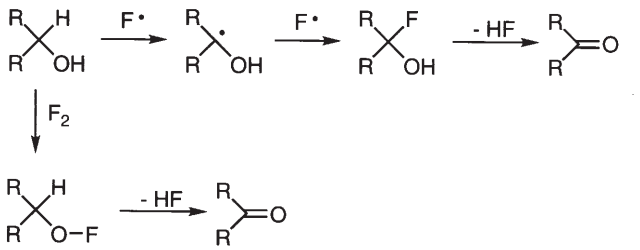


Fig. 84

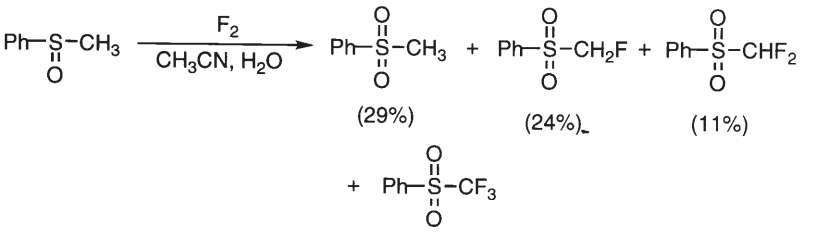


Fig. 85

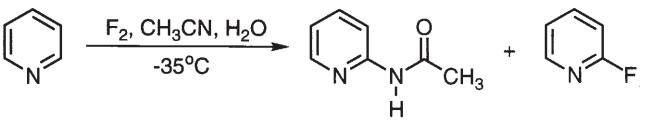


Fig. 86

Reaction with oxygen nucleophiles provides a simple route for the oxidation (Fig. 88) [229] and alkoxylation [230] (Fig. 89) of pyridine and related heteroaromatics.

Fluorine has been used for the generation of extremely strong electrophilic halogenating agents in electrophilic iodination and bromination of deactivated aromatic substrates in highly acidic reacton media. Polyhalogenation of more activated aromatic substrates is also possible (Fig. 90) [231–233].

Fluorination of 1,3-dithiolanes in aqueous acetonitrile offers novel methodology for the deprotection of thiolanes to the parent ketones (Fig. 91) [162].

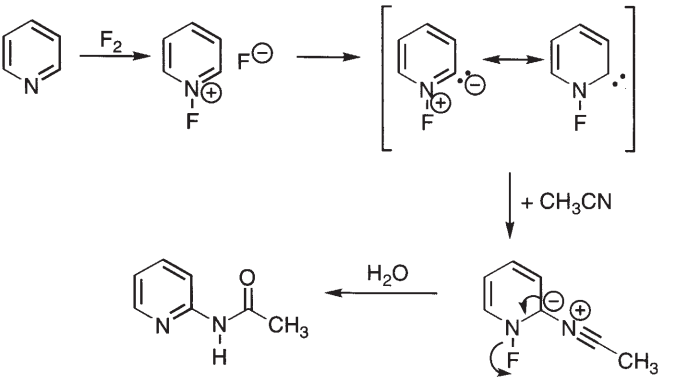
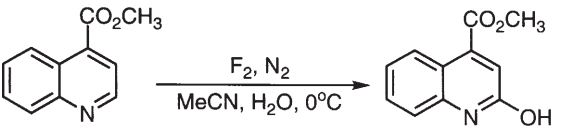
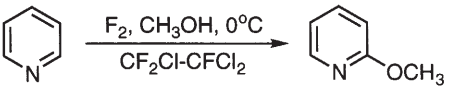


Fig. 87



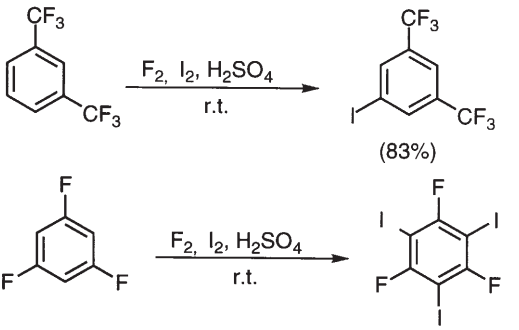
(75%)

Fig. 88



(57%)

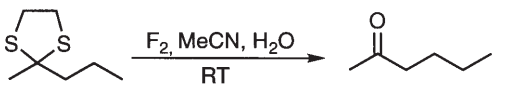
Fig. 89



(83%)

(63%)

Fig. 90



(79%)

Fig. 91

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