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Organofluorine Chemistry

Techniques and Synthons

Volume Editor: R.D. Chambers

With contributions by
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T. Yamazaki

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Preface

Fluorine is unique in that it is possible to replace hydrogen by fluorine either singly or multiply, in an organic molecule and, in so-doing create a potentially infinite extension to organic chemistry that is entirely synthetic. The excitement of the chemistry of these systems stems from the unique reactions that ensue and the "special-effects" that introduction of fluorine impart. Indeed, these effects are now exploited in a remarkable array of applications across the whole of the chemical, pharmaceutical, and plant-protection industries, although this is not widely appreciated. In this book, we have gathered authors with immense experience in various aspects of their field and each is a world-authority on the important topics they have described. Some topics, like the use of elemental fluorine, and enzymes in synthesis, are relatively new areas that are rapidly growing.

We dedicate the book to a long standing friend, Professor George Olah, in the year of his 70th birthday, in recognition of his massive achievements.

Durham, May 1997 Dick Chambers

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Organofluorine Chemistry: Fluorinated Alkenes and Reactive Intermediates

Volume Editor: R. D. Chambers

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.

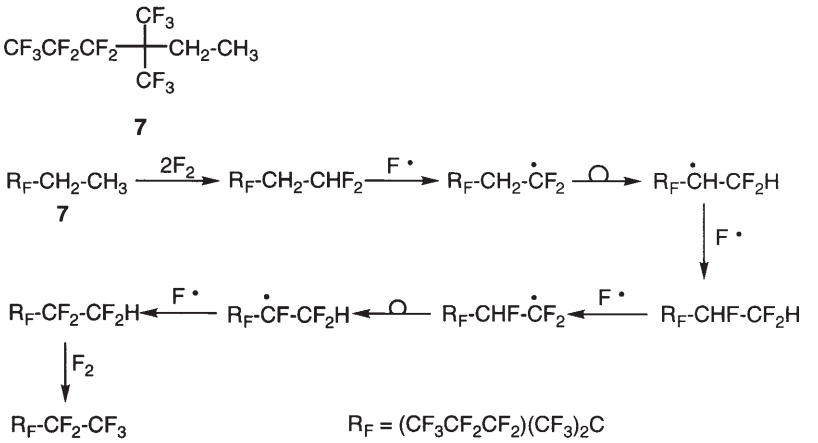


Fig. 2

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.

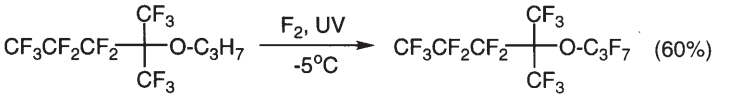


Fig. 3

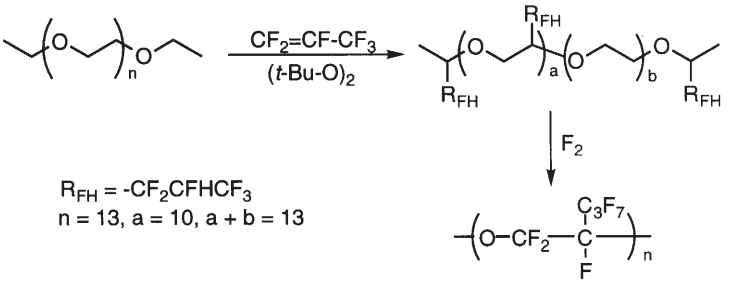


Fig. 4

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).

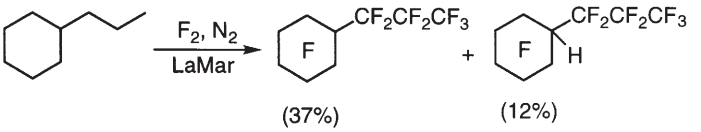


Fig. 5

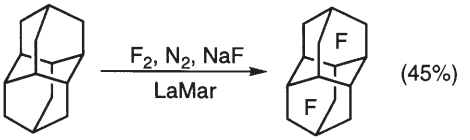


Fig. 6

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.

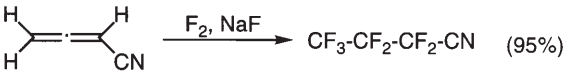


Fig. 7

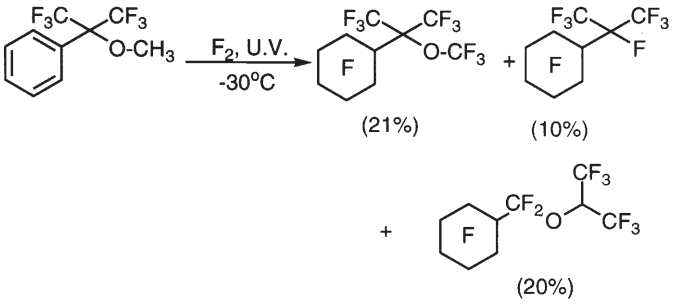


Fig. 8

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.

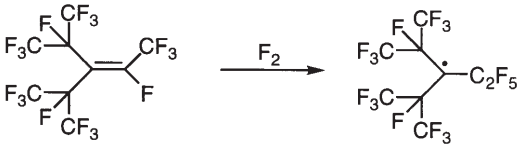


Fig. 9

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).

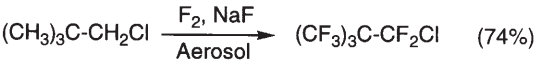


Fig. 10

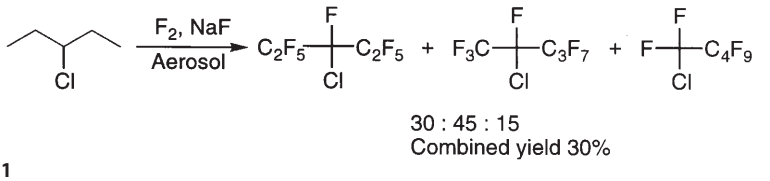


Fig. 11

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].

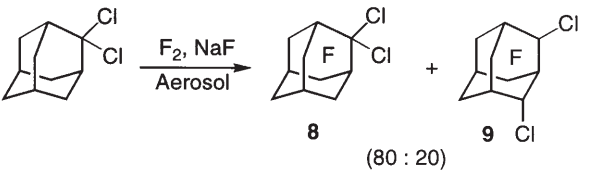


Fig. 12

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 σ-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].

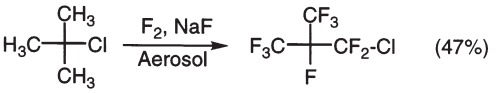


Fig. 13

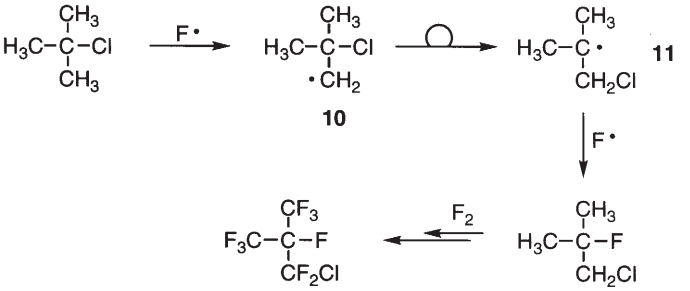


Fig. 14

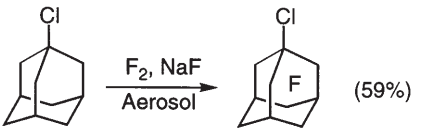


Fig. 15

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].

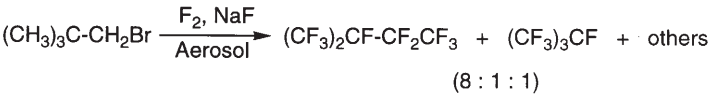


Fig. 17

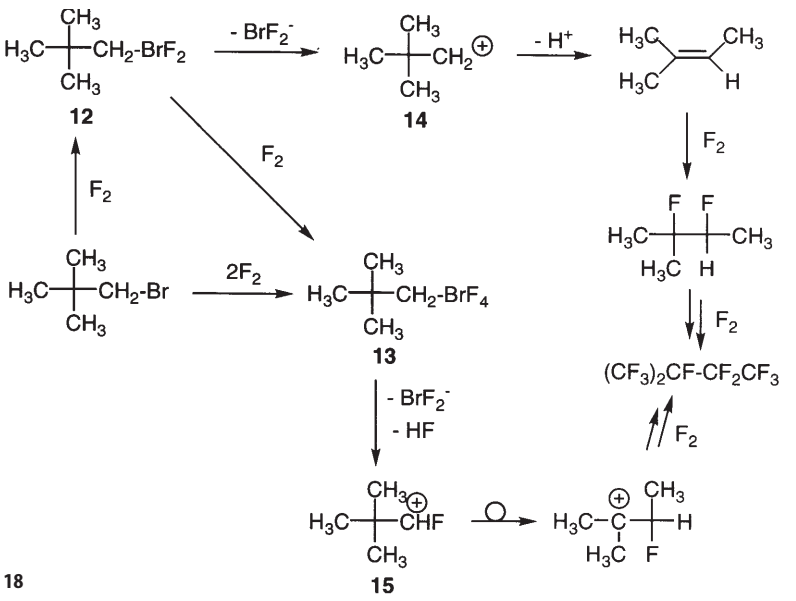


Fig. 18

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].

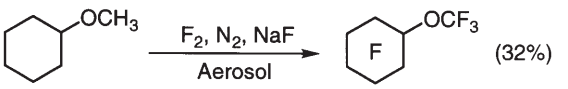


Fig. 19

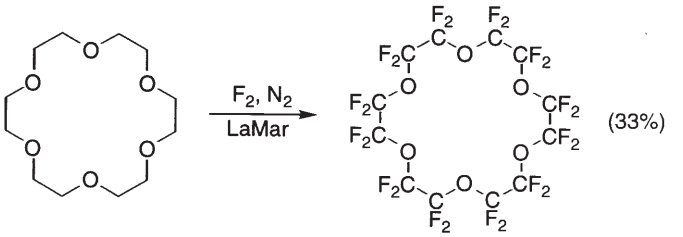


Fig. 20

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].

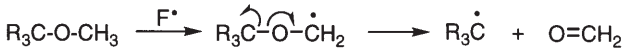


Fig. 21

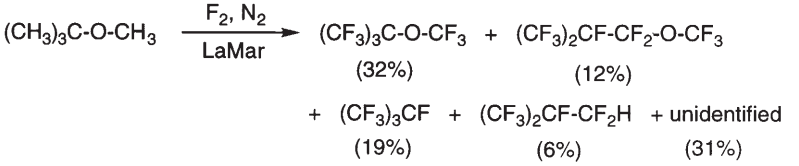


Fig. 22

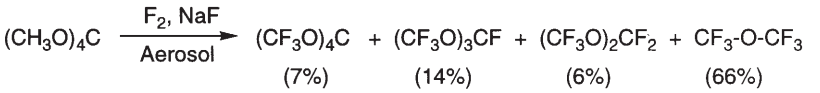


Fig. 23

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

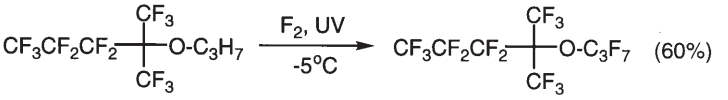


Fig. 24

Fig. 25

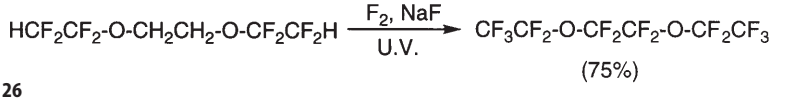
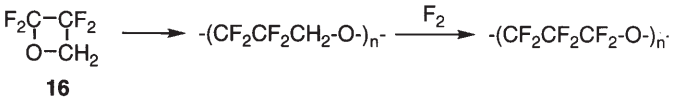


Fig. 26

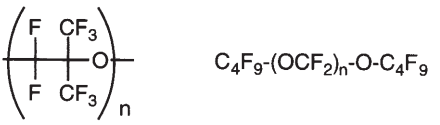
Perfluoropolyethers have found widespread use as high-performance lubricants and several companies manufacture a range of these materials (Krytox®, Du Pont; Fomblin®, Montefluos; Demnum®, Daikin). The Fomblin® fluids and Krytox® require the use of fluorine in the finishing stages [81] whilst Demnum® 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).

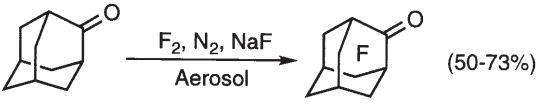


Fig. 29

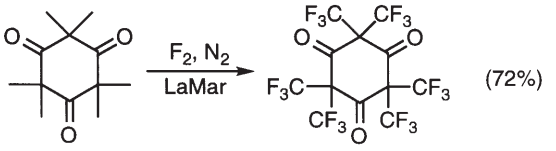


Fig. 30

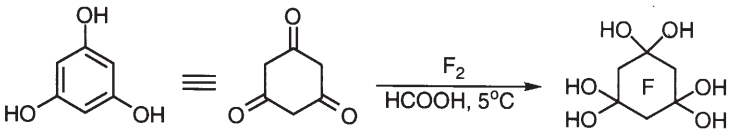


Fig. 31

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.

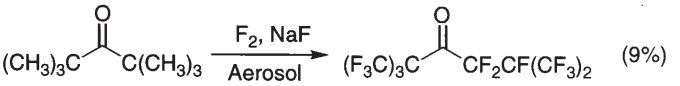


Fig. 32

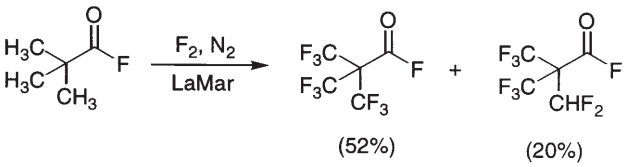


Fig. 33

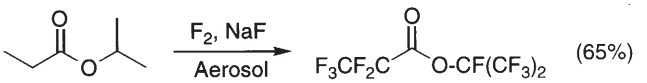


Fig. 34

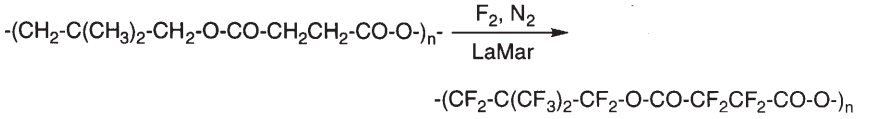


Fig. 35

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].

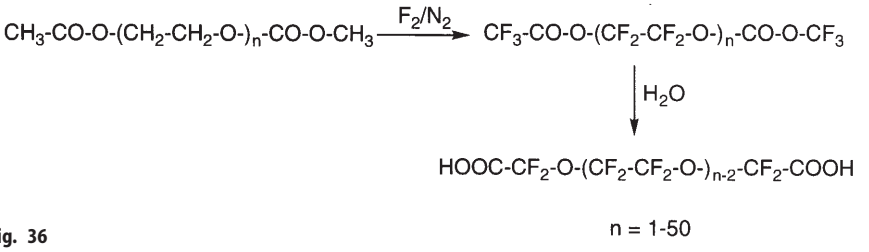


Fig. 36

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].

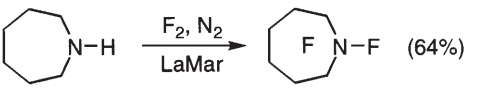


Fig. 37

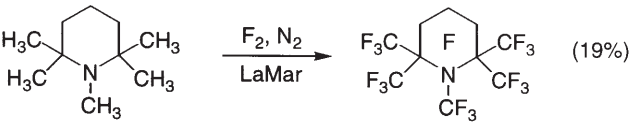


Fig. 38

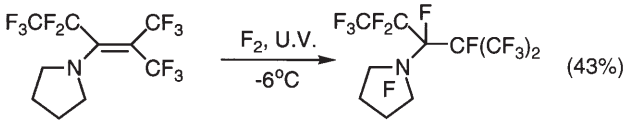


Fig. 39

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].

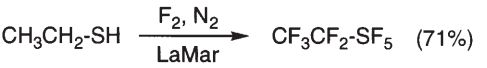


Fig. 40

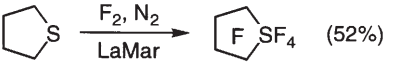


Fig. 41

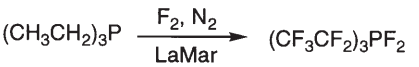


Fig. 42

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].

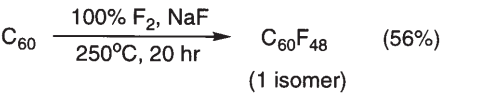


Fig. 43

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.

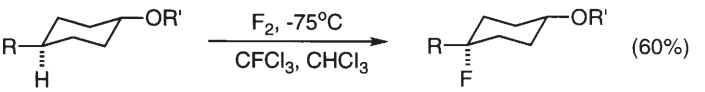
Most successful selective fluorination reactions are carried out under conditions which limit any free radical processes and encourage nucleophilic attack on fluorine either by a one- or two-electron transfer process (see Sect. 3.1.1.3).

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.

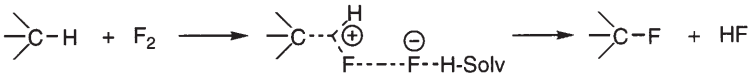


Fig. 45

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].

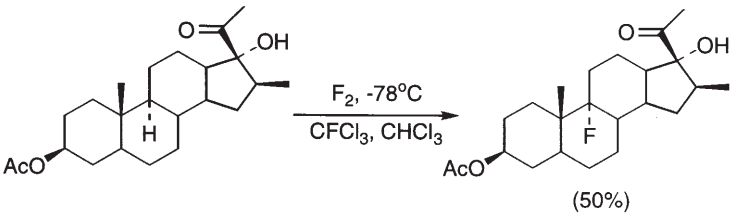


Fig. 46

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.

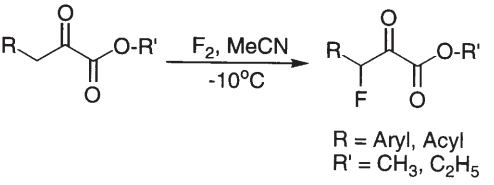


Fig. 47

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].

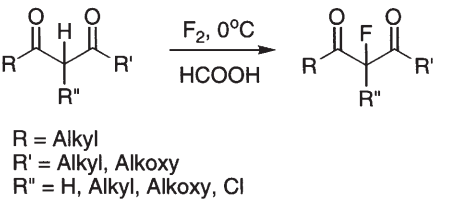


Fig. 48

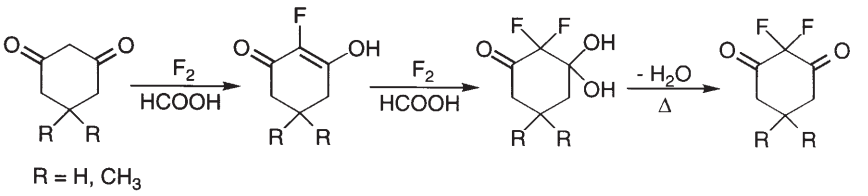


Fig. 49

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].

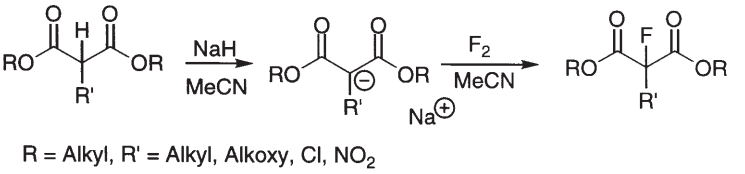


Fig. 50

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].

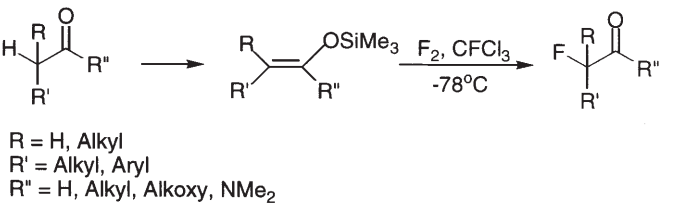


Fig. 51

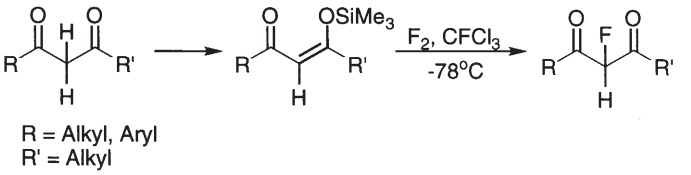


Fig. 52

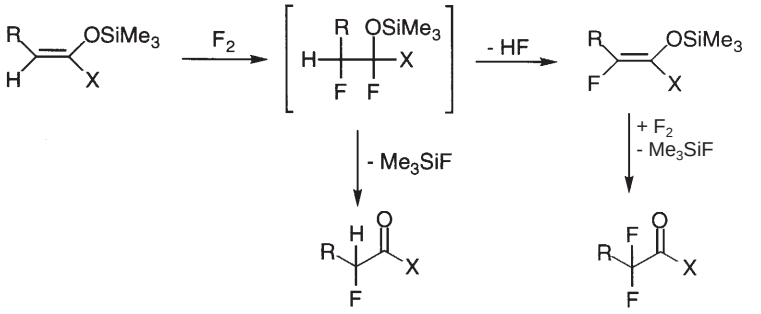


Fig. 53

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].

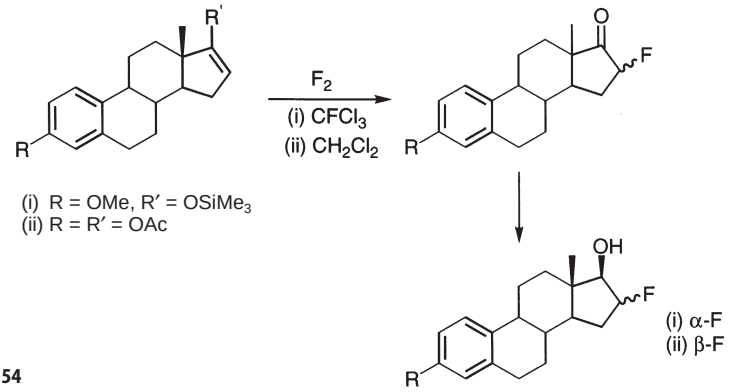


Fig. 54

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.

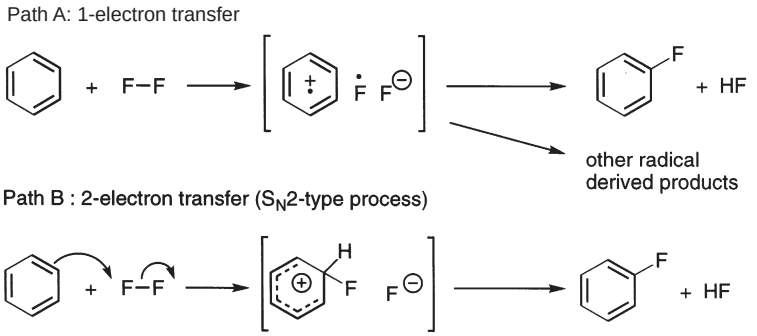


Fig. 55

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].

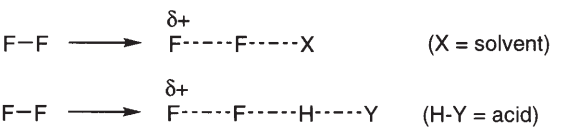


Fig. 56

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].

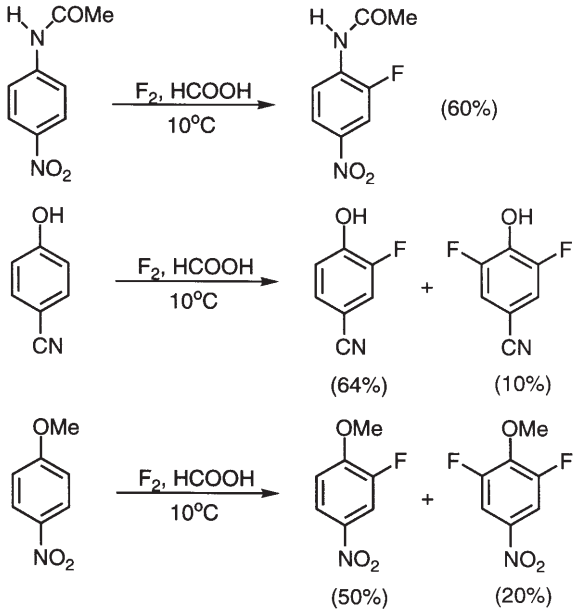


Fig. 57

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.

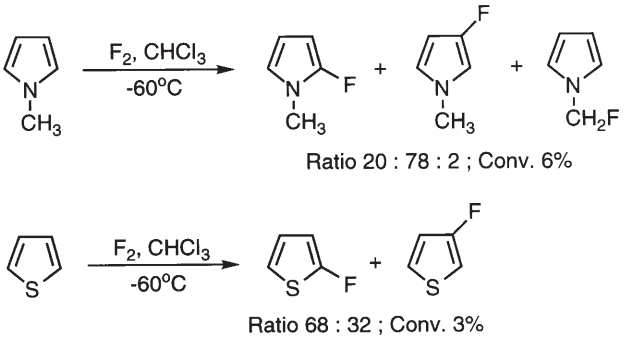


Fig. 58

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.

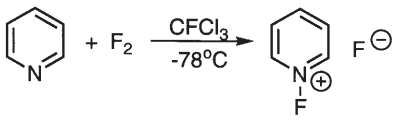


Fig. 59

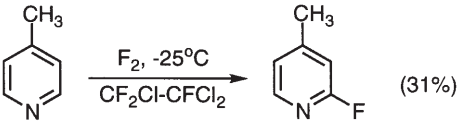


Fig. 60

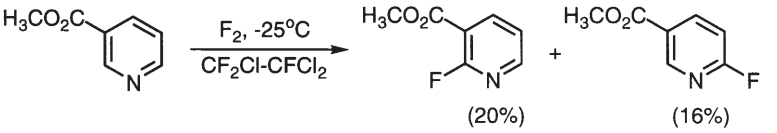


Fig. 61

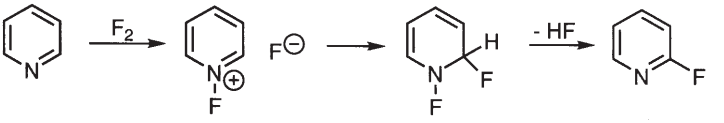


Fig. 62

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].

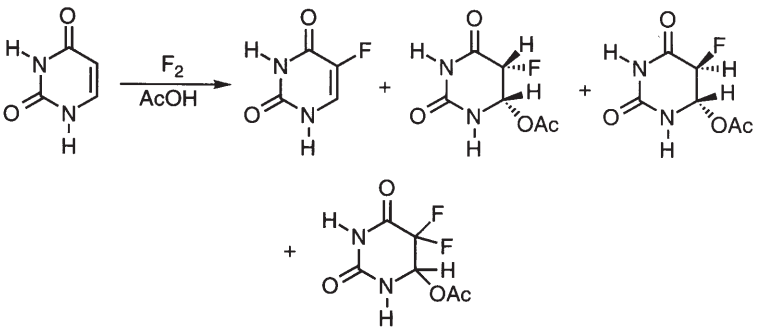


Fig. 63

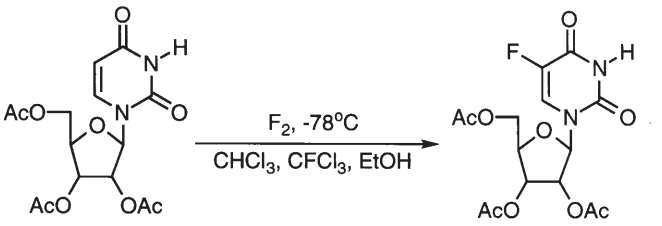


Fig. 64

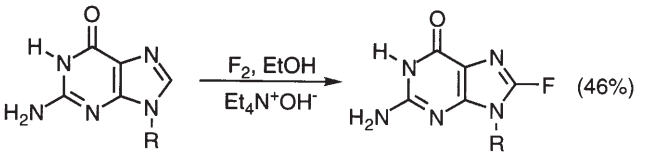


Fig. 65

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.

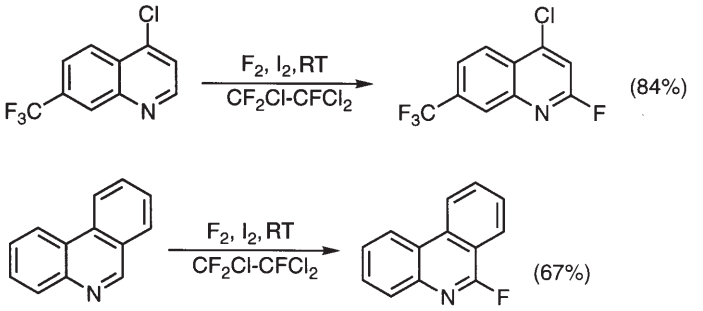


Fig. 66

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.

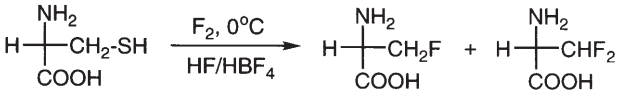


Fig. 67

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].

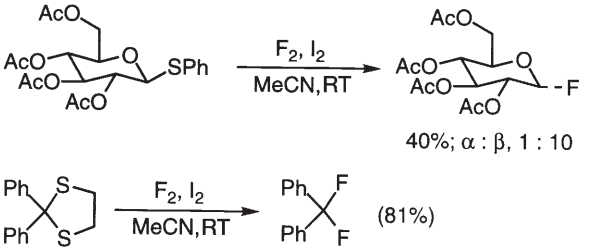


Fig. 68

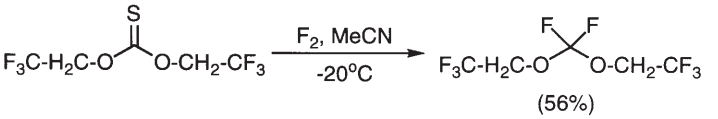


Fig. 69

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.

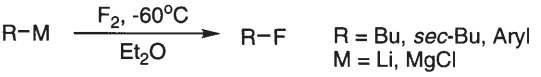


Fig. 70

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].

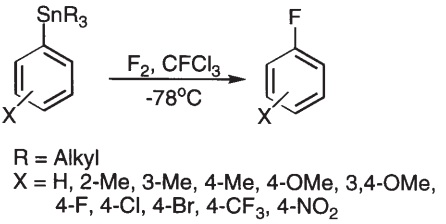


Fig. 71

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].

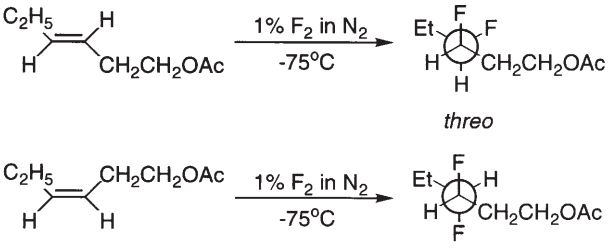


Fig. 72

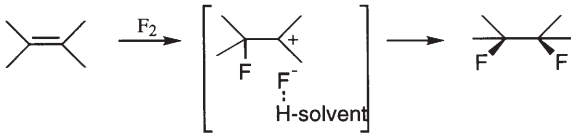


Fig. 73

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]

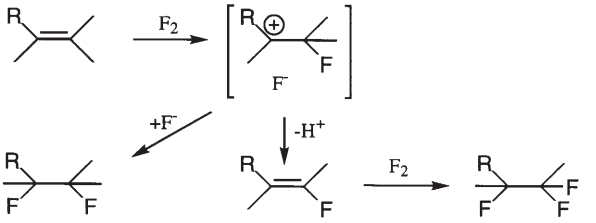


Fig. 74

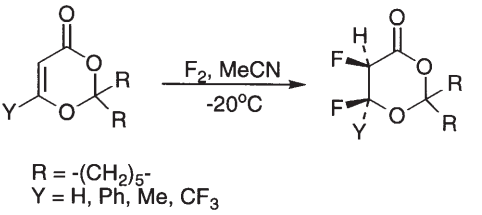


Fig. 75

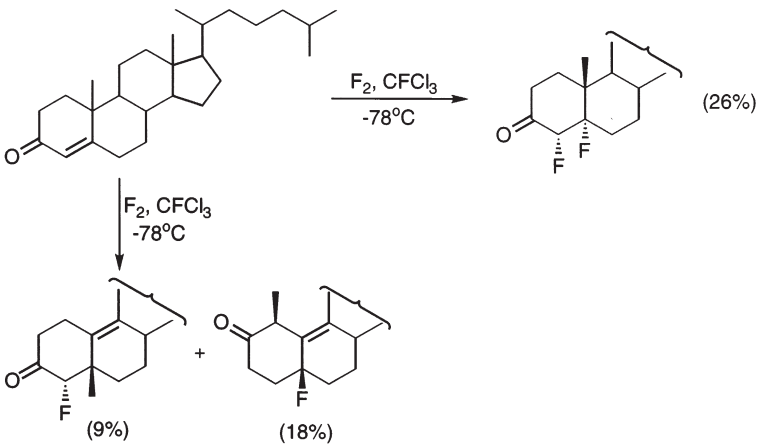


Fig. 76

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].

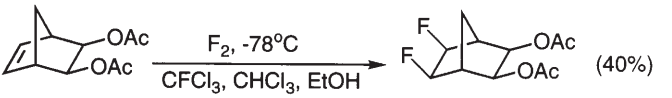


Fig. 77

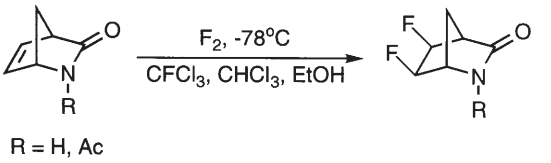


Fig. 78

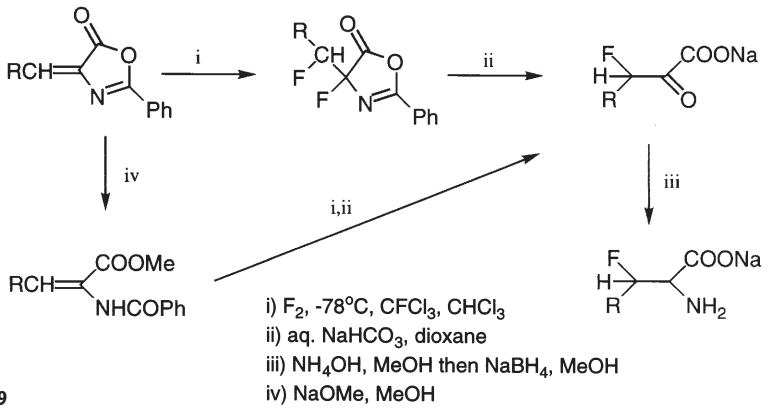


Fig. 79

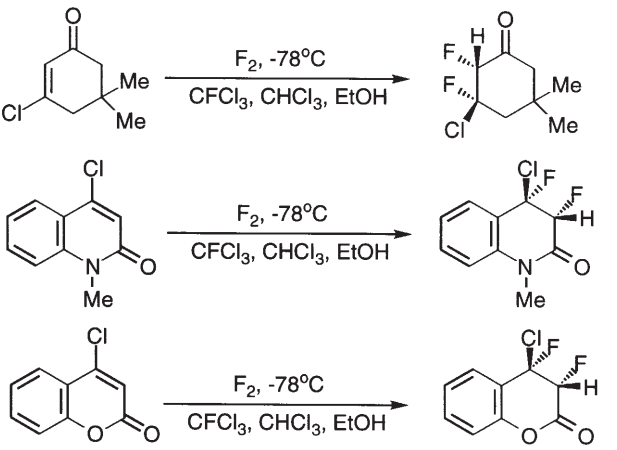


Fig. 80

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].

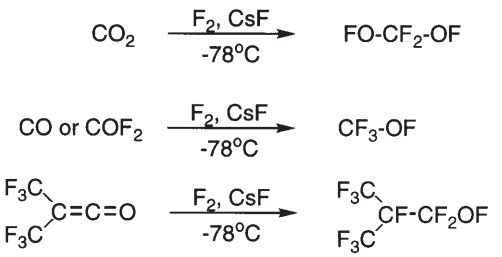


Fig. 81

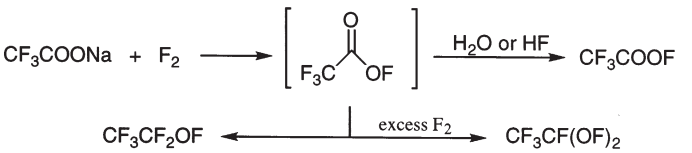


Fig. 82

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

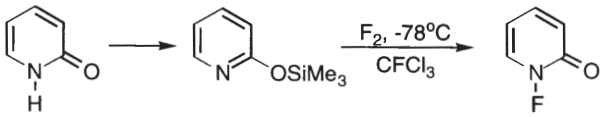
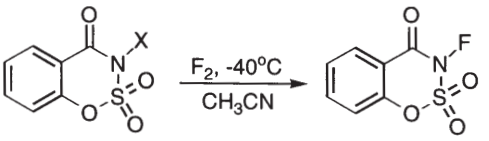
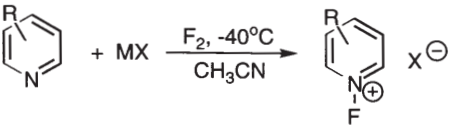
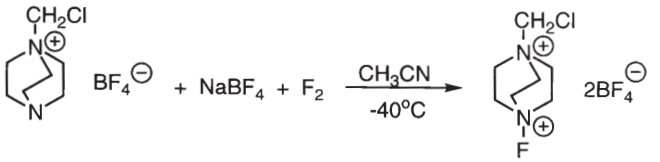
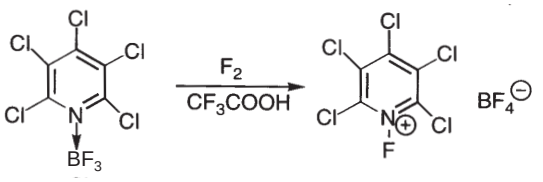
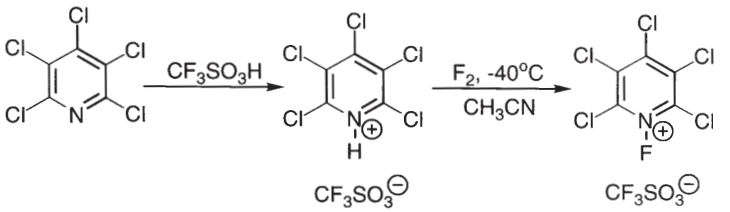
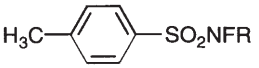
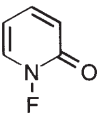
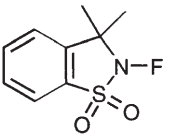
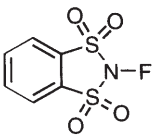
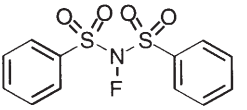
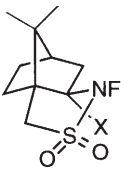
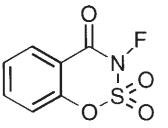
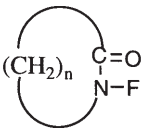
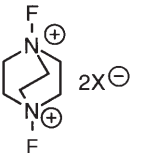
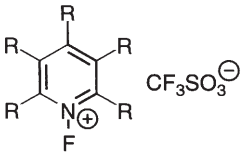
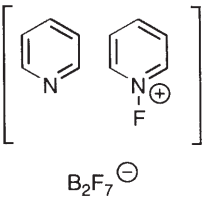
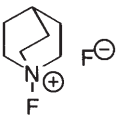
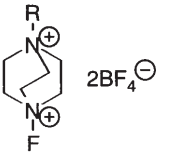
Reaction	Ref.
	[212]
 X = H, Na, K	[213]
 X = TfO, BF_4, PF_6, SbF_6, ClO_4 M = Na, K	[204]
 (89%)	[214]
	[204]
	[204]

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]

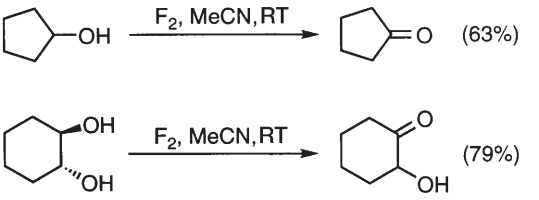


Fig. 83

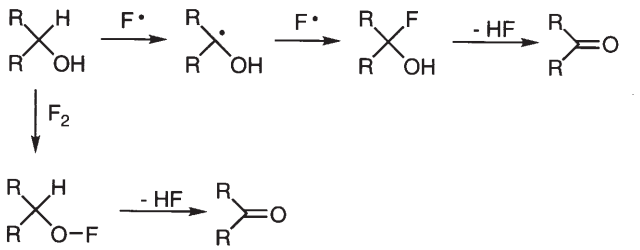


Fig. 84

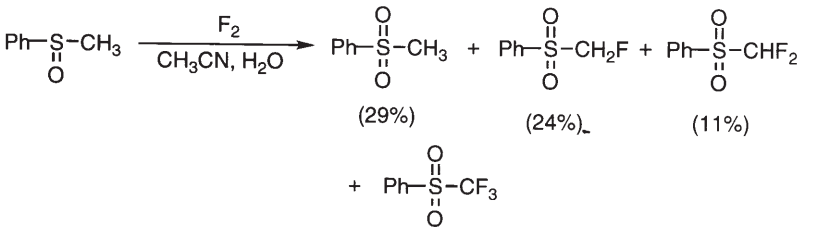


Fig. 85

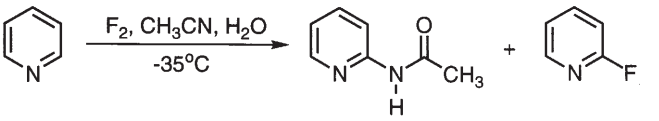


Fig. 86

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].

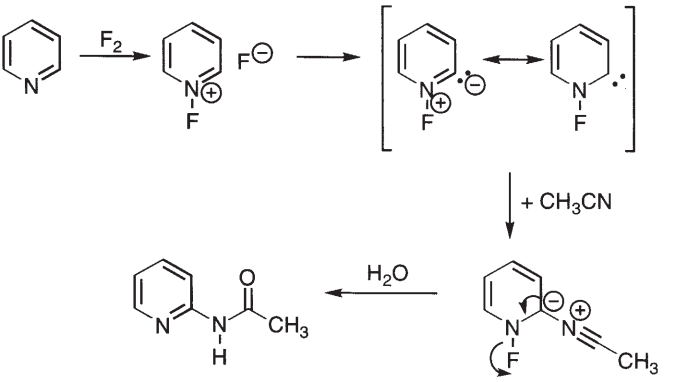
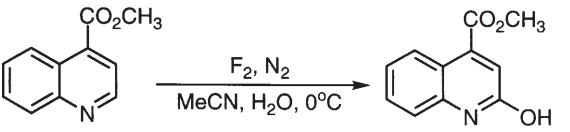
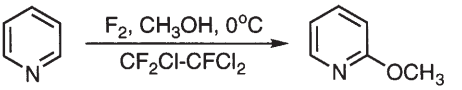


Fig. 87



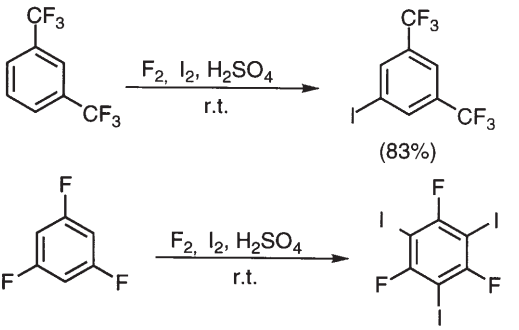
(75%)

Fig. 88



(57%)

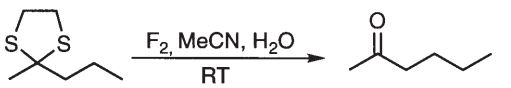
Fig. 89



(83%)

(63%)

Fig. 90



(79%)

Fig. 91

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Fluorinated Organometallic Compounds

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Recent preparation of various types of fluorinated organometallic reagents is described, including perfluoroalkyl, perfluoroalkenyl, perfluoroaryl, carboalkoxydifluoromethylene, dialkoxyphosphinylidifluoromethyl and α,α-difluoroallyl and α,α-difluoropropargyl organometallics. Application of these reagents for the preparation of fluorine-containing compounds is presented with typical illustrative examples. Emphasis is focused on preparations and applications described during the past ten years.

Keywords: Fluorinated organometallics; organofluorine compounds; organofluorine synthesis.

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List of Abbreviations

BOC	*N-tert*-Butoxycarbonyl
DMAC	*N,N*-Dimethylacetamide
DME	Ethylene glycol dimethyl ether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
HMPA	Hexamethylphosphoramide (Hexamethylphosphoric triamide)
hv	Photolysis
LDA	Lithium diisopropylamide
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
MEM	(2-Methoxyethoxyl)methyl
NMP	1-Methyl-2-pyrrolidinone
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TG	Triglyme (triethylene glycol dimethyl ether)
THF	Tetrahydrofuran
TMEDA	*N,N,N,N*- Tetramethyl-1,2-ethylenediamine
TMS	Trimethylsilyl
TNS-Tf	*N*-trifluoromethyl-*N*-nitrosotrifluoromethanesulfonamide
Ts	*p*-Toluenesulfonyl

1 Introduction

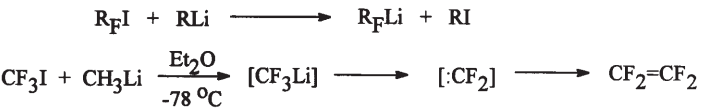
Fluorinated organometallic reagents provide a general method for the incorporation of fluorine into organic molecules. The chemistry of fluorinated organometallic reagents has been well documented recently [1, 2]. In this chapter we will present a short and compact review which focuses on the progress made in this field during the past ten years. We apologize to authors whose excellent work may not have been included here due to space limitations.

2
Fluorinated Alkyl Organometallics

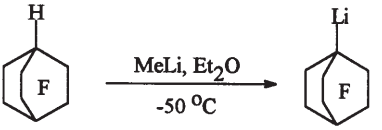
2.1
Perfluoroalkyl Lithium Reagents

Halogen-lithium exchange reaction is the most general method for the preparation of perfluoroalkyl lithium reagents [3–5]. Perfluoroalkyl lithium reagents such as perfluoroethyl and propyl lithium reagents etc. have been prepared via treatment of perfluoroalkyl iodides with organolithium reagents, such as methyl and butyl lithium, in diethyl ether at low temperature [6]. However, attempts to generate and capture trifluoromethyllithium failed, presumably due to the facile decomposition to difluorocarbene and lithium fluoride [7] (Scheme 1).

Hydrogen-lithium exchange reaction was first utilized to prepare the stable perfluorobicyclo[2, 2, 2]oct-1-yl lithium reagent [8] (Scheme 2).



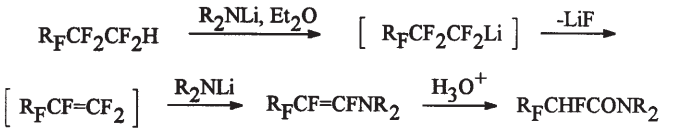
Scheme 1



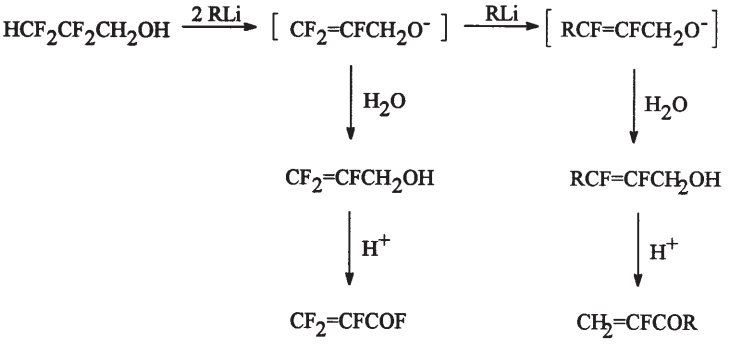
Scheme 2

Similarly, perfluoroalkyl lithium reagents, generated from the reaction of 1-hydroperfluoroalkanes with alkyl lithium [9] or LDA [10], undergo β-fluoride elimination to form perfluoroalkenes which reacted further with excess LDA to yield the corresponding amides via an addition-elimination reaction followed by hydrolysis (Scheme 3). 2-Fluoroacrylic acid and 1-fluorovinyl ketone have been prepared from the readily available 2,2,3,3-tetrafluoro-1-propanol via a similar procedure, followed by an acid-catalyzed rearrangement reaction [11] (Scheme 4).

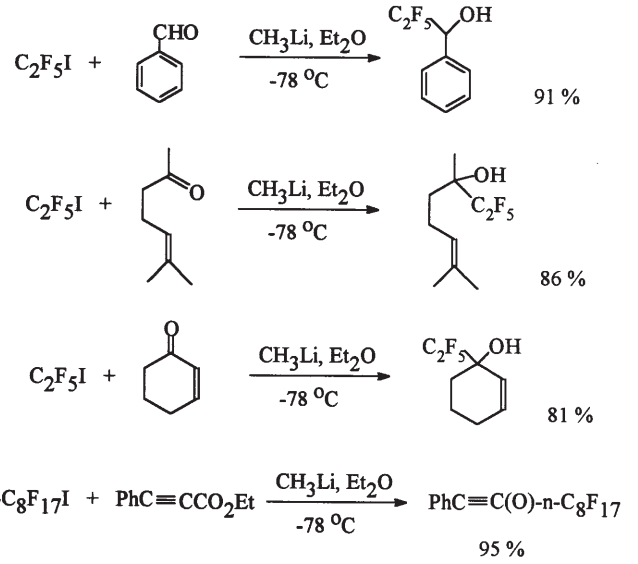
Perfluoroalkyl lithium reagents undergo reactions typical of their hydrocarbon analogs. For example, perfluoroalkyl lithium reagents generated in situ from perfluoroalkyl iodides and alkyl lithiums reacted readily with aldehydes and ketones to yield the corresponding secondary and tertiary carbinols, and with esters to give either ketones or tertiary carbinols [12]. No 1,4-addition product is observed when α,β-unsaturated ketones and esters are employed. [12, 13] (Scheme 5).



Scheme 3



Scheme 4



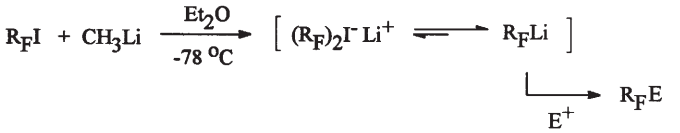
Scheme 5

Recently Uno and Suzuki have described a new concept for the formation of perfluoroalkyl lithium reagents [14]. The initially formed perfluoroalkyl lithium reagent reacted with the starting perfluoroalkyl iodides during the in situ generation of perfluoroalkyl lithium reagents to yield the bis(perfluoroalkyl)iodinanides. This complex itself did not transfer perfluoroalkyl group to electrophiles but was proposed to be a stable carrier of the reactive perfluoroalkyl lithium reagent which reacted with electrophiles (Scheme 6).

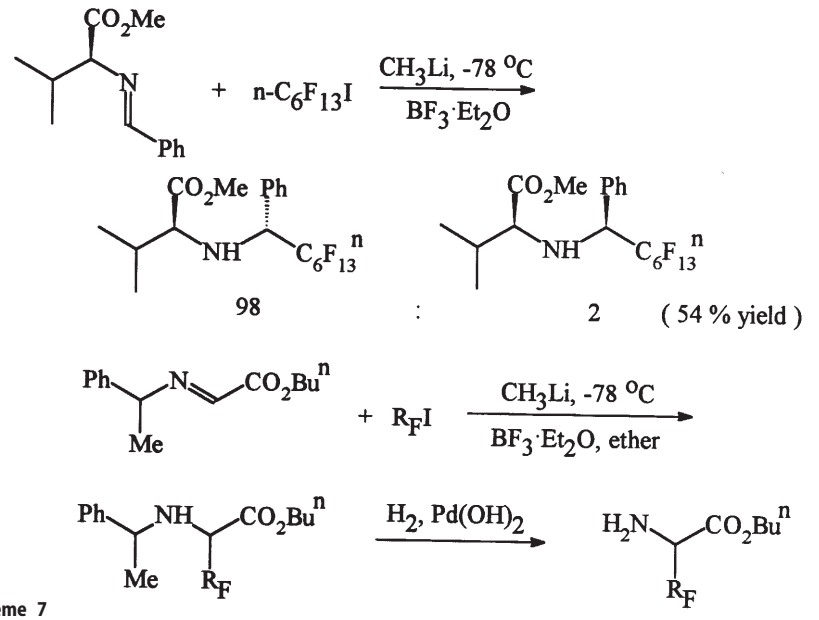
Perfluoroalkyl lithium reagents reacted with imines in the presence of boron trifluoride to give the corresponding adducts in good yields [15], and this methodology has been applied to the synthesis of perfluoroalkyl-containing amino acids [16] (Scheme 7).

2.2 Perfluoroalkyl Magnesium Reagents

In contrast to the difficulty encountered in the direct reaction of perfluoroalkyl iodides with lithium metal [17–19], perfluoroalkyl magnesium reagents can be



Scheme 6



Scheme 7

prepared directly in 40–60% yields by the reaction of perfluoroalkyl iodides with magnesium metal [20–23]. However, a facile exchange route to perfluoroalkyl magnesium reagents via the reaction of perfluoroalkyl iodides and phenylmagnesium bromide has been developed by McBee and co-workers [24], which was the key to the further application of these reagents. The perfluoroalkyl Grignard reagent was obtained in quantitative yield and, except for trifluoromethyl analog [25], was stable at –78 °C. At elevated temperature, perfluoroalkyl magnesium reagents undergo β-elimination in THF to form perfluoroalkenes [26] (Scheme 8).

The perfluoroalkyl Grignard reagents participate in a wide variety of functionalization reactions with electrophiles as illustrated in Scheme 9 [27–35].

For the last reaction, if the intermediate adduct was allowed to warm to room temperature for several hours before hydrolysis, a Brook rearrangement occurred to yield the enone [28] (Scheme 10).

2.3
Perfluoroalkyl Zinc Reagents

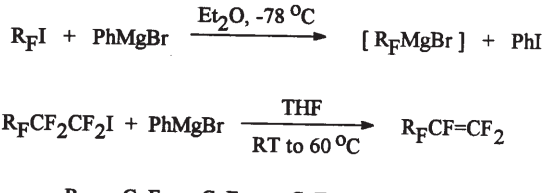
Solvated perfluoroalkyl zinc reagents have been prepared by reaction of perfluoroalkyl iodides with zinc in ethereal solvents such as dioxane [36, 37]. Self-coupled and cross-coupled products can be formed when a mixture of acetic anhydride and methylene chloride was used [38–40] (Scheme 11).

The exchange reaction of perfluoroalkyl iodides and iodopentafluorobenzene with dialkylzinc in the presence of Lewis base, such as diglyme or pyridine, afforded the corresponding bis(trifluoromethyl)zinc and bis(pentafluorophenyl)zinc in high yield [41] (Scheme 12).

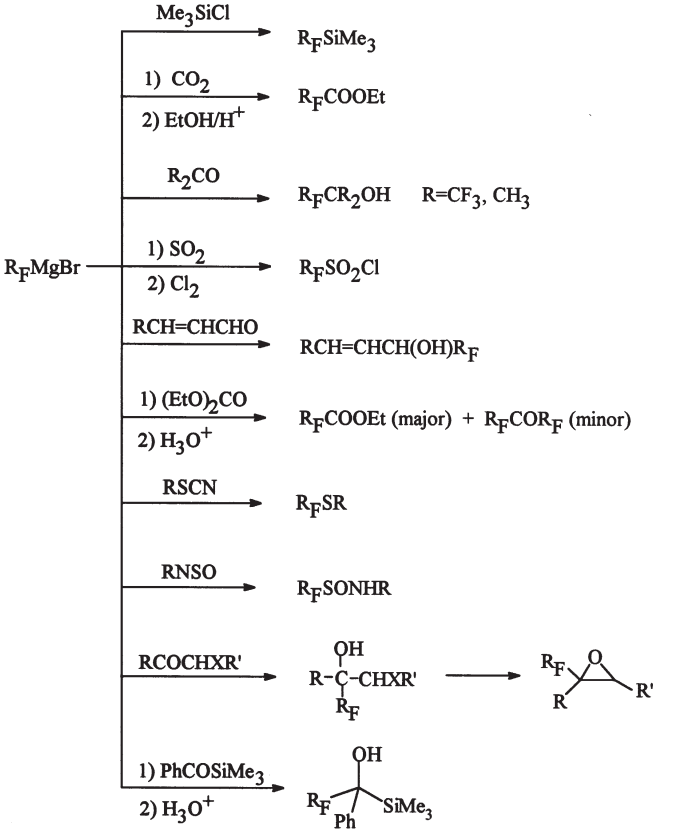
Trifluoromethylzinc reagent can be prepared from the direct reaction of dihalodifluoromethane and zinc in DMF [42] (Scheme 13). In this remarkable reaction, DMF functions both as a solvent and reactant, and difluorocarbene is the reactive intermediate, based on mechanistic experiments. Dolbier et al. have utilized this reaction as a difluoromethylene cyclopropanation reaction [43] (Scheme 14).

Trifluoromethylzinc reagent can also be prepared by the reaction of the readily available bromotrifluoromethane with zinc in pyridine [44] (Scheme 15).

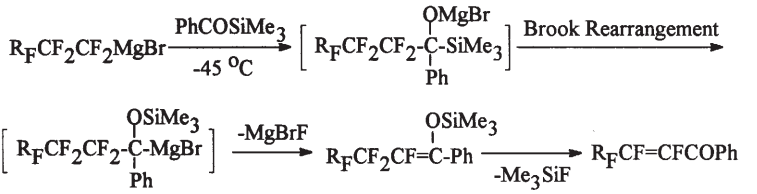
Under ultrasonic conditions, the reaction of perfluoroalkyl iodides with zinc has been utilized by Ishikawa to effect perfluoroalkylation of a variety of organic



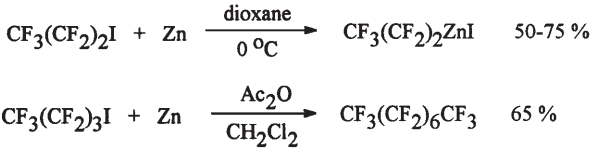
Scheme 8



Scheme 9



Scheme 10



Scheme 11

$$CF_2ClCFClI + CF_2ClCFClCF_2CFClI \xrightarrow[CH_2Cl_2]{Ac_2O} CF_2ClCFClCFClCF_2CFClCF_2Cl + (CF_2ClCFClCF_2CFCl)_2 + \text{others}$$

46 % 40 %

Scheme 11 (continued)

$$2\,R_FI + R_2Zn \longrightarrow (R_F)_2Zn + 2\,R$$

R_F=CF_3, C_2F_5, $(CF_3)_2CF$, C_6F_5

Scheme 12

$$CF_2X_2 + Zn \xrightarrow{DMF,\ RT} CF_3ZnX + (CF_3)_2Zn$$

X=Br, Cl 80-85 %

Scheme 13

Scheme 14

$$CF_3Br + Zn \xrightarrow[60\ ^oC]{pyridine} CF_3ZnBr + (CF_3)_2Zn$$

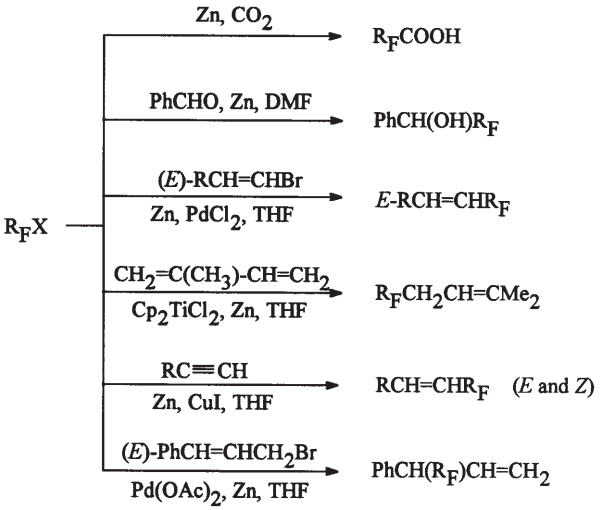
Scheme 15

compounds [45–48] (Scheme 16). Pefluoroalkyl radical intermediates have been proposed by the authors to be the reactive transient intermediate.

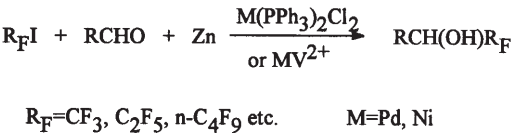
Similarly, palladium, nickel complex [49] or methyl viologen (MV^{2+}) [50] have also been used to catalyze the reaction of perfluoroalkyl iodides with aldehydes in the presence of zinc to give the corresponding α-perfluoroalkyl carbinols (Scheme 17).

Barbier conditions have been utilized by Wakselman et al. to carry out reactions of trifluoromethyl bromide with aldehydes, α-keto esters, activated esters and anhydrides in the presence of pyridine to give trifluoromethylated compounds [51, 52] (Scheme 18).

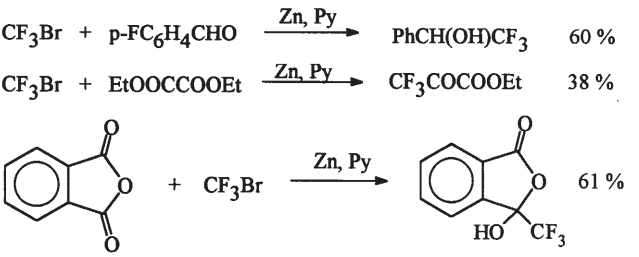
Triflic acid can be prepared from the reaction of trifluoromethyl bromide with sulfur dioxide and zinc followed by oxidation [53] (Scheme 19). This reac-



Scheme 16



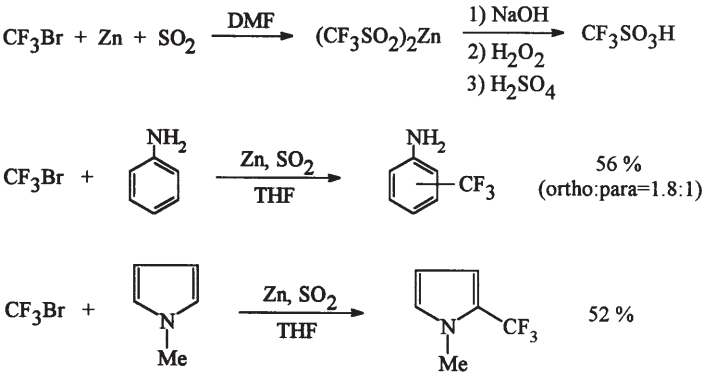
Scheme 17



Scheme 18

tion involves a trifluoromethyl radical intermediate which can be trapped by electron-rich aromatics to give the corresponding trifluoromethylated aromatics [54].

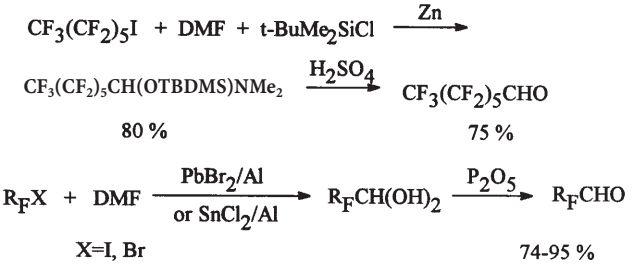
Perfluoroalkyl iodides reacted with trialkylsilyl chloride in DMF in the presence of zinc followed by hydrolysis with acid to give perfluoroaldehydes in good yields [55]. Recently, Hu reported a new preparation of perfluoroalkyl aldehydes via reaction of perfluoroalkyl halides and DMF, initiated by redox



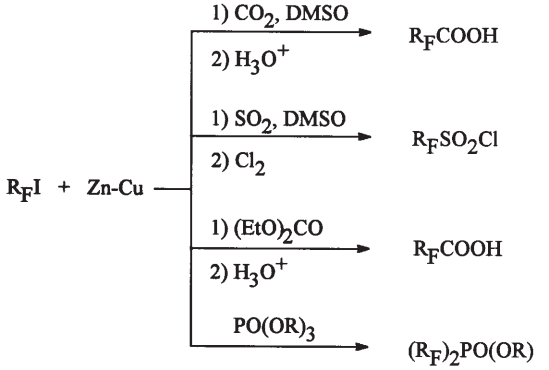
Scheme 19

systems such as catalytic $PbBr_2$ or $SnCl_2$ with aluminum powder followed by the dehydration with P_2O_5 [56] (Scheme 20).

Perfluoroalkyl iodides reacted with ethyl carbonate, carbon dioxide, sulfur dioxide, and alkyl phosphates in the presence of a more active zinc-copper couple to afford the corresponding perfluoroalkylated products [57–59] (Scheme 21).



Scheme 20



Scheme 21

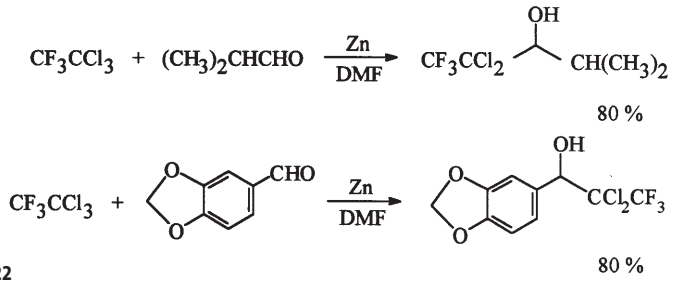
Recently, 1,1-dichlorotrifluoroethyl zinc chloride [60, 61] has received significant attention due to the readily available starting material, 1,1,1-trichlorotrifluoroethane and potential industrial applications. This zinc reagent undergoes a variety of functionalization reactions, particularly addition to aldehydes [62, 63] (Scheme 22).

In the presence of excess zinc and acetic anhydride, 1,1,1-trichlorotrifluoroethane reacts with aldehydes to yield trifluoromethyl substituted *Z*-alkenes as the major isomer [64], which has been utilized to prepare artificial pyrethroids containing the $CH=ClCF_3$ moiety [65, 66] (Scheme 23).

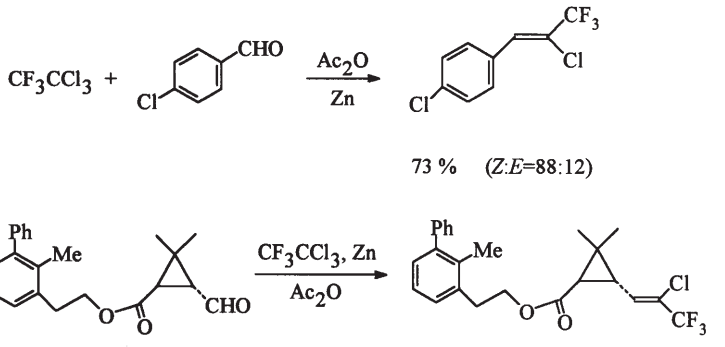
1,1-Dichlorotrifluoroethyl zinc chloride also reacts with DMF in the presence of a chlorosilane followed by acid hydrolysis to give the corresponding aldehyde [55] similar to that observed with perfluoroalkylzinc reagents. Reaction of CF_3CCl_3 with formaldehyde provides the corresponding 2,2-dichloro-3,3,3-trifluoropropanol [67] (Scheme 24).

2.4 Perfluoroalkyl Copper Reagents

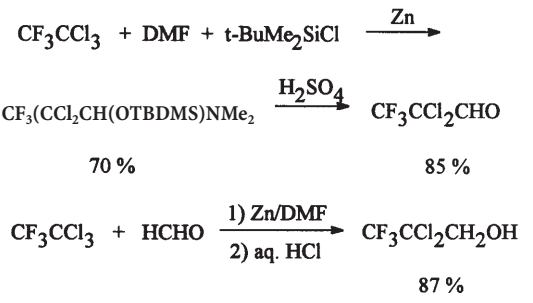
The first preparation of perfluoroalkyl copper reagents was reported by McLoughlin and Thrower in 1969 [68]. Perfluoroalkyl iodides react with copper



Scheme 22

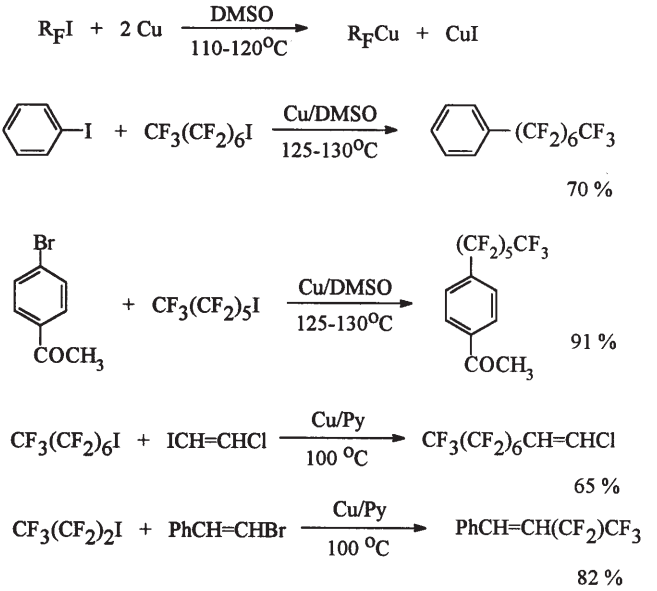


Scheme 23



Scheme 24

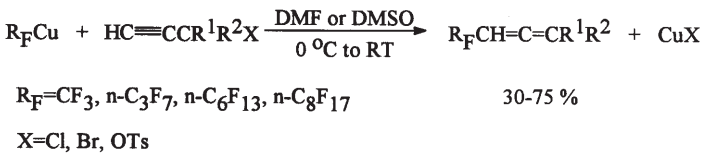
metal (2.5–3.0 eq.) in DMSO at 110–120 °C to produce the corresponding perfluoroalkyl copper reagents in good yields, which can participate in a wide variety of coupling reactions with vinyl and aryl halides [68–79] (Scheme 25). Several typical examples are outlined below:



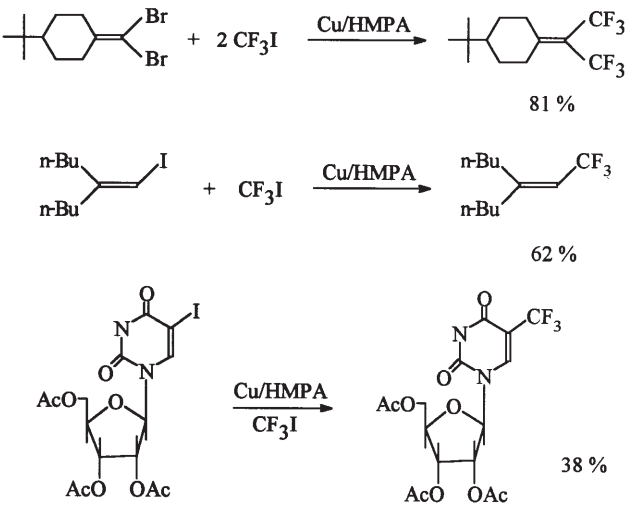
Scheme 25

Reactions of perfluoroalkyl copper reagents with propargyl halides or tosylates in DMSO or DMF afforded the corresponding allenes in good yields [80–82] (Scheme 26).

Trifluoromethylation is the most important perfluoroalkylation reaction. Kobayashi and co-workers reported the trifluoromethylation of aryl, vinyl, alkyl halides with trifluoromethyl iodide in the presence of copper powder in aprotic solvents such as HMPA at 120–150 °C [83, 84], and this methodology has been applied to the preparation of fluorinated pyrimidine and purine nucleosides [85, 86] (Scheme 27).



Scheme 26

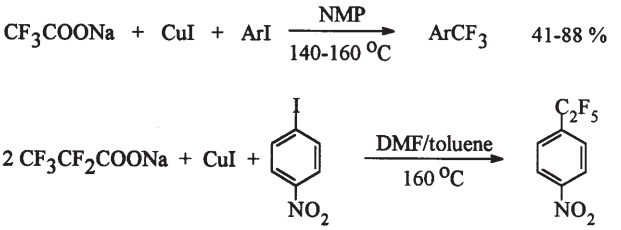


Scheme 27

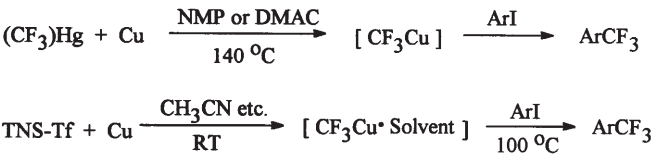
Due to the cost of trifluoromethyl iodide, other cheaper sources have been investigated for trifluoromethylation. Sodium trifluoroacetate reacted with aryl iodide in the presence of copper (I) iodide in NMP at 140 – 160 °C to afford the corresponding coupling product [87]. No trifluoromethylation was observed without CuI. Under similar reaction conditions, sodium pentafluoropropionate worked well to give the pentafluoroethylated compounds [88, 89] (Scheme 28).

A CF_3Cu solution can also be prepared by the reaction of bis(trifluoromethyl) mercury [90] or *N*-trifluoromethyl-*N*-nitrosotrifluoromethanesulfonamide (TNS-Tf) [91] with activated copper powder in dipolar aprotic solvents. Reaction with aryl iodides gave the corresponding trifluoromethylated aromatics in good yields. (Scheme 29).

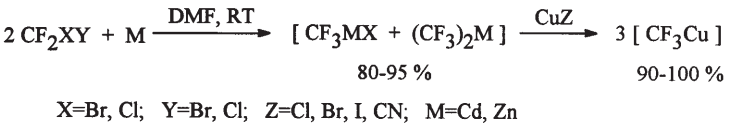
Dihalodifluoromethanes react readily with acid-washed cadmium or zinc powder in DMF at room temperature to produce stable solutions of trifluoromethyl cadmium and zinc reagent, respectively in high yields [42], which undergo a metathesis reaction with copper (I) salts to give a trifluoromethylcopper solution [92] (Scheme 30).



Scheme 28



Scheme 29



Scheme 30

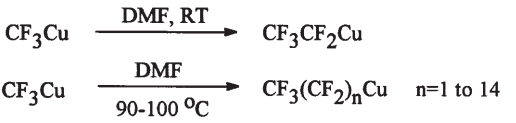
The DMF solution of CF_3Cu slowly decomposes at room temperature to form pentafluoroethylcopper [92] and at higher temperature to form an oligomeric mixture of perfluoroalkylcopper reagents [93] (Scheme 31).

Addition of HMPA or potassium fluoride to the CF_3Cu/DMF solution suppressed the oligomerization and allowed this reagent to be employed for the trifluoromethylation of aryl iodides even at elevated temperature [92–94] (Scheme 32).

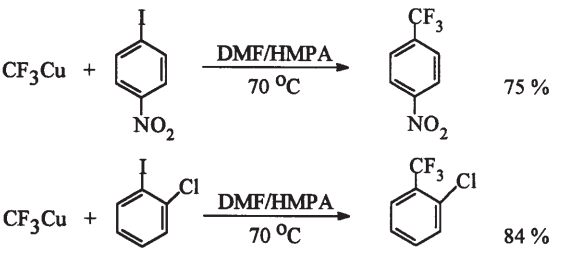
This reaction has been carried out in DMAC for the trifluoromethylation of activated aryl chlorides such as 2,4-dinitro-1-chlorobenzene [95–97]. Similar trifluoromethylation can be accomplished with trifluoromethylcopper generated from trifluoromethanesulfonyl chloride and copper powder in DMAC [98] (Scheme 33).

The mechanism of the CF_2XY-Cu reaction involves a difluorocarbene intermediate, and is outlined below [42] (Scheme 34):

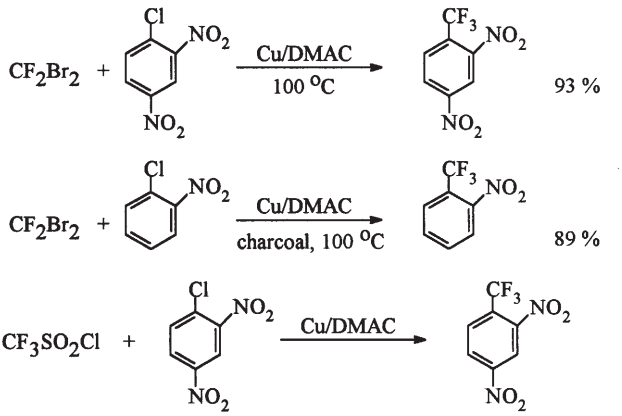
Recently, a variety of difluorocarbene precursors such as methyl fluorosulfonyldifluoroacetate (FO_2SCF_2COOMe), fluorosulfonyldifluoromethyl iodide (ICF_2SO_2F) and methyl α-halodifluoroacetates (XCF_2COOMe, X = I, Br, Cl) have been utilized by Chen and co-workers to trifluoromethylate aryl, alkenyl and alkyl halides [99, 100] (Scheme 35).



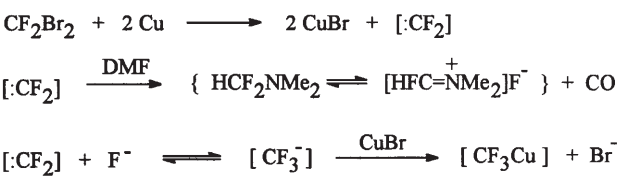
Scheme 31



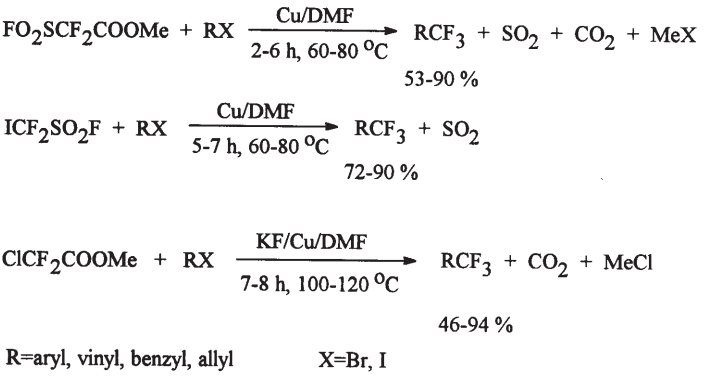
Scheme 32



Scheme 33



Scheme 34



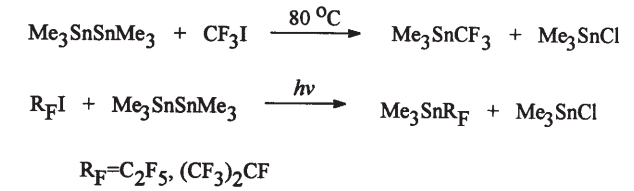
Scheme 35

2.5
Perfluoroalkyl Tin Reagents

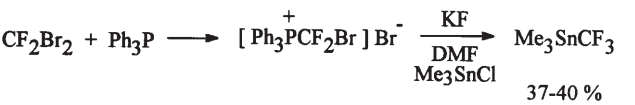
Trimethyl(trifluoromethyl)tin was first prepared via reaction of hexamethylditin with excess iodotrifluoromethane under pressure at 80 °C [101]. Later this reaction was accomplished with ultraviolet light for the preparation of longer chain perfluoroalkyl analogs [102, 103] (Scheme 36).

The trialkyl(trifluoromethyl)tin can also be prepared via the reaction of triphenylphosphine and dibromodifluoromethane followed by the treatment with potassium fluoride and trialkyltin chloride [104, 105] (Scheme 37).

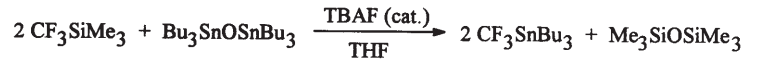
Recently, Olah and co-workers reported a new route to tributyl(trifluoromethyl)tin via in situ formation and capture of the trifluoromethyl anion by trialkyltin oxide [106]. Reaction of trimethyl(trifluoromethyl)silane with tributyltin oxide in the presence of catalytic TBAF in THF afforded the corresponding tributyl(trifluoromethyl)tin in good yield (Scheme 38). This reaction system was first reported by Warner and Buchwald [107].



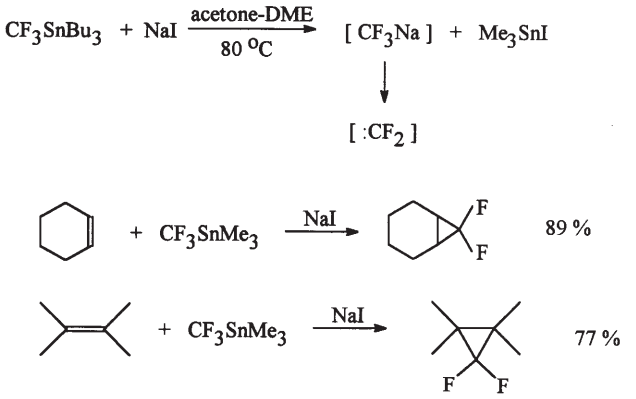
Scheme 36



Scheme 37



Scheme 38



Scheme 39

Trialkyl(trifluoromethyl)tin reacted with sodium iodide at 80 °C to form difluorocarbene in situ, which gave the difluorocyclopropane derivatives in the presence of olefins [108–110] (Scheme 39).

3
Fluorinated Alkenyl Organometallics

3.1
Fluorinated Alkenyl Lithium Reagents

Trifluorovinyllithium was first prepared by Seyferth et al via the reaction of phenyltris(trifluorovinyl)tin and phenyllithium in ether at –40 °C [111] and then more conveniently obtained via lithium-halogen exchange reaction of bromotrifluoroethylene with *n*-butyllithium or methyllithium at –78 °C [112]. Later Normant reported an inexpensive route to trifluorovinyllithium by reaction of the readily available chlorotrifluoroethylene with *sec*-butyllithium or *tert*-butyllithium [113] (Scheme 40).

Reactions of trifluorovinyllithium with a variety of electrophiles such as proton, halogen, trialkylsilyl chloride, trialkyltin chloride, methyl iodide, carbon dioxide, sulfur dioxide afforded the corresponding trifluorovinylated derivatives [111, 113, 114] (Scheme 41).

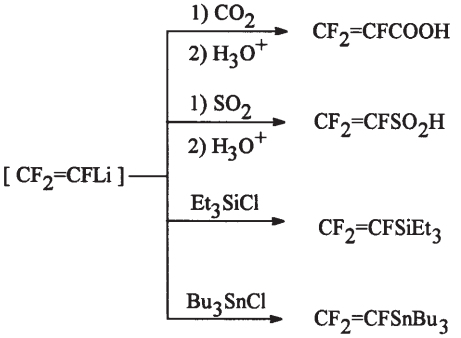
Trifluorovinyllithium also reacted with aldehydes or ketones to give the corresponding carbinols, which could be further converted to α-fluoro-α,β-unsaturated acid fluoride via acid- or thermally-promoted rearrangement [115–118] (Scheme 42).

$$(CF_2{=}CF)_3SnPh + 3\ PhLi \xrightarrow[-40\ ^oC]{ether} 3\ [CF_2{=}CFLi] + Ph_4Sn \quad (> 64\ \%)$$

$$CF_2{=}CFBr + n\text{-}BuLi \xrightarrow[-78\ ^oC]{ether} [CF_2{=}CFLi] + n\text{-}BuBr \quad (> 73\ \%)$$

$$CF_2{=}CFCl + sec\text{-}BuLi \text{ or } tert\text{-}BuLi \xrightarrow[-60\ ^oC]{ether} [CF_2{=}CFLi] \quad (> 95\ \%)$$

Scheme 40



Scheme 41

$$[\ CF_2{=}CFLi\ ] \xrightarrow[2)\ H_3O^+]{1)\ R^1R^2CO} R^1R^2C(OH)\text{-}CF{=}CF_2 \xrightarrow{H_2SO_4} R^1R^2C{=}CFCOF$$

(82-91 %; 75-82 %)

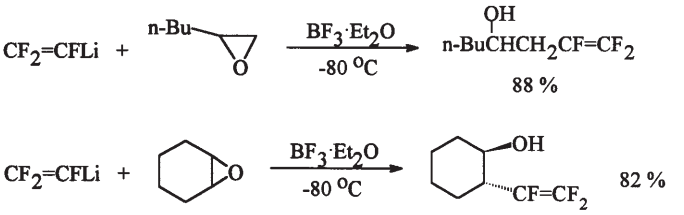
Scheme 42

No reaction occurred when trifluorovinyllithium was treated with epoxides or oxetanes, but with boron trifluoride catalysis the corresponding trifluorovinylated alcohols were obtained in good yields [119] (Scheme 43).

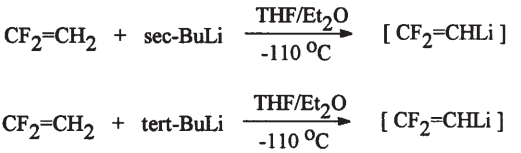
2,2-Difluorovinyllithium was prepared in high yield via reaction of 1,1-difluoroethylene with *sec*-butyllithium in THF and ether (80/20) [120, 121] or *tert*-butyllithium [122] in pentane and ether at –110 °C (Scheme 44).

Similarly, 2,2-difluorovinyllithium reacted with triethylsilyl chloride, tributyltin chloride [122], carbon dioxide [123] or aldehydes [124] to give the corresponding 2,2-difluorovinylated derivatives (Scheme 45).

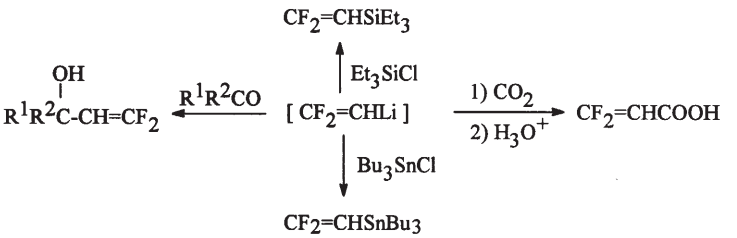
trans and *cis*-1,2-Difluoroalkenyllithium could be prepared via lithium-hydrogen exchange reactions of the corresponding *trans* and *cis*-1,2-difluoroalkenes with *n*-butyllithium [115, 125], but *trans*-1,2-difluoroalkenyllithium reagents are more stable than their *cis*-analogs (Scheme 46). Both lithium



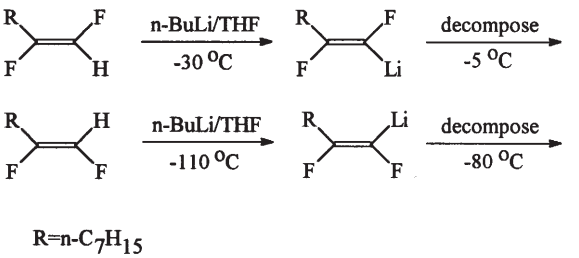
Scheme 43



Scheme 44



Scheme 45

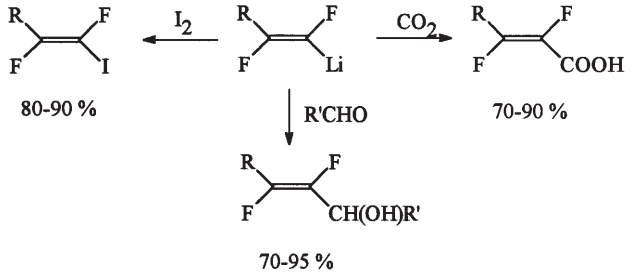


Scheme 46

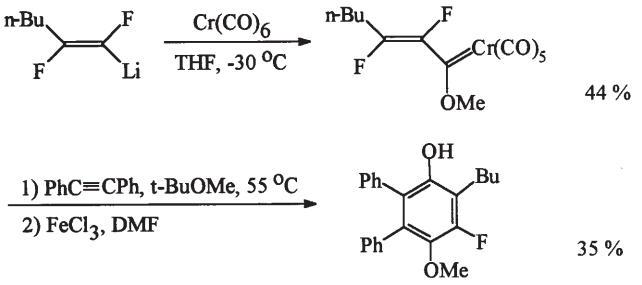
reagents react with electrophiles such as iodine and aldehydes to give the corresponding iodides and alcohols, respectively [119, 126] (Scheme 47).

Recently, reaction of this lithium reagent with $Cr(CO)_6$ followed by the treatment with 1,2-diphenylacetylene afforded a highly substituted fluorophenol via a chromium carbene intermediate [127] (Scheme 48).

trans-1,2-Difluoro-2-triethylsilylvinyllithium, prepared in a similar way, reacts with a variety of electrophiles and is a useful *trans*-1,2-difluoroethylene



Scheme 47



Scheme 48

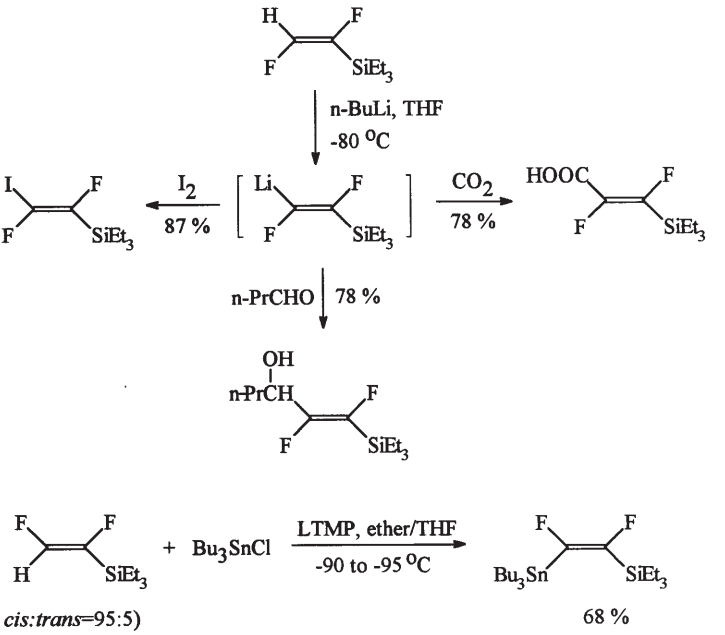
synthon [128]. However, the *cis* analog, generated with hindered base, is extremely unstable even at –110 °C and could only be trapped in situ in good yield with tributyltin chloride [129] (Scheme 49).

1-Pentafluoropropenyllithium could be prepared by lithium-hydrogen exchange of pentafluoropropene with *n*-butyllithium in ether at –78 °C [130], but a bulky base such as *tert*-butyllithium or LDA had to be employed for the preparation of 2-pentafluoropropenyllithium from the corresponding 2-hydropentafluoropropene in ether and pentane solution at –78 °C [131] (Scheme 50).

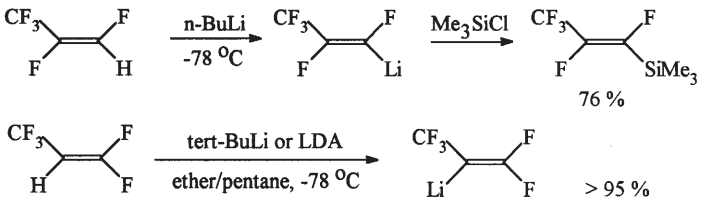
Recently, starting from readily available 2,2,2-trifluoroethanol, α-oxygen-substituted difluorovinyllithium reagents have received much attention. The preparation of several α-oxygen-substituted difluorovinyllithium reagents are outlined below [132–138] (Scheme 51).

They could be trapped with a variety of electrophiles such as aldehydes, water, carbon dioxide, trimethylsilyl chloride, tributyltin chloride to give the corresponding difluorovinyl derivatives [132–138] (Scheme 52), which were demonstrated to be versatile and useful building blocks for the synthesis of organofluorine compounds.

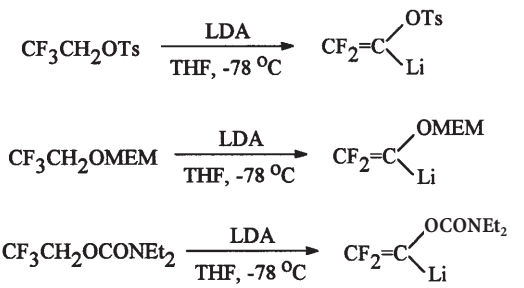
2,2-Difluoro-1-tosyloxyvinyllithium reacted with trialkylboranes to give 2,2-difluorovinylboranes, which underwent a variety of interesting functionalizations to the corresponding difluoromethylene-containing compounds [139–145] (Scheme 53).



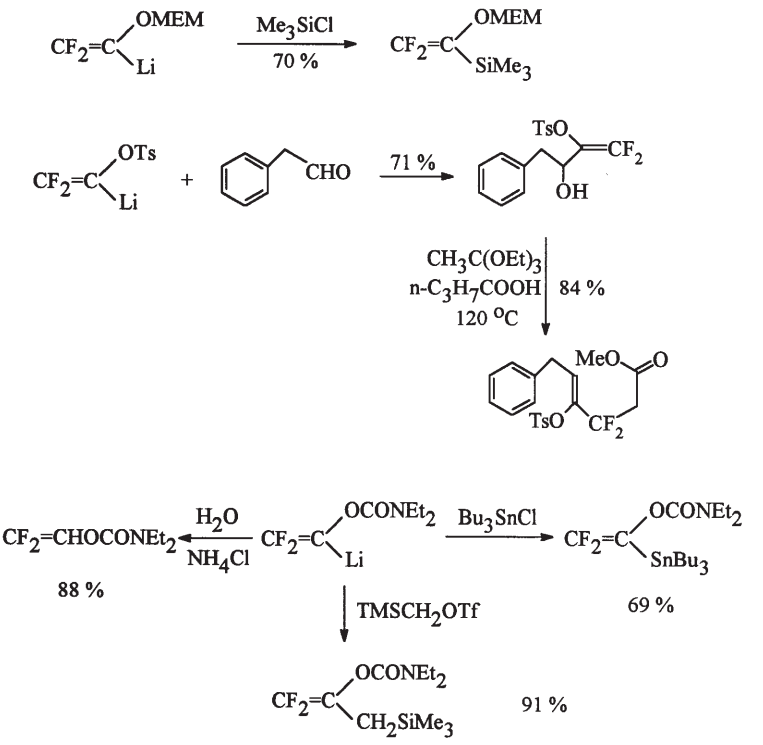
Scheme 49



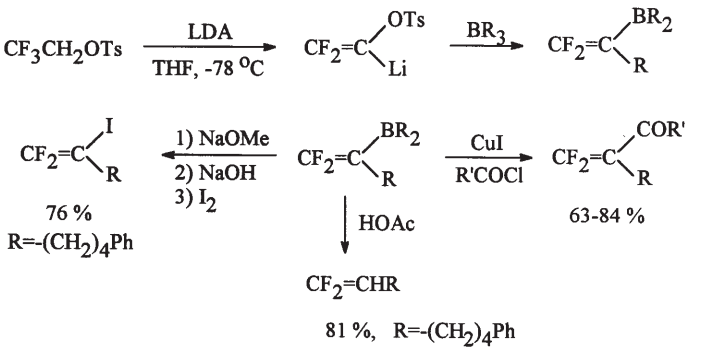
Scheme 50



Scheme 51



Scheme 52



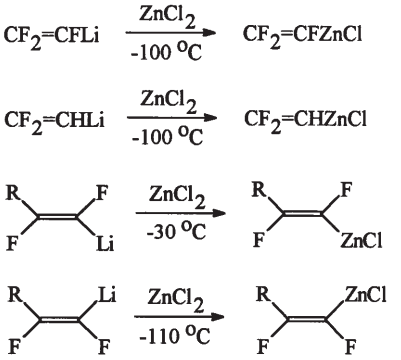
Scheme 53

3.2
Fluorinated Alkenyl Zinc Reagents

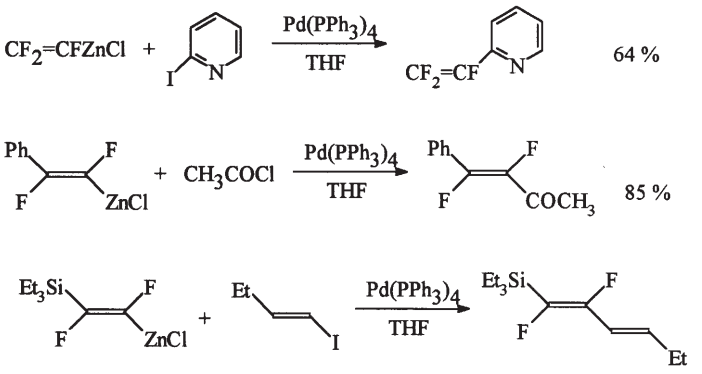
Fluorinated alkenyl zinc reagents can be prepared by two different routes: 1) exchange of the corresponding alkenyl lithium reagents at low temperature with zinc chloride; 2) direct insertion of zinc into the carbon-halogen bond of fluorinated alkenyl halides.

A variety of fluorinated alkenyl zinc reagents such as $CF_2=CFZnCl$, $CF_2=CHZnCl$, *E* and *Z*-RCF=CFZnCl have been prepared by the first method (Scheme 54). In the presence of palladium catalyst, these fluorinated alkenyl zinc reagents undergo cross-coupling reactions with aryl iodides, vinyl iodides, acid chlorides and 1-iodo-1-alkynes to give the corresponding fluorinated alkenyl derivatives [127, 146–153], which have been utilized in the synthesis of fluorinated codlemones [154]. Typical examples are outlined below (Scheme 55).

The second method for the preparation of fluorinated alkenyl zinc reagents involves the reaction of alkenyl bromides or iodides with acid-washed zinc in a



Scheme 54



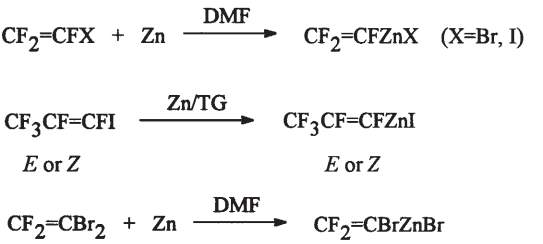
Scheme 55

variety of solvents such as DMF, DMAC, diglyme, THF [155–163] (Scheme 56). In the presence of a palladium catalyst, these alkenyl zinc reagents undergo cross-coupling reactions with aryl or vinyl halides [161, 164–166].

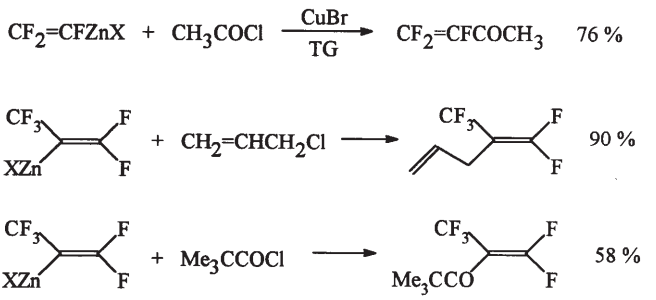
The coupling reaction with active halides such as allyl halides or acid chlorides catalyzed by cuprous halides afforded the corresponding alkenylated compounds [131, 167, 168] (Scheme 57).

Recently, 3,3,3-trifluoro-2-propenyl zinc reagent has been prepared by the reaction of 2-bromo-3,3,3-trifluoropropene with Zn(Ag) and TMEDA in THF in good yield [169]. TMEDA is essential to the preparation of this zinc reagent, presumably by formation of a chelate structure which can stabilize the zinc reagent (Scheme 58).

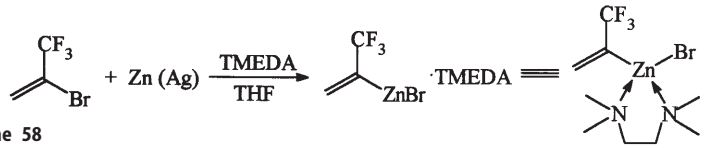
3,3,3-Trifluoro-2-propenyl zinc reagent can undergo palladium-catalyzed cross-coupling reaction with aryl or vinyl halides [169, 170], which provides a novel method for the introduction of the trifluoromethyl group into organic molecules (Scheme 59). The trifluoro analogue of Naproxen has been prepared by this method [169] (Scheme 60).



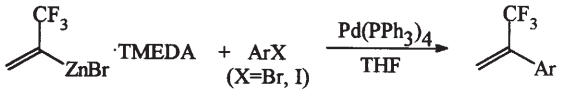
Scheme 56



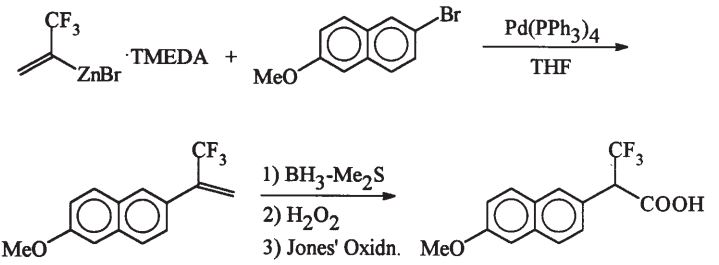
Scheme 57



Scheme 58



Scheme 59 80-99 %



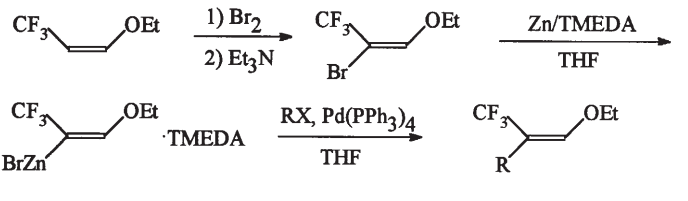
Scheme 60

More recently, the α-trifluoromethyl substituted β-ethoxyvinyl zinc reagent has been prepared in a similar way and coupled with aryl or vinyl halides in the presence of $Pd(PPh_3)_4$ [171] (Scheme 61).

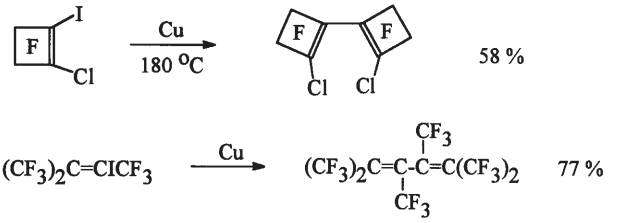
3.3
Fluorinated Alkenyl Copper Reagents

Attempted preparation of fluorinated alkenyl copper reagents from the corresponding alkenyl iodides with copper powder was not successful. The symmetric dimer was obtained in good yield [172–179] (Scheme 62).

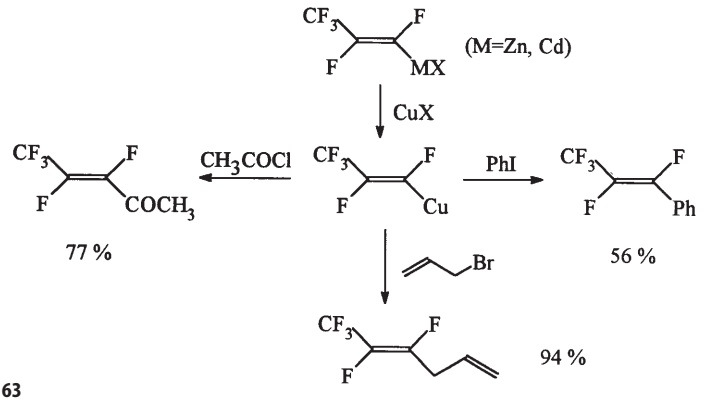
A practical method for preparation of fluorinated alkenyl copper reagents has been recently developed from cuprous halides metathesis of the corresponding zinc or cadmium reagents [180]. These copper reagents exhibit excellent stability at room temperature and undergo a variety of coupling reactions with methyl, allyl, vinyl, aryl and acid halides [180] (Scheme 63). More recently, preparation of cyclic perfluoroalkenyl copper reagents has been reported by the same route [156–158].



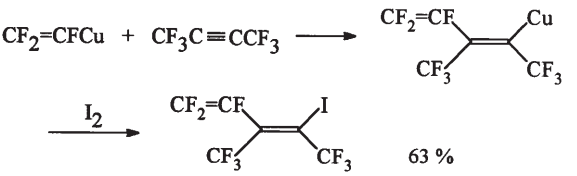
Scheme 61



Scheme 62



Scheme 63



Scheme 64

Trifluorovinylcopper reacted readily with perfluoroalkynes to give stereospecific *syn* addition products, which were quenched with iodine to afford the corresponding iodide [181] (Scheme 64).

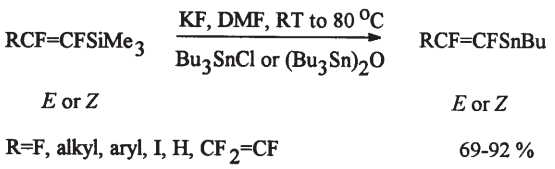
3.4
Fluorinated Alkenyl Tin Reagents

Reaction of fluorinated alkenyl Grignard reagents or lithium reagents with organotin halides has been utilized for the preparation of fluorinated alkenyl tin reagents [111, 182–184]. Recently, a novel, general and convenient method has been developed for the preparation of a variety of fluorinated alkenylstannanes

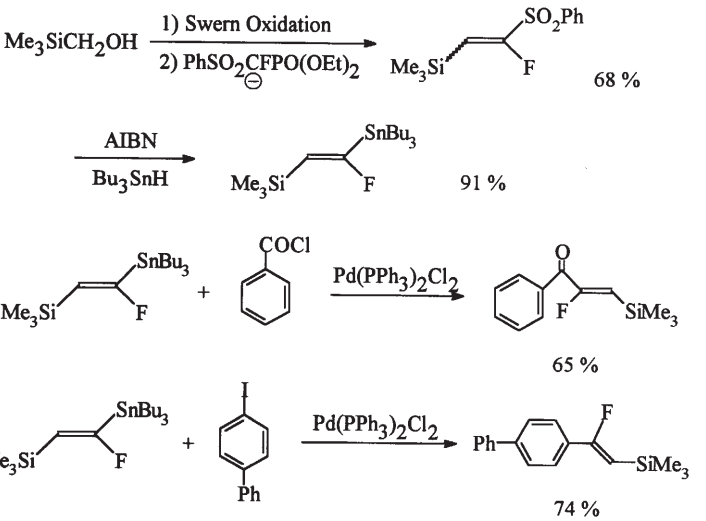
from the corresponding alkenylsilanes [185]. Reaction of *trans*-2-substituted-1,2-difluoroethenylsilanes with tributyltin chloride or tributyltin oxide in DMF in the presence of dry potassium fluoride at room temperature to 80 °C stereospecifically afforded the corresponding stannanes in good yields (Scheme 65).

The stereospecific preparation of *E*- and *Z*-α-fluorovinylstannanes via the radical reaction of the corresponding α-fluorovinylsulfones with tributyltin hydride has been reported by McCarthy et al. These reagents undergo a variety of destannylation reactions including protolysis, deuterolysis, acylation, iodination, electrophilic fluorination and the Stille coupling reaction [186–189] (Scheme 66). The last reaction has been employed successfully in the synthesis of a fluorinated thymidylate synthetase inhibitor [189] (Scheme 67).

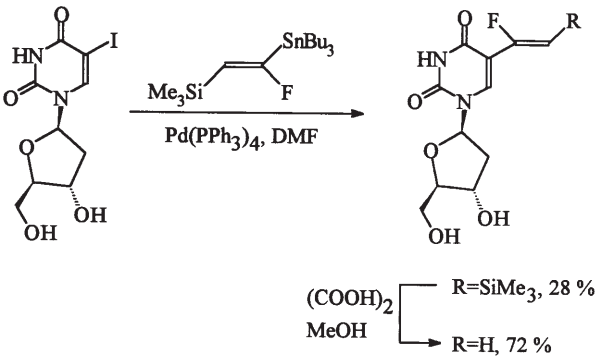
Trifluorovinylstannane has been successfully employed in the Stille cross-coupling reaction with aryl or vinyl halides in the presence of a palladium catalyst [190, 191] (Scheme 68). Recently, ethyl 3-(tributylstannyl)-2-methoxyacrylate was prepared from ethyl trifluoropyruvate in several steps and used in the Stille reaction for the synthesis of α-fluoro–keto acid derivatives [192] (Scheme 69).



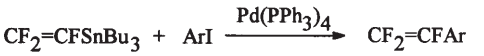
Scheme 65



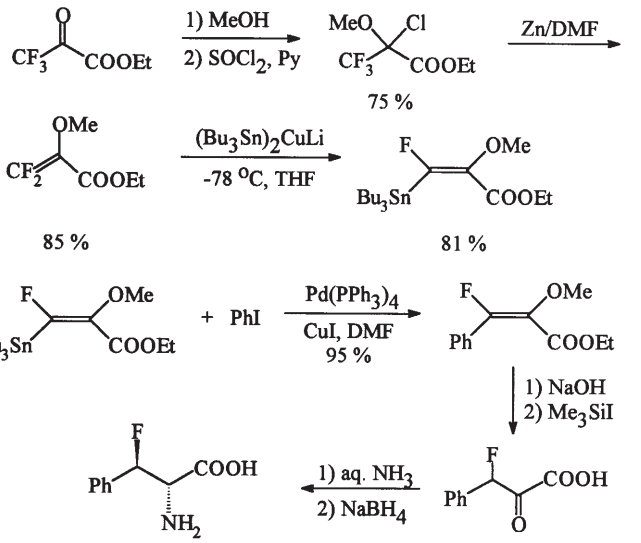
Scheme 66



Scheme 67



Scheme 68

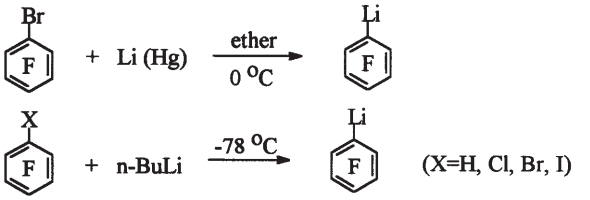


Scheme 69

4
Fluorinated Aryl Organometallics

4.1
Perfluoroaryl Lithium Reagents

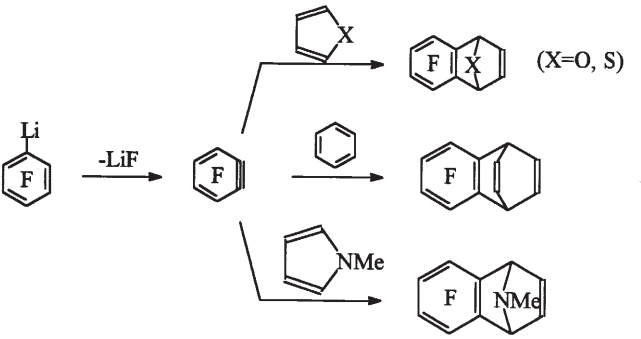
Pentafluorophenyllithium can be readily prepared by direct reaction of pentafluorophenyl halides with lithium amalgam [193, 194] or lithium-hydrogen and lithium-halogen exchange reactions of pentafluorophenyl halides with alkyllithiums [195–205] (Scheme 70).



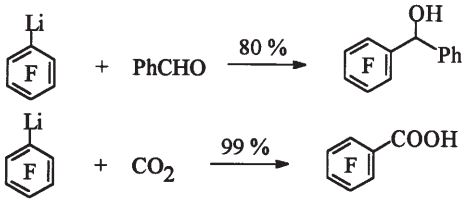
Scheme 70

Pentafluorophenyllithium is thermally unstable and decomposes to generate tetrafluorobenzyne by β-elimination of lithium fluoride. The benzyne can be trapped by a variety of dienes to give the corresponding Diels-Alder adducts [193, 196, 197, 206] (Scheme 71).

Pentafluorophenyllithium readily reacted with electrophiles to give the pentafluorophenylated compounds in good yield [195, 197, 207–211]. The addition-elimination product was obtained instead of the displacement product when pentafluorophenyllithium was reacted with iodotrifluoroethylene [212] (Scheme 72).



Scheme 71



Scheme 72

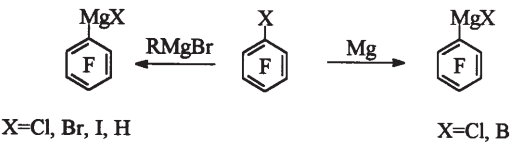
4.2
Perfluoroaryl Magnesium Reagents

Similarly, pentafluorophenylmagnesium halides can be prepared either by direct reaction of magnesium with pentafluorophenyl halides or by an exchange reaction of alkylmagnesium halides with hydro-, bromo- and chloropentafluorobenzenes [195, 213–217] (Scheme 73).

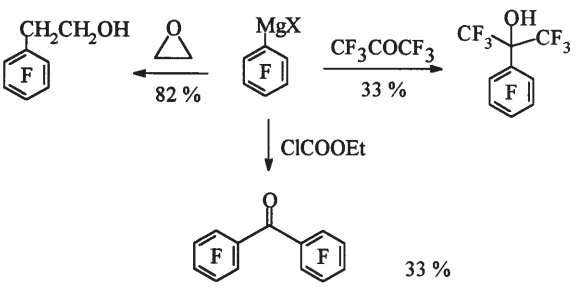
The pentafluorophenylmagnesium reagents exhibit greater thermal stability than the corresponding lithium reagents [215, 218] and also afford Diel-Alder adducts of tetrafluorobenzyne in the presence of dienes [219]. Pentafluorophenylmagnesium reagents react with a variety of electrophilic substrates to give the expected fluorinated aromatics [194, 215, 220–225] (Scheme 74).

4.3
Perfluoroaryl Copper Reagents

Pentafluorophenylcopper was prepared by the metathesis of pentafluorophenyl magnesium, pentafluorophenyllithium or pentafluorophenylcadmium reagents



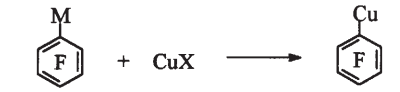
Scheme 73



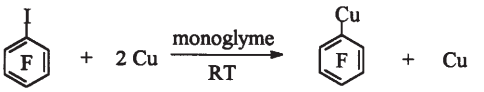
Scheme 74

with cuprous halides [226–230] (Scheme 75). Pentafluorophenylcopper can also be prepared by the reaction of iodopentafluorobenzene with highly activated copper [231–234] (Scheme 76).

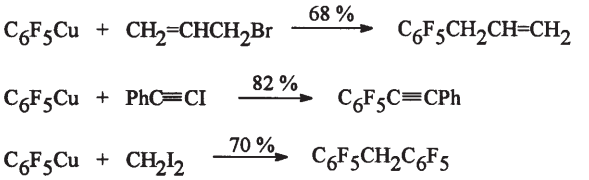
Pentafluorophenylcopper exhibits high reactivity towards a variety of organic substrates such as aryl, vinyl, alkynyl, allyl halides etc. [226, 227, 229, 235–238] (Scheme 77). Similar to trifluorovinylcopper, pentafluorophenylcopper readily adds to hexafluoro-2-butyne to form the *syn* addition product, which can be quenched with electrophiles [230] (Scheme 78).



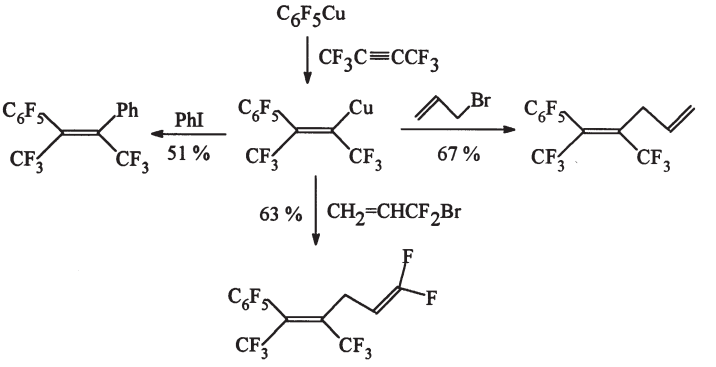
Scheme 75



Scheme 76

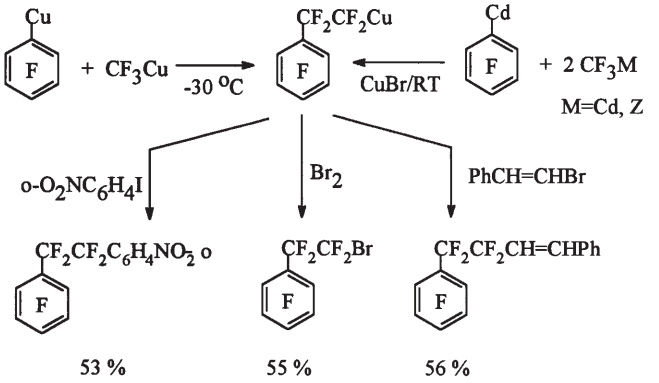


Scheme 77



Scheme 78

Recently, a unique double difluoromethylene insertion into the carbon-copper bond of pentafluorophenylcopper has been reported [239]. Pentafluorophenylcopper reacted with trifluoromethylcopper in DMF at –30 °C to room temperature to form perfluoro-2-phenylethylcopper ($C_6F_5CF_2CF_2Cu$) in high yield, which readily underwent a variety of functionalization reactions with electrophiles [239] (Scheme 79).



Scheme 79

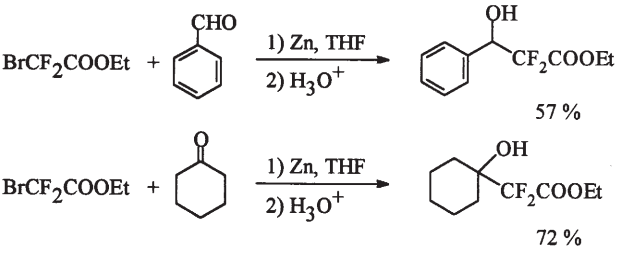
5
Carboalkoxydifluoromethylene Organometallics

5.1
Carboalkoxydifluoromethylene Zinc Reagent

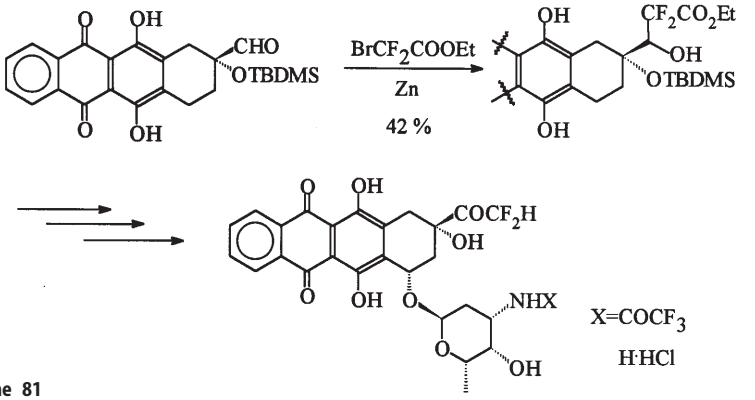
In 1984, Fried et al. reported the reaction of bromodifluoroacetate with carbonyl substrates in the presence of zinc. The α,α-difluoro β–hydroxyester was obtained in good yield without isolation of the Reformatsky reagent [240, 241] (Scheme 80) Later, this zinc reagent has also been prepared via reaction of ethyl bromodifluoroacetate with zinc amalgam in triglyme [242] or reaction of methyl iododifluoroacetate with zinc in acetonitrile [243].

This Reformatsky reagent has been widely utilized for the incorporation of $-CF_2CO-$ into organic molecules, which often exhibit enhanced biological activity [244–258]. For instance, 14, 14-difluoro-4-demethoxydaunorubicin was found to exhibit antitumor activity against P388 murine leukemia [246] (Scheme 81). An inhibitor of interleukin-1 converting enzyme [257] (Scheme 82), a renin inhibitor [251] (Scheme 83) and a 4,4-difluoro-L-arginine analog [258] (Scheme 84) were also prepared via this reagent.

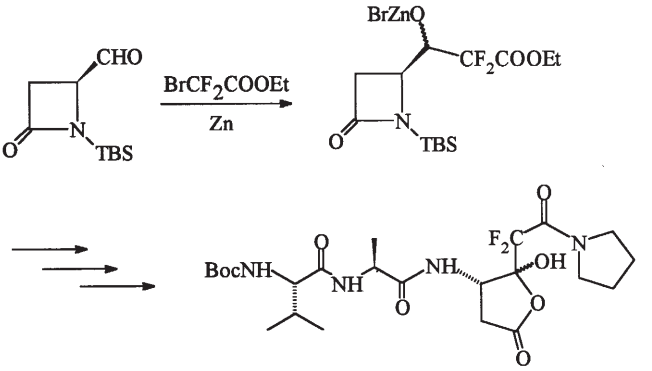
A similar Reformatsky reaction, prepared from the cheaper precursor, ethyl chlorodifluoroacetate in dry DMF, has been reported by Lang and Schaub [259] (Scheme 85). Later, Lang demonstrated the preparation of 2,2-difluoro-4-pente-



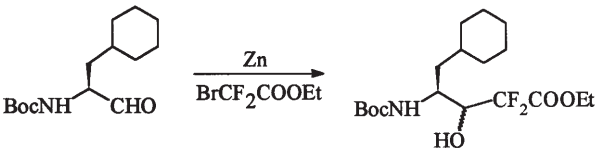
Scheme 80



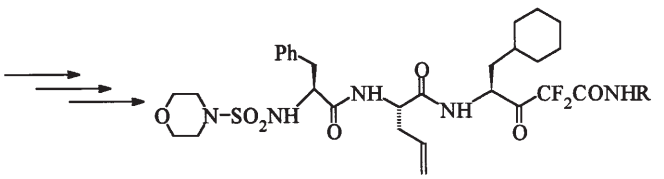
Scheme 81



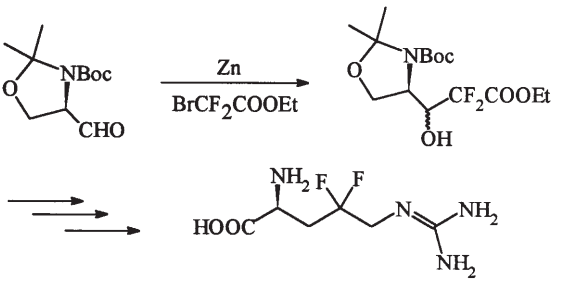
Scheme 82



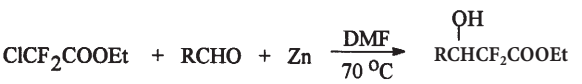
Scheme 83



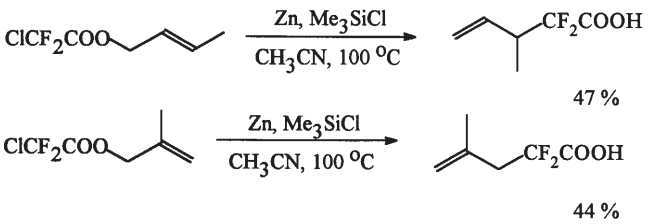
Scheme 83 (continued)



Scheme 84



Scheme 85

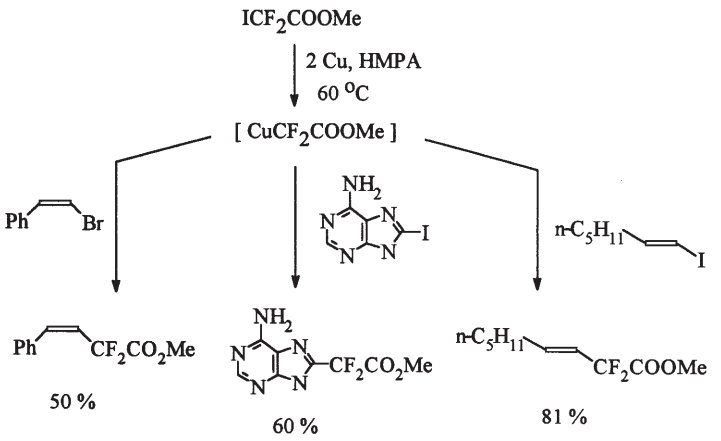


Scheme 86

noic acid derivatives via the silicon-induced Reformatsky-Claisen reaction followed by hydrolysis of the silyl ester [260] (Scheme 86).

5.2 Carboalkoxydifluoromethylene Copper Reagent

Reaction of methyl iododifluoroacetate with copper in HMPA affords the carboalkoxydifluoromethylene copper reagent, which couples with aryl, alkenyl, alkyl, alkynyl and allyl halides to give the corresponding 2,2-difluoroester derivatives [261] (Scheme 87).



Scheme 87

6
Dialkoxyphosphinydifluoromethyl Organometallics

6.1
Dialkoxyphosphinydifluoromethyl Lithium Reagents

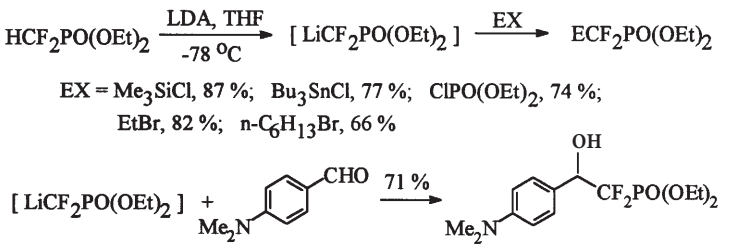
Treatment of difluoromethylphosphonate with LDA in THF at –78 °C afforded dialkoxyphosphinydifluoromethyllithium, which can be captured by a variety of electrophiles [262] (Scheme 88).

Recently, lithiodifluoromethylphosphonate was reacted with methyl vinyl ketone followed by rearrangement of the allylic alcohol to give the difluoromethylphosphonate derivative as the E isomer [263] (Scheme 89). This lithium reagent was also reacted with nitroalkenes in the presence of $CeCl_3$ to produce the corresponding Michael addition products in moderate yield [264] (Scheme 90).

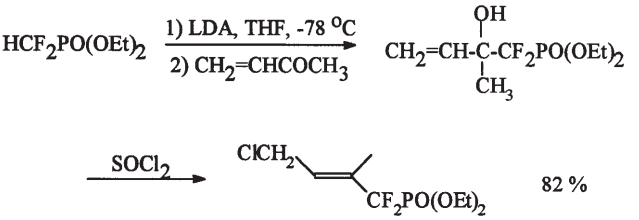
The dialkoxyphosphinydifluoromethyllithium reagent has also been used in the preparation of bioactive compounds such as 2-amino-7,7-difluoro-7-phosphonoheptanoic acid for evaluation in the *N*-methyl-D-aspartic acid binding assay [265], 9-(5,5-difluoro-5-phosphonopentyl)quanine as a multisubstrate analog inhibitor of purine nucleoside phosphorylase [266], fluorinated phosphoserine analog [267, 268] (Scheme 91) and nucleoside 5′-deoxy-5′-difluoromethylphosphonates [267, 269] (Scheme 92).

6.2
Dialkoxyphosphinydifluoromethyl Cadmium Reagent

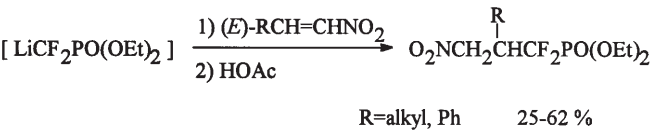
Dialkoxyphosphinydifluoromethyl cadmium reagent can be readily prepared via reaction of diethyl bromodifluoromethylphosphonate with acid-washed cadmium powder [270] (Scheme 93). This cadmium reagent exhibits remarkable stability and versatile chemical reactivity. Typical examples are outlined below [271 – 273] (Scheme 93).



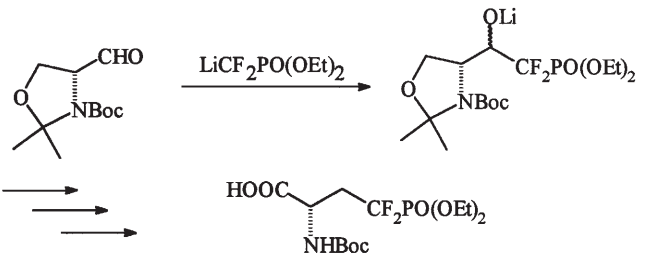
Scheme 88



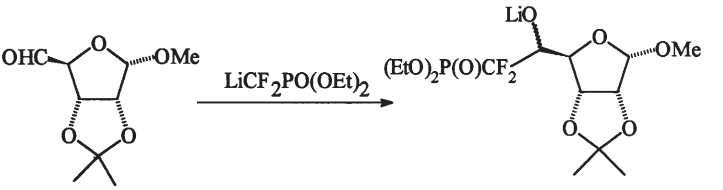
Scheme 89



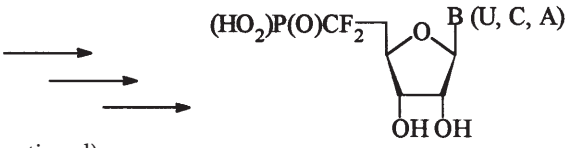
Scheme 90



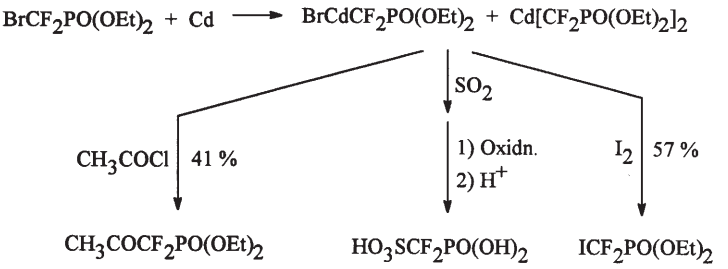
Scheme 91



Scheme 92



Scheme 92 (continued)



Scheme 93

6.3
Dialkoxyphosphinydifluoromethyl Zinc and Copper Reagent

Dialkyl bromodifluoromethylphosphonates are treated with acid washed zinc dust or powder in ethereal solvents at room temperature to 60 °C to give the corresponding dialkoxyphosphinydifluoromethyl zinc reagents in good yields [274] (Scheme 94).

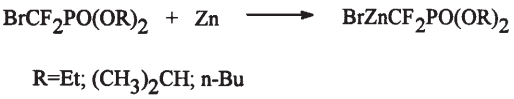
These zinc reagents also exhibit excellent thermal stability but still react with strong electrophiles [275–277]. With less reactive electrophiles, addition of catalytic cuprous bromide can improve the reaction with dialkoxyphosphinydifluoromethyl zinc reagents [278, 279]. Presumably, this reaction involves a dialkoxyphosphinydifluoromethyl copper reagent intermediate (Scheme 95).

7
α,α-Difluoroallyl and α,α-Difluoropropargyl Organometallics

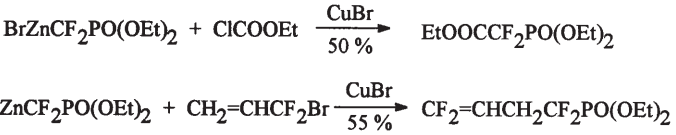
7.1
α,α-Difluoroallyl Organometallics

3-Bromo-3,3-difluoropropene reacted with *n*-butyl lithium in the presence of carbonyl compounds or trialkylsilyl chloride to give the corresponding α,α-difluoroallylic derivatives. The difluoroallyllithium was proposed as an intermediate [280–282] (Scheme 96).

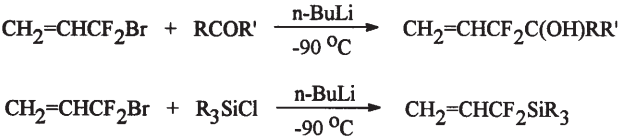
In the presence of zinc, cadmium or tin, 3-bromo-3,3-difluoropropene also reacted with carbonyl compounds to give the α,α-difluoroallylic alcohols in good yields [283] (Scheme 97).



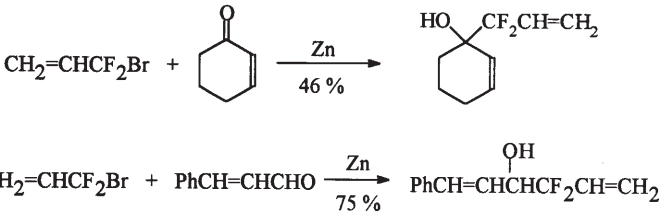
Scheme 94



Scheme 95



Scheme 96

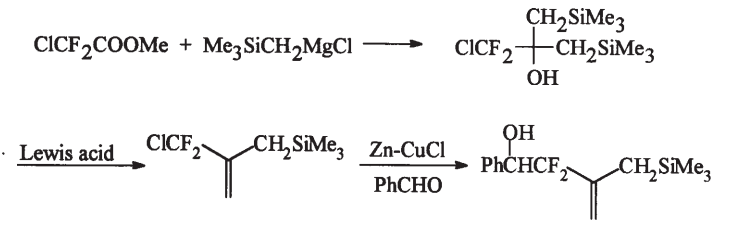


Scheme 97

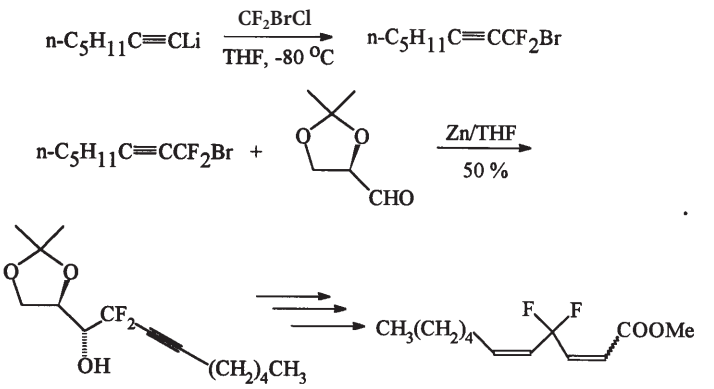
Recently, Ishihara reported the preparation and reaction of 2-(trimethylsilyl)methyl-3-chloro-3,3-difluoropropene with carbonyl compounds in the presence of Zn-CuCl or Zn-AgOAc in DMF or DMAC [284] (Scheme 98).

7.2 α,α-Difluoropropargyl Organometallics

Similarly, 1-bromo-1,1-difluoro-2-alkynes, which were prepared by the reaction of lithium acetylides with CF_2ClBr [284] or CF_2Br_2 [285], also reacted with carbonyl compounds in the presence of zinc to afford the corresponding α,α-difluoropropargyl alcohol [285]. This reaction has been utilized for the preparation of 3-fluoro-2,5-disubstituted furans [286] and other fluorinated biologically active compounds [285, 287] (Scheme 99).



Scheme 98



Scheme 99

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Enzymatically Controlled Reactions of Organofluorine Compounds

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The biotransformation of organofluorine materials into optically active functionalized fluorinated materials along with a discussion on the effect of fluorine atom(s) during enantioselective and/or diastereoselective transformations is described. The ability of microorganisms to discriminate between enantiomers is particularly important regarding resolution and asymmetric synthesis. Furthermore, the use of chiral fluorinated materials in the design and preparation of new types of biologically active materials is discussed.

Keywords: Chiral fluorinated materials, microbial transformation, enzymatic optical resolution, microorganisms, stereochemistry.

1 Introduction

Extensive research has already been carried out on incorporation of fluorine into molecules which can lead to profound and unexpected results on biological activities and/or physical properties [1–5]. In particular, optically active fluorine-containing molecules have been recognized as a relatively important class of materials because of their interesting characteristics and potential applicability to optical devices such as ferroelectric or antiferroelectric liquid crystals [6–11]. Recent investigations in this field have opened up the possibility for the

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introduction of chirality via asymmetric reduction or enzymatic optical resolution by employing biocatalysts [12], along with conventional chemical methods [13–15]. In this chapter the authors review recent progress made in the synthesis of optically active fluorinated materials via biotransformation. The microorganism outcomes are analyzed mechanistically to see how fluorine substitutions influence factors such as the reactivity, selectivity and electronic effects on stereochemical recognition in the transformation.

2
Asymmetric Induction via the Reduction of a Carbonyl Group

The reduction of fluorinated carbonyl compounds with microorganisms is a convenient method used to synthesize optically active materials. in particular, baker's yeast is known as one of the most convenient and readily available biocatalysts and promotes introduction of asymmetry via reduction, oxidation, hydrolysis, or carbon-carbon bond formation [16–19]. The mode of reduction is predictable by the empirical Prelog rule (Fig. 1). Reduction proceeds smoothly in many instances as shown in Table 1 and absolute configurations of the newly created chiral centers, R in every case, results from the *si*-face introduction of hydride. The supposition that Prelog's rule is effective in these cases led to the conclusion that all fluoromethyl moieties (R_f) used here were recognized by the enzyme as smaller than an R group. Thus, we can empirically consider that the fluorine atom is only regarded as the "second smallest element" and its electronegative nature seemingly gives very little effect, if any, on stereoselectivity [20–22]. On the other hand, it is interesting that perfluorodecanone was not a substrate. Presumably this lack of reactivity is caused by its poor solubility in the aqueous medium, or the ready reactivity of the strongly electron deficient carbonyl group to form hydrates or a complex with enzymes [23, 24].

In this reduction system, several methods have been developed to control the stereochemistry of the reaction to obtain both enantiomers of the reduction products in high enantiomeric excess. For example, 2,2,2-trifluoroacetophenone was reduced to produce both enantiomers with a growing culture of *Aspergillus niger* and *Geotrichum candidum* or baker's yeast. This may be explained by the presence, in each microorganism, of several oxidoreductases, which generate secondary alcohols of opposite configuration. The configuration and the enantiomeric purity of the alcohol obtained depend on how many, and which, oxidoreductases operate on the carbonyl compound [25].

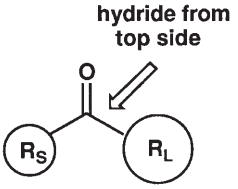


Fig. 1. Prelog Rule

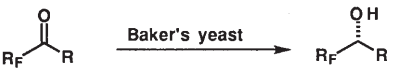
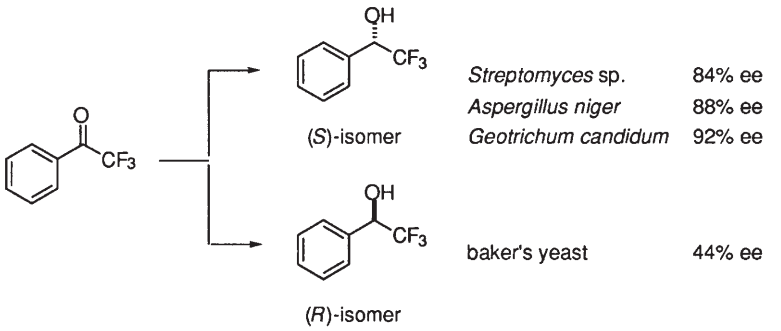


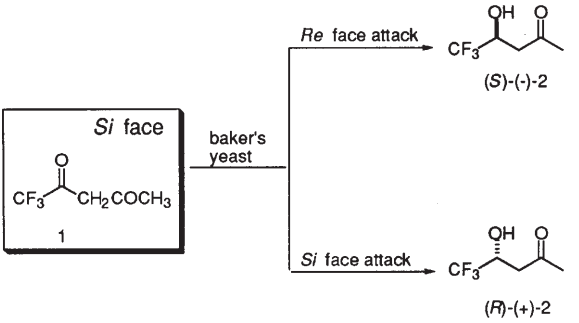
Table 1. Baker's Yeast Reduction of Fluorinated Ketones

R_F	R	Yield (%)	Optical purity[a] (% ee)
CH_2F	Ph[b]	58	90 (R)
	CH_2CH_2Ph	54	32 (R)
	CH_2SPh	40	70 (S)
CHF_2	Ph	81	88 (R)
	CH_2CO_2Et	68	63 (R)
CF_3	CH_2CH_2Ph	72	82 (R)
	n-C_8H_{17}	34	64 (R)
	CH_2CO_2Et	92	50 (R)
CF_2Cl	*n*-C_8H_{17}	no reaction	
	Ph	85	7 (7)

[a] In the parentheses are shown their absolute configurations.
[b] This product was obtained from ethyl α-fluorobenzoylacetate via enzymatic hydrolysis and decarboxylation, which was followed by baker's yeast redution of the resultant monofluoroacetophenone.



In addition, the use of enzyme selective inhibitors has turned out to be very effective. Reductions were performed by adding 1,1,1-trifluoro-2,4-pentanedione **1** to a yeast-water suspension with selected additives such as methylvinylketone, allyl alcohol, alkanoic acids, ethyl chloroacetate or allyl bromide, all of them reported to affect the stereochemical course of baker's yeast reduction. In some cases, both the influence of the yeast/substrate ratio and the influence of the presence of glucose were considered. In the presence of alkanoic acids (acetic, fumaric, or oleic acid), no significant effect was observed. However, addition of methylvinylketone, allyl alcohol, ethyl chloroacetate and allyl bromide to the reaction system affected the stereochemical course of the reduction of **1**. In particular, (*R*)-(+)-**2** was produced in the presence of ethyl chloroacetate and allyl bromide as additive.



	gl^{-1}	% ee
non additive		72
allyl alcohol	3	88
	6	92
methylvinylketone	1.5	83
	3	86
allyl bromide	1.5	64
	3	81
ethylchloroacetate	3	20

The most representative results of these additive systems are: (1) allyl alcohol seems to inhibit the *Si*-face attack of the hydride, and (2) allyl bromide inhibits the *Re*-face attack. In this system, if it is assumed that CF_3 is sterically less demanding than the CH_2COCH_3 substituent, Prelog's rule holds for the yeast-allyl bromide additive reduction system, whereas it is not followed when the additive is allyl alcohol [26].

3
Lipase-catalyzed Asymmetric Induction

3.1
Asymmetric Hydrolysis

Yeast-mediated reductions predominantly form a single enantiomer and it is often difficult to find conditions which produce the opposite stereoisomer selectively. It has, however, been possible to obtain both enantiomers in 50% yield in 100% ee via enzymatic optical resolution. Chiral fluorinated secondary alcohols possessing the mono-, di- and/or trifluoromethyl group have been prepared by enzyme-catalyzed kinetic resolutions [27].

For example, the acetate prepared from 1,1,1-trifluoro-2-octanol was transformed into (*R*)-1,1,1-trifluoro-2-octanol in 96% ee when hydrolyzed with lipase MY at 40% conversion. Other, trifluoromethylated chiral secondary alcohols shown in Table 2 were prepared by the same procedure. The corresponding alcohols were converted to their acetate, followed by asymmetric hydrolysis to attain the higher enantiomeric excess [28].

Such resolution could be readily optimized by use of an appropriate acyl group which reacts efficiently with the enzyme employed [29]. For example, the acetate prepared from monofluorinated α-phenetyl alcohol was hydrolyzed with lipase MY at 34% conversion to afford the product only with 26% ee. Enhancement of optical purity to 73% ee was observed when the corresponding isobutyrate was hydrolyzed. The best results were obtained for hydrolysis of the isobutyrate by lipase PS, which afforded the product in 82% ee at 47% hydrolysis. Experience has shown (see Table 3) that one of the best combinations was hydrolysis of acetate with lipase MY or isobutyrate with lipase PS [30].

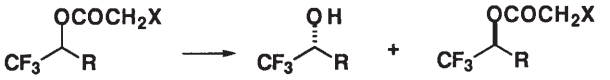


Table 2. Asymmetric hydrolysis

R	X	Time (hr)	$[\alpha]_D$/MeOH	Optical purity %ee
C_2H_5	Cl	1	+28.9	91
C_3H_7	Cl	5	+30.6	97
C_4H_9	Cl	6	+29.5	97
C_5H_{11}	Cl	5	+29.8	97
C_6H_{13}	Cl	6	+24.0	97
C_7H_{15}	H	43	+23.8	98
C_8H_{17}	H	45	+25.4	98

Lipase MY (Candida rugosa; Meito Sangyo Co. Ltd.) was used.

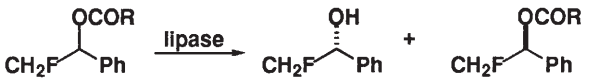


Table 3. Effect of acyl group and enzyme towards asymmetric hydrolysis

R	Lipase	Hydrolysis conversion (%)	Optical purity (% ee)	*E* value
CH_3	lipase MY	34	26	1.9
i-C_3H_7		33	73	9.1
n-C_4H_9		46	52	4.8
c-C_6H_{11}		11	7	1.2
Ph		28	63	5.6
i-C_3H_7	lipase MY	33	73	9.1
	lipase PS	47	82	21.9

[a] Lipase MY (*Candida rugosa*: Meito Sangyo Co. Ltd.), lipase PS (*Pseudomonas cepacia*.: Amano Pharmaceutical Co. Ltd.).
[b] Optical purity was determined by HPLC using Chiralcel OB (Daicel Chemical Industries Ltd.).

The authors have also investigated the action of enzymes on phenetyl alcohols containing various fluoroalkyl groups. As described in Table 4, when the alcohols are ordered according to the increasing size of **R**, a consistent trend was observed between a decrease in the reaction rate of hydrolysis and an increase in the optical purity of the alcohol [27, 30]. Another interesting point is the reversal of enantiomeric recognition by lipase MY between *i*-Pr and CF_3 substituted alcohols. These trends suggest that the active site of enzymes may be surrounded with various types of electrophobic functional groups such as amines, amides, or hydroxyls. Unfavorable interactions of these groups which

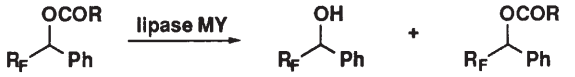


Table 4. Asymmetric hydrolysis of esters from fluoroalkylated benzyl alcohol

R_F	Hydrolysis conversion (%)	Time (hr)	Optical purity (% ee)	Absolute config.	*E* value
CH_3	25	1	6	(R)	1.2
CH_2F	34	1.5	26	(S)	1.9
CHF_2	35	2	30	(S)	2.2
i-C_3H_7	5	24	57	(R)	3.8
CF_3	40	24	57	(R)	5.2
CF_2Cl	25	7.5	73	(R)	8.1
CF_3CF_2	23	23	racemic	–	–
i-C_3F_7	0	24	–	–	–

occur when R_f is CF_3 or $CClF_2$ can be obviated by association to form the opposite enantiomer. This concept is not generally applicable but rationalizes one special aspect of fluorination [27, 30].

Table 5 shows selected examples of the enzymatic resolution of esters with various structures. As discussed above, enhancement of the optical purity was

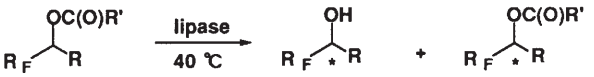


Table 5. Lipase-catalyzed Asymmetric Hydrolysis of Fluorinated Esters

Run	R_F	R	R′	Lipase[d]	Hydrolysis (%)	Optical purity of carbinol (% ee)
1	CH_2F	Ph	Me	MY	34	26 (S)
2		Ph	*i*-Pr	PS	47	82 (S)
3		$PhCH_2CH_2$	Me	MY	34	81 (R)
4	CHFCl	Ph[b]	*i*-Pr	PS	32	>99 (S)[c]
5		$PhCH_2CH_2$[b]	*i*-Pr	PS	31	>99 (S)[c]
6	CHF_2	Ph	Me	MY	35	30 (S)
7		Ph	*i*-Pr	PS	38	>98 (S)
8		$PhCH_2CH_2$	Me	PS	55	73…[a]
9		*n*-C_6H_{13}	Me	MY	51	33 (R)
10		CH_2CO_2Et	Me	MY	39	90 (R)
11	CF_3	Ph	Me	MY	40	57 (R)
12		$PhCH_2CH_2$	Me	MY	44	98 (R)
13		*Z*-PhCH=CH	Me	MY	28	>99 (R)
14		*E*-PhCH=CH	Me	MY	36	94 (R)
15		CH_2COPh	Me	MY	23	92 (R)
16		$CH_2COC_6H_{13}^n$	Me	MY	37	90 (R)

Table 5 (continued)

Run	R_F	R	R′	Lipase	Hydrolysis (%)	Optical purity of carbinol (% ee)
17		CH_2CO_2Et	Me	MY	41	96 (R)
18	CF_2Cl	Ph	Me	MY	25	73 (R)
19		$PhCH_2CH_2$	Me	MY	42	>95 …[a]
20		*n*-C_6H_{13}	Me	MY	44	88 …[a]
21	CF_3CF_2	*n*-C_8H_{17}	*i*-Pr	MY	60	50 …[a]
22		CH_2CH_2OH	Me	MY	33	99 …[a]
23	CF_3CCl	Ph	Me	PS	27	92 …[a]

[a] Stereochemistry was unknow.
[b] Diastereomeric ratio of starting material and product, 97:3 and >99:1; 77:23 and >99:1 (R = $PhCH_2CH_2$).
[c] Stereochemistry at the carbon bearing a hydroxy group.
[d] lipase MY (*Candida rugosa*: Meito Sangyo Co. Ltd.); lipase PS (*Pseudomonas cepacia*.: Amano Pharmaceutical Co. Ltd.).

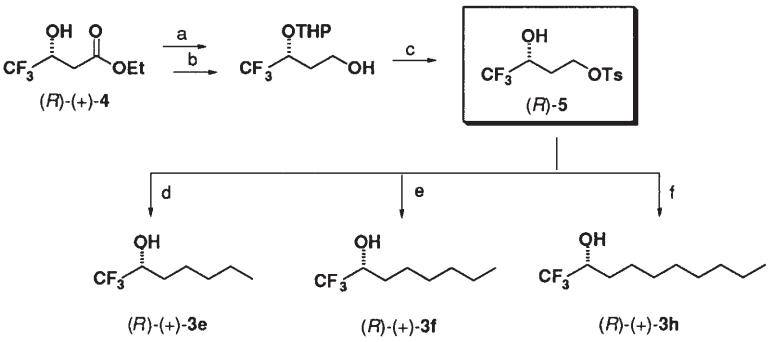
possible by changing the acyl group and/or the enzyme. Interestingly, esters with a trifluoromethyl group were converted by lipase MY into the alcohol with **R** absolute configuration in every case when stereochemistry was determined. However, substrates with mono- or difluoromethyl substituents furnished alcohols whose asymmetric configuration depended on their structures. Particularly interesting are runs 4 and 5, when resolution was accompanied with simultaneous separation of diastereomers [31]; the separation of both diastereomers and enantiomers by enzymatic hydrolysis in the same transformation.

3.2 Determination of Absolute Configuration

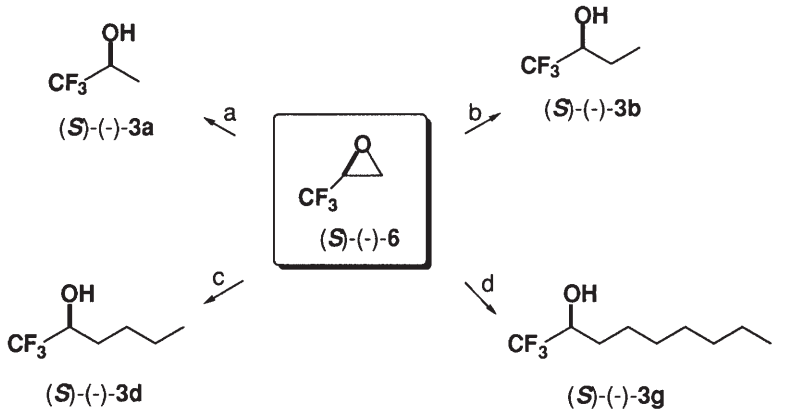
The authors have also investigated the absolute configuration of optically active carbinols with a trifluoromethyl group. The synthetic strategies employed are shown in Scheme 1. The absolute stereochemistry of the synthetic intermediate (*R*)-(+)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate (**4**) was confirmed by X-ray analysis. It has been prepared by asymmetric hydrolysis (>95% ee) and the (*S*)-enantiomer was prepared by enzymatic hydrolysis of the recovered acetate.

The protected (*R*)-(+)-**4** was selectively reduced with lithium aluminum hydride to give the optically pure alcohol in good yield which was then reacted with tosyl chloride to give the synthon. Treatment with a variety of cuprates gave materials with known absolute configurations. Results shown in Scheme 1 suggest that (+)-1,1,1-trifluoro-2-heptanol, (+)-1,1,1-trifluoro-2-octanol and (+)-1,1,1-trifluoro-2-decanol produced from the asymmetric hydrolysis are the *R* enantiomers [30].

The absolute configuration of other compounds [$CF_3CH(OH)R$; R = Me, Et, Bu, C_7H_{15}] was determined from *S*-(-)-trifluoropropene oxide, which was produced from the direct oxidation of 3,3,3-trifluoropropene with microorganism.



Scheme 1. a) DHP, CH_2Cl_2; b) $LiAlH_4$, Et_2O; c) TsCl, pyridine; d) PrMgBr, Et_2O; e) *n*-Bu_2CuLi, Et_2O; f) *n*-$C_6H_{13}MgBr$, Et_2O



Scheme 2. a) $LiAlH_4$; b) Me_2CuLi, Et_2O; c) *n*-Bu_2CuLi, Et_2O-hexane; d) *n*-$C_7H_{15}MgBr$, THF-Et_2O

3.3
Diastereocontrolled Reaction

Chiral fluorinated allylic alcohols obtained by enzymatic resolution (Table **5**, Runs **13** and **14**) were employed in diastereoselective cyclopropanation using the carbenoid from samarium and di-iodomethane [32]. This reaction proceeded smoothly at –78 °C to 0 °C, but not as smoothly as the case of non-fluorinated allylic alcohols at –78 °C.

The electron deficient nature of the carbon-carbon double bond due to the strong electron withdrawing trifluoromethyl group may account for this finding. While the absolute stereochemistry was not defined, Molander's mechanism predicts that the cyclopropane derivatives would be formed in a highly *syn* selective manner. The corresponding *anti*-isomer was prepared via oxidation and reduction of the resulting carbonyl group [19]. These high selectivities may

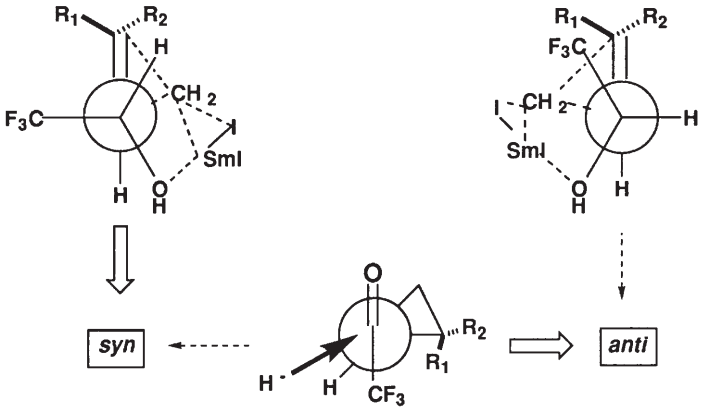


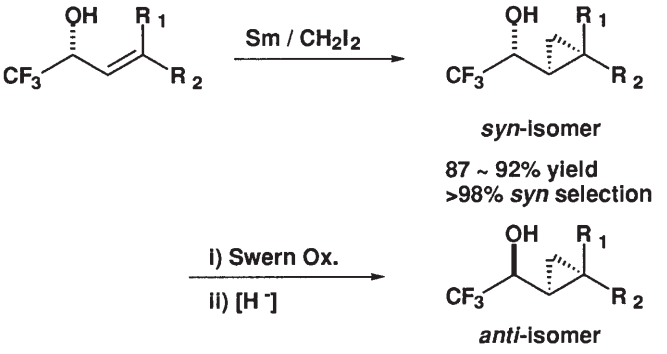
Fig. 2. Possible mechanisms for diastereoselective cyclopropanation and reduction

be explained by the transition state models in Fig. 2. The trifluoromethyl group, a steric equivalent to the isopropyl group [30c], would be located perpendicular to the π system to minimize steric repulsion.

The incoming carbenoid approaches from the side opposite to the CF_3 moiety, interacting with the hydroxyl oxygen, to yield the *syn*-isomer predominantly. As reported in the literature [33, 34], a relatively large substituent such as *i*-Pr or *t*-Bu is required for the realization of high diasteroselectivity when introduced to the position of R_2. However, less sterically demanding Me or *n*-Bu groups led to a drastic decrease in the syn:anti ratio (syn:anti = 1:6 for Me, 1:1.4 for *n*-Bu, but 200:1 for *i*-Pr). Our results corroborate the hypothesis that the trifluoromethyl group is sterically equivalent to an isopropyl moiety. On the other hand, hydride would approach from the less hindered side of the carbonyl group in the Felkin–Anh model [35, 36] depicted below to produce cyclopropyl alcohols in an anti selective manner. This explanation is verified by the fact that ketone from *Z*-olein (R^1 = Ph, R^2 = H) gave much better diastereofacial selection than the other (R^1 = H, R^2 = Ph) when reduced by $NaBH_4$. The latter ketone was transformed with high anti selectivity when a bulkier reducing agent, l-selectride was employed.

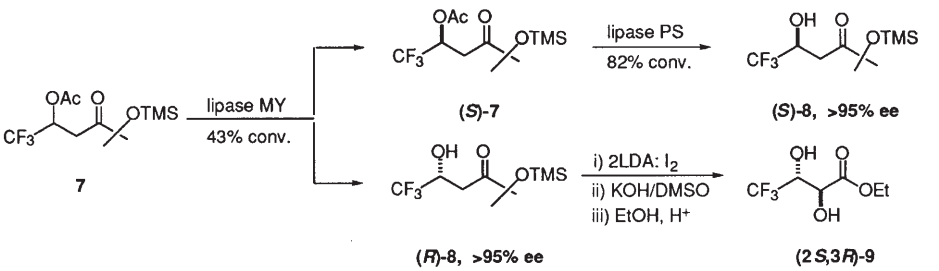
Construction of two consecutive stereocenters bearing a CF_3 group with a diastereo as well as enantiomerically form has been achieved in the following scheme. The *anti*-diol was synthesized via optically active β-hydroxyketone (*R*)- or (*S*)-**8**, both were resolved in > 95 % ee by lipase MY catalyzed asymmetric hydrolysis (Scheme 2). These materials were readily converted into the diol esters possessing the desired configuration via intramolecular epoxide formation and regioselective ring opening, followed by esterification.

The corresponding *syn*-isomer was, on the other hand, prepared from the potassium permanganate-mediated oxidation of trifluorocrotonate **10**, derived from β-hydroxy-butyrate. In this procedure, the diol ester with *syn* relative configuration was the only product detected. After acetylation, ***syn*-11** was employed as a substrate for the enzymatic resolution affording both (2*S*,3*S*)-**11**

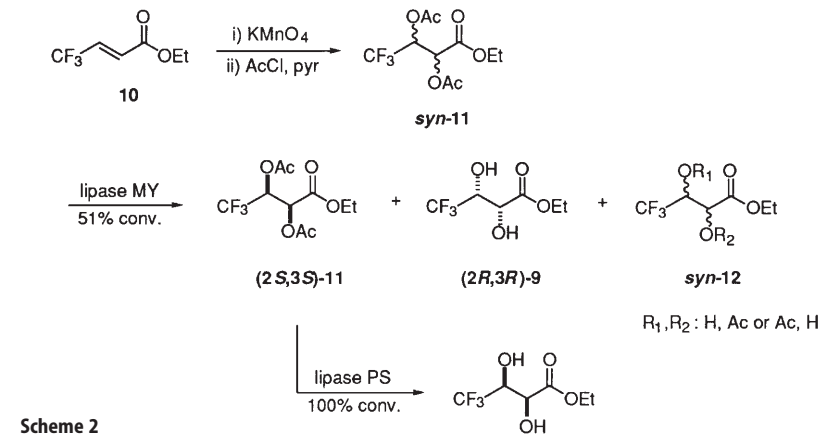


R_1	R_2	[H^-]	Selectivity (*syn*:*anti*)
H	Ph	$NaBH_4$	32 : 68
H	Ph	L-Selectride	<1 : 99
Ph	H	$NaBH_4$	2 : 98

Preparation of optically active *anti*-diol ester (2*S*,3*R*)-9



Preparation of optically active *syn*-diol ester (2*S*,3*S*)-9



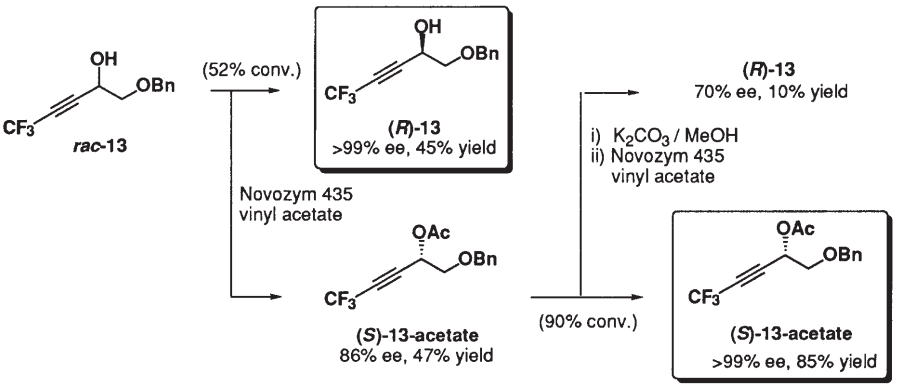
Scheme 2

and the corresponding diol ester (2*R*,3*R*)-**9** with concomitant formation of a small amount of mixture of monoacetates ***syn*-12**. Two acetyl groups in (2*S*,3*S*)-**11** were removed by another lipase hydrolysis with high regioselectivity. This procedure could be also substituted by tetraalcoxytitanate-mediated transesterification. On the other hand, because of the difficulty in separating ***syn*-12** from the diol, an effective preparation of the enantiomeric *syn*-isomer, (2*R*,3*R*)-**9**, has not yet been found. However, the desired conversion would be realized by searching for a better combination of enzyme and an acyl group selectively yielding this isomer [37].

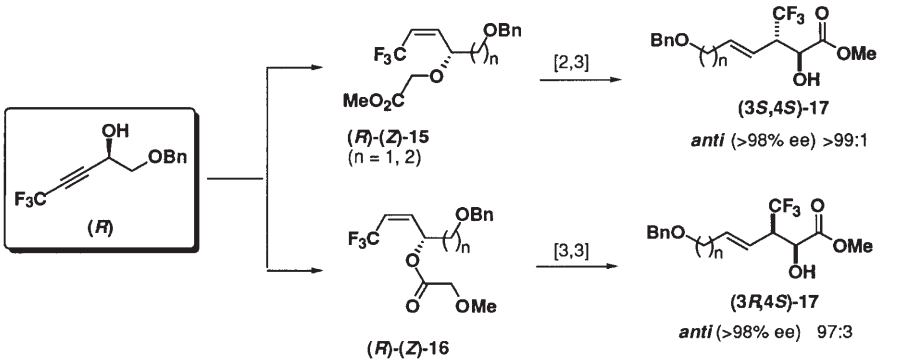
In the next stage of construction of two consecutive stereocenters bearing a CF_3 group, ester-enolate [2, 3]-Wittig and Ireland–Claisen rearrangements have been found useful. This remarkable pathway enabled us to prepare all possible stereoisomers with high stereoselectivity. Initial efforts were directed at the examination of ester-enolate [2, 3]-Wittig rearrangement. The authors have examined enzymatic kinetic resolution for ***rac*-13** to acertain [1, 3]-chirality transfer of this reaction and to obtain **17** in an optically active form [38]. After several explorations of reaction conditions, the authors found that lipase (Novozym 435; *Candida antarctica*: Novo Nordisk) in hexane with vinyl acetate preferentially acetylates *R* alcohol (*E* value >100). Thus, this system allowed us to obtain the unreacted chiral alcohol, **(*R*)-13** (>99% ee, 45% yield) at 52% conversion. In this reaction, **(*S*)-13**-acetate with 86% ee (47% yield) was also isolated, which was resolved by further enzymatic esterification using the same condition (>99% ee, 85% yield). The absolute configuration of **(*S*)-13**-acetate was assigned as ***S*** by its conversion into known diacetate **(*R*)-14**, followed by comparison of their optical rotation values. On the other hand, **(*R*)-13** (99% ee) was prepared according to the literature. The authors have also attempted enzymatic resolution of ***rac*–13** to clarify that lipase PL (*Alcaligenes* sp. Meito Sangyo Co. Ltd.) was effective (*E* value = 78), affording (*S*)-alcohol (>99% ee, 45% yield) and (*R*)-acetate (81% ee, 51% yield) at 56% conversion. The obtained chiral materials, along with racemic propargylic alcohol, were converted into the corresponding allylic alcohols by the same method as described in the literature, followed by etherification with bromoacetic acid and esterification, giving substrates in high overall yield [38].

After establishing the easy access to substrates **13** by the combination of the convenient synthetic method of propargylic alcohols and effective enzymatic resolution, the [2, 3]-Wittig rearrangements were carried out.

Subjection of (*Z*)-α-allyloxyacetate **(*R*)-(*Z*)-15** to 1.2 equivalents of LDA in THF at –78 °C in the presence of HMPA as a cosolvent resulted in the rapid (<10 min) formation of α-hydroxy-β-trifluoromethyl-γ,δ-unsaturated ester ***anti*-17** in 63% chemical yield as the sole detectable isomer. The obtained material was converted into the corresponding diol, followed by esterification using MTPA-Cl. The ^{19}F NMR of the MTPA ester showed only one set of peaks (doublet and singlet), strongly suggesting that the rearranged product was in an optically pure form and that [1, 3]-chirality transfer occurred completely. All of the (*Z*)-substrates examined exhibited high *anti* stereoselection, and high *E* selection was shown in the newly created olefinic bond. In addition, complete transfer of chirality was achieved leading to highly functionalized trifluoro-



methylated materials in enantiomerically pure forms. On the other hand, (*E*)-**15a** and **15b** rearranged to give *syn* isomers in a lower diastereoselective manner (*syn*: *anti* = *ca.* 4:1). A significant influence of the substituent R was observed, and the syn isomer was a 4:1 ~ 1:1 mixture of *E* and *Z* forms. The driving force for the accelerated rearrangement is probably the decrease of LUMO level of the allylic part by the introduction of an electron-withdrawing (CF_3) group.



As described above, the desired compound **17** with high degree of *anti* selectivity could be obtained from the starting materials, propargylic alcohols in only three steps. Thus, ester-enolate [2, 3]-Wittig rearrangement can be considered as one of the most attractive synthetic methods for new types of trifluoromethylated intermediates. However, switching of (*E*)- and (*Z*)-substrates did not lead to the diastereoselective construction of the different stereoisomers. The next [3, 3]-Ireland–Claisen rearrangement as an alternative approach to the *syn* isomer with a high degree of diastereoselectivity was also examined. This reaction might be similar to the system of ester-enolate [2, 3]-Wittig shift in the case of OR (R = protective group).

(*E*)- and (*Z*)-Substrates provided *syn* and *anti* isomers, respectively. High diastereo- and regioselection as well as complete transfer of chirality were observed in both isomers, and the diastereomeric excesses of *syn* isomers were found to be a little higher than those of *anti* isomers. Furthermore, the regioselection of *syn* isomers depended on the substituent, R. On the other hand, the diastereomeric excesses of *anti* isomers were a little lower than those of [2, 3]-Wittig rearranged products derived from (*Z*)-substrates. It is possible that this rearrangement proceeded via a six-membered transition state in which a lithium atom co-ordinates to an oxygen atom of a methoxy group to afford (*Z*)-ketene silyl acetal preferentially [38]. (Fig. 3)

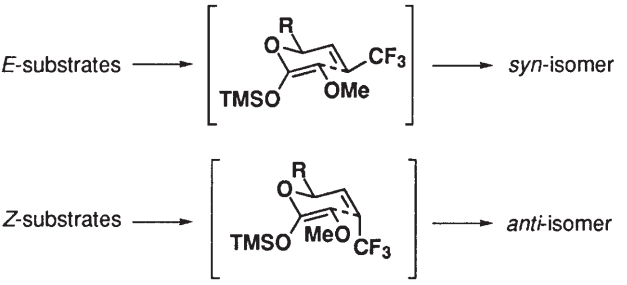
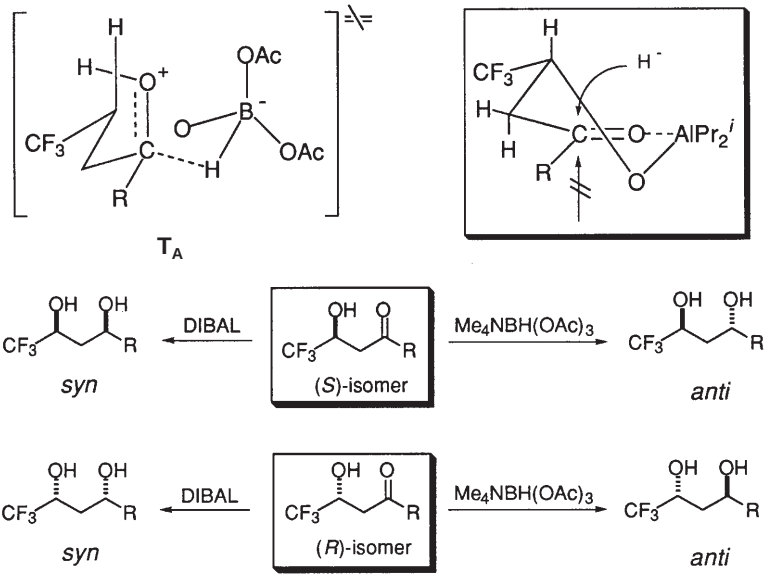


Fig. 3

Examples of the stereoconstruction of 1,3-positions bearing a CF_3 group include 1,3-diols and/or 1,3-amino alcohols. The stereoselective reduction of β-hydroxy ketones possessing a CF_3 group with diisobutylaluminum hydride might be expected to proceed through cyclic transition states, yielding the *syn* diols as indicated by the formation of the metal oxygen chelate in Fig. 4 [30].

The reduction of β-hydroxy ketones with a tetramethylammonium triacetoxyborohydride-anhydrous acetic acid system yielded the *anti* diols via the transition state (T_A). The stereochemistry of the 1,3-diols was assigned by using ^{1}H NMR coupling constants after their conversion to the corresponding cyclic acetonide.

The syntheses of 1,3-amino alcohols from β-hydroxy ketones were examined with *O*-benzyloximes possessing a CF_3 group based on the following hypothesis. In these reduction systems, the intramolecular reduction might be expected to proceed through cyclic transition states to form *syn* 1,3-amino alcohol as indicated by the formation of the aluminum fluoride chelate (seven-membered chelate) in Fig. 5 [30].



Preparation of 1,3-diols

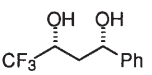
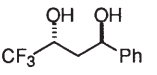
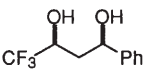
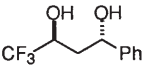
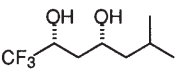
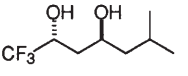
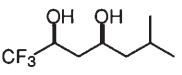
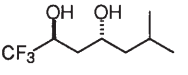
	diastereomeric ratio (% de)		diastereomeric ratio (% de)
	97		94
	96		96
	97		95
	95		97

Fig. 4

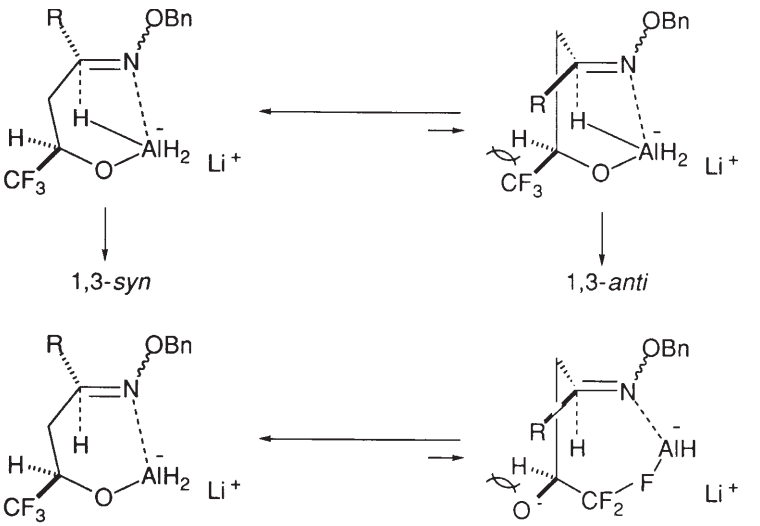
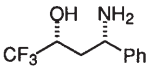
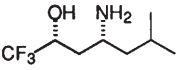
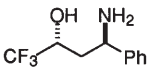
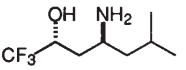
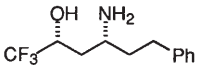
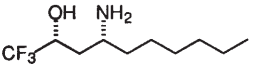
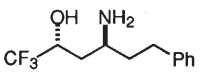
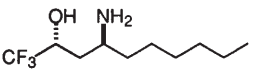


Fig. 5. Transition-state model

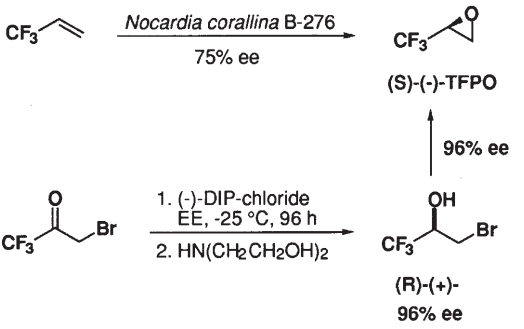
Preparation of 1,3-amino alcohols

	syn : anti		syn : anti
	87 : 13		82 : 18
			
	79 : 21		83 : 17
			

4
Building Blocks derived from Microbial Transformation

4.1
Epoxidation with Microorganisms

The ability of the microorganism to discriminate between enantiomers is very important regarding resolution and asymmetric synthesis. The ability of microorganisms to exert prochirality stereospecific control in their catalyses overcomes this problem because it permits direct asymmetric synthesis of chiral products from symmetric starting materials. *Norcadia corallina* B-276 is a



powerful microorganism used in the oxidation of 3,3,3-trifluoropropene to produce a very useful building block (*S*)-(-)-3,3,3-trifluoropropene oxide (TFPO: 75% ee) [39–41]. It is known that under basic conditions the nucleophilic ring opening of (*S*)-(-)-TFPO and its hydrocarbon analog occurs exclusively at C_1 to provide the substituted secondary alcohol as the sole product. Treatment of (*S*)-(-)-TFPO with potassium hexamethyl-disilazide and work up with anhydrous HCl provided the corresponding amine in 61% yield with retention of chirality. The other route to the same chiral amine was achieved by ring cleavage of (*S*)-(-)-TFPO with sodium azide followed by hydrogenation (101 101Fig. 6).

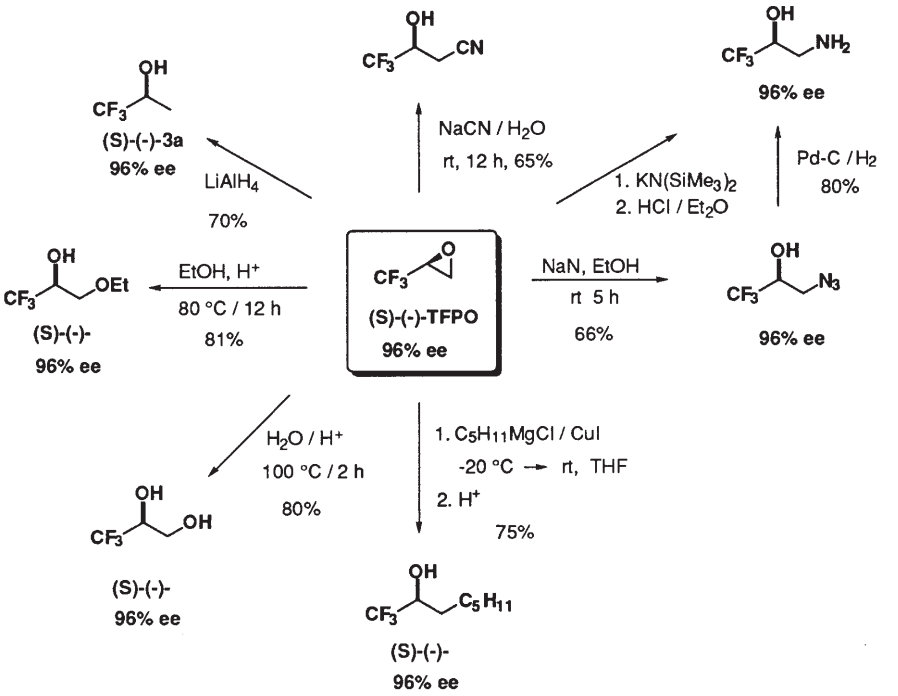
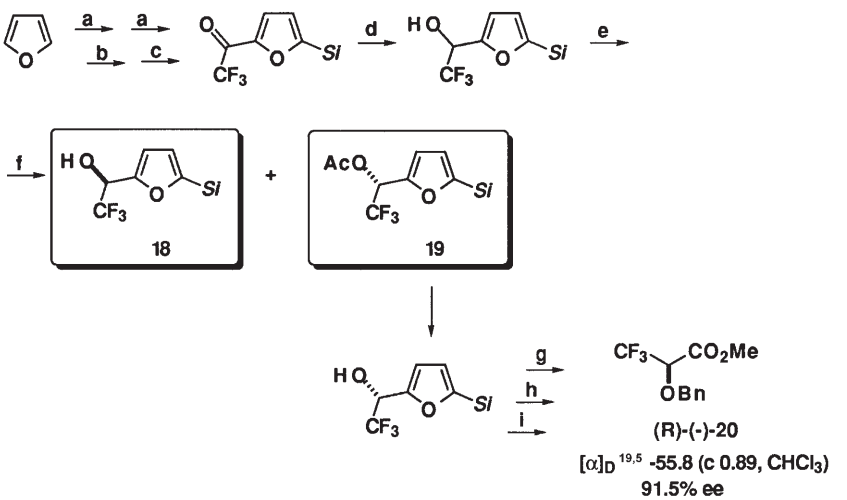


Fig. 6. Utilization of ring opening reactions

Furthermore, nucleophilic reaction of (*S*)-(-)-TFPO with NaCN produces 1-cyano-3,3,3-trifluoro-2-propanol as an versatile synthetic intermediate, which can be transformed into the chiral trifluoromethylated *β*-amino alcohol, *β*-hydroxy acid or ester, etc. Depending on the nucleophiles used such as lithium aluminum hydride or organometallic species, the desired (*S*)-1-trifluoromethyl alkyl carbinols are prepared. The Friedel–Crafts reaction of (*S*)-(-)-TFPO with benzene, opens the epoxide ring so as to place the phenyl group at C_1 to provide the corresponding carbinol. In Fig. 6, utilization of the ring-opening reactions of (*S*)-(-)-TFPO is summarized.

4.2
Fluorinated Building Blocks for Sugar Derivatives

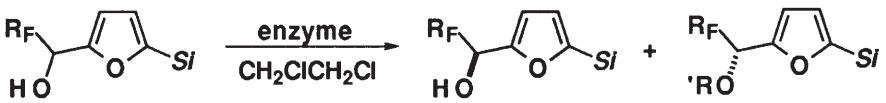
Building blocks derived from microbial transformations are usually employed as the key units of fluorinated analogs of appropriate natural products or synthetic biologically active materials [42–45]. Among such useful compounds, trifluoromethylated carbohydrates constitute one of the most interesting fields for intensive study. Novel and efficient routes to access a variety of chiral 6-deoxy-6,6,6-trifluorosugars by way of enzymatic optical resolution as well as 1,2-*O*,*O*-silyl migration as key steps are being developed. The starting materials for the enzymatic resolution were conveniently prepared by standard methods as shown in Scheme 6 [43]. Thus, repetitive anion generation and trapping with electrophiles in a one-pot manner afforded silylated furyl ketones. These compounds were further reduced and acylated to yield the lipase-catalyzed hydrolysis substrates. Of the enzymatic systems investigated, the highest efficiency was demonstrated by the combination of lipase PS (*Pseudomonas cepacia*, Amano



Scheme 6. (a) n-BuLi; (b) Si-Cl; (c) CF_3CO_2Et; (d) $NaBH_4$; (e) AcOCl, pyr.; (f) lipase PS; (g) NaH, BnBr; (h) O_3; i) CH_2N_2; (j) K_2CO_3/MeOH

Pharmaceutical Co. Ltd., Japan) and acetate. Absolute configuration of the recovered acetate was unambiguously determined as *R* by comparison of its optical rotation after derivatization into the known methyl *O*-benzyl-3,3,3-trifluorolactate **20**.

In the enzymatic resolution using water media it is not easy to separate the product from the enzyme-water system on a large scale. A practical enzymatic resolution of a furanol with a fluoroalkyl group is achieved in organic media. This sequence is used for the large scale production of optically active furanol with a CF_3 group [25].



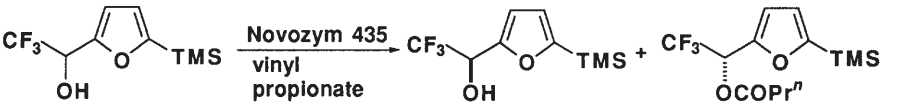
R_F	*Si*	Enzyme	Time (h)	Conv. (%)	Optical purity (% ee) Ester	Alcohol	*E* value
CHF_2	TBS	Novozyme 435	70	36	>99	53	584
CF_3	TMS		114	33	97	46	117
			18	44	98	79	276
			18	49	95	98	129
			24	42	95	61	85
		lipase QL	48	17	-	22	-
		LIPASE	48	50	90	87	61
		lipase PS	144	14	-	-	-
C_2F_5		LIPASE	48	19	98	22	156

(a) Novozyme 435 (*Candida antarctica*, Novo Nordisk Co. Ltd.), lipase QL (*Alcligenes* sp., Meito Sangyo Co. Ltd.), lipase PS (*Pseudomonas cepacia*, Amano Pharmaceutical Co. Ltd.), LIPASE (*Pseudomonas* sp. Toyobo Co. Ltd.)
(b) CH_2ClCH_2Cl was used as a solvent

Initially, kinetic resolutions of 2-(trimethylsilyl)-5-[1′-(2′, 2′, 2′-trifluoro-1′-hydroxy-ethyl)]furan with a wide variety of lipases and vinyl alkanoates were examined in 1,2-dichloroethane. On the basis of these results, the system consisting of an enzyme (Novozym 435, *Candida antarctica*, Novo Nordisk Co. Ltd.) and vinyl propionate was sufficient to obtain optical pure alcohol and ester with a high *E*-value. Moderate effect on the optical purity was observed on changing the organic solvents. Obviously, Novozym 435-CH_2ClCH_2Cl system is the most convenient practical system for obtaining the optically pure alcohol and the ester on the basis of comparison of the reaction time and the *E*-value.

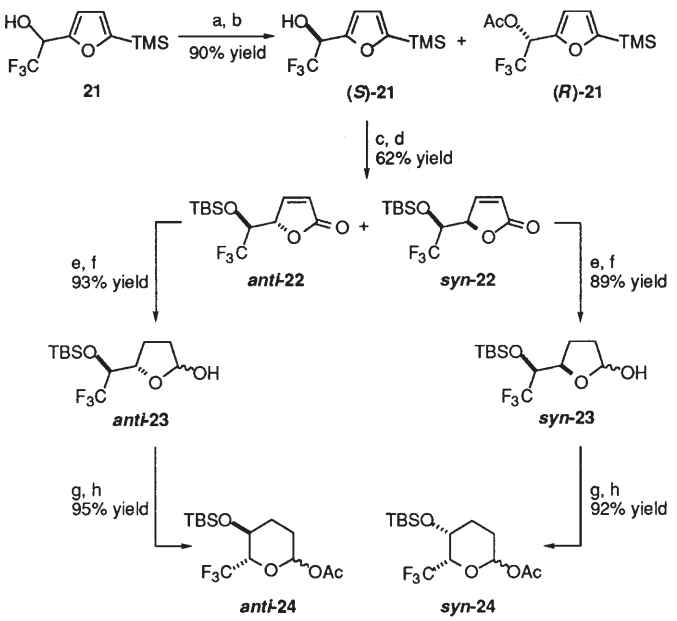
Generally, it was found that a CF_3 group attached to the stereogenetic center improved the optical purity of the enzymatic transesterification relative to CHF_2 or C_2F_5 groups [46].

After optical resolution by lipase, the silylated furanol with a trifluoromethyl group, was converted into the corresponding butenolide by oxidation with magnesium monoperoxyphthalate (MMPP). Ring opening of this butenolide



Organic solvent	Time (h)	Conv. (%)	Optical purity (% ee) Ester	Alcohol	*E* value
CH_2ClCH_2Cl	18	44	98	79	276
CCl_4	26	49	97	92	229
$CHCl_3$	41	48	93	93	72
$CHCl_3$	168	42	>99	72	536
CH_3CN	168	42	>99	72	534
$PhCH_3$	168	33	96	46	74

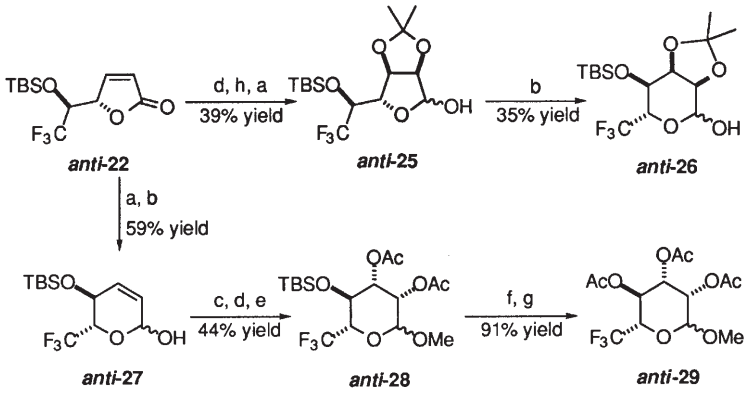
might lead to the formation of the triol, and, considering that the terminal primary hydroxyl group can be selectively protected with groups such as *tert*-butyldimethylsilyl (TBS) or trityl groups, discrimination of the other two hydroxyl functionalities at the 4 and 5 positions was a problem. 6,6,6-Trifluorinated rhodinose and amicetose as target materials were produced from chiral silylated furanol with a CF_3 group.



Scheme 7. Preparation of 6,6,6-Trifluoro Analogs of D-Amicetose and D-Rhodinose. (a) AcCl, pyr.; (b) lipase PS; (c) TBS-Cl, imidazole; (d) MMPP (Magnesium monoperoxyhthalate)/AcOH; (e) Pd/C, H2; (f) DIBALH; (g) KOBu^t; (h) Ac_2O

The preparation of 6,6,6-trifluoro analogs of d-rhamnose and 6-deoxy-d-allose from the same furanol derivatives with a CF_3 group was achieved by the application of the 1,2-*O*,*O*-silyl migration strategy shown in Scheme 8.

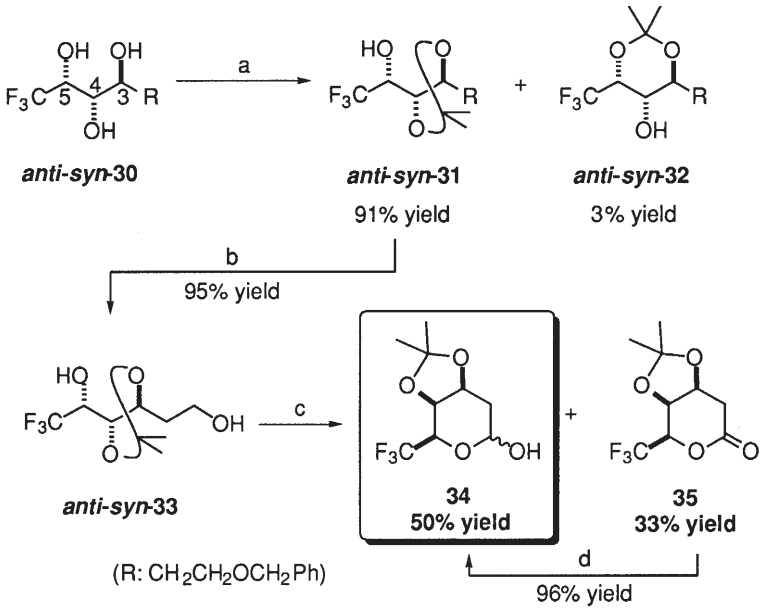
In this type of study, the terminally-CF_3 propargylic alcohol (*S*)- derived from the enzymatic resolution is also a useful intermediate. This material is transformed into the corresponding *E*- and *Z*-allylic alcohols after successful enzymatic optical resolution. OsO_4-catalyzed oxidation eventually led to the formation of the desired triols **30** in a diastereoselective manner.



Scheme 8. Preparation of 6,6,6-Trifluoro Analogs of D-Rhamnose and 6-Deoxy-D-allose. (a) DIBALH; (b) $KOBu^t$; (c) MeOH, H^+; (d) $KMnO_4$, cat. 18-crown-6; (e) Ac_2O, pyr.; (f) TBAF; (g) Ac_2O; (h) $Me_2C(OMe)_2$, H^+

At this stage, compound **30** contained three hydroxyl groups at the 3, 4, and 5 positions with one benzyl group (X = Bn) at the terminus (see the drawing on the right), and the above discussion allowed us to expect the OH functionality at the 5 position to be the least nucleophilic and the most stable of the three as its anionic form. These electrostatic properties would allow the regioselective protection of hydroxyl groups at positions 3 and 4 while leaving the other unprotected. Furthermore, the subsequent deprotection at the terminal would afford a 1,5-diol and the same idea might lead to the conclusion that the hydroxyl group at position 1 would be much more readily oxidized than the one at position 5. If this were the case, then the syntheses of our final products would be possible via a very short reaction course by eliminating the tedious protection-de-protection processes.

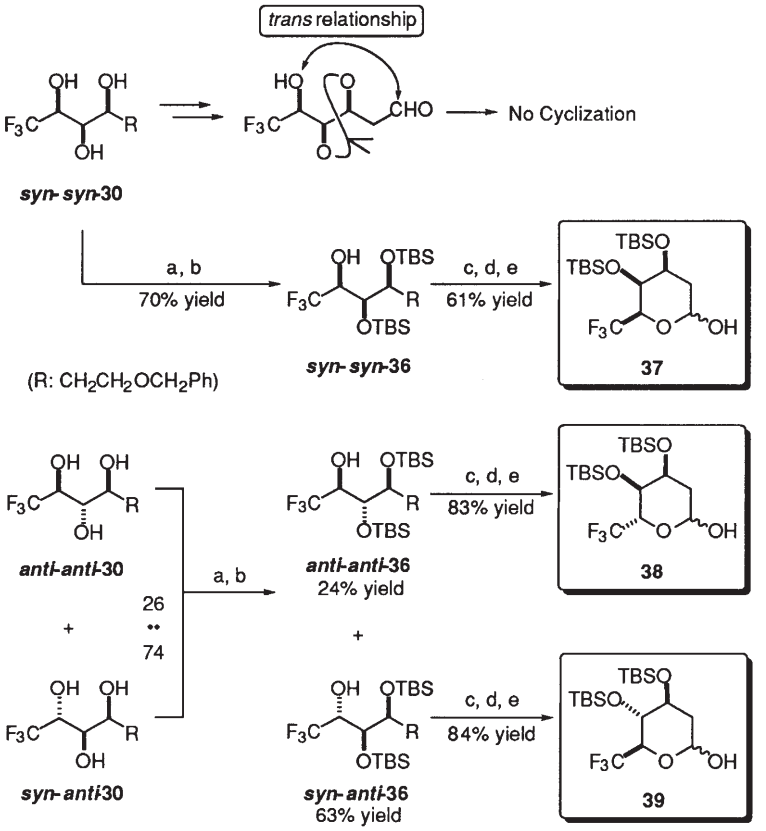
As shown in Scheme 9, when ***anti-syn*-30** was subjected to the usual acetonide formation condition, the corresponding 5- and 6-membered acetonides, ***anti-syn*-31** and ***anti-syn*-32**, respectively, were obtained in a ratio of 91:3 in spite of the steric congestion in the major product by the *syn* relationship of the two substituents, which would be a clear reflection of the above hypothesis. ***Anti-syn*-31**,



Scheme 9. Preparation of 6,6,6-Trifluoro-L-oliose. (a) $Me_2C(OMe)_2$, H^+; (b) Raney Ni, H_2; (c) PDC; (d) DIBALH

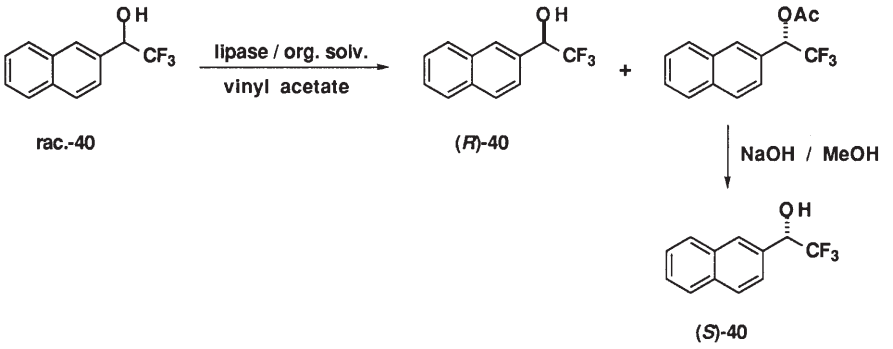
after separation by column chromatography, was de-protected and oxidized with an excess amount of PDC and converted into a mixture of **34** and **35,** the latter was readily transformed into the corresponding lactol **34** in high yield. At this stage, no isomeric product based on the oxidation of an OH group at position 5 was formed. On the other hand, the authors were confronted with the difficulty which called for an alternative route to access the targets because of the failure to utilize the same strategy for the diastereomeric *syn-**syn**-**30** due to the *anti* relationship of the substituents required for pyranose ring formation.

Taking the electrostatic factor into consideration and the above into account, the protective group was changed to a TBS group. In contrast to our expectation, reaction of *syn-**syn**-**30** with 3 equivalents TBS chloride did not lead to complete conversion (22% of mono-silylethers were produced at the same time) nor regio-selection for the synthesis of bis-silylethers, while the latter problem was solved by the subjection of the mixture to the previous 1,2-*O*,*O*-silyl migration condition, affecting the smooth and perfect conversion to the thermodynamically more favorable *syn-**syn**-**36**. Transformation of this product to the 6,6,6-trifluoro-d-boivinose was successfully carried out in a similar way (13% recovery of *syn-**syn**-**36** at the de-protection step) and the target material was obtained in 61% yield from these three steps. In spite of the inseparable nature of ***anti-anti***- and *syn-**anti**-**30**, ready separation after the silylation-silyl migration procedure to the corresponding bis-silylethers ***anti-anti***- and *syn-**anti**-**36** realized the construction of 6,6,6-trifluoro-d-digitoxose and l-olivose, respectively (Scheme 10) [44, 45].



Scheme 10. Preparation of 6,6,6-Trifluorinated Analogs. a) TBS-Cl, imidazole; b) KOBu^t; c) Raney Ni, H_2; d) PDC; e) DIBALH

Gaspar and Guerrero showed a practical route for the synthesis of both enantiomers of β-naphthyl trifluoromethyl carbinol **40** through enzymatic resolution in organic mediaβ [47]. For the enantioselective resolution of alcohol **40**, various commercially available lipases were examined, *i. e.,* lipase AY, lipase AP6, lipase PS, CCL (*Candida cylindracea*) and PPL (porcine pancreatic lipase). Among them, only lipase PS (*Pseudomonas cepacia*) successfully produced chiral β-naphthyl trifluoromethyl carbinol **40** through acylation of the racemic alcohol with vinyl acetate. Further, the effect of organic solvents on the enantioselectivity was examined. Several kinds of solvents were examined with the log P values ranging from –0.23 (acetone) to 6.6 (dodecane). Although good to excellent *E* values were generally obtained, excellent results were achieved with non-polar solvents (hexane, dodecane), yielding in all cases the *S* isomer. However, excellent ee was also obtained in more polar solvents, such as THF or acetone, although they required considerably longer reaction times to achieve ca. 50% conversion. In contrast, no correlation was obtained after plotting E



values vs hydrophobicity (log P), although the acylation rate increased with hydrophobicity of the solvent.

When the approach of chiral auxiliary is used to generate a chiral center in a molecule, enzymatic resolution has become a frequently used methodology for the synthesis of biologically interesting materials with high optically active forms.

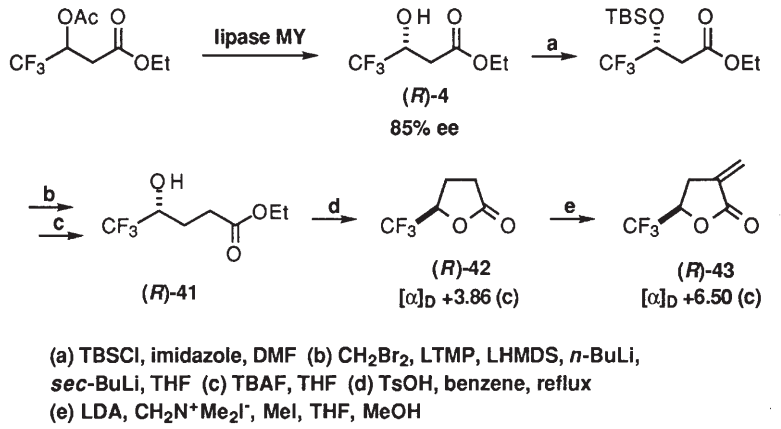
The effect of organic solvents on the lipase PS-mediated acylation of alcohol **40**

Solvent	log P	Time (hr)	Conv. (%)	% ee (*R*)-40	% ee (*S*)-40	*E* value
tetrahydrofuran	0.49	25	7	8	>99	215
		240	51	>99	95	206
acetone	-0.23	25	8	9	99	217
		240	52	>99	91	111
diethyl ether	0.85	25	17	20	96	60
toluene	2.5	25	25	32	96	67
benzene	2.0	25	25	32	98	135
dodecane	6.6	25	41	66	94	64
hexane	3.5	25	42	69	94	67

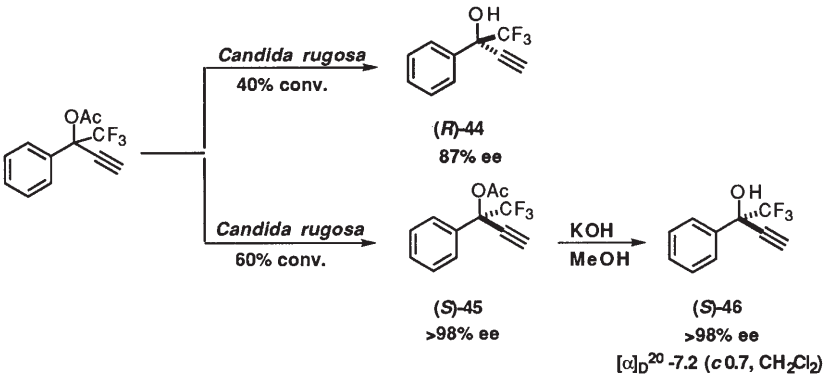
log P values were taken from the literature (Laane, C.; Boeren, S.; Vos, K.; Veeger, C. Biotech. Bioeng. **1987**, *30*, 81)

(*R*)-(+)-Ethyl 4,4,4-trifluoro-3-hydroxybutyrate **4** derived from enzymatic resolution was transformed to (*R*)-(+)-γ-trifluoromethyl-γ-butyrolactone **42** which were elaborated to give the corresponding (*R*)-(+)-γ-trifluoromethyl-α-methylene-γ-butyrolactone **43** [48].

Some other cases in the following scheme will be considered whose starting framework still contains a CF_3 alcohol. (*R*)-γ-Phenyl-γ-(trifluoromethyl)-butyrolactone **50** and (*R*)-1,1,1-trifluoro-2-methoxy-2-phenyl-3,4-epoxybutane **53**



Scheme 11. γ-Trifluoromethyl-α-methylene-γ-butyrolactone

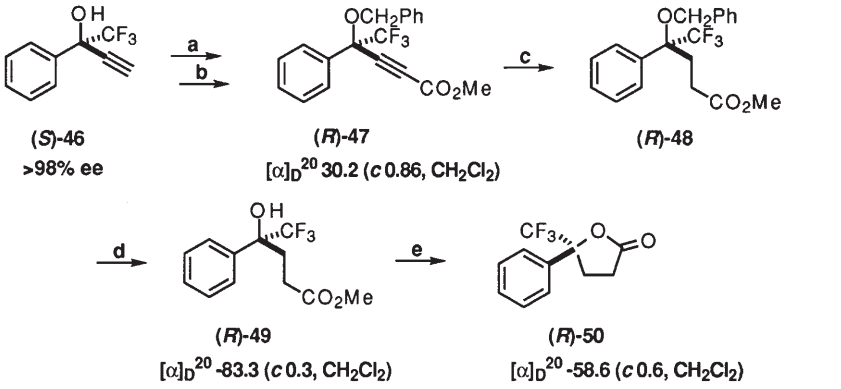


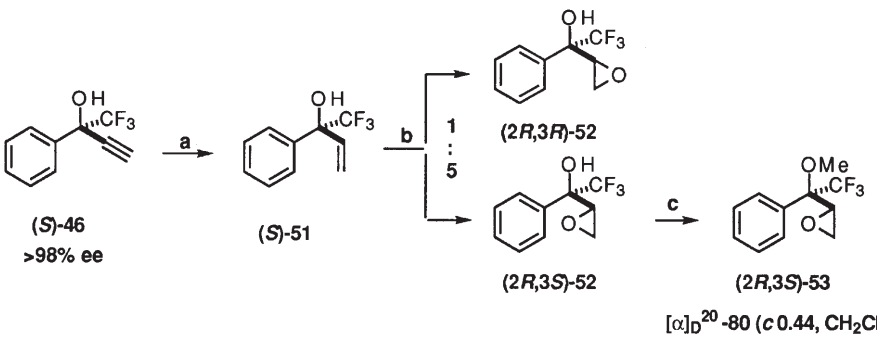
Scheme 12. Synthesis of (*R*)-γ-phenyl-γ-(trifluoromethyl)butyrolactone

have been synthesised in high optically pure form from the tertiary (*S*)-(**45**)-acetate which was resolved using the lipase (from *Candida rugosa*).

In step **b**, Mander's reagent was used to recover (*R*)-**47** after treatment of the intermediate with LDA, followed by methyl chloroformate. Reduction of the acetylene functionality to (*R*)-**48** was proceeded with Adam's catalyst in MeOH under hydrogen. Final cyclization could not be achieved with NaH, although more vigorous reaction conditions using *n*-BuLi gave (*R*)-**50** in moderate yield.

Treatment of (*S*)-**51** with mCPBA resulted in a 5:1 diastereomeric mixture of hydroxy epoxide (2***R***,3***S***)-**52** and (2***R***,3***R***)-**52**. The diastereomer was separated by two recrystallizations, giving the predominant diastereomer (2***R***,3***S***)-**52** whose the relative stereochemistry was confirmed with X-ray structure analysis. The target material (2***R***,3***S***)-**53** was obtained after treatment with NaOHMeI system [49].



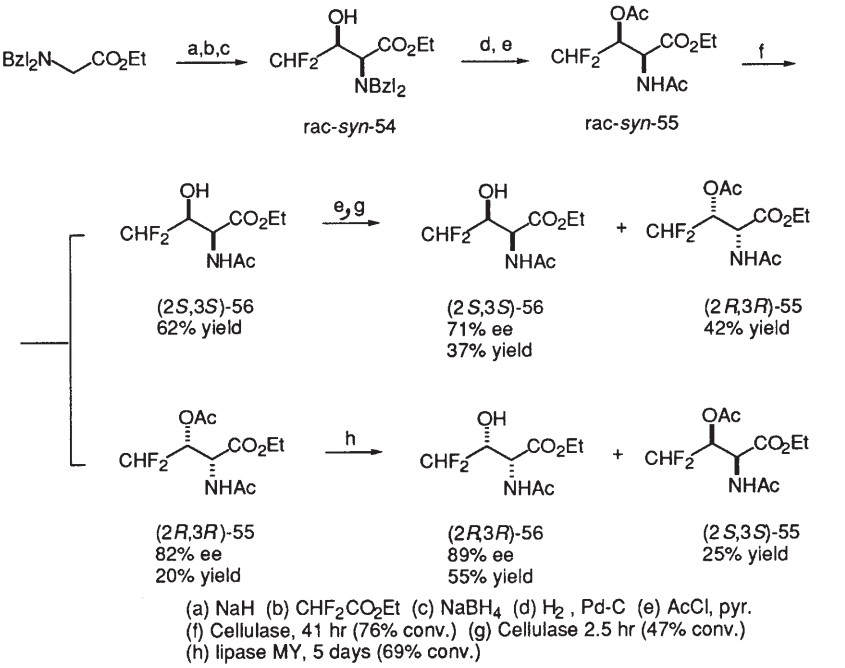


Scheme 13. Synthesis of (2*R*,3*S*)-1,1,1-trifluoro-2-methoxy-2-phenyl-3-4-epoxybutane; (a) Lindlar catalyst, quinoline, H_2, 1 atm; (b) mCPBA, CH_2Cl_2; (c) NaH, Et_2O, DMSO, MeI

4.3 Fluorinated Amino Acids

Since the pioneering work of Kollonitsch and co-workers on the preparation of 3-fluoro-d-alanine-2*d* [50], unnatural fluorinated amino acids have drawn significant attention because they frequently have profound and unexpected results on biological activity. Fluorinated threonines at position 4 (F_n-Thr; n = 1, 2, or 3) have been the focus of special interest, not only because of their potential use in the pharmaceutical field as reported for other fluorinated amino acids, but also because of their versatility as chiral building units with three easily differentiated functional groups.

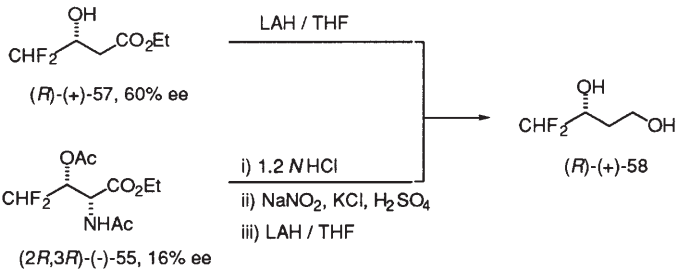
Stereoisomers of 4,4-difluorothreonine [51] were prepared via the synthetic strategy shown in the following scheme. Condensation of ethyl *N*,*N*-diben-



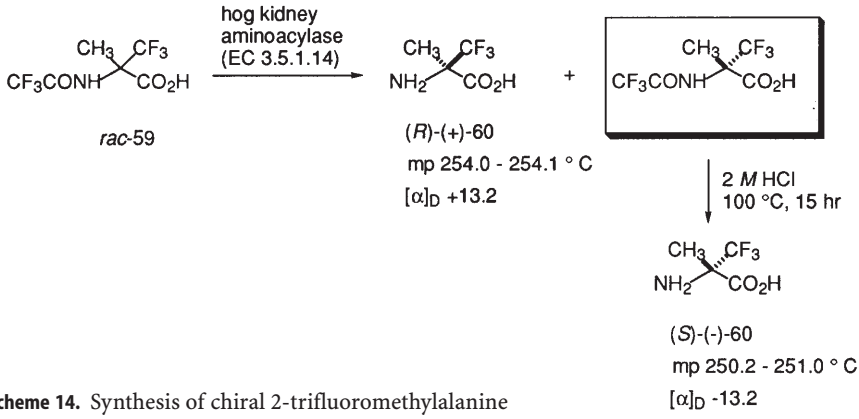
zylglycinate with ethyl difluoroacetate, followed by reduction with $NaBH_4$ yielded racemic **54** with *syn* configuration. No trace of the corresponding *anti* isomer was detected by ^1H, ^{13}C, and ^{19}F NMR spectroscopy. Deprotection of the amino group and acetylation of both amino and hydroxyl moieties furnished the substrate rac-*syn*-**56** for the enzymatic resolution. Cellulase (from *Trichoderma viride*) was found to preferentially transform (2***S***,3***S***)-**56**, with the recovery of enantiomeric (2***R***,3***R***)-**55**. To further enhance the optical purity, these compounds were subjected to the enzymatic process employing cellulase or lipase MY (from *Candida rugosa*) independently to form the enantiomeric *N*-acetylated threoninates. The optically active threonines thus obtained were successfully converted into the free amino acids via usual acidic hydrolysis (7 h reflux in 1.2 *N* HCl).

Absolute stereochemistry was determined by the following chemical correlation. Thus, (2***R***,3***R***)-(-)-**55** was transformed into the diol **58**, whose sign of the optical rotation ($[\alpha]_D^{20}$ +6.68° (*c* 0.61, MeOH) was consistent with that for the same molecule obtained from configuration (*R*)-(+)-**57** ($[\alpha]_D^{20}$ +29.10° (*c* 1.05, MeOH)) [52].

In connection with the relative configurational argument as in reference [52], stereochemistry of the compound preferentially hydrolyzed by cellulase was unambiguously determined as (2***R***,3***R***). On the other hand, the optical purity was determined by the integration of a CH_3O group after derivatization into the corresponding (*R*)-MTPA ester (δ 3.49, q, J=1.2 Hz) for (2***S***,3***S***) isomer (minor) and 3.58 (δ 3.49, q, J=1.3 Hz) for (2***R***,3***R***) isomer.



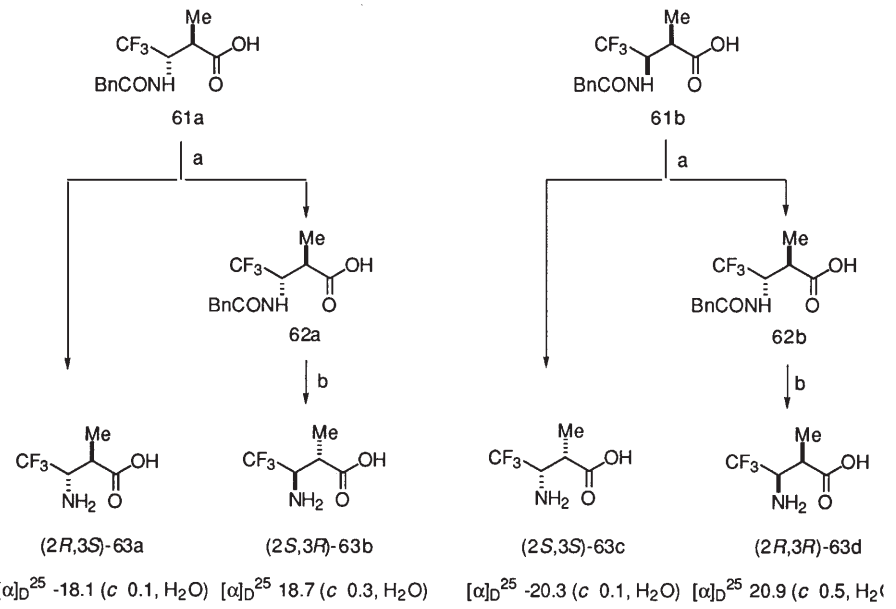
A particularly interesting case is the partial hydrolysis of the racemic *N*-trifluoroacetyl derivative **59** with hog kidney aminoacylase (HKA) (EC 3.5.1.14) to prepare chiral isomers of 2-trifluoromethylalanine **60** [53]. The stereochemical preference of hog kidney aminoacylase is to hydrolyze amino acid amides bearing the larger C-2 substituent in the pro-*S* position [54]. The enzymatic hydrolysis of compound **60** follows this trend.



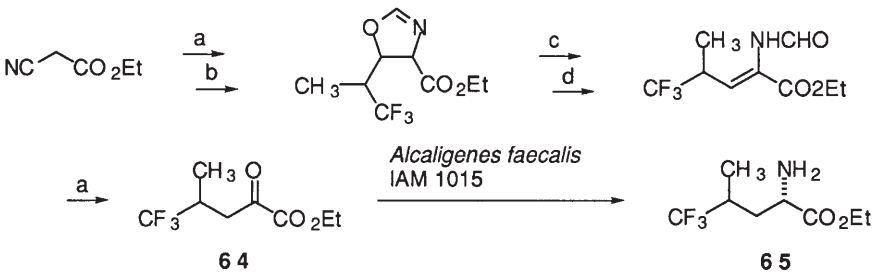
Scheme 14. Synthesis of chiral 2-trifluoromethylalanine

Another interesting example of resolution through formation of diastereomers is the isolation of four stereoisomers of 3-amino-2-methyl-3-trifluoromethyl butanoic acid [55]. In this process, the chemical-enzymatic method by the combination of chemical and enzymatic reaction is a very convenient. At first, *N*-phenylacetyl derivatives **61a** and **61b** were prepared in excellent isolated yields via the Schotten–Baumann procedure. After these materials were hydrolysed with penicillin acylase (EC 3.5.1.11) from *Escherichia coli* until attainment of 50% conversion, enzymatically unconverted *N*-phenylacetyl derivatives **62a** and **62b** (organic layer) and amino acids **63b** and **63d** (aqueous layer) were separated. Acidic hydrolysis of unconverted materials produced other stereoisomers **63a** and **63c** in high optical pure form.

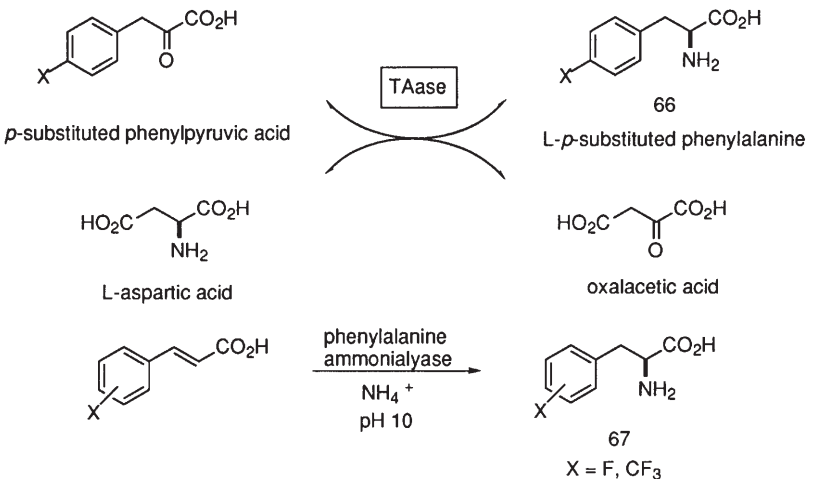
The employment of living organisms, such as transamination and a well-defined oxygenative catabolic pathway, seems to be particularly promising as it has produced the predicted absolute configuration of chiral products starting from fluorinated α-ketocarboxylic acids. For example, *Alcaligenes faecalis* afforded a 1:1 mixture of diastereomer of (2*S*, 4*S*)- and (2*S*, 4*R*)-5,5,5-trifluoroleucine **65** starting from 5,5,5-trifluoro-4-methyl-2-oxopentanoic acid **64**. These diastereomers were isolated after purification by ion exchange chromatography [56]. This procedure was carried out using the resting cells of *Alcaligenes faecalis* IAM 1015 grown in a nutrient medium (50 ml, initial pH 7.0) in a shaking flask at 30 °C.



Scheme 15. Chemico-enzymatic approach to chiral β-trifluoro-β-amino acid. (a) penicillin acylase, pH 7.5, 4–5 h; (b) 6*N*HVl, 70 °C, 12 h



Scheme 16. Enzymatic transamination to γ-5,5,5-trifluoroleucine. (a) LiN(i-Pr)$_2$, $CF_3(CH_3)$CHO, THF, –78 °C, 1 h; (b) H_2O, Et_3N, 100 °C, 1 h; (c) MsCl, Et_3N, 25 °C, 9 h then 40 °C 2 h; (d) 1 N HCl, EtOH, 80 °C, 40 min



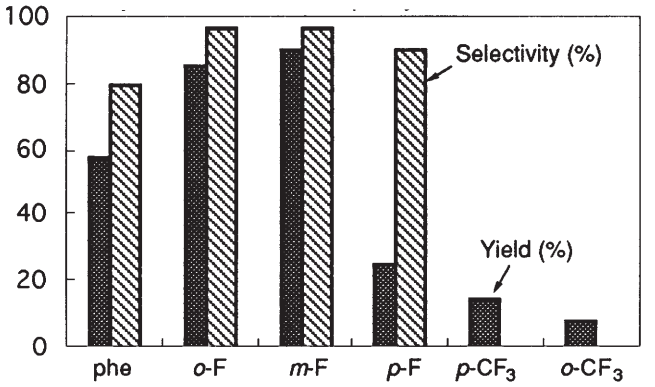
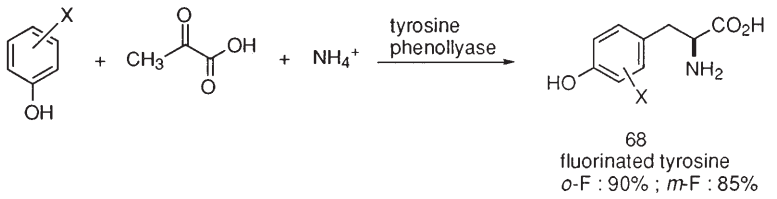


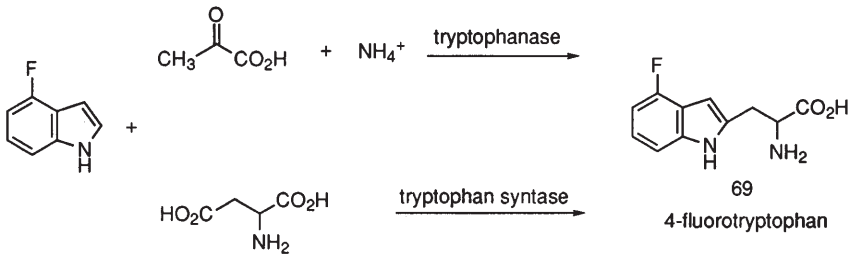
Fig. 7. Synthesis of fluorinated phenylalanine with PAL

In this transamination, the effect of *para* substitient groups has been studied using fluorinated phenylpyruvic acids and L-aspartic acid. From these results, the migratory preference is H > F > Cl > Br > CF_3. This order has been attributed to the bulkiness of the substituted group [57]. Direct amination of *p*-substituted succinic acid with phenylalanine ammonialyase (EC 4.3.1.5) has suggested very high substrate specificity that the order of reaction rate is *m*-F ≧ *o*-F ≫ *p*-F ≫ CF_3.

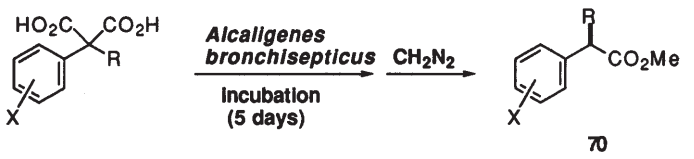
In the microbial transformations, it is possible to use several kinds of synthetase in the case of some materials which have no reaction site modified by fluorine(s). For instance, tyrosine phenollyase (*β*-tyrosinase, EC 4.1.99.2) afforded *o*- or *m*-fluorotyrosine with high yields starting from the corresponding fluorophenol and pyruvic acid-ammonium system, however *p*-fluorophenol did not react in this system [58].



Another interesting microbial condensation reaction was the synthesis of 4-fluoro-tryptophan. One possible approach was the use of tryptophanase (EC 4.1.99.1) in the 4-fluoroindole and pyruvic acid-ammonium salt system, to give 4-fluorotryptophane **69** in 43% yield [59a]. In another route, tryptophan synthase (EC 4.2.1.20) from *E. coli* was used in the 4-fluoroindole and serine to obtain 4-fluorotryptophan **69** in 90% yield [59b].



Furthermore, microbial decarboxylation of α-aryl-α-methylmalonic acids [60] with *Alcaligenes bronchisepticus* proceeds selectively to produce pure (*R*)-α-arylpropionic acid enantiomers **70** as shown in Scheme 17.

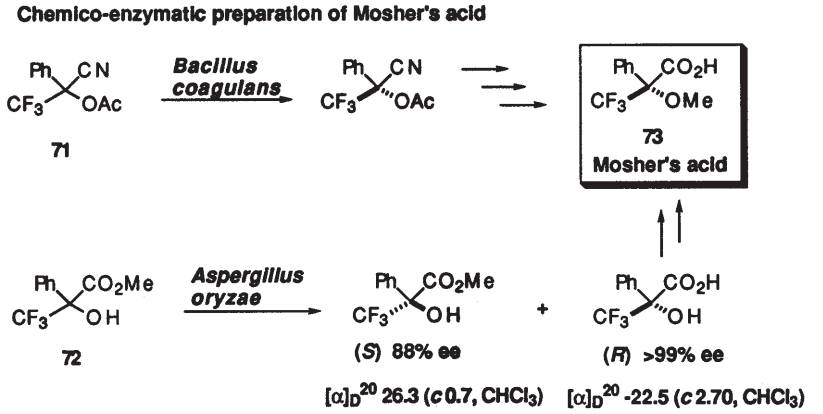


X	R	Yield (%)	Opt. purity (% ee)	X	R	Yield (%)	Opt. purity (% ee)
o-F	Me	12	54	*m*-CF_3	Me	99	95
m-F	Me	75	97	*p*-CF_3	Me	88	97
p-F	F	54	97	H	Me	64	95

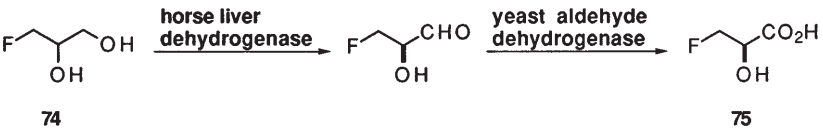
Scheme 17. Microbial decarboxylation of fluorinated malonic acids

5
Useful Reagents and Materials

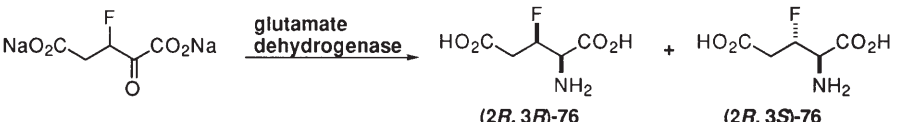
Chiral Mosher's acid **73** is established as a useful reagent for the determination of optical purity and absolute configuration [61–64], and several different approaches for its chemical synthesis have been described. In contrast, two different enzymatic approaches to Mosher's acid have been reported as following, (1) microbial hydrolysis of cyanohydrin acetate **71** with *Bacillus coagutans* leading to a precusor of Mosher's acid [65], and (2) resolution of α-trifluoromethyl mandelic methyl ester **72** with a protease from *Aspergillus oryzae* [66].



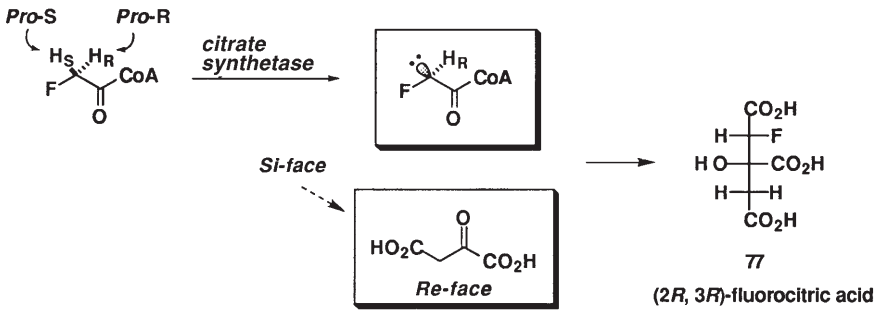
Similarly, horse liver dehydrogenase oxidized 3-fluoro-1,2-propanediol **74** to the aldehyde which further transformed into (*R*)-β-fluorolactic acid **75** with optically pure form by yeast aldehyde dehydrogenase [67, 68].



Transformation using glutamate dehydrogenase is an elegant approach to (2*R*,3*R*)- and (2*R*,3*S*)-3-fluoroglutamic acid **76** [69].



To date, the biosynthesis of fluoroacetic acid and its derivatives, such as fluorocitrate, ω-fluorooleate, and ω-fluoropalmitate, by bacteria and higher plants have been known, and these materials were isolated from plants growing in Africa, South America, and Australia [70–74]. In addition, citrate synthetase is an interesting enzyme to acylate the stereospecific abstraction of the *pro*-S proton from fluoroacetyl-CoA and the nucleophilic attack of the generated anion on the *Si*-face of oxalacetic acid to produce (2***R***,3***R***)-fluorocitric acid **77** [75–78]. (Scheme 18) This process, which produces the (2***R***,3***R***)-stereoisomer (much more toxic than the other possible ones) inhibited the biotransformation (tricarboxylic acid cycle; TCA cycle) with aconitase in mitocondria, is a very useful synthetic method [77–79]. This process is known as the "lethal synthesis" of an anti-metabolite, and is used in the design of enzyme inhibitors modified by fluorine(s).

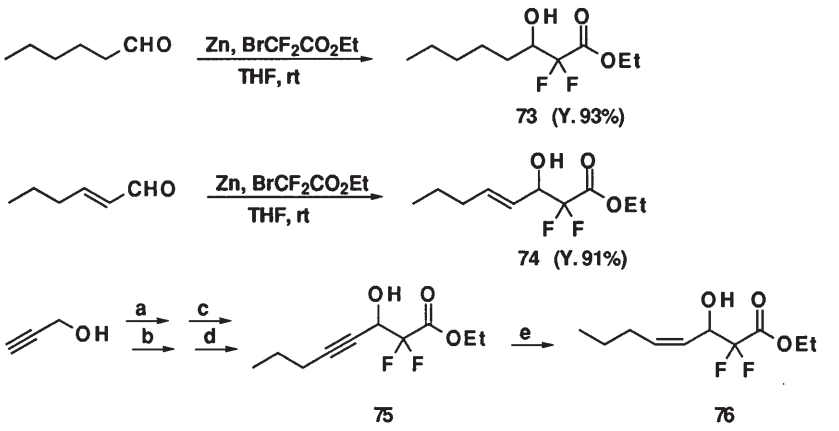


Scheme 18. Biosynthesis of (2*R*, 3*R*)-fluorocitric acid with citrate synthetase

More interestingly, the ability of a microorganism (*Streptomyces cattleya*) can be used to produce a 4-fluorothreonine from inorganic fluoride (KF, NaF) or any one of a number of organofluorine materials *m*- or *p*-fluorophenylalanine, fluoroacetic acid) [80].

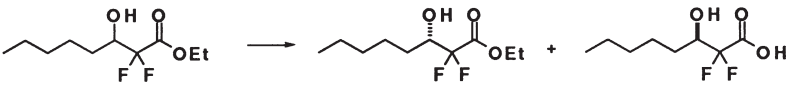
A skeleton of β-hydroxyketone is frequently found in natural products, and simple molecules bearing this framework are widely used as key intermediates in organic synthesis to afford highly functionalized compounds. Such molecules have a relatively acidic methylene moiety and tend to undergo some chemical or biochemical transformations, among which dehydration is observed most frequently. Substitution of the two methylene hydrogens for fluorines would inhibit such reactions because of the difficulty in generating a fluorocarbonated species, and would exert a pronounced influence on the chemical property with no significant effect on the steric bulkiness, leading to the possible unexpected biological properties. Currently, studies of some fluorinated ketones suggest that these molecules are transition-state analogue inhibitors [81]. The enhanced electrophilic nature of the fluorinated ketone carbonyl was expected to facilitate an enzyme-catalyzed addition of the active site, the hydroxy group in serine, forming a stable hemiketal which is a structural mimic of the putative tetrahedral intermediate that forms during the enzymatic cleavage of a peptide substrate.

Based on the recent impressive progress made on asymmetric hydrolysis, the design and bio-transformation of the optically active ethyl 2,2-difluoro-3-hydroxyoctanoate **78** and synthesis of optically active fluorinated [6]-gingerol derivatives are reported [82]. The following criteria were used in the search for a practical route to chiral ethyl 2,2-difluoro-3-hydroxyoctanoate with a high *E*-value: (1) the search of an additive to enhance the enantioselectivity of asymmetric hydrolysis by lipases, and (2) the modification of ethyl 2,2-difluoro-3-hydroxyoctoate. α,α-Difluoro-β-hydroxyesters (**78**), (**79**), (**80**), (**81**) for the enzymatic transformation were prepared by synthetic strategies shown in Scheme 19.



Scheme 19. (a) DHP, TsOH, TsOH/CH_2Cl_2, rt; (b) *n*-BuLi, HMPA, $CH_3CH_2CH_2I$/THF, –78 °C → rt; (c) TsOH/EtOH, reflux; (d) MnO_2/THF: Zn, $BrCF_2CO_2Et$/THF, rt, Y. 39%; (e) Lindlar/hexane, Y. 97%

At first, kinetic resolution of ethyl 2,2-difluoro-3-hydroxyoctoate **78**, with a wide range of lipases were examined under different reaction conditions: (a) enzymatic resolution in water, (b) addition of 1*N* NaOH to a water medium for neutralization, and (c) medium in KH_2PO_4-NaOH, pH 7.0 buffer. Since the *E* value was found to be insufficient for practical resolutions, various additives, such as LiCl, quinidine,18-crown-6,12-crown-4, were examined to increase enantioselectivity of biocatalytic resolution. Unfortunately additives were not effective in enhancing the *E* value. To improve the scope and limitation of lipase-catalyzed asymmetric hydrolysis modification of material was examined at the next stage. By controlling the extent of hydrolysis conversion, either product or unreacted substrate would be obtained with high enantioselectivity. Thus highly enantiomerically enriched ethyl 2,2-difluoro-3-hydroxyoctoate can be prepared by extension of the conversions, while reacted 2,2-difluoro-3-hydroxyoctanoic acid is obtained with high ee values by stopping the reactions at low conversion. Thus, enzymatic hydrolysis of ethyl 2,2-difluoro-3-hydroxyoctanoate **78** (64% conversion) afforded (*S*)-(–)-**78** in 92% ee, while enzymatic hydrolysis of **78**

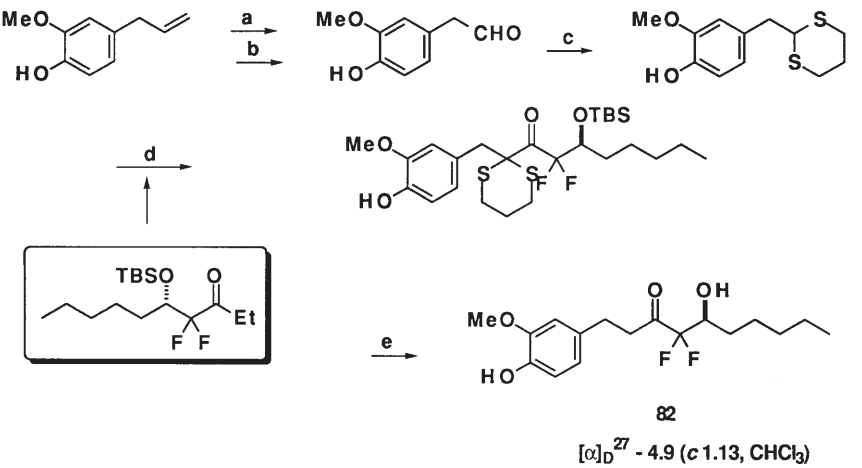


78 (*S*)-(-)-78

Enzyme	Compound[a] no	Method[b]	Time (hr)	Conversion (%)	Optical purity (% ee)	*E* value
olipase/4S	1	A	11	40	55	18
olipase/4S	1	B	4	81	79	3
lipase AK	1	A	8	19	20	15.3
lipase AK	2	A	0.5	39	21	2.3
lipase AK	4	A	2	54	12	1.4
lipase AK	3	A	1	61	61	4
olipase/2S	2	A	1	44	62	24
olipase/2S	4	A	14	13	8	3.6
olipase/2S	3	A	43	39	33	4.3

a) olipase/4S (*Rhizopus japonicus*), lipase AK (*Pseudomonas fluorescens*)
b) Method A: 0.1 *M* H_2O, 6000 unit/mmol, 30 °C; Method B: 0.1 *M* H_2O, 6000 unit/mmol, 30 °C, added 1 *N* NaOH to neutralize acid

(36% conversion)and the following recrystalization from diethyl ether-ethyl acetate afforded (*R*)-(+)-**78** in 81% ee. The enantiomeric purity was determined by gas chromatography after conversion of the (*R*)-(+)- and (*S*)-(–)-ethyl 2,2-difluoro-3-hydroxyoctanate **78** to their diastereomeric ester by optically active PPPA (perfluoropropoxypropionic acid).



82

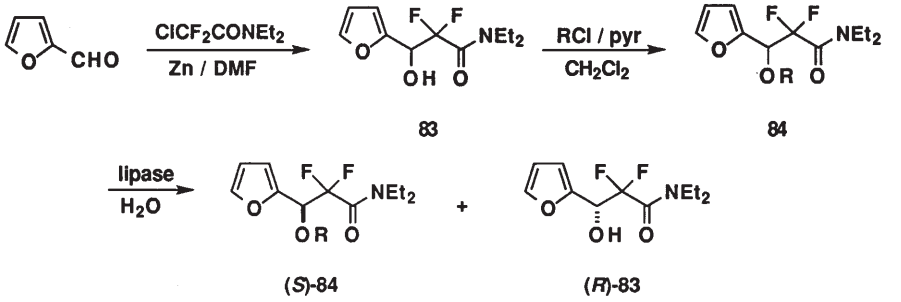
$[\alpha]_D^{27}$ - 4.9 (*c* 1.13, $CHCl_3$)

(a) O_3 / MeOH-CH_2Cl_2 (2:1), -78 °C (b) Me_2S, rt: Y. 86% (86%) (c) $HS(CH_2)_3SH$, $BF_3 \cdot Et_2O$ / THF, 0 °C: Y. 81% (81%) (d) n-BuLi / THF, -78 °C: Y. 65% (49%) (e) Raney Ni / EtOH, reflux: Y. 95% (49%) (f) $Bu_4N^+F^-$ / THF, rt: Y. 80% (80%); yield in parentheses is a case of enantiomer: $[\alpha]_D^{24}$ + 4.4 (*c* 1.54, $CHCl_3$)

Scheme 20. Total synthesis of difluorinated [6]-gingerol

It was also possible to synthesize optically active difluorogingerol starting from (*S*)-(−)-ethyl 2,2-difluoro-3-hydroxyoctanoate (**78**, 92% ee) and the corresponding (*R*)-isomer (**78**, 81% ee). Both enantiomers were first protected with chloro *t*-butyldimethylsilyl and imidazole, giving silyl ether. On the other hand, unprotected eugenol was converted into the corresponding aldehyde by ozonolysis in MeOH-CH_2Cl_2 solution followed by reductive treatment with Me_2S. The thioacetal compound was derived from the aldehyde with 1,3-propylilditiol and borane trifluoride diethyl ether complex. The gingerol skeleton was obtained by the coupling of lithium thioacetal and silyl ether. Finally, [6]-2,2-difluorogingerol **82** was synthesized from the coupling compound by carrying out reductive desulfidation with raney nickel followed by desilylation with tetrabutylammonium fluoride.

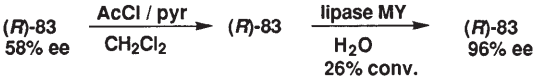
Malic acid is also an important intermediate of the tricarboxylic acid cycle and is found in a wide variety of organisms. The incorporation of two fluorine atoms into the methylene group would exert a pronounced influence on its chemical property with no significant effect on its geometry. Such a compound is potentially useful as a probe in the study of the tricarboxylic acid cycle and also can be used as chiral building blocks for the synthesis of highly functionalized *gem*-difluorinated compounds [83]. The facile synthesis of chiral *β*, *β*-difluoromalic acid **85** via enzymatic resolution was carried out by the following route. At first, the kinetic resolution of various acylated compounds **83** with lipase MY (*Candida rugosa*) and lipase PS (*Pseudomonas cepacia*) was examined as shown in Table. When the substrate **84a** was hydrolyzed with lipase MY, both (*S*)-**84** and (*R*)-**83** were obtained in the highest optical purities, which were

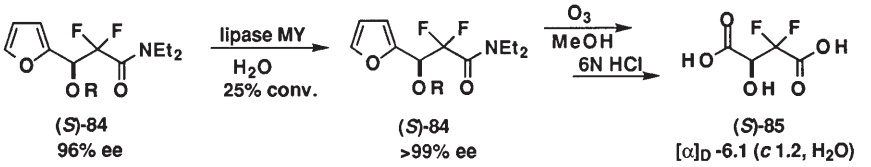


further enhanced by repeating procedures as follows. Reacetylation of (*R*)-**83** provided (*R*)-**84**, which was again treated with lipase MY (26% conversion) to give (*R*)-**83** in 96% ee, while additional enzymic hydrolysis (25% conversion) of (*S*)-**84a** afforded (*S*)-**84a** in >99% ee. Ozonolysis of (*S*)-**84a** followed by acid hydrolysis gave (*S*)-*β*, *β*-difluoro-malic acid **85** in 64% yield [84].

In the next stage the introduction of a fluorine atom onto the chiral center was examined with some 2-fluoro-2-alkyl malonic acid diesters with lipases. When the hydrolysis of 2-fluoro-2-methyl malonic aicd diester was examined with pig

Substrate	R	lipase	time (hr)	conv. (%)	optical purity(% ee) (*S*)-84	(*R*)-83
84a	COMe	MY	5	61	96	58
84a	COMe	PS	8	26	20	53
84b	COEt	MY	2	95	4	-
84b	COEt	PS	15	55	65	55
84c	COPr^i	MY	2	55	20	17
84c	COPr^i	PS	24	0	-	-



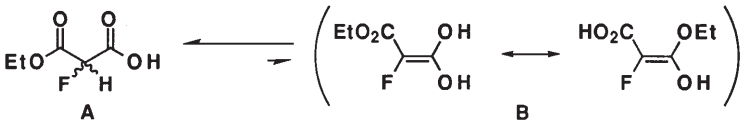


$$RCF(CO_2Et)_2 \xrightarrow[\text{40-41 °C}\\ \text{buffer sol.}]{\text{hydrolase}} RCF(CO_2Et)CO_2H$$

R	origin of hydrolase	yield (%)	$[\alpha]_D$ MeOH	optical purity (% ee)
H	*Candida rugosa*	79	(+)	82
	Trichoderma viride	73	(+)	38
Me	*Candida rugosa*	87	(-)	91
	Trichoderma viride	42	(+)	56
Et	*Candida rugosa*	87	(-)	93
	Trichoderma viride	-		-
n-Pr	*Candida rugosa*	30	(-)	33
n-Bu	*Candida rugosa*	78	(-)	11

liver esterase (PLE), the optically active (–)-2-fluoro-2-methyl malonic acid monomethyl ester (16% ee) or monoethyl ester (24% ee) were obtained. Since the optical purity is insufficient as a practical chiral synthon, a wide variety of lipases or cellulases were examined to search for practical routes to monofluorinated chiral synthons with high optical purity. The asymmetric hydrolysis by lipase MY (*Candida rugosa*) proceeded smoothly to afford the (*S*)-(–)- 2-fluoro-2-methyl malonic aicd monoethyl ester **86** and by cellulase (*Trichoderma viride*) to afford the enantiomic (*R*)-(+)-**86** [85]. However, in the case of 2-fluoromalonic acid monoethyl ester **87**, only the (+)-**87** was formed. Surprisingly, it is possible to

isolate chiral material **87**. This result clearly suggests the great advantage of the fluorine atom to obviate racemization under these condition. The isolation of material **87** suggests the very important fact in fluorinated compounds that the structure **B** is unstable because of the $2p$-$2p\,\pi$ electron repulsion between the lone pair of fluorine atom and carbon-carbon double bond.



It is of particular interest to compare fluorine with other halogens or alkyl groups in order to confirm that fluorine mimics hydrogen. Comparison of the fluorine atom with the methyl group clearly indicates that the difference in van der Waals radii is an important factor in this lipase system.

Mimic effect of fluorine atom at the 2-position

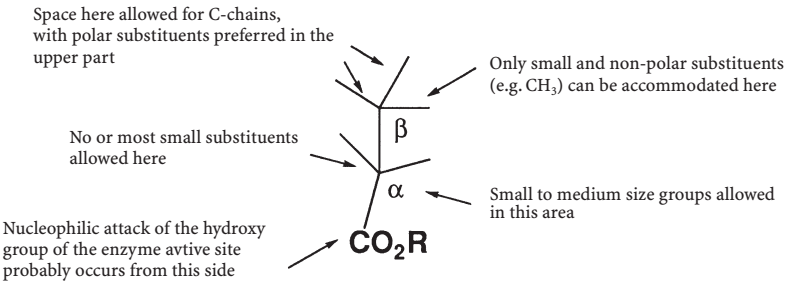
$$MeCX(CO_2Et)_2 \xrightarrow[\text{40-41 °C}]{\text{lipase MY}} MeCX(CO_2Et)CO_2H$$

X	yield (%)	optical purity (% ee)
H	83	a
F	60	91
Cl		no reaction
Br		no reaction
CH_3		no reaction

a) Cannot be determined because of racemization

The general rule based on the study of stereoselective hydrolysis of symmetrical diesters with pig liver esterase (PLE) by Tamm also predicts formation of the *S* enantiomer [86].

A study of stereoselective hydrolysis of symmetrical diesters with pig liver esterase



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Building Block Approaches to Aliphatic Organofluorine Compounds

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This review deals with general and significant developments in the area of building block chemistry of lightly-fluorinated aliphatic compounds, that is, those that contain one, two, or three, fluorine atoms. For the purposes of the review, building blocks are small readily-available materials that already contain fluorine atoms. They are classified according to the number of carbon atoms supplied to the target molecule, rather than according to the number of fluorine atoms. Finally, certain fluorinated motifs which may be generated easily, and are then transformable in useful ways, are discussed.

Keywords: Organofluorine; building blocks; synthesis; fluoroaliphatic; methodology.

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List of Abbreviations

acac	acetylacetonyl
AIBN	azo*iso*bisbutyronitrile
DAST	diethylaminosulfur trifluoride
dba	dibenylidineacetonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAl-H	di*iso*butylaluminium hydride
DMAD	dimethylacetylenedicarboxylate
DMDO	dimethyl dioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
ee	enantiomeric excess
HMPA	hexamethylphosphoric triamide
HOAc	ethanoic acid
LDA	lithium di*iso*propylamide
LiHMDS	lithium hexamethyldisilazide
*m*CPBA	*meta*-chloroperoxybenzoic acid
MsCl	methanesulfonyl chloride
PDC	pyridinium dichromate

PMP	*para*-methoxyphenyl
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrogensulfate
TBHP	*tert*-butyl hydroperoxide
TEBAB	tetrabenzylammonium bromide
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMP	2,4,6-trimethylphenyl
Tol	*para*-toluenesulfonyl

1 Introduction

The chemistry of fluorinated building blocks involves methods for the construction of fluorine-containing target molecules from fluorine-containing starting materials by carbon-carbon bond formation to the fluorinated fragment. Ideally, the fluorinated building block should be easy to handle and relatively readily available. This could mean that the material is available commercially, or can be synthesised from such a compound via a short reaction sequence.

If we can begin to systematise the current literature into synthetic equivalents of various synthons, and if we can identify methods corresponding to various retrosynthetic transforms, then synthetic analyses, and therefore route selection, should be facilitated. In addition, we should also be able to identify areas where new knowledge and methodology is required. This review will attempt to initiate this process of systematisation so the chemistry will be classified according to building block size. Reactions arising directly from these uses will be discussed as they arise, but more general reactions and transformations will be covered in Sect. 7 which deals with elaboration and transformation of readily available fluorinated motifs.

Clearly, there are thousands of reactions of fluorinated building blocks mentioned in the literature; this reviewer has concentrated on reactions which show generality, or solve important problems, so the review is highly selective rather than exhaustive.

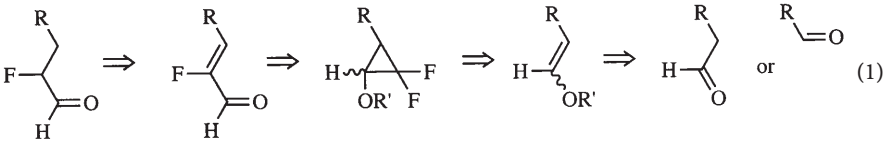
2 One-Carbon Fluorinated Building Blocks

2.1 Fluorohalomethanes as Carbene Precursors

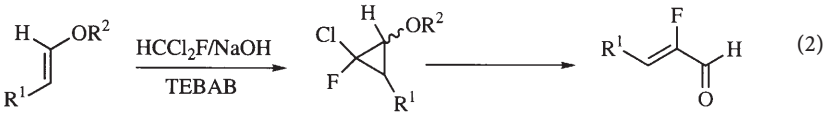
This is an extensive area, reviewed recently with great scholarship by Brahms and Dailey [1]. The relatively high acidity of fluorohalomethanes affords access

to conjugate bases from which α-elimination of halide occurs relatively rapidly; the halocarbenes that result add to a variety of alkenes to afford fluorinated cyclopropanes, which have some interesting chemistry.

The classic method for the addition of a monofluorinated carbon atom involves the reaction shown in Eq. (1), which uses Freon-21 as the building block; for other methods (of which there are many), see [1]. Chlorofluorocarbene reacts efficiently with electron-rich alkenes such as enol ethers, and the alkoxycyclopropane products undergo extremely valuable solvolysis reactions leading to high yields of α-fluoro-*Z*-enals [2]. This approach has been used in elegant biomimetic cascade syntheses of steroid analogues by the Johnson group [3–6], and the chemistry of the enal products has also been reviewed [7]. Single or double fluoro-homologation of aldehydes is thus enabled by the sequence shown in Eq. (2).

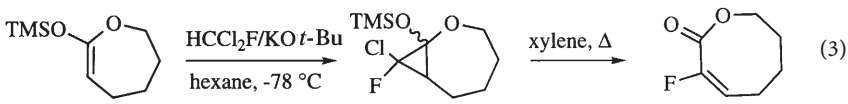


(1)

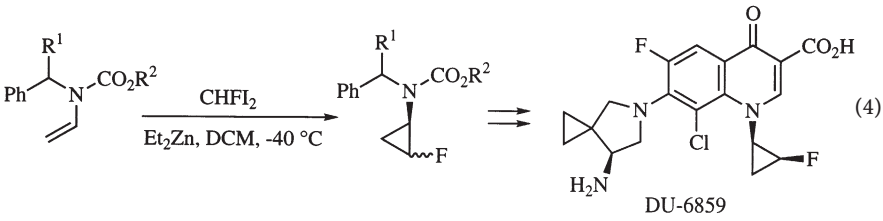


(2)

In related chemistry (Eq. 3), the chlorofluorocyclopropanes derived from medium-ring lactones underwent ring opening to the α-fluoroenolides in refluxing xylene [8]. Reductive dehalogenation of the products has been achieved in a number of different ways [9], affording adducts of fluorocarbene addition and the general chemistry of dihalocyclopropanes has been reviewed [10]. More recently, the Simmons-Smith reaction was used for the direct fluoromethylenation of alkenes in an asymmetric synthesis of antibiotic DU-6859 (Eq. 4) [11, 12].



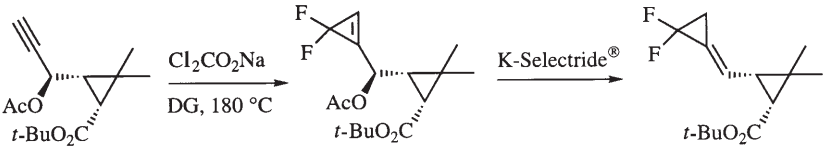
(3)



(4)

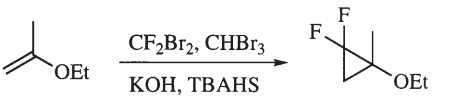
The scope of this reaction remains to be seen but the fluorine atom appeared to exert a significant effect upon the stereochemical outcome of the reaction (under carefully optimised conditions).

The literature concerning difluorocyclopropanes is much more extensive. The most reliable and reproducible protocol is the classical thermolysis of sodium chlorodifluoroacetate in diglyme. The building block in this case is chlorodifluoroacetic acid, an inexpensive material which is converted to the sodium salt using a simple procedure. Even relatively sensitive alkene substrates have been converted to cyclopropanes using this method. For example, a difluorocyclopropene product was obtained successfully from a propargylic acetate using the thermolysis method (Eq. 5). Conjugate reduction of the reaction product with K-selectride afforded a difluorocyclopropylidene [13].



(5)

Methylene difluorocyclopropanes are relatively rare and their rearrangement chemistry has been reviewed recently [14]. In addition, electron deficient alkenes such as sesquiterpenoid methylene lactones may be competent substrates. Two crystal structures of compounds prepared in this way were reported recently [15, 16]. Other relatively recent methods use dibromodifluoromethane, a relatively inexpensive and liquid precursor. Dolbier and co-workers described a simple zinc-mediated protocol [17], while Balcerzak and Jonczyk described a useful reproducible phase transfer catalysed procedure (Eq. 6) using bromoform and dibromodifluoromethane [18]. The only problem here appears to be in separating cyclopropane products from alkene starting material (the authors recommend titration with bromine which is not particularly amenable for small scale use). Schlosser and co-workers have also described a mild ylide-based approach using dibromodifluoromethane [19] which reacts particularly well with highly nucleophilic alkenes such as enol ethers [20], and remarkably, with alkynes [21] to afford labile difluorocyclopropenes (Eq. 7).



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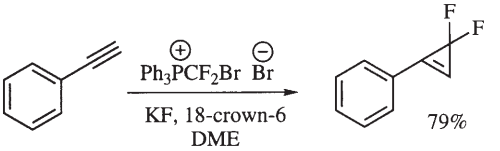
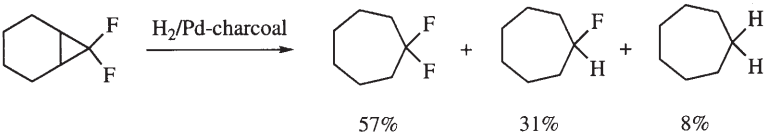


(7)

Even this very general method failed with 1,2-diarylcyclopropene substrates [22]. With less reactive alkenes, the chlorodifluoroacetate thermolysis is the method of choice though care must be taken if the products are volatile because of the potential difficulty of separating them from diglyme. Both the substrate and products must be thermally stable and the precursor may be required in a sacrificial stoichiometry. Conceptually different developments in difluorocyclopropane chemistry have emerged recently from the Taguchi group in Tokyo; these will be reported later in Sect. 5.2.

Cyclopropane ring opening reactions are useful for the synthesis of acyclic mono- and *gem*-difluoro compounds. As there are relatively few rational methods for the formation of cyclic difluoroalkane derivatives via the building block approach, efficient cyclopropane ring expansion chemistry would be extremely valuable. Catalytic hydrogenolysis of difluorocyclopropanes over a Pd/charcoal catalyst proceeds via predominant cleavage of the distal bond to afford mixtures of di-, mono- and des-fluoro ring expansion products (Eq. 8). Defluorination occurred to a lesser extent when a rhodium catalyst was used [23]. Kobayashi and co-workers described a ring opening reaction initiated by ester hydrolysis, though C-F bond heterolysis and cationic ring opening, leading to the formation of monofluoro products, competed under the polar reaction conditions (Eq. 9) [24]. Vinyl cyclopropane rearrangements appear to receive little or no advantage from the distal bond weakening effect exerted by the CF_2 centre [25, 26]. However, a facile divinyl cyclopropane rearrangement was described as a key step in the synthesis of an analogue of a marine Brown algae sex attractant Dictyopterene B [27] (Eq. 10).



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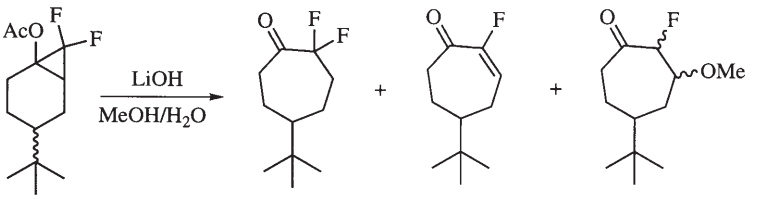

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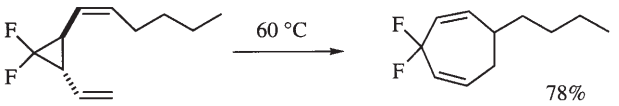


(10)

Other ring opening reactions were achieved under carbanionic conditions leading to stereocontrolled formation of fluorinated dienes [28–30]. One area which appears to be underexploited concerns free radical ring opening and subsequent trapping, though some mechanistic information is available [31].

2.2 Fluorohalomethanes as Electrophiles

Many of these reactions also involve carbene intermediates [32] but they are treated separately because their synthetic equivalence is different. The chemistry described in this section allows the disconnection of targets to carbon nucleophiles and one-carbon fluorinated electrophiles.

Electrophilic fluoromethylation is not a synthetic procedure used widely though dibromofluoromethylation of phosphorus nucleophiles has some important applications in fluorophosphonate chemistry (Sect. 2.3.2).

However, difluoromethylation occurs when nucleophiles intercept difluorocarbene generated under basic conditions, providing a route to difluoromethylethers of phenols [33] and thiophenols [34]. The reaction with phosphite anion leads to the corresponding difluoromethyl phosphonate (see Sect. 2.3.2) while nucleophilic carbanions such as alkynes [35] also undergo formal alkylation, as do malonates [36, 37]. An *N*-difluoromethylaziridine was reported in a reaction with a glycine imine [38]. The scope of the established chemistry is summarised in Fig. 1. Bromodifluoromethylation occurs with a similar range of nucleophiles [39, 40], and also with carbonyl-stabilised carbanions such as malonates [41, 42].

Figure 2 represents both alkylation reactions mechanistically. More recently, reactive enolates were bromodifluoromethylated successfully via difluorocarbene formed in situ. [43, 44]. The reaction solvent was critical for the outcome of the reaction (Eq. 11).

In particular, it was essential that traces of diisopropylamine were removed in vacuo before the addition of monoglyme, followed by the halofluoromethane.

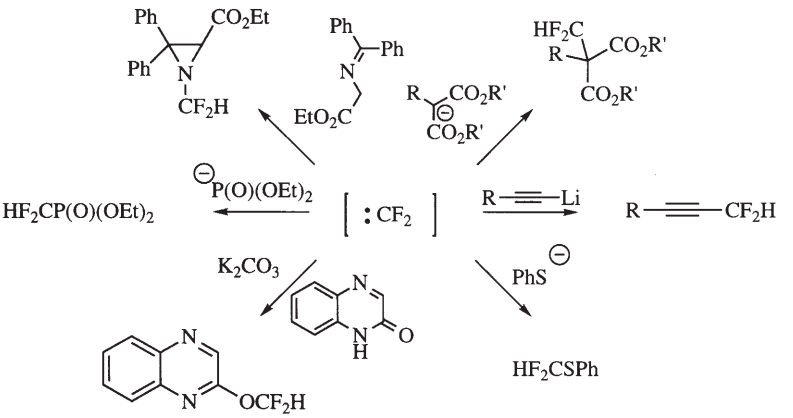


Fig. 1. Difluoromethylation by nucleophilic trapping of difluorocarbene in situ

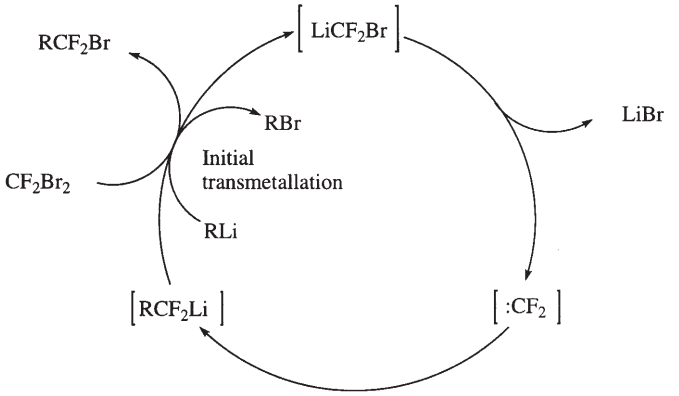
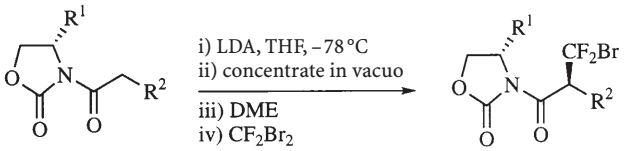
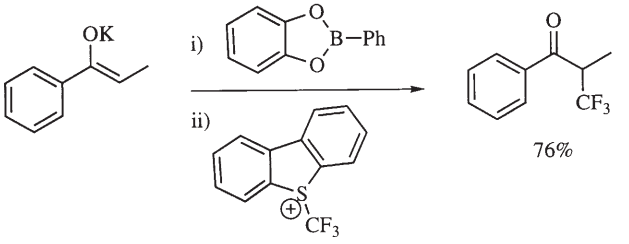


Fig. 2. Bromodifluoromethylation of an organolithium species



(11)

This result may have particularly general and important implications, and is an extremely useful link with asymmetric methodologies. Umemoto [45] has reviewed many elegant examples of electrophilic trifluoromethylation reactions. A range of nucleophilic substrates has been transformed including boron enolates of ketones (Eq. 12) [46]; a particularly appealing feature of the chemistry is the variable reactivity which can be tuned by varying the heterocyclic leaving group.



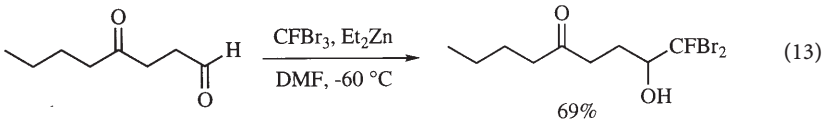
(12)

The main challenge in this approach lies in the synthesis of the electrophilic reagent, and indeed in understanding the mechanism, which shows some most unusual characteristics [47], and therefore the operating limits of the trifluoromethylation reaction. Chemistry in this area is developing rapidly and further significant progress may be anticipated.

2.3
Fluoromethane-derived Nucleophiles and Free Radicals

2.3.1
Unstabilised Species

Organometallic reagents derived from highly fluorinated species are described elsewhere in the literature [48] and in this volume so this section will concentrate on a selection of recent examples. Both organolithium [49, 50] and organozinc [51] reagents derived from fluorotribromomethane have been described. In the former case, the reagent must be generated at very low temperature (–130 °C) under trapping conditions, while the more recent procedure, involving halogen metal exchange with diethylzinc, operates at a more convenient higher temperature (–60 °C) and shows good chemoselectivity (Eq. 13). Dibromodifluoromethane undergoes addition to electron-deficient and electron-rich alkenes in the presence of a $CrCl_3$/Fe system, presumably via a free radical mechanism [52]. A similar addition was described by Elsheimer and co-workers [53] though a CuCl/ethanolamine system was used in this case (Eq. 14), leading to the formation of a promising γ,γ-difluoroallylsilane (Sect. 4.3).



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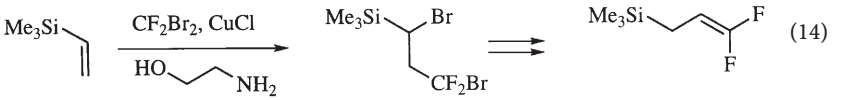
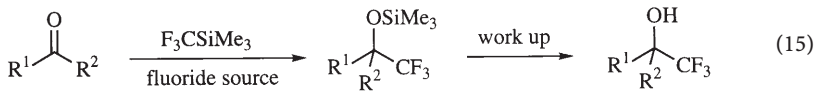


(14)

A most useful recent development in trifluoromethylation concerns Rupperts reagent (trifluoromethyl trimethylsilane) [54, 55] which adds smoothly to carbonyl derivatives under fluoride ion mediation. The reagent is available commercially, and an Organic Syntheses procedure from bromotrifluoromethane has been published [56] in which the scope of the chemistry of this useful reagent has been reviewed. Most of the examples deal with additions to ketones (shown generally in Eq. 15), though lactones and oxazolidinones have been deployed in syntheses of sugar analogues [57, 58] and α-amino trifluoromethylketones [59].



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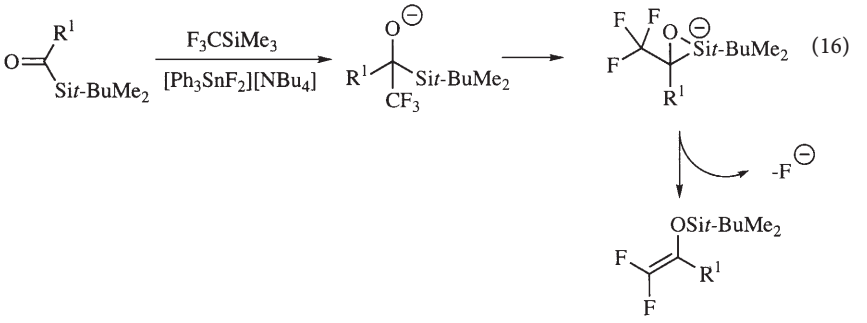


(16)

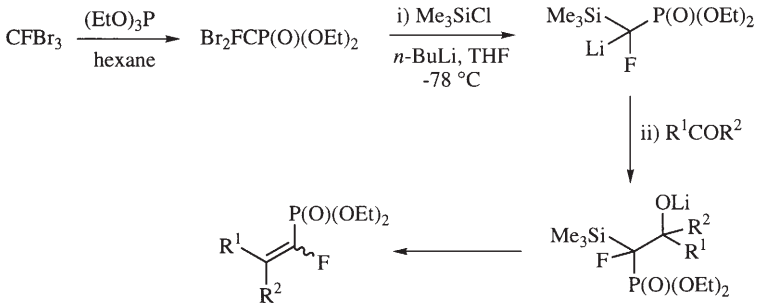
Recently, analogues of nucleosides [60], natural products Huperzine-A [61] and Hydroartemisinin [62], and inhibitors of metallo-β-lactamases have been synthesised [63]. With acylsilane electrophiles, the initial adducts undergo Brook rearrangement which is interrupted by C-Si bond fission with loss of fluoride anion (Eq. 16), leading to the formation of extremely useful difluoroenol silanes [64]. Of the various fluoride sources employed, the tetrabutylammonium triphenyldifluorostannate described by Gingras appears to be particularly effective. The numerous other methods for trifluoromethylation formed the subject of an exhaustive review [65]. More recently, the Olah group described a chlorodifluoromethyl trimethylsilane which is expected to have a rich chemistry [66].

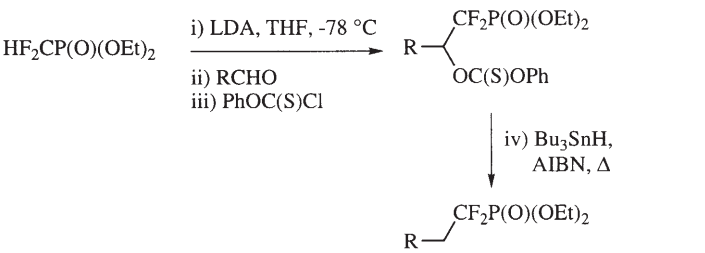
2.3.2 *Stabilised Species*

Mono- and di-fluoromethylphosphonates and sulfones are well known and have been deployed in a number of strategic roles.

The phosphonates are of interest as reagents for the synthesis of difluoroalkenes, and as building blocks for the synthesis of analogues or chemical mimics of important phosphate esters. The chemistry was reviewed recently [67] but there have been significant developments which are summarised here. The Savignac group has described (in full) [68] the sequence shown in Eq. 17. The key step is the in situ silylation of the first-formed lithiophosphonate; this manoeuvre solves many of the problems encountered earlier with monofluorophosphonates. Similar methodology was employed in the synthesis of a glycerol phosphate analogue, in which the key reaction was an alkylation of the intermediate carbanion [69] using a reactive alkyl triflate electrophile.

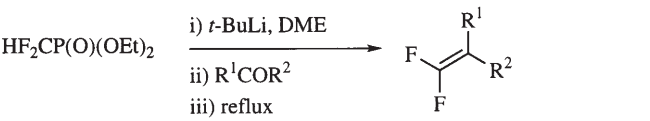
The literature dealing with difluoromethylphosphonates is considerably more extensive; The well-known lithiophosphonate adds to (hard) electrophiles such as aldehydes to afford alcohol products which can be deoxygenated (Eq. 18) affording the products of formal alkylation [70]. This method has been utilised in total syntheses of Phospholipase C inhibitors [71], phosophoserine [72] and nucleotide 5′-deoxy-5′-difluoromethylphosphonate analogues [73]. Direct alkylation is also possible though restricted to highly reactive primary





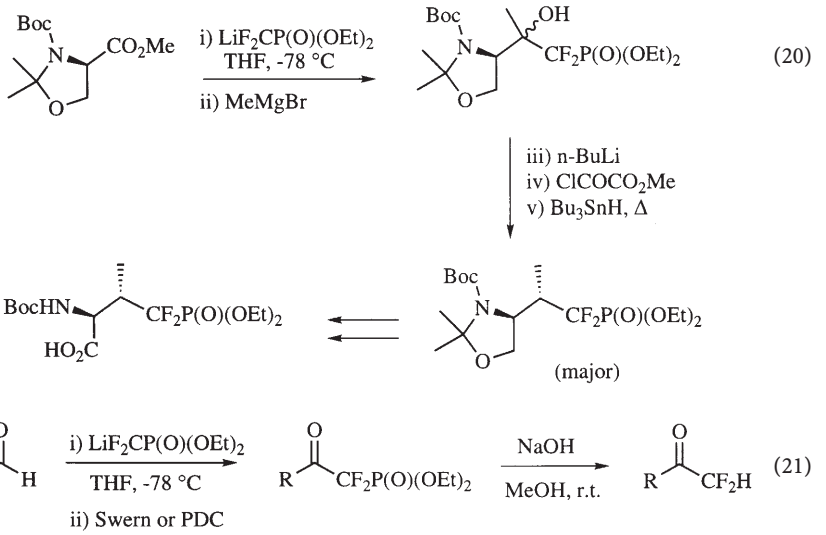
alkyl triflates [74]. The alternative use of the lithiophosphonate is in difluoroalkene synthesis, following elimination of dialkylphosphate monoanion. Piettre and Cabanas [75] attempted to optimise this reaction, in view of the notoriously low reproducibility of the original (preliminary) publication in this area. A more reliable protocol is represented in Eq. 19.

The lithiophosphonate adds to carboxylic esters to afford ketophosphonates, which were trapped with Grignard reagents in situ [76]. Free radical reduction of the tertiary alcohol adducts afforded the products of formal secondary alkylation (Eq. 20) [76].



An *allo*-threonine analogue was prepared in this way. The Nebraska group has also explored the use of diallyl phosphonates driven by the need to develop mild deprotection methods [77]. Treatment of ketophosphonates with alkoxide base led to the formation of difluoroenolates and thus difluoromethylketones [78]. The lithiophosphate then acts as a synthetic equivalent for the difluoromethyl anion synthon (Eq. 21).

The reviewers research group had already described a highly-reproducible cerium(III)-mediated synthesis of ketophosphonates [79], and conjugate addition



reactions to nitroalkenes facilitated by the same lanthanide [80]. Similar results have been obtained with cyclic vinylsulfones [81]; Fig. 3 summarises these developments. These reactions fail to afford useful yields of products when the lithiophosphonate is generated in the absence of cerium(III). Direct organometallic coupling of the readily available diethyl bromodifluoromethylphosphonate has been described with vinyl and aryl halide electrophiles. The recent key developments by Shibuya and co-workers (superceding an earlier report of organocadmium methodology by the Iowa group [82]) are represented in Fig. 4. The key methodology involves copper-mediated coupling of the zinc phosphonate with the unsaturated electrophiles, though the mechanism is far from clear. With vinylic electrophiles [83], the reaction is catalytic in copper(I), while a stoichiometric amount is required with the aryl substrates [84], which also require sonication.

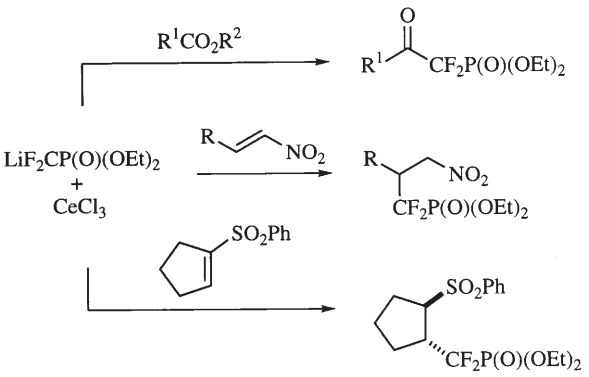


Fig. 3. Cerium(III)-mediated reactions of diethl lithiodifluoromethylphosphate

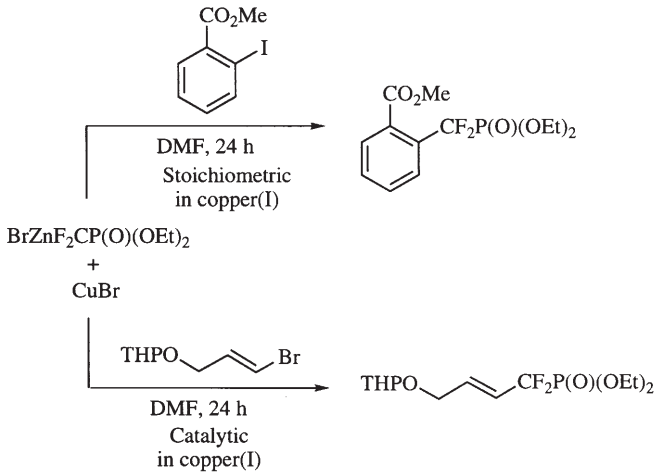
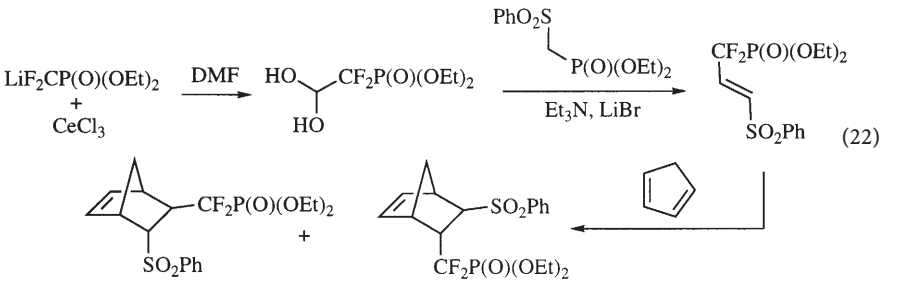


Fig. 4. Copper(I)-mediated reactions of diethyl bromozincdifluoromethylphosphonate

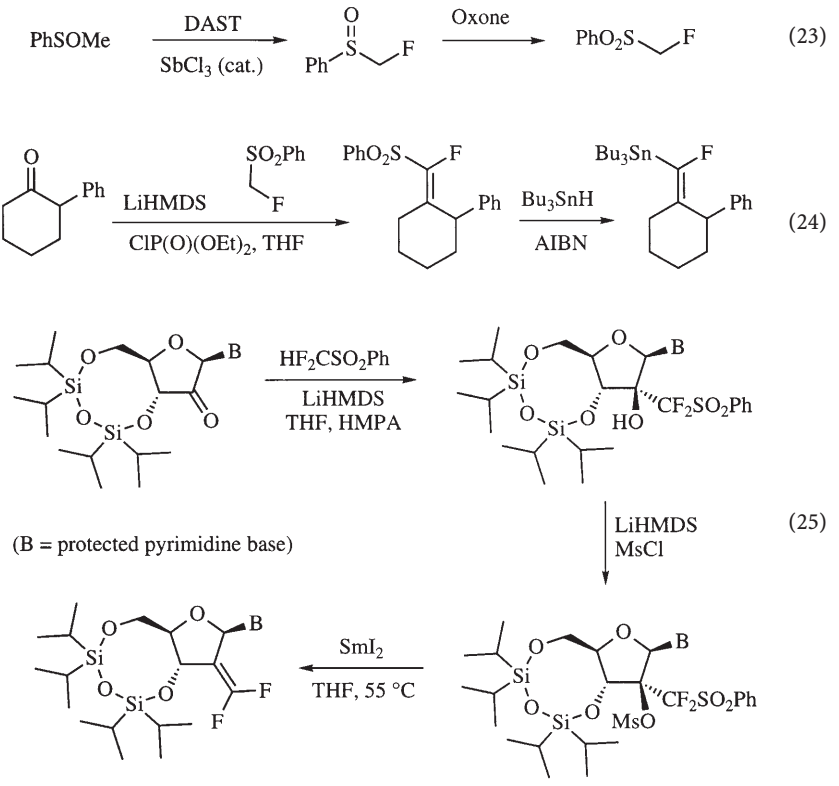


(22)

Nevertheless, the latter method represents a potentially significant improvement on published routes to analogues of phosphotyrosine [85–87]. Competitive methodology is available for the synthesis of the vinylic compounds [88]. When a suitable LUMO-lowering group is present, they are competent dienophiles, opening the way to a general strategy for the construction of cyclic compounds containing the difluoromethylenephosphonato group; for example, see Eq. 22. Difluoroallylic phosphonates have also been synthesised by free radical additions to alkynes [89].

According to a recent Organic Syntheses procedure, fluoromethyl phenyl sulfone, which can be prepared on a large scale [90] (Eq. 23), undergoes a number of useful reactions. A Wadsworth-Emmons-type procedure affords α-fluorovinylsulfones [91], which undergo tin-sulfur exchange under free radical conditions (Eq. 24). The products may be protodestannylated [92], fluorinated [93], or coupled under palladium catalysis [94]. The difluoromethyl phenyl sulfone also shows some useful chemistry.

Originally, Stahly [34] showed that deprotonation and trapping with aldehyde electrophiles could be achieved in concentrated sodium hydroxide solution;



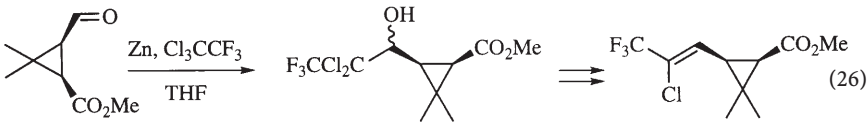
however, more recent investigators have used strong base/aprotic solvent conditions during a synthesis of difluoromethylene nucleoside analogues (Eq. 25) [95]. Fluoro- and di-fluoromethylene analogues of nucleosides have formed the subject of recent reviews [96, 97].

3
Two-Carbon Fluorinated Building Blocks

3.1
Halofluoroalkanes as Building Blocks

Perfluoroalkyl organometallic reagents were reviewed fairly recently [48] so a few typical examples are included here. Trichlorotrifluoroethane (FC-113a) has been used to effect the introduction of a (trifluoromethyl)chloromethylene group into synthetic pyrethroid derivatives (Eq. 26) [98].

Zinc-mediated addition to aldehydes achieves the key carbon-carbon bond forming reaction. Similar adducts were described in a recent paper concerning 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123) which also underwent zinc-mediated addition to aldehydes to afford the two series of adducts shown in Eq. 27 [99].



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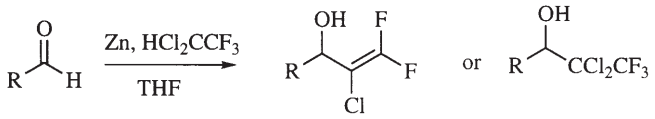
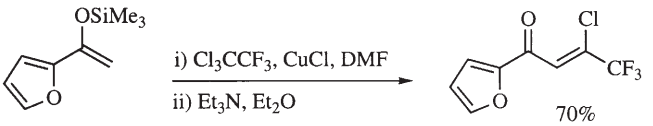


(27)

In the presence of copper(I) chloride, FC-113a adds to silyl enol ethers affording adducts which can be transformed into the β-chloro-β-trifluoromethyl enones in moderate yields [100]. The carbon-carbon bond is formed via a free radical addition reaction (Eq. 28). Free radical addition mediated by iron pentacarbonyl was also described recently during a synthesis of a modified pyrethroid [101].



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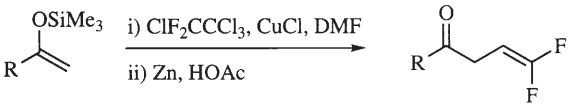
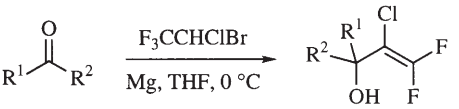


(29)

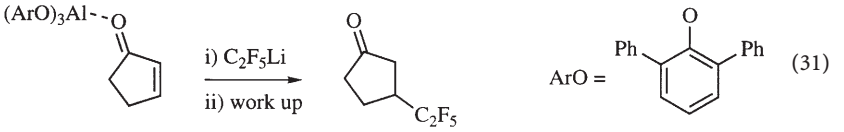
The related 1,1-difluoro-1,2,2,2-tetrachloroethane (FC-112) undergoes a similar reaction to afford adducts which can be cleaved reductively to γ,γ-difluoro-β,γ-enones in moderate yields (Eq. 29) [102]. Kumadaki's group in Osaka have described a number of interesting reactions of 1-bromo-1-chloro-2,2,2-tetrafluoroethane (FC-123B1, Halothane), which include the so-called anomalous Grignard reaction (Eq. 30) [103, 104].



(30)

The normal reaction (metal-insertion into the carbon-bromine bond) proceeded in the presence of zinc metal to afford good to moderate yields of alcohol adducts under mild conditions [105]. This section would be incomplete without mention of a new reaction of the remarkable pentafluoroethyllithium

reagent; conjugate addition of the reagent to enones was described mediated by Yamamoto's triaryloxyaluminium Lewis acid (Eq. 31) [106].

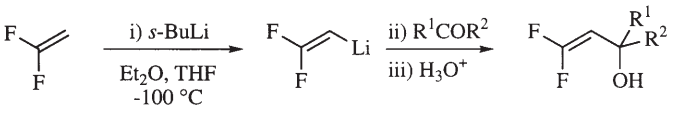


(31)

3.2 Fluoroalkene Building Blocks

3.2.1 Metallated Fluoroalkenes

This section should be read in conjunction with Sect. 7.2 where transformations of fluoroallylic alcohols are discussed. The seminal work in the area was conducted by Normant and Sauvêtre, who showed that difluoroethene underwent deprotonation under scrupulously controlled conditions in a reaction which was neither reported in full, nor reproducible at the published yields [107]. The problems with metallated difluoroalkenes are two-fold; firstly, the two fluorine atoms depress the nucleophilicity by an inductive effect, so reactions such as alkylations usually fail, and secondly, the antiperiplanar arrangement between carbon-fluorine and carbon-lithium bonds presages a facile elimination of lithium fluoride, followed usually by decomposition [108]. For more exhaustive coverage, the reader is referred to a relatively recent review [109]. Nevertheless, reactions with hard electrophiles such as aldehydes and ketones were successful and this technology (Eq. 32) has been applied [110] in the target synthesis of analogues of insect pheromones [111]. Transmetallation extends the temperature range [112] and palladium-catalysed coupling chemistry is available [113]. Direct palladation of difluoroethene has also been achieved recently in a rare example of a Heck reaction via (very slow) oxidative insertion of a palladium(0) species into a carbon-fluorine bond of difluoroethene (Eq. 33) [114]. This reaction effectively provides a synthetic equivalent to the α-fluoroethenyl anion synthon, for which two other equivalents exist.



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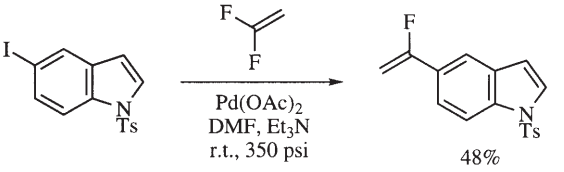

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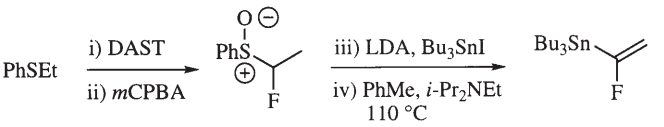
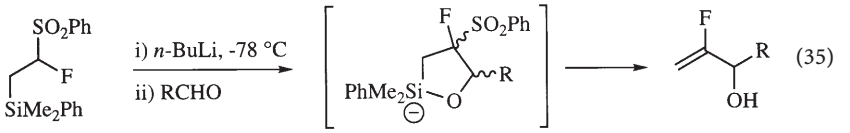


(34)

The Neurocrine group reported the sequence shown in Eq. 34, affording a stannane that undergoes palladium-catalysed (Stille) couplings in moderate to high yields [115, 116]. A strongly complementary and extremely elegant procedure was reported by Tokoroyama et al., in which metallation of an α-fluoro-β-(dimethylphenylsilyl) sulfone followed by addition to an aldehyde or ketone electrophile sets the stage for desulfinylation with 1,4-migration of silicon (Eq. 35) [117].



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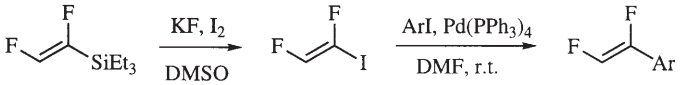


(36)

55-93%

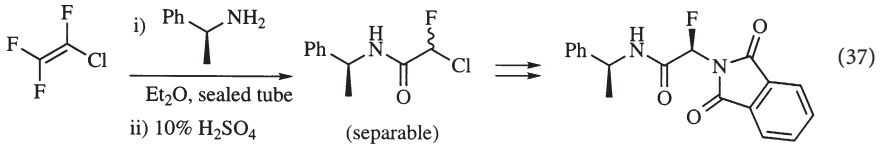
Transmetallation to copper allowing alkylation, allylation and conjugate addition reactions forms a notable absence from the repertoire. There are (to the reviewer's knowledge) no examples of transfers of simple fluoroalkenyl ligands to substrates from cup*rate* reagents. However, vinylcopper reagents have some utility and conjugate addition has been achieved using the Yamamoto Lewis acid (see Eq. 31) [106]. Trifluoroethenyllithium was already available [118] but a more recent method allows its preparation from 1,2,2,2-tetrafluoroethane (HFC-134a) [119]; the higher thermal stability of this vinylmetal derivative reflects the additional electron-withdrawing effect of the α-fluorine atom. Stereoselective reduction of trifluoroethenyl trimethylsilane affords the difluoroethenyl congener which can be remetallated β-to the trialkylsilyl group [120]. More recently, Burton and co-workers have described related chemistry represented in Eq. (36) affording a general route to *cis*-1,2-difluoro-1-arylethenes [121] and related compounds [122].

3.2.2
Miscellaneous Fluoroalkene Reactions

Even simple fluoroalkenes display exploitable electrophilic character. Bailey described an asymmetric synthesis of protected difluoroglycines initiated by nucleophilic addition/elimination at the difluorocentre of chlorotrifluoro-

ethene, represented in Eq. (37) [123]. Hydrolysis followed by (slow) halogen exchange set the stage for the introduction of the amino-function as a phthalimide. The alkene is therefore a synthetic equivalent for a fluoroacetyl cation synthon. The reaction of the sodium salt of an allyl alcohol (Eq. 38) with tetrafluoroethene triggered [124] a [3,3]-rearrangement affording an interesting *gem*-difluoro compound in situ. This appears to be a valuable yet under-utilised procedure, deployed in this instance in a synthesis of PLA_2 inhibitors.

More recently, radical additions to fluoroethenes have attracted attention. Eguchi et al. [125] applied the Barton decarboxylation procedure to add a range of alkyl radicals to 1,1-dichloro-2,2-difluoroethene. Addition was regioselective and the terminal carbon could be hydrolysed to a carboxyl group with silver(I) mediation (Eq. 39). The fluoroalkene is effectively an equivalent for either difluoroacetyl anion or cation synthons, because the adding radical can be approached from either polarity manifold.



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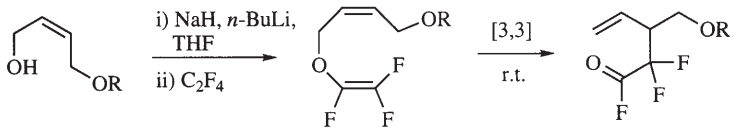

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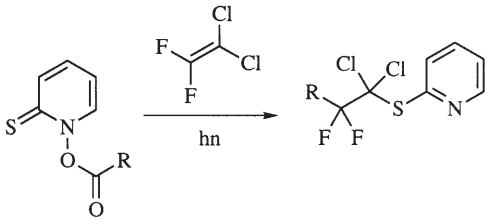
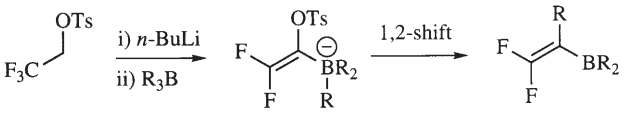


(39)

3.3
Fluoroethanol Building Blocks

Trifluoroethanol is an extremely attractive building block. The alcohol is available in industrial quantities and is a stable liquid with a rich chemistry. The initial contributions in the area were made by Nakai et al. [126]; conversion to the tosylate (itself a stable, crystalline commercial material) followed by exposure to LDA in THF at –78 °C led to the formation of difluorovinyl tosylate which reacted efficiently with hard electrophiles such as aldehydes and ketones. Ichikawa has converted this initial result into a powerful and versatile metho-

dology [127] by intercepting the difluorovinyl tosylate with a trialkyl borane. The boron *ate* species that resulted lost tosylate anion via a 1,2-alkyl shift from boron to carbon and a difluorovinyl borane was formed. Protiolysis of the carbon-boron bond at this point results in the formation of difluoroalkenes (Eq. 40). Alternatively, the borane can be halogenated to afford products with clear potential for further elaboration [128]. Subsequent transmetallation with copper(I) iodide in HMPA afforded a most useful vinylcopper nucleophile.



(40)

Figure 5 shows the range of coupling reactions achieved using this general synthetic equivalent for difluoroalkenyl anion synthon [129–133]. Of particular note is the Nazarov cyclisation sequence leading to the formation of a fluorocyclopentenone [134]. When the difluoroalkenyl double bond is activated by a carbonyl group, one or both fluoride ions can be displaced selectively [135–137]. More recent results have explored the reaction shown in Eq. (41); the zirconacyclopropane undergoes ring opening with loss of tosylate to afford a difluorovinylzirconium derivative, a reactive carbon nucleophile (in the presence of zinc(II) iodide) and a synthetic equivalent for the difluoroethenyl anion synthon [138].

Trifluoroethanol has also been used in carbon-carbon bond-forming chemistry in which the oxygen function is retained. We have described dehydrofluorina-

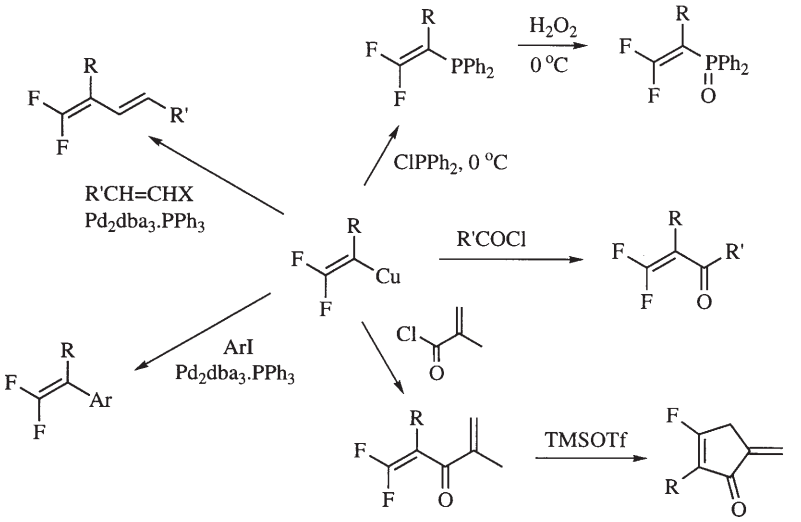
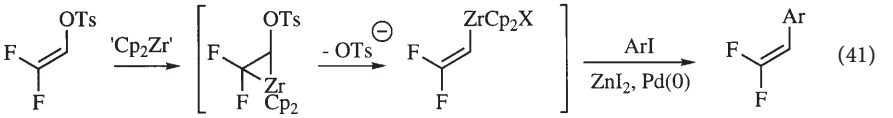


Fig. 5. Coupling reactions of Ichikawa's difluorovinylcopper reagent



(41)

tion/metallation chemistry of the MEM ether (in fact an acetal) of trifluoroethanol under the Nakai conditions [139]. The inclusion of the lithium atom within a chelate in which the lithium atom is coordinated to two oxygen atoms ensures that defluorination is attenuated, at least at –78 °C. Details for the generation and trapping of this species have been published in full; aldehydes, ketones, Group(IV) halides have all been used successfully (Fig. 6). Transmetallation with zinc bromide allows access to iodide while boron trifluoride-mediated ring opening of epoxides proceeded in moderate yield. Similar chemistry, described by the Snieckus group [140] and the reviewer's group [141] is available from the *N,N*-diethylcarbamate of trifluoroethanol (Eq. 42). An additional feature of this chemistry is the transcarbamoylation reaction which results in the formation of a difluoroenolate in situ. Upon protic work-up, ketones can be isolated so that the metallated difluoroenol carbamate is a synthetic equivalent for the difluoroacetyl anion synthon. The vinyl silanes that arise upon trapping with trialkyl chlorosilanes undergo addition/elimination upon treatment with reactive alkyllithium reagents to afford E-fluoroenol carbamates upon fluorodesilylation.

Transmetallation chemistry of the metallated difluoroenol carbamate is not extensive but a useful reaction with a CuX_3Li_2 reagent has been described allowing elaboration to difluoroenones, useful building blocks in cycloadddition chemistry (Eq. 43) [142]. Difluoroethanol (which is considerably more

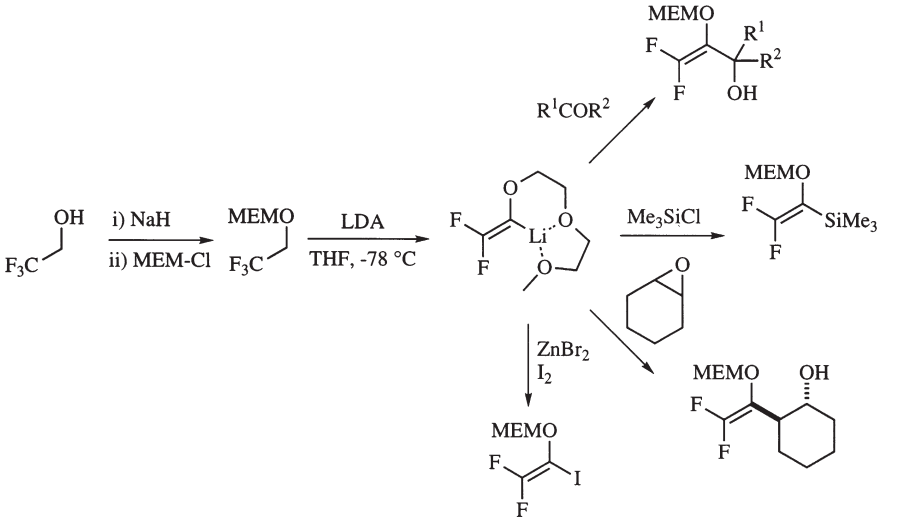
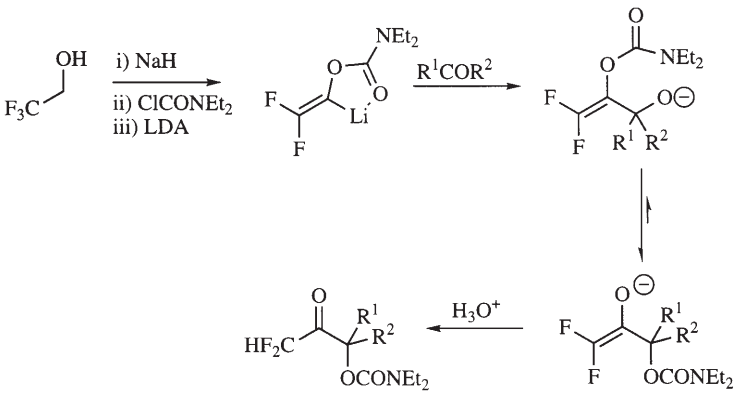


Fig. 6. Generation and reactions of a metallated difluoroenol acetal



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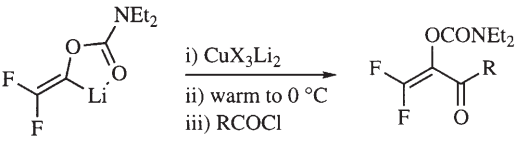
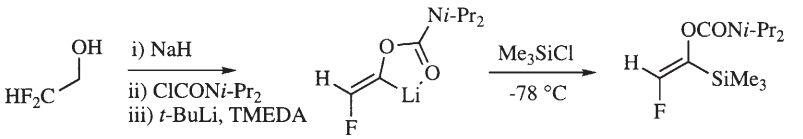


(43)

expensive) has also been converted to a metallated fluoroenol carbamate (Eq. 44) [143]. The more hindered di*iso*propyl carbamate substrate was used and more strongly basic conditions were required. Though starting material was consumed completely, yields of products failed to exceed 40%, even when the most competent Group(IV) halides were added. This reaction conceals a familiar stereoelectronic effect; the two metallated intermediates differ in the relationship between the carbon-lithium and carbon-fluorine bonds. In the absence of a second fluorine atom, the stereoisomer with a *trans* arrangement undergoes elimination, even at –78 °C, whereas the *cis* diastereoisomer (shown) is stable and is duly trapped. The reviewer is unaware of useful reactions of fluoroethanol.



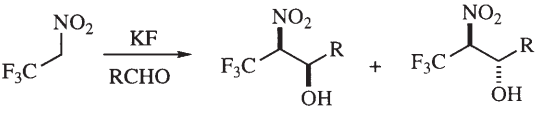
(44)

3.3
Other Fluoroethyl Building blocks

Though not available commercially, trifluoronitroethane shows some interesting chemistry consistent with the powerful electron-withdrawing effect exerted by the nitro group. Fluoride-mediated nitroaldol reactions were reported [144] with aldehydes affording a valuable entry to trifluoromethyl amino alcohols

(Eq. 45) while a more recent publication described diastereoselective reactions of two trifluoromethyl silyl nitronates [145].

Derivatives of trifluoroethanethiol have limited though interesting chemistry. Unfortunately, metallated difluorothioenol chemistry has not been reported, because rapid nucleophilic attack occurs even by hindered bases such as LDA. Nakai et al. exploited this high electrophilicity in a tandem addition/elimination-rearrangement sequence [146], but more recent applications have concerned free radical chemistry (Eq. 46). Chlorination of trifluoroethyl phenyl sulfide followed by exposure to tin hydride in the presence of an allylstannane resulted in C-C bond formation with a reasonable level of stereocontrol [147].



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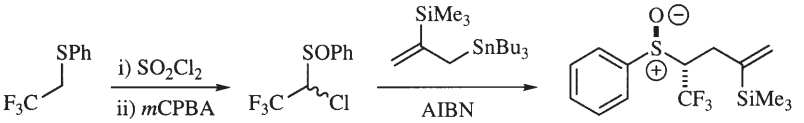


(46)

major (*anti*) diasteroisomer

3.4
Fluorinated Acetaldehyde Derivatives

Fluoroacetaldehyde was generated and trapped in situ in a recent synthesis of a fluoromethylketone inhibitor of Interleukin-1β converting enzyme [148]. The interception of fluoroacetaldehyde derivatives by nitrocarbanions has been used by a number of groups. The usual starting material is the ethyl hemiacetal which is available commercially in the trifluoro-series. The TIT group [149] has developed versatile chemistry based on the difluoro-congener, which is summarised in Fig. 7.

The reactions with nitrocarbanions, leading ultimately to fluoroanalogues of aminosugars, are particularly interesting. The ethyl hemiacetal of difluoroacetaldehyde has also been used to prepare an imine which underwent stereoselective Lewis acid-catalysed Diels-Alder cycloadditions with Danishefsky's diene to afford a difluoromethyl pyridone in good yield (Eq. 47); the adduct was elaborated to 1,6-dideoxy-6,6-difluoroazasugar derivatives [150]. Zinc-mediated allylation reactions of the imine leading to pyrrolidone products were also described (Eq. 48) [151]. The analogous trifluoromethyl imine *failed* to react under these conditions. Ishihara and co-workers [152] described a useful general method for the preparation in situ of fluorinated aldehyde equivalents which uses DIBAl-H reduction of the corresponding esters, followed by Lewis acid mediated allylation by stannane nucleophiles (Eq. 49).

The chemistry of trifluoroacetaldehyde is more extensive. Inhibitors of Human Leukocyte Elastase [153–155] and antagonists of Leukotrienes D_4 and E_4 [156] were prepared recently using trifluoral chemistry.

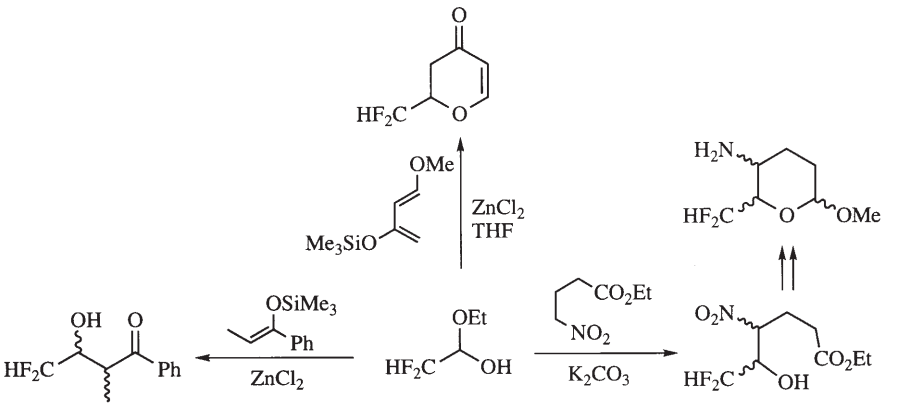
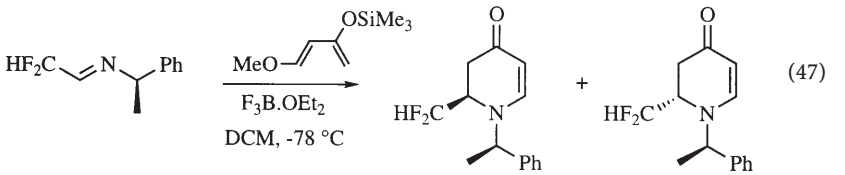


Fig. 7. Reactions of a difluoroacetaldehyde equivalent with nucleophiles



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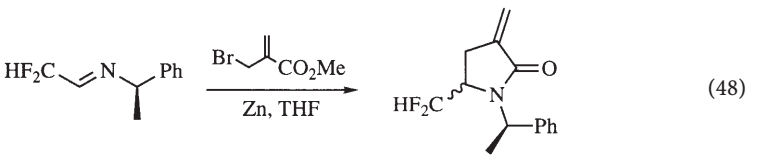

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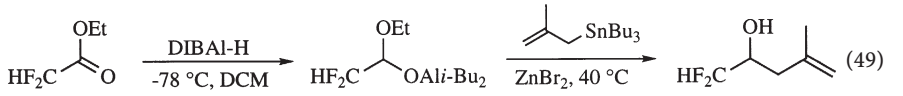

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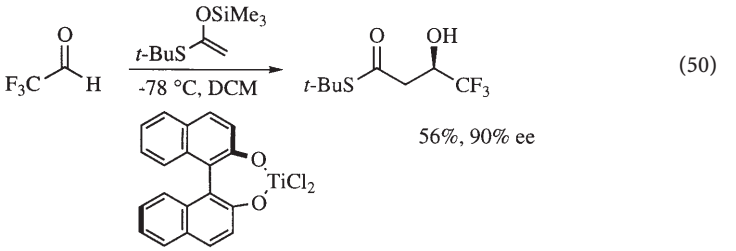
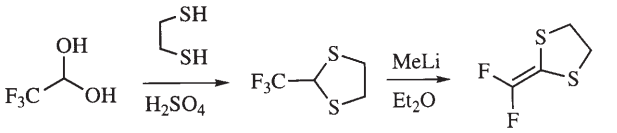


(50)

Trifluoral is also a highly reactive substrate in the carbonyl-ene reaction [157, 158], though in these cases the aldehyde must be isolated and distilled freshly before use. Mikami has shown that a number of other nucleophilic species such as vinyl sulfides undergo addition with asymmetric catalysis to afford useful homoallyl trifluoromethyl alcohols (Eq. 50) [159, 160]. Oxidative cleavage of the ene products then affords *syn*-aldols which are also available directly via the catalytic asymmetric aldol reaction [161]. It follows that fluorinated acetaldehydes are reactive and well-behaved electrophiles. The author is unaware of reverse polarity methods; clearly any attempt to deprotonate the former acyl carbon would be followed most probably by a defluorination reaction; Eq. (51) illustrates this perfectly [162]. This reaction is relatively unusual in that the reaction between the aldehyde and the thiol has progressed beyond the hemiacetal stage (normally a high carbenium ion energy prevents loss of water) and the product dithioketene acetal has not been attacked by the methyllithium.

Trifluoral was also converted to a *C*-(trifluoromethyl)nitrone [163] which underwent regio- and stereo-selective cycloaddition with alkenes, affording potentially useful aminoalcohols after N-O bond cleavage (Eq. 52)



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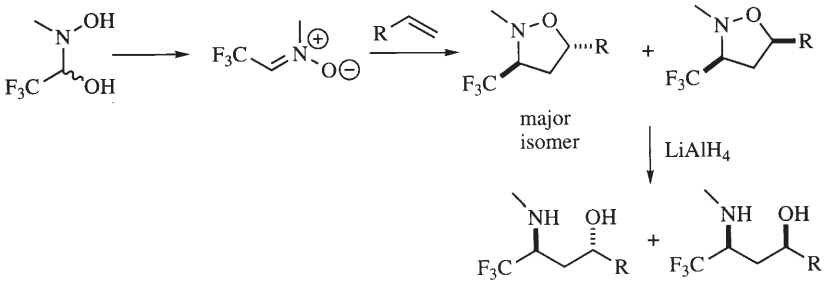


(52)

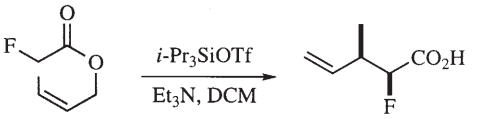
3.5
Fluorinated Acetic Acid Derivatives

Most of the C-2 building block chemistry derives from trihaloacetic acid derivatives, though reactions of dihalo-congeners are also extremely useful.

Allylic esters of fluoroacetic acid were used in the Ireland silyl ketene acetal rearrangement procedures by the Welch group at Albany [164]. For example, Eq. (53) shows a highly diastereoselective rearrangement which formed an early stage in syntheses of 2,3-dideoxy-2-fluoro-3-*C*-methyl pentose nucleosides [165, 166]. If a stereoselective synthesis of a functionalised monofluorocompound is

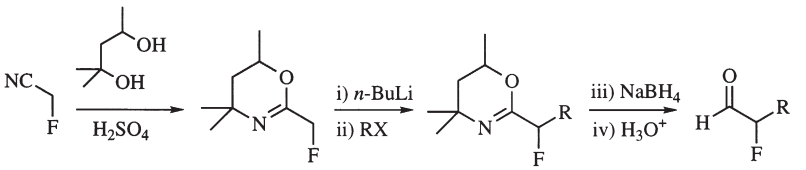
required, this methodology is probably the one of choice. Other rearrangements based on fluoroacetic acid orthoesters (derived from fluoroacetonitrile, an expensive building block) have been reported though they offer a considerably lower level of control [167].

Fluoroacetonitrile has also been transformed into a trimethyloxazine, which can be deprotonated, alkylated and then hydrolysed to the aldehyde (Eq. 54); overall, the reagent functions as a synthetic equivalent for fluoroacetaldehyde enolate [168]. Condensation of fluoroacetonitrile with carbon disulfide (Eq. 55) affords an α-fluoroacrylate-β-cation equivalent [169]. Fluoroacetyl chloride can also be converted to fluoroketene (Eq. 56) which undergoes the ketene-imine cyclisation in a stereoselective manner [170]. Fluorinated β-lactams have been synthesised using this method, followed by stereoselective alkylation of the lactam enolate and the products have been converted to peptide retroamide isosteres [171, 172]. Recently, fluoropropionate thioester has been used in a preparation of similar azetidinones [173] (Eq. 57). A powerful new aldol methodology is also being developed based on the metal enolate of this fluoroester [174]. Though not completely general in aldehyde, the reaction shows great promise for the location of fluorine atoms at teriary stereocentres. The alternative approach developed by Takeuchi et al. from ethyl dibromofluoroacetate lacks any obvious means of asserting stereocontrol [175].



(53)

>95% (15:1 *syn*:*anti*)



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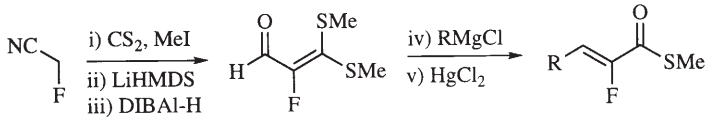

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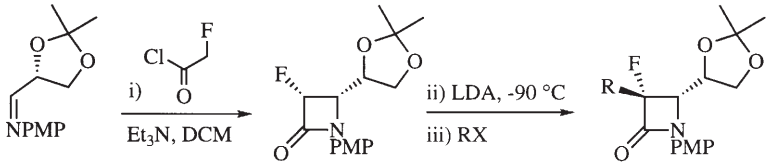

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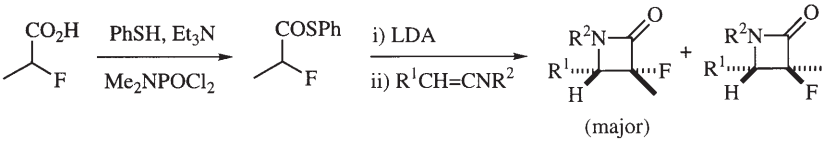

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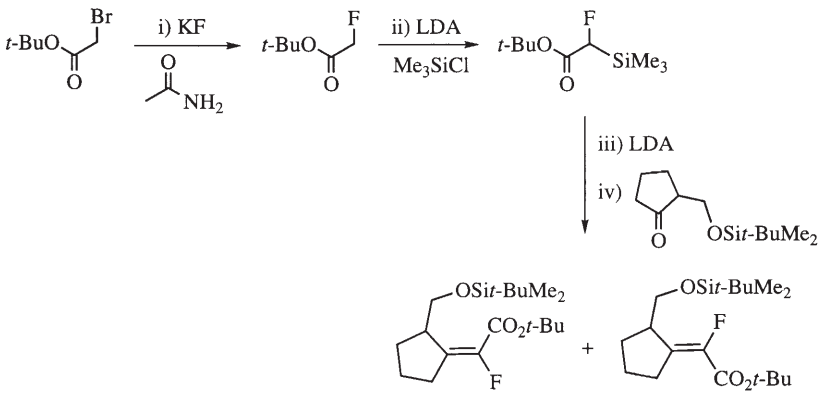
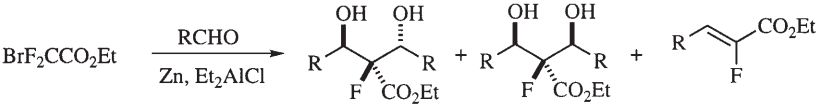


(58)

Peterson olefination chemistry based upon *tert*-butyl fluoroacetate, generated in situ from the corresponding bromoester, has also been used in the synthesis of peptide isosteres [176, 177]. Equation (58) shows the crucial early steps in the synthesis of an inhibitor of Dipeptidyl Peptidase IV.

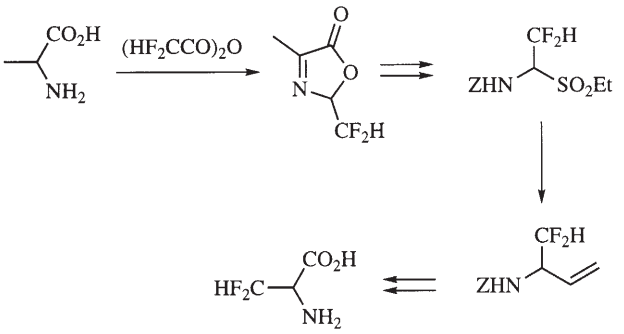
Ethyl dibromofluoroacetate has been used as a fluoroacetate enolate equivalent in Reformatsky chemistry developed by the Kyoto group [178]. Addition mediated by zinc and chloro diethylaluminium occurs with modest stereoselectivity to afford the bromofluoro hydroxyesters.



(59)

The reaction could be continued (in the presence of excess aldehyde and mediator) to afford the double aldol products (Eq. 59). A fluoroacetate equivalent was also deployed in the recent synthesis of a 1β-fluorocarbapenem derivative [179]. Difluoroacetic acid was used by d'Orchymont [180] in a synthesis of 3,3-difluoro-DL-alanine. Condensation of the anhydride with alanine set the stage for a Steglich-Weygand procedure (Eq. 60); the key step appears to involve vinyl Grignard addition to an imine of difluoroacetaldehyde, generated in situ. Chlorodifluoroacetic acid, its esters and anhydride are used widely.

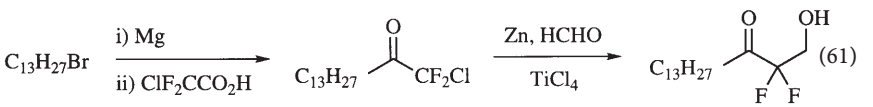
Grignard addition to chlorodifluoroacetic acid constitutes the classic method for the synthesis of chlorodifluoromethyl ketones. A recent example [181] was



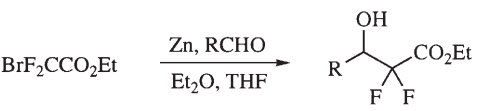
(60)

provided in a synthesis of substrate analogues of *N*-myristoyltransferase (Eq. 61). However, the successful application of Wittig chemistry by Bégué et al. (see Eq. 67) to esters of chlorodifluoroacetic acid offers an attractive alternative route [182]; hydrolysis of the enol ether affords the ketone. Both methods are limited to fairly simple substrates because strongly basic reaction conditions are involved. Useful reactions of chlorodifluoroketones are described in Sect. 7.1.

Ethyl bromodifluoroacetate is one of the fluorinated building blocks used most widely. There are scores of examples of the important Reformatsky reaction with aldehydes which occurs in THF/ether solvent mixtures, sometimes under sonication conditions (Eq. 62).



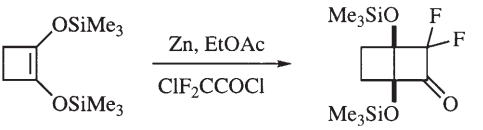
(61)



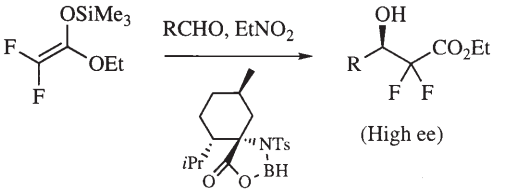
(62)

Targets are typically inhibitors of protease enzymes [183–186]. The method has also been used for the synthesis of analogues of TXA_2 [187], aminoacids [188], nornicotinic acids [189] and [6]-gingerol [190], and is used in large scale production of at least one important pharmaceutical compound, the Eli Lilly anti-tumour agent Gemcitibine [191]. Asymmetric methodology has been developed based on ephedrine-derived chiral auxiliaries though ees appear to be highly substrate dependent and maximal at 84% for the addition to aromatic aldehydes [192, 193]. Variations in the established procedure involve the use of the more economical chlorodifluoroacetate ester (in which case DMF is the solvent, and 70 °C the temperature, of choice) [194], and the use of samarium diiodide [195] with both substrates. The lanthanide reagent allowed very short reaction times (ca. 1 min) in ether solvent at room temperature, even with the less reactive chloro ketone which may be advantageous for sensitive substrates.

Reactions with imines also occur under similar conditions leading to the formation of difluorinated β-lactams [196, 197]. Formally, this reaction corresponds to a [2+2]-cycloaddition across an imine; there is also an isolated report of a difluoroketene reaction, shown in Eq. (63) [198]. Useful chemistry of a silyl difluoroketene acetal was reported recently; Eq. (64) shows the efficient asymmetric reaction between this reactive carbon nucleophile and aldehydes catalysed by chiral Lewis acids [199].

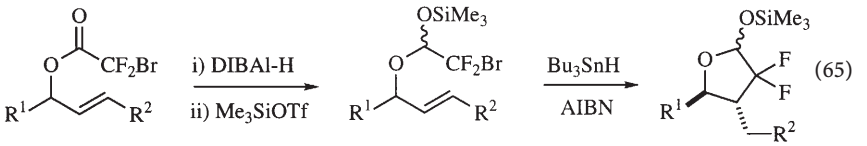


(34%) (63)



(High ee) (64)

A conceptually different C-C bond forming reaction involving intramolecular radical cyclisation of allylic esters of bromodifluoroacetic acid was described by Itoh et al. [200]. Reduction to the acetal sets the stage for a tin hydride-mediated cyclisation (Eq. 65).

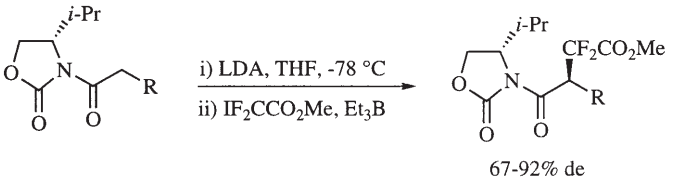


(65)

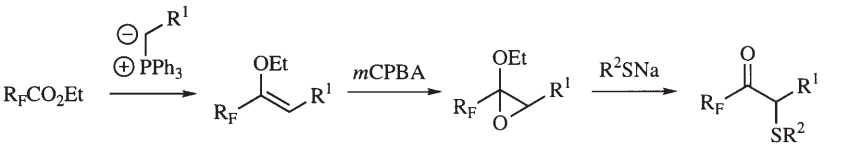
The most reactive ester in the series is the iodo species; nucleophilic organometallic reagents have been prepared [201], while Eq. (66) shows an alternative and reversed polarity method of C-C bond formation in which the ester acts as an electrophile. Iseki and co-workers at Daikin [202] showed that the (presumably highly electrophilic) free radical derived from the ester reacted with enolates derived from chiral *N*-acyloxazolidinones in a highly diastereoselective process. The mechanism has strong parallels with Taguchi's cyclopropanation methodology reported in Sect. 5.3. Some potentially useful manipulations of the carboxyl group were also reported. Atom-transfer procedures have also been exploited in this area with addition of the iododifluoroacetate across alkenes mediated by copper in DMF [203, 204] and by nickel dichloride [205].

Trifluoroacetic acid is a most useful building block for a wide range of trifluorocompounds, particularly trifluoromethyl ketones [206]. Esters are useful

electrophiles, towards organolithium and ylid reagents for example. Wittig reactions afford the corresponding enol ethers [182] which can be oxidised (Eq. 67) to the epoxy enol ethers with surprising ease [207]. Ring opening then occurs readily at the less hindered position with sulfur [208] and nitrogen [209] nucleophiles. The TIT group have used ethyl trifluoroacetate to gain access to 6-deoxy-6,6,6-trifluorosugars [210–214]. Equation (68) shows the opening steps in the sequence.



(66)



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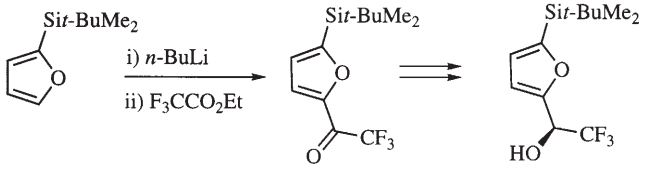
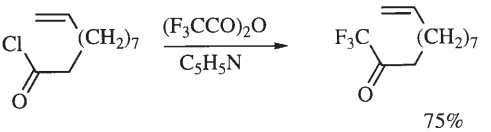


(68)

Alkynyllithium reagents react with ethyl trifluoroacetate (and the difluoro congener) to afford valuable substrates for conjugate addition reactions [215]. These reactions represent normal polarity applications as trifluoroacetyl cation equivalents. The more reactive trifluoroacetic anhydride can be used in the same way, reacting with acid chlorides via acylketene intermediates to afford trifluoromethyl ketones (Eq. 69) [216]. In the presence of boron trifluoride dimethylsulfide complex, alkynes were trifluoroacetylated [217] with concomitant addition of dimethylsulfide, while enol ethers and thioenol ethers reacted smoothly with trifluoroacetic anhydride in the presence of pyridine [218] to afford extremely useful C-4 building blocks. More reactive carbon nucleophiles such as arylcopper reagents also react efficiently with this reagent [219]. A strategically different and powerful methodology has been developed by the Uneyama group in Okayama. Trifluoroacetimidoyl halides [220] were synthesised from trifluoroacetic acid according to Eq. 70 [221]. The iodide is most useful, undergoing iodine-lithium exchange readily [222] and converting the electrophilic carbonyl carbon into a nucleophilic centre which could be trapped with carbonyl electrophiles in some cases. This therefore constitutes a polarity reversal

method. Direct zincation of the iodide afforded a reagent that could be trapped with aldehyde electrophiles [223].

Palladium-catalysed coupling also proceeded readily, carbonylative coupling in the presence of alcohols affording some particularly useful C-3 building blocks (Sect. 4.6) (Eq. 71) [224]. A metal-free method for generation of the trifluoroacetimidoyl carbanion has also been reported involving silic-*ate* formation and trapping [225].



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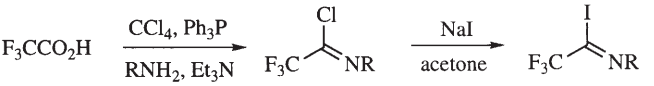
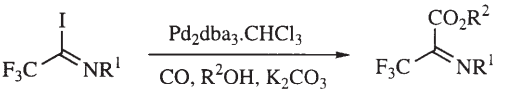


(70)

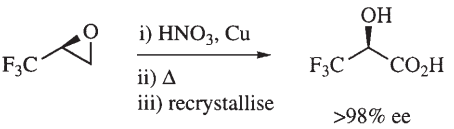


(71)

4
Three Carbon Fluorinated Building Blocks

4.1
Trifluoropropene Derivatives

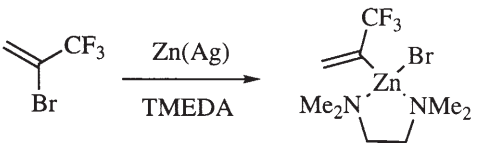
Asymmetric microbial oxidation afforded the (–)-epoxide which has been explored as a building block; ring opening reactions with organometallic nucleophiles, and via Friedel-Crafts reactions have been reported. [226, 227]. A non-biotransformative approach to this epoxide has also been described [228]. Copper(II)-catalysed oxidative hydrolysis (Eq. 72) affords a lactic acid analogue in high enantiomeric purity [229].



(72)

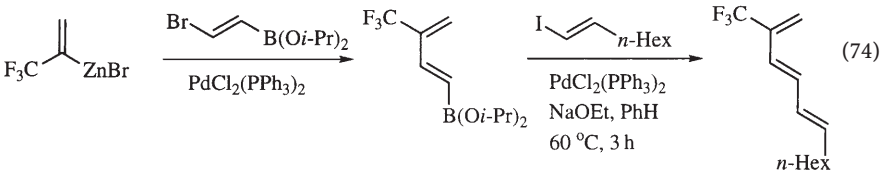
Conversion of trifluoropropene to the bromide allows access (via halogen-metal exchange) to organometallic reagents, synthetic equivalents for the trifluoropropenyl anion synthon. Clearly, defluorometallation (leading to allene formation [230]) is a potential problem so the electropositivity of the metal

must be limited. A remarkably stable zinc reagent was prepared according to Eq. (73). The presence of TMEDA was critical for the success of the procedure, as was the use of chlorotrimethyl silane in activating the Zn(Ag) couple [231].

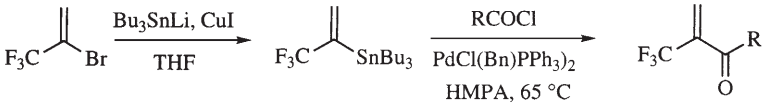


(73)

Palladium(0)-catalysed coupling proceeded smoothly with aryl bromides and iodides, and the reaction has been extended to include bromovinyl boronate esters [232], which then undergo further coupling, resulting in triene formation (Eq. 74). Tin-bromine exchange has been achieved by treatment with a trialkylstannyl homocuprate, though copper iodide must be used to make the cuprate if a controlled reaction is to be achieved (Eq. 75). Coupling with acid chlorides then occurred under forcing palladium-catalysed conditions [233]. Direct Sonogashira coupling of the bromide led to the formation of trifluoromethyl enynes [234]; in the case shown in Eq. 76, where an alkynyl silane was used as the nucleophile, further carbon-carbon bond formation with aldehydes was possible in the presence of catalytic fluoride ion [235]. Barbier-type chemistry has also been reported in which the bromide adds to aliphatic or aromatic aldehydes in DMF initiated by a Zn(Cu) couple [236].



(74)



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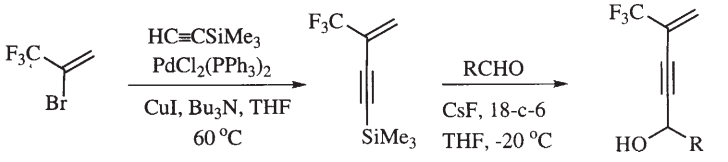
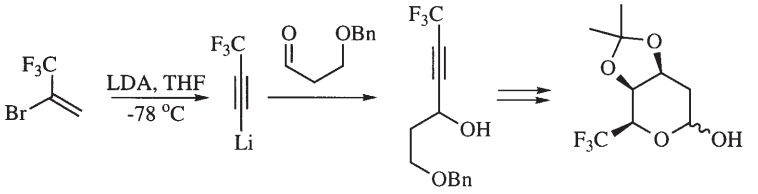
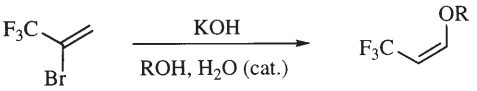


(76)

Dehydrobromination of bromotrifluoropropene affords the more expensive trifluoropropyne [237], which was metallated in situ and trapped with an aldehyde in the TIT group's [238]synthesis of 2,6-dideoxy-6,6,6-trifluorosugars (Eq. 77). Allylic alcohols derived from adducts of this type have been transformed into trifluoromethyl lactones via [3,3]-Claisen rearrangements and subsequent iodolactonisation [239]. Relatively weak bases such as hydroxide anion can be used to perform the dehydrobromination and when the alkyne is generated in the presence of nucleophilic species, addition usually follows. Trifluoromethyl enol ethers were prepared (stereoselectively) in this way (Eq. 78); the key intermediate is presumably a transient vinyl carbanion which protonates before defluorination can occur [240]. Palladium(II)-catalysed alkenylation or arylation then proceeds [241].

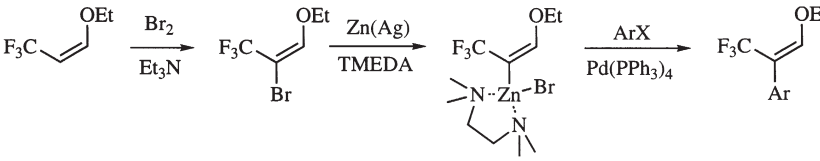


(77)



(78)

Bromination of the enol ether product with two equivalents of bromine followed by dehydrobromination afforded the *Z*-bromoenol ether (Eq. 79) which could be converted to the zinc reagent and cross-coupled with aryl halides [242]. Dehydrobromination in the presence of thiophenol followed by bromination/dehydrobromination affords an enol thioether [243]. Oxidation to the sulfone, followed by exposure to triethylamine in ether, resulted in dehydrobromination to the unstable alkynyl sulfone which could be trapped with dienes in situ. Alternatively, dehydrobromination of the sulfide in the presence of allylic alcohols results in the formation of allyl vinyl ethers which undergo Claisen rearrangements [244]. Further oxidation followed by sulfoxide elimination results in highly unsaturated trifluoromethyl ketonic products (Eq. 80).



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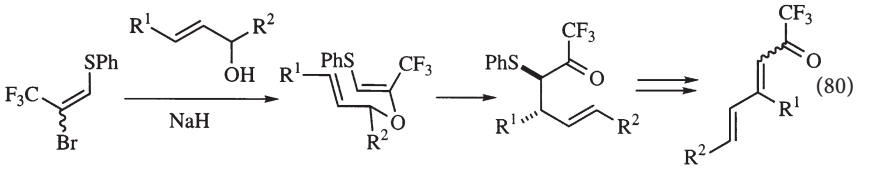
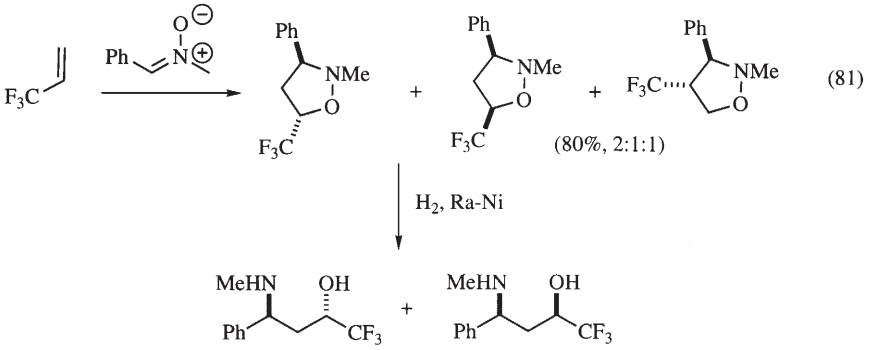
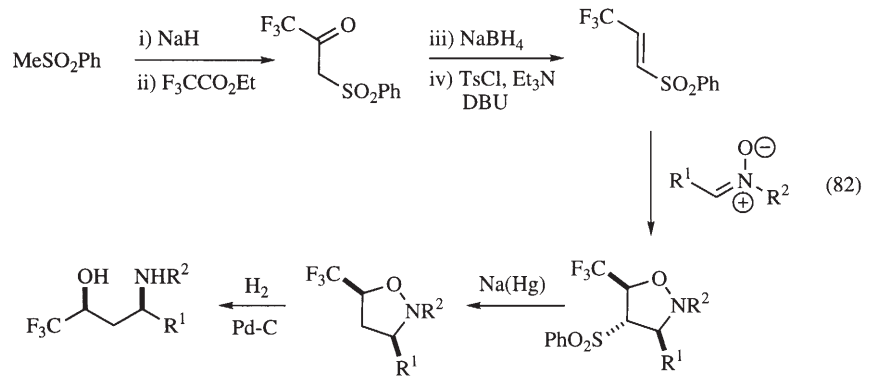


4.2
Activated Trifluoropropene Derivatives

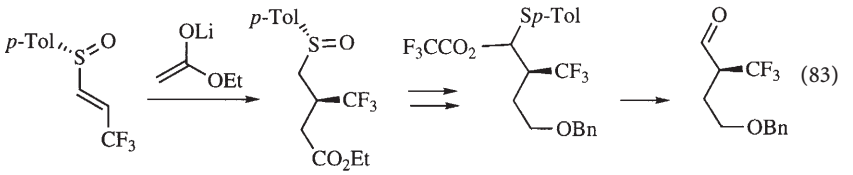
Trifluoropropene itself undergoes a dipolar cycloaddition with *C*-phenyl-*N*-methylnitrone under reasonably mild conditions (Eq. 81); reduction of the adducts leads to the formation of aminoalcohols though the regio- and stereoselectivities are relatively low [245]. Low regioselectivity reflects the non-π acceptor nature of the trifluoromethyl group. Much higher reactivity accrues when a π acceptor group is also present. Dipolar cycloaddition of 1,1,1-trifluoro-3-phenylsulfonylpropene occurs with high regio- and stereoselectivity (Eq. 82).





The dipolarophile was prepared in a short (three-step) sequence from methyl phenyl sulfone (38% overall yield) and ethyl trifluoroacetate. Desulfonation, followed by reductive N-O cleavage afforded the *syn* aminoalcohols [246]. Conjugate additions to the sulfone were described some years earlier [247]; more recently, trifluoromethyl pyrroles have been synthesised from the nitropropene [248].

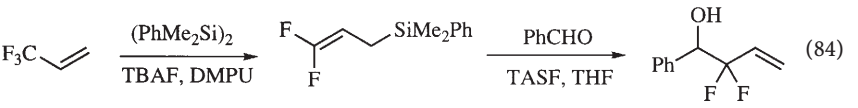
Conjugate addition reactions to enantiomerically pure tolylsulfinyl trifluoropropene were used recently to prepare α-trifluoromethyl aldehydes [249]. Conjugate adducts were elaborated by Pummerer rearrangement of the sulfoxyl group to install the aldehydic carbonyl (Eq. 83).



(83)

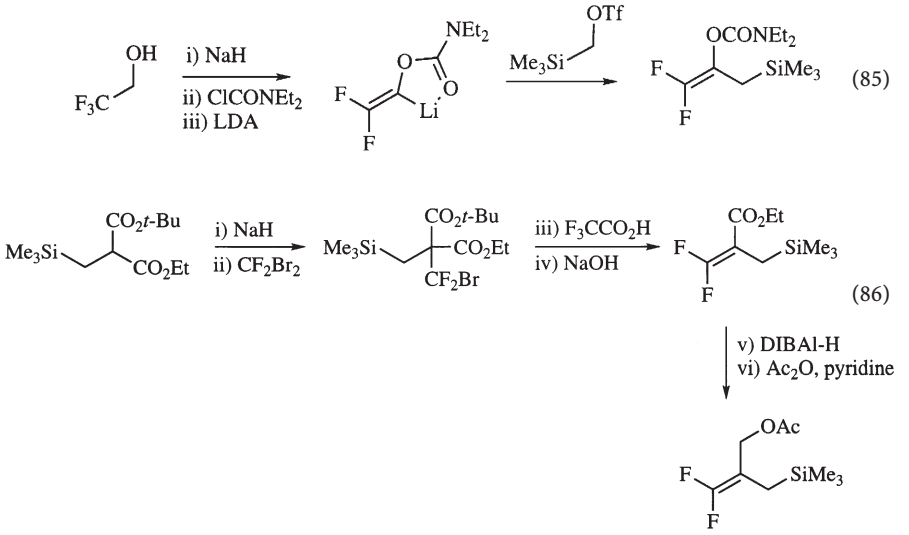
4.3 γ,γ-Difluoroallylic Derivatives

There are two main entry points to nucleophilic difluoroallylic species. Trifluoropropene undergoes S_N2' displacement of fluoride anion when treated with trialkylsilyl anion equivalents (Eq. 84) [250]. The γ,γ-difluoroallyl silane products undergo fluoride-mediated attack upon carbonyl electrophiles to afford homoallylic alcohol products [251]. Amazingly, this reviewer failed to find a single application of this chemistry in target synthesis! A more recent route to the silanes was shown in Eq. (14) and alternative routes to the homoallyl products have been published, using bromodifluoropropene as a starting material.



(84)

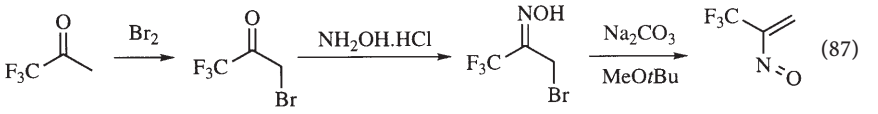
The original chemistry, described by Seyferth et al. [252] required low temperature conditions; a more recent method used zinc to mediate the addition [253]. The chlorodifluoropropene can also be used with copper(I) chloride or silver acetate and zinc mediation [254]. Trapping a metallated difluoroenol carbamate with (trimethylsilyl)methyl triflate [255] affords a useful C-3 building block (Eq. 85) while a much longer sequence (Eq. 86) afforded a related silane [256]. γ,γ-Difluoroallylic derivatives are also available by the addition of nucleophiles to difluoroallenes; Huang and co-workers reported the addition of thiolates to afford allylic sulfides recently [257] though there are no applications



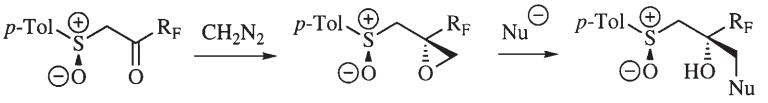
to date. The cycloaddition chemistry of fluoroallenes has been studied extensively, and reviewed by Dolbier [258].

4.4 Fluoroacetone Derivatives

Welch and Seper explored the deprotonation chemistry of ketimines derived from fluoroacetone [259]. The cyclohexylimine could be alkylated regioselectively at either the methylene or the fluoromethylene carbon atom, so fluoroacetone is a versatile (though expensive) building block for higher fluoroketones. Trifluoroacetone was converted to 1,1,1-trifluoro-2-nitrosopropene (Eq. 87), a useful heterodiene which reacts with a wide range of alkenes [260] to afford oxazinyl products. Subsequent lithiation and stereoselective alkylation of these products has been achieved, though trapping the oxazinyllithium with carbonyl electrophiles was unsuccessful [261].



Bravo and coworkers explored the chemistry of an enantiomerically pure p-toluenesulfinyl trifluoroacetone (indeed other perhaloalkyl groups were also explored) (Eq. 88) [262, 263]. Treatment with diazomethane led to the stereoselective formation of epoxides, potentially useful C-4 building blocks with a high level of functionality [264]; there are many published variations on this basic theme.

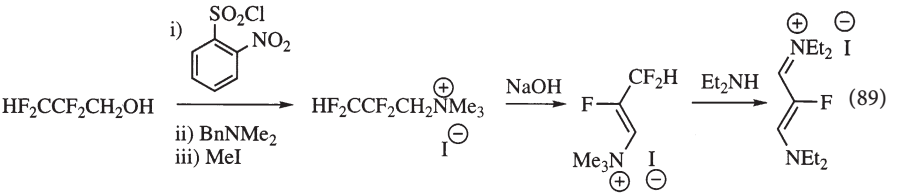


(88)

4.5
Tetrafluoropropanol Derivatives

The Kyoto group has developed some interesting chemistry based upon this readily available alcohol. β-Fluoro vinamidinium salts with potential for the synthesis of fluorinated heterocycles were prepared according to Eq. (89) [265]. Treatment of the tosylate of tetrafluoropropanol with *n*-butyllithium achieves regioselective dehydrofluorination; a short reaction time appears to be critical [266].

Treatment of the enol tosylate obtained with amines led to the formation of β-amino-α-fluoro acrylaldehydes (Eq. 90); when bifunctional nitrogen nucleophiles were used, pyrazoles and pyrimidines were obtained [267]. More recently the reaction has been used to prepare the alkyl- or arylthio congeners [268].



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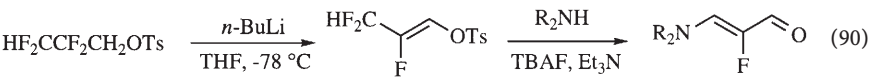
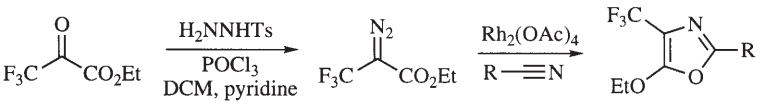


(90)

4.6
Trifluoropyruvic Acid Derivatives

The Shanghai group has developed two strategically different methods for using this commercially-available compound. Conversion to the diazopropionate was achieved according to Eq. (91) by treating the ketoester with tosyl hydrazine in the presence of a dehydrating agent [269]. Rhodium-catalysed decomposition in the presence of nitriles led to the trifluoromethyl oxazoles [270]. Allylic sulfides reacted as nucleophiles with the rhodium carbenoid to afford products that underwent [2, 3]-sulfonium ylid rearrangement (Eq. 92) in situ.

Further sulfoxide elimination led to the formation of dienoate esters, including a novel retinoid analogue (Eq. 93) [271]. More recent chemistry involved 1,2-Stevens rearrangement to gain access to aminoacid analogues (Eq. 94) [272]. The second strategic use involves the addition of alcohols to the



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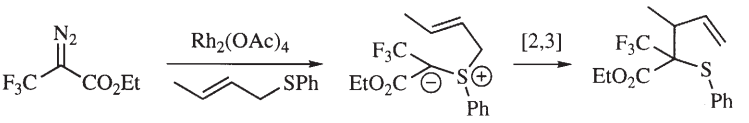

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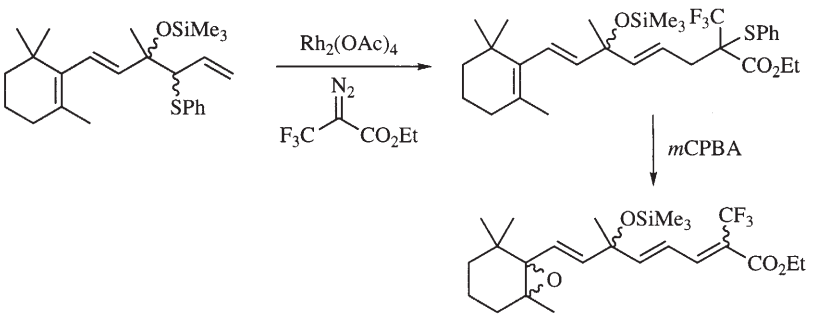

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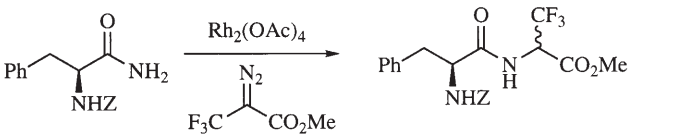
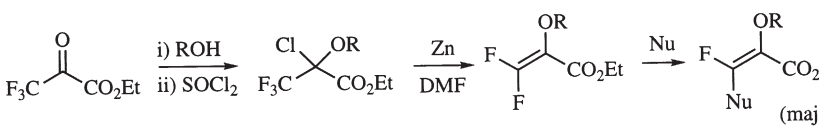


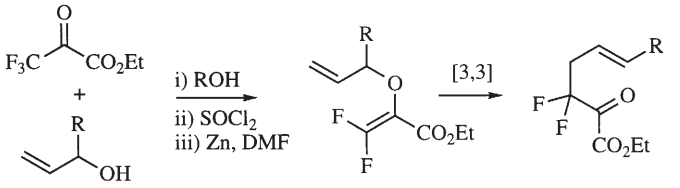
(94)

ketonic carbonyl group to afford relatively stable hemiketals which can be chlorinated affording the α-chloroethers. Dechlorofluorination then affords the rather attractive α-alkoxy-β,β-difluoroalkenoates. Nucleophilic displacement of one fluorine atom has been achieved stereoselectively (Eq. 95) [273]. A potentially useful C-3 allylic alcohol has been produced by a (long) related procedure [274]; however, when allylic alcohols are used to form the hemiketal, [3, 3]-rearrangement could be induced under mild conditions [275], transferring the CF_2 group into mid-chain (Eq. 96).



(95)

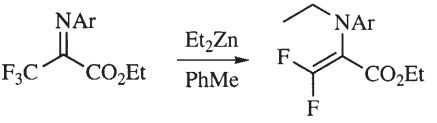
Reconversion of the ketonic carbonyl group into a diazo group sets the stage for intramolecular carbenoid addition to an alkene [276]. A recent paper described syntheses of 2-*C*-trifluoromethyl 3-deoxypentoses [277] from ethyl trifluoropyruvate; other approaches to heterocycles containing trifluoromethyl groups were reviewed recently and will therefore not be discussed further here [278].



(96)

Uneyama has described some interesting reactions of the *N*-aryl imines of ethyl trifluoropyruvate. Tandem alkylation/defluorination occurred (Eq. 97) upon exposure to diethylzinc, via attack at *nitrogen* and S_N2' displacement of fluoride anion [279]. Interestingly, an alkylzinc halide reagent attacked regioselectively at carbon, perhaps the more expected outcome.

The difluoroalkenoate products should have some interesting chemistry. Asymmetric reduction (Eq. 98) occurred with moderate ee to afford an enantiomerically-enriched alanine analogue [280].



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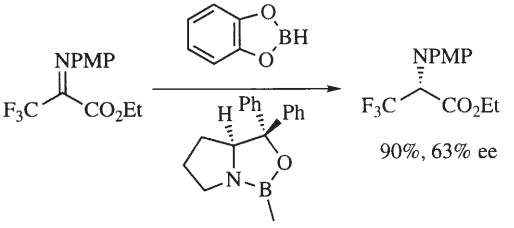

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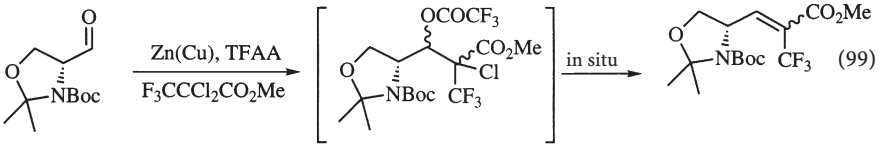
5
Four-Carbon Fluorinated Building Blocks

5.1
2-(Trifluoromethyl)propenoic Acid

This material is available commercially, or can be prepared by palladium(0)-catalysed carbonylation [281] of bromotrifluoropropene. Carbonylation routes to (trifluoromethyl)propanals were described in the same paper. A route to higher 2-trifluoromethyl 2-alkenoates was described by the Ciba-Geigy group [282]; Reformatsky reaction of methyl 2,2-dichloro-3,3,3-trifluoropropionate with aldehydes in the presence of acetic or trifluoroacetic anhydride resulted in elimination forming the alkenoate in situ (Eq. 99).

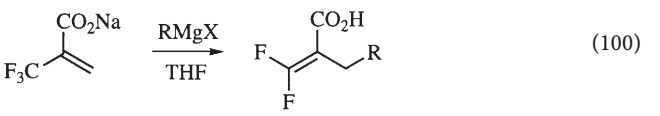
Fluoride ion can be displaced from the sodium salt of 2-(trifluoromethyl)propenoic acid with some control; Fuchikami [283] and co-workers showed that

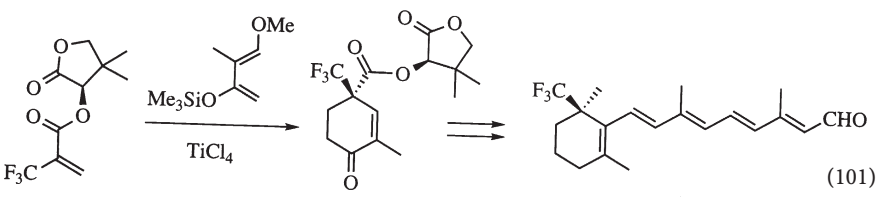


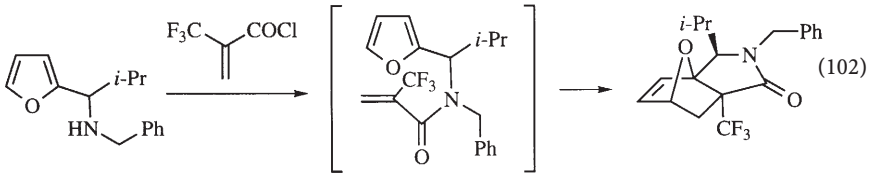
Grignard reagents and lithium tetrahydridoaluminate achieved S_N2' displacement of fluoride anion (Eq. 100). Displacement of a second fluoride ion occurred with excess reducing agent, and upon the action of butyllithium. These reactions have not found extensive use in target synthesis.

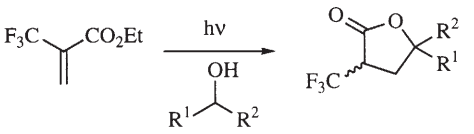
At Tokyo College of Pharmacy [284], esters of 2-(trifluoromethyl)propenoic acid were used to synthesise 16,16,16-trifluororetinal (Eq. 101). Intermolecular Lewis acid-catalysed Diels-Alder reaction with a pantolactone chiral auxiliary allowed the diastereoselective construction of the core cyclohexenone portion with the quaternary centre set in the desired absolute configuration.

The same ester also undergoes useful ene reactions, again with high diastereoselectivity [285]. An intramolecular Diels-Alder system was set up when the corresponding acid chloride reacted with furfurylamine derivatives [286]. Large R^1 groups resulted in a highly stereoselective formation of the *trans* product (Eq. 102) under mild conditions. The α-methyl compounds were much less reactive and afforded products from the opposite sense of stereoselection. More recently, photochemical additions of alcohols to 2-(trifluoromethyl)propenoic acid led directly [287] to the formation of trifluoromethyl butyrolactones in good yield (Eq. 103).





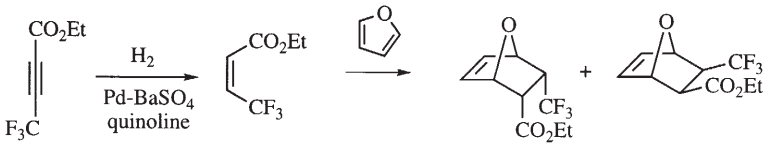




(103)

5.2
Ethyl 4,4,4-Trifluoro-2-butenoate and Related Compounds

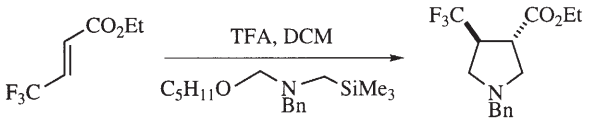
These compounds have some interesting chemistry, particularly when another halogen atom replaces the third fluorine atom. Ethyl 4,4,4-trifluoro-2-butenoate is available commercially (E-isomer) and is easy to prepare. The highly electron-deficient alkenoate has been used as substrate in a range of pericyclic reactions; for example, Wakselman et al. used the intermolecular Diels-Alder reaction with furan during syntheses of analogues of shikimic acid [288]. The Z-diastereoisomeric ester was also reported for the first time during this study (Eq. 104). The key step in its synthesis was the controlled hydrogenation of the corresponding propynoate, itself a reactive dienophile [289].



(104)

The E-alkenoate reacted efficiently with 1,3-dipoles; Bégué and co-workers [290] described a reaction forming a trifluoromethylpyrrolidine via an azomethine ylid (Eq. 105), while a recent study examined the reaction of the methyl ester with a nitrone. The presence of the trifluoromethyl group reverses the stereoselectivity to the sense opposite to that observed with the non-fluorinated alkenoate [291]. Carbocyclic and heterocyclic ring systems can therefore be assembled in a concise manner using this compound [292]; the effect of the trifluoromethyl group on reactivity is comparable to that which would be exerted by a second alkoxycarbonyl group.

Conjugate addition reactions to the E-alkenoate proceeded fruitfully [293]. Remarkably, ketone enolates added to the alkenoate (Eq. 106) to afford the Michael adducts; in the absence of the three fluorine atoms, the retro-Michael reaction dominates, because a ketone enolate is more stable that the ester enolate generated by the conjugate addition process; therefore some special driving



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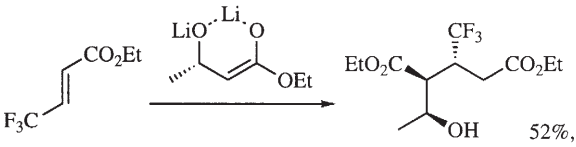
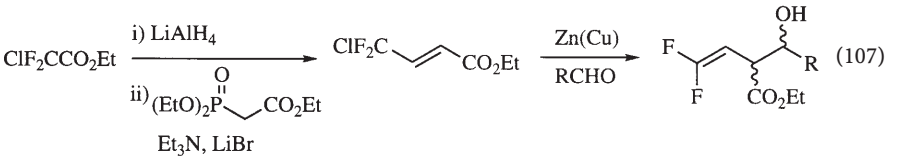


(106)

force must be operating when the the fluorine atoms are present. Coordination of lithium gegenion to one of the fluorine atoms, closing a chelate, was suggested on the basis of ab initio calculations on a simple model compound.

The chlorodifluoroalkenoate was prepared according to Eq. 107, undergoing a Reformatsky-type addition to aldehydes through the α-position in the presence of a Zn(Cu) couple [294]. However, it is the bromodifluoroalkenoate that has the most interesting chemistry. Michael reaction with an amide or ester enolate in the presence of oxygen and triethylborane results in cyclopropanation [295] which is diastereoselective when a chiral auxiliary is employed [296] (Eq. 108). The ring closure step is a fascinating one; presumably, it involves 3-*exo* attack of a difluoromethyl radical on an enolate, implying that the radical is *strongly electrophilic*. Glycine imine anions could also be used to trigger the cyclopropanation, allowing the synthesis of more highly functionalised derivatives [297].



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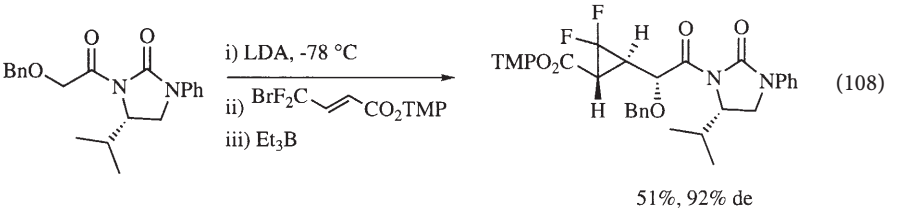
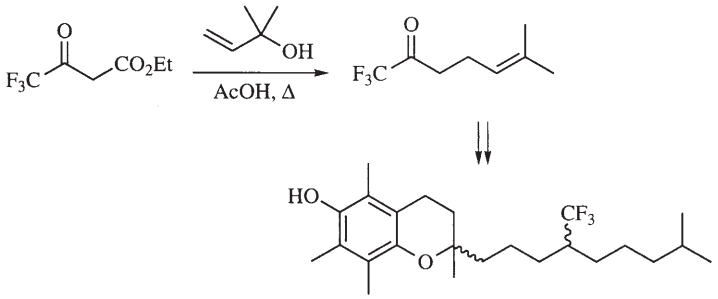


(108)

5.3
Ethyl 4,4,4-Trifluoro-3-oxobutanoate and Related Compounds

The fluorinated ketoester shows some unusual chemistry; the enol tautomer can be trapped directly with 1,3-dipoles [298], while alkylation occurs initially and reversibly at oxygen, followed by isomerisation to the *C*-adduct [299]. The Kumadaki group used the ketoester during syntheses of Vitamin E analogues; Eq. 109 shows the preparation of a key enone [300].

Conversion to the R-hydroxyester set the stage for the synthesis of an enantiomerically-pure epoxide, a versatile C-4 building block (Eq. 110) [301].



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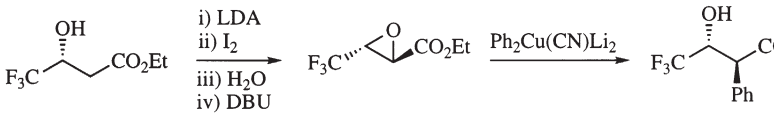
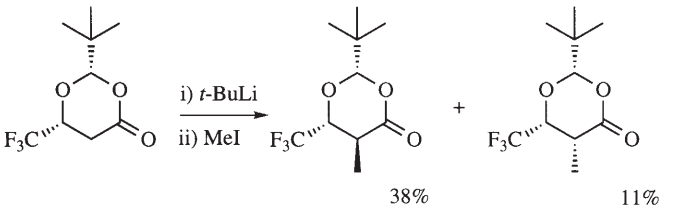


(110)

Hard organometallic nucleophiles (Grignard, organolithium reagents) reacted at the ester carbonyl initially, whereas a higher order heterocuprate reacted cleanly at the less hindered (and more activated) end of the epoxide. The ETH group also prepared interesting 6-trifluoromethyl-1,3-dioxan-4-ones [302]; the enolates were generated and trapped to afford the *trans, trans* compounds in very varied yields (Eq. 111).

The related 6-trifluoromethyl-1,3-dioxin-4-ones underwent conjugate addition reactions with Gilman reagents, or with Grignards with copper(I) catalysis (Eq. 112). The 6-substituted compounds were also available, and were used to synthesise threonine and *allo*-threonine analogues [303]. Stark contrast between the behaviour of fluorinated and non-fluorinated compounds is revealed in Eq. (113). While benzylmagnesium chloride adds smoothly to the 6-methyl



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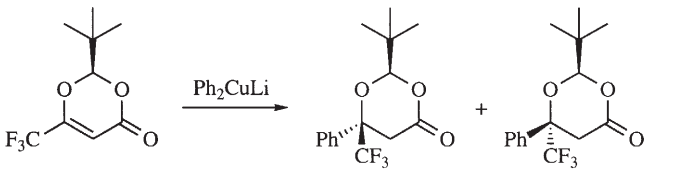

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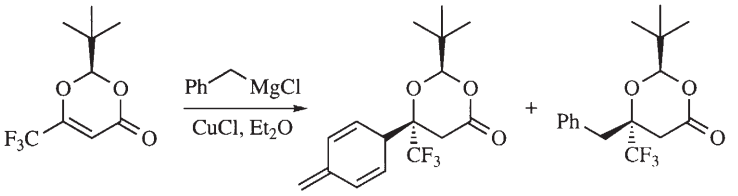
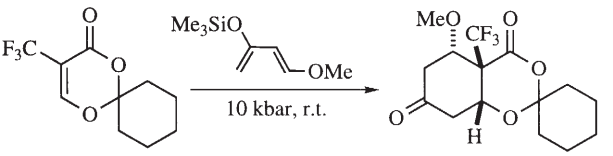


(113)

compound in the expected way in the presence of catalytic copper(I) chloride, the unusual quinone methide product was formed from the trifluorinated congener (Eq. 113) [304].

The related 5-trifluoromethyl-1,3-dioxin-4-ones underwent high pressure Diels-Alder reactions with Danishefsky's diene (Eq. 114), and [2+2] photocycloadditions with alkenes [305]. The former reaction failed entirely when attempted in the absence of the fluorine atoms.

Fluorinated dicarbonyl triphenylphosphoranes, easy to prepare (by trifluoroacetylation of the stabilised ylides), have been transformed stereoselectively into β-substituted β-trifluoromethyl alkenoates by treatment with organolithium reagents (Eq. 115) [306]. The stereoselectivity could be reversed by O-methylation of the initial adduct followed by protonation [307].



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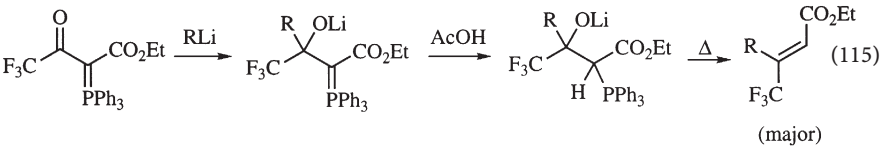
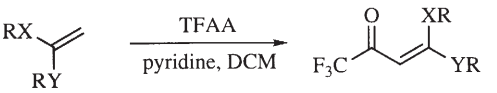


(115)

5.4
1,1,1-Trifluorobut-3-en-2-one and Related Compounds

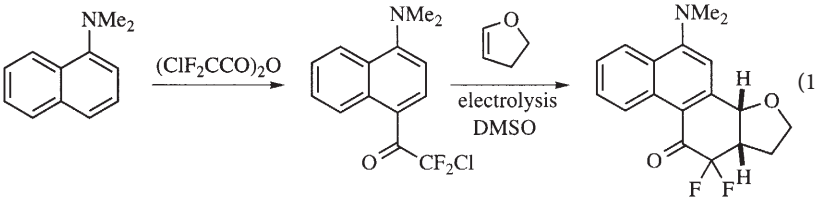
Hojo et al. [218, 308, 309] described the trifluoroacetylation of alkenes activated by heteroatom donors such as vinyl ethers and ketene acetals (Eq. 116); the reaction occurs under mild conditions and can be used to prepare bis(trifluoroacetyl) products from highly activated derivatives [310]. The main use of the products appears to be in the synthesis of trifluoromethyl heterocycles; both 1,2- and 1,4-attack by nucleophiles occur readily [311–315].

The reaction also runs smoothly for chlorodifluoroacetic anhydride and difluoroacetic anhydride, but less reactive electrophiles fail to react. There appear



(116)

X, Y = NR, O or S



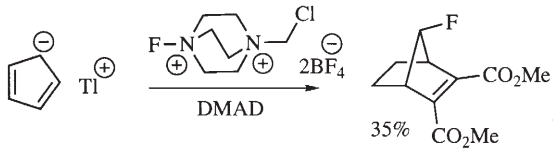
(117)

to be few applications in aliphatic chemistry apart from the electrochemical transformations described by Medebielle [316]. Electrochemical generation of a free radical by carbon-chlorine bond reduction sets the stage for some useful cyclisation processes (Eq. 117) [304].

6 Larger Fluorinated Building Blocks

Fluorinated cyclopentadienes would be ideal components for cycloaddition reactions leading to fluorinated carbocycles. However, there are few reports of such species. Treatment of the thallium(I) salt of cyclopentadiene with Selectfluor led to the formation of fluorocyclopentadiene (Eq. 118), which reacted with dienophiles to afford cycloadducts in the *syn* orientation [317].

Difluorocyclopentadiene was prepared via a pyrolysis reaction; the difluoromethylene centre was installed (Eq. 119) using a DAST fluorination [318]. A fluorobutenolide building block was prepared by a Wadsworth-Emmons reaction of isopropylidene glyceraldehyde; removal of the ketal protecting group led to the formation (Eq. 120) of the unsaturated lactone in acceptable overall yield



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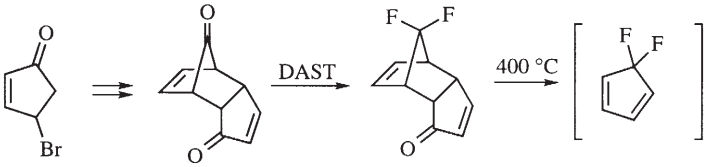

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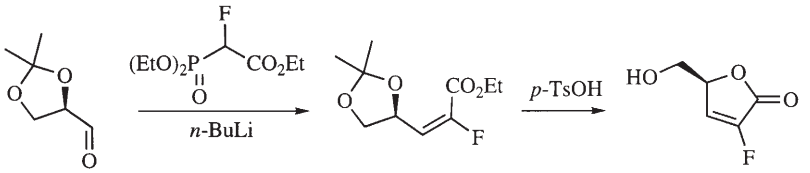
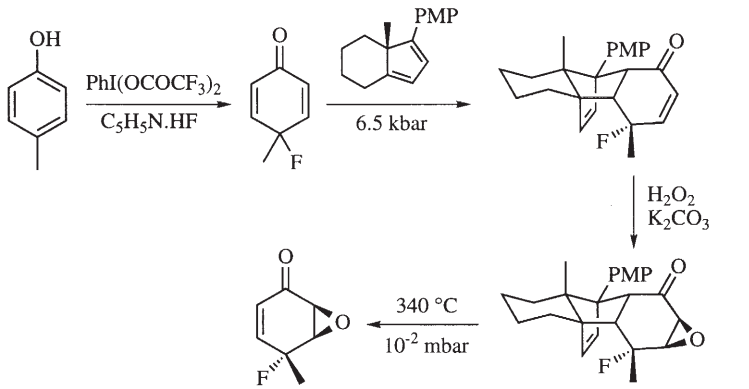


(120)

[319]. A related compound was available as a racemic modification from 3-fluorocatechol. Other C-6 building blocks include the fluorobenzene diol, obtained by *Pseudomonas putida* oxidation of fluorobenzene. Carless and Oak described the preparation of a fluoroconduritol from this attractive intermediate [320] though there are few other citations of the building block. A simple route to an enantiopure fluorocyclohexenone was described by Weinmann and Winterfeldt [321]. Fluorination of *p*-cresol, mediated by a hypervalent iodine reagent, afforded the fluorocyclohexadienone which was trapped with an enantiopure cyclopentadiene under high pressure conditions. Modification of the exposed double bond followed by flash vacuum pyrolysis afforded the fluorocyclohexenone (Eq. 121).

Other fluoroaromatic compounds such as fluorobenzene, trifluorotoluene and their derivatives may be elaborated to more complex aromatic compounds by directed metallation reactions (in itself, the subject of another large review [322–324]). Wakselman and co-workers described the conversion of 3-trifluoromethylphenol into 2-(trifluoromethyl)-1,3-cyclopentadienone, an intermediate they used to synthesise angularly trifluoromethylated steroid analogues [325]. The reaction, which involved an interesting ring contraction reaction, occurred with rather low efficiency (Eq. 122) [326].



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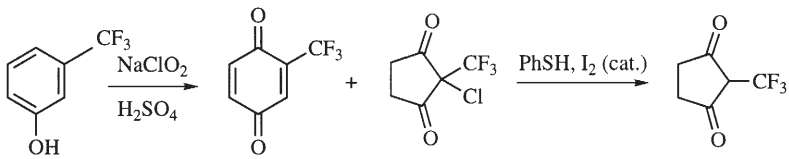


(122)

7
Transformations of Fluorinated Motifs

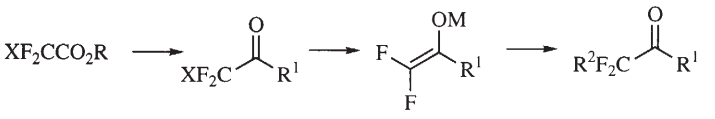
Certain fluorinated motifs can be installed easily using the building block methods described in the previous sections. The existence of transformation methods adds considerably to the scope of building block chemistry. Again, there are many methods available so this section will attempt to highlight those of strategic importance, and to show where the repertoire lacks strength.

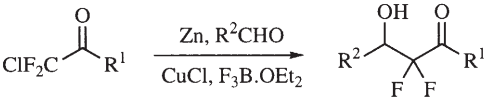
7.1
Aldol and Related Reactions involving Fluoroenolates and Equivalents

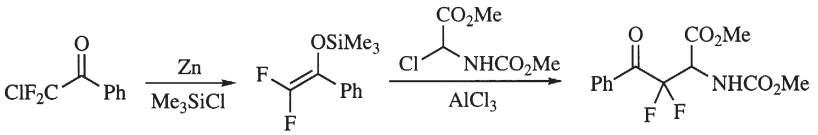
The extension of an array to include, for example, a halodifluoromethyl ketone sets the stage for a second carbon-carbon bond forming reaction via a difluoroenolate or synthetic equivalent (Eq. 123). Despite the obvious power of this approach for the assembly of more complex molecules around a C-2 fluorinated unit, there are relatively few examples in the literature.

Chlorodifluoromethylketones underwent aldol reactions (Eq. 124) via zinc enolates, to afford good yields of α,α-difluoro-β-hydroxy ketones, in a study by the Kyoto group [327]. Copper(I) or silver salt catalysis was essential and boron-trifluoride additive appeared to exert a key role in the conversion to the enolate. Earlier [328], chlorodifluoromethyl ketones had been converted to the difluoroenoxy silanes by the action of zinc in the presence of chlorotrimethyl silane. A difluoroenoxy silane was used by McCarthy and co-workers [329] to synthesise a kynureninase inhibitor (Eq. 125); Lewis acid-mediated reaction with a chloroglycinate installed the key carbon-carbon bond.

An alternative approach to difluoroenoxy silanes developed by the Reims group was described in Sect. 2.3.1 (Eq. 16). Lewis acid-mediated reactions with aldehydes and with alkyl halides were also described, constituting a valuable complementary approach to the Ishihara chemistry. The third approach to the



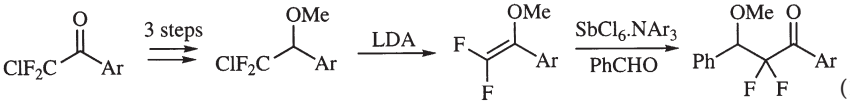




synthesis of a difluoroenoxy silane involves introducing the alkyl chain as a Grignard reagent in the reaction with a trifluoromethyl acyl silane. Xu and co-workers have published extensively on the chemistry shown in Eq. (126), but full details for the preparation of the key acyl silane have never been published. Nevertheless, a brassinosteroid analogue was prepared using this chemistry.

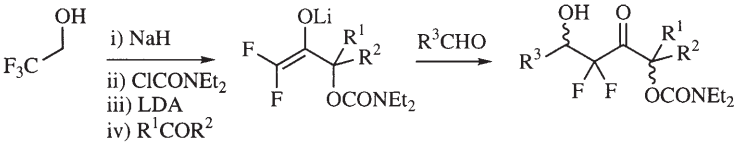
More stable difluoroenol ethers were prepared in four steps from ethyl chlorodifluoroacetate by the Taguchi group (Eq. 127). Lewis acid-mediated additions to aldehydes [330], and to *N*-acyliminium species [331], were described. The choice of Lewis acid was critical for the success of these reactions, particularly in the former case where Lewis acids capable of activity in SET processes were effective, whereas more conventional agents such as trimethylsilyl triflate were not.

(126)



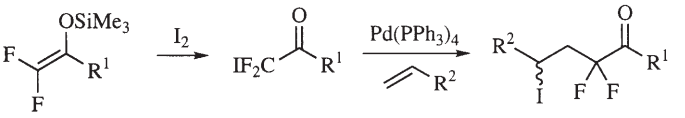
(127)

Metallated difluoroenol carbamate chemistry can be used as a flexible entry point to difluoroenolates and to difluoroenoxy silanes (Sect. 3.3, Eq. 42). Trapping the difluoroenolates with non-enolisable aldehydes affords aldol products (with low stereoselectivity and in variable yield) (Eq. 128) [332], while difluoroenoxy silanes result when the enolate is intercepted with a chlorotrialkyl silane [333].



(128)

The difluoroenoxy silanes can be converted to any of the possible halodifluoromethyl ketones upon treatment with the appropriate electrophile (NCS, NBS or ICl). Iododifluoromethyl ketones are a valuable class of intermediate; Qiu and Burton [334–336] have shown that they add efficiently to alkenes in the presence of catalytic palladium(0), or under photolysis conditions (Eq. 129). A radical mechanism is claimed for the process and while there is evidence to support this hypothesis, results which contradict it are discussed later in this section.



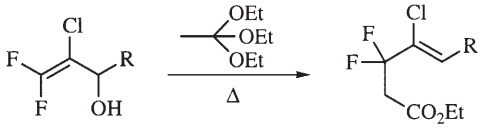
(129)

7.2
Transformations of Fluoroallylic Compounds

7.2.1
γ,γ-Difluoroallylic Compounds

These compounds are available directly using metallated difluoroalkenes or metallated difluoroenol derivatives and show considerable potential for the synthesis of mono-, di- or tri-fluorocompounds. Sigmatropic rearrangements [337,338] are attractive reactions for the transformation of the vinylic chain-end CF_2 motif into a mid-chain position [339] with carbon-carbon bond formation and Dolbier et al. showed [340] that some acceleration accrued with rehybridisation of the fluorinated centre from sp^2 to sp^3 [341]. Isolated but preparatively useful Claisen rearrangements were described by the groups of Taguchi [342] and Metcalf [343] and the high reactivity of the substrates was noted. Lang and co-workers described a complementary and useful Reformatsky-Claisen procedure [344], but there were no systematic studies. More recently, the groups of Kumadaki (Eq. 130) [345] and the reviewer [346] have re-examined the Claisen rearrangement with difluoroallylic alcohol substrates.

While Eschenmoser and Johnson variants of the Claisen ran smoothly on difluoroallylic alcohol substrates, the Dauben-Dietsch conditions afforded a dienal product somewhat unexpectedly (Eq. 131). This product arises because of the high acidity of the *β,β*-difluoroaldehydic product, which may be enhanced further by an interaction between the carbonyl oxygen and Brönsted or Lewis acid in the medium. The reader should note also the high reactivity of the rearrangement substrate. Remarkable differences in reactivity between primary, secondary and tertiary substrates were also exposed. The [2, 3]-Wittig rearrangement has also proved effective in elaborating simple difluoroallylic alcohols [347].



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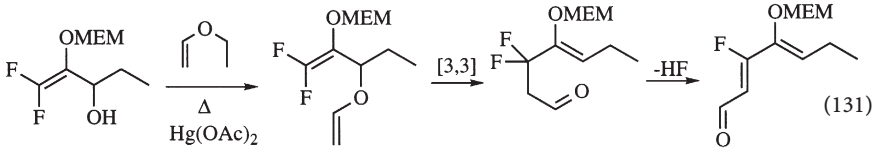
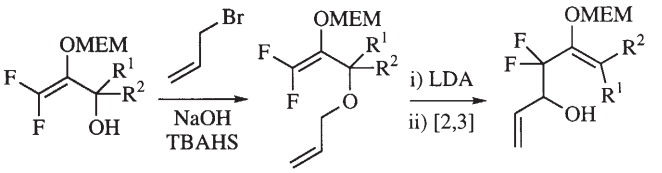


(131)

A range of ethers rearranged smoothly (Eq. 132) affording products with an attractive level of differentiated functionality. Indeed, the high reactivity of the difluoroallylic moiety was revealed when the dienyl allyl ether in Eq. (133) rearranged exclusively on the difluoroallylic unit. Nucleophilic (S_N2') displacement of an allylic acetoxy group would constitute an alternative method for the formation of a carbon-carbon bond to the fluorinated centre. Copper-catalysed reactions of Grignard reagents with difluoroallylic acetates (Eq. 134) afford a solution to this problem [348].



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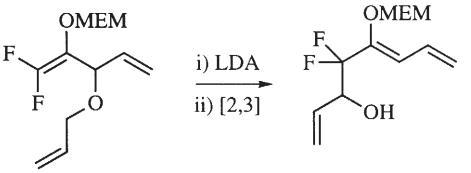

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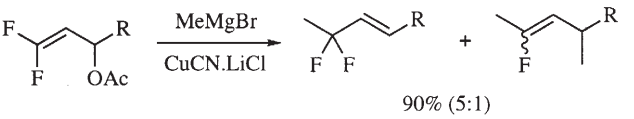
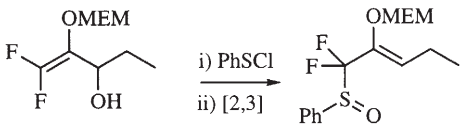


90% (5:1)

(134)

Other groups can be attached to the fluorinated carbon atom.

Treatment of difluoroallylic alcohols with sulfur(II) or phosphorus(III) halides resulted in [2, 3]-rearrangement (Eq. 135) under mild conditions [349]. This method constitutes a potential alternative route to difluorophosphonates, and to difluorosulfoxides and sulfones. The Jussieu group showed that thionyl chloride or bromide converted difluoroallylic alcohols to the corresponding halodifluoromethyl allylic compounds (Eq. 136) [350]. Exposure to DAST afforded the trifluoromethyl congeners [351, 352] and Kumadaki showed that β-chloro-γ,γ-difluoroallylic alcohols afforded the trifluoromethyl alkene products upon treatment with HF.



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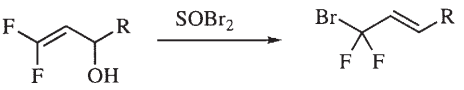
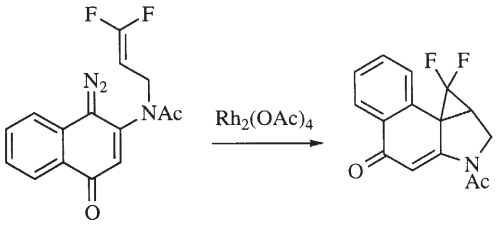


(136)

Carbenoid additions to γ,γ-difluoroallylic compounds represent valuable methodology complementary to the difluorocarbene chemistry described in Sect. 2.1. One example was provided by Boger and Jenkins [353] at Scripps during a synthesis of a duocarmycin analogue. Intramolecular rhodium-catalysed carbenoid addition of a p-quinonediazide to a protected difluoroallylic amine formed a key intermediate (Eq. 137).

Reductive defluorination reactions have also been described; in ether, difluoroallylic alkoxides undergo stereoselective reduction (Eq. 138) to the E-monofluoro derivatives upon treatment with lithium tetrahydridoaluminate [354]. Sodium borohydride [355] and Red-Al [346] have also been used to achieve this transformation.



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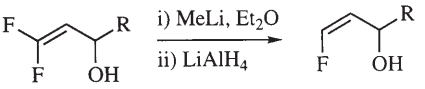
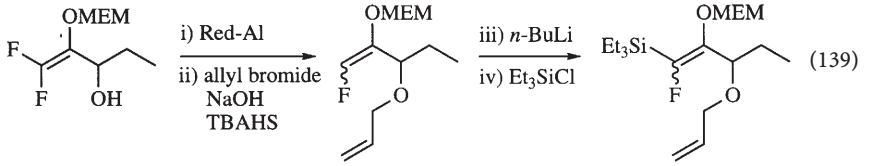


(138)

Both stereoisomeric reduced products can be remetallated at the γ-position following protection of the hydroxyl group [356]; the new metallated difluoroenol derivatives can be quenched with electrophiles and separated (Eq. 139), affording an entry to highly-functionalised monofluorocompounds with the prospect for elaboration with a high level of stereocontrol. Similar γ-metallation chemistry has been described [49, 357] using 1-bromo-1-fluoroalkenes (which undergo coupling reactions with alkynes [358, 359]) and dibromofluoromethyl alcohols.

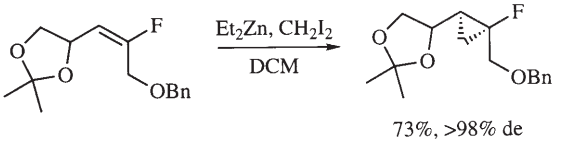


(139)

7.2.2
β-Fluoroallylic Compounds

The presence of an excellent recent review in this area [7] will curtail discussion to three papers. Taguchi et al. [360] showed that protected *β*-fluoroallylic alcohols underwent Simmons-Smith reactions more slowly than the non-fluorinated congeners, but still afforded useful yields of cyclopropane products (Eq. 140) with an excess of the methylene transfer reagent.

Epoxidation also proceeds (Eq. 141) under mild conditions and with high stereoselectivity (95:5 *erythro*: *threo*) despite the deactivating effect of the fluorine atom [361]. At a higher oxidation level, the Lausanne group described chemistry of a metallated azomethine derived from *α,β*-unsaturated-*α*-fluoroaldehydes [362]. Highly flexible chemistry allowed alkylation at nitrogen, or at the (fluorinated) *α*-position, or at the *γ*-position (Fig. 8).



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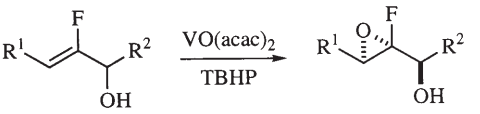

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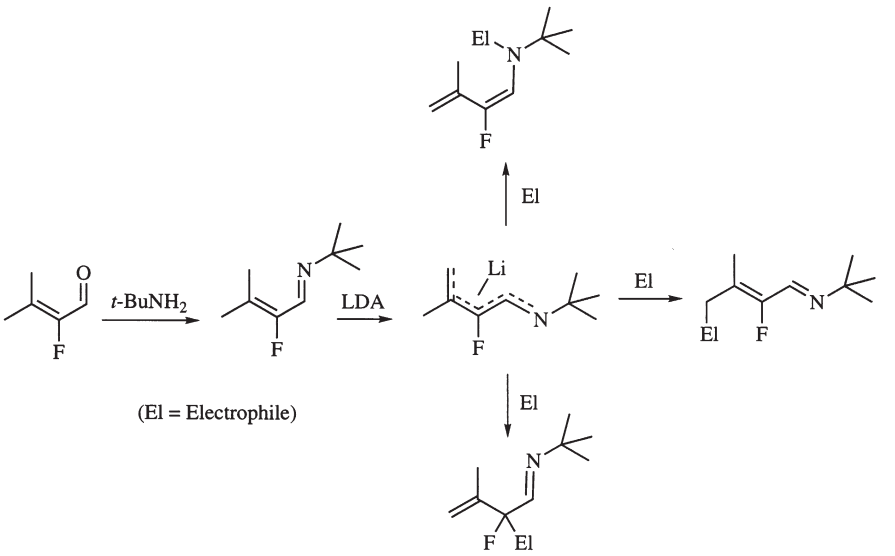
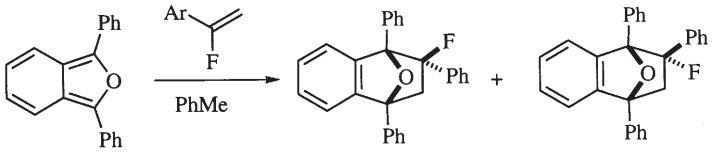


Fig. 8. Chemistry of another 3-azapentadienyllithium reagent

7.3
Cycloaddition Reactions with Fluorinated Components

This section deals with fluorinated dienes and fluorinated dienophiles in which the fluorine atom(s) are attached directly to the double bond(s). The reason for highlighting work in this area is to show how there is a significant need for new methodology; indeed, the formation of cyclic mono- or di-fluorocompounds remains the one significant area where building block chemistry is weak.

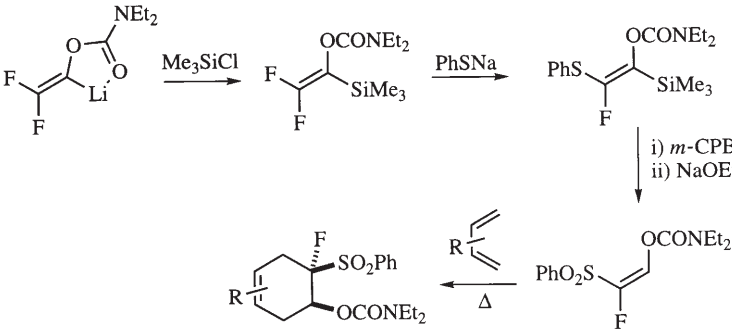
Since the seminal work of Bartlett [363] there have been relatively few reports of useful cycloadditions of fluoroalkenes. Recent work by Haufe showed that fluorine atom substituents depress the reactivity of styrene derivatives in the Diels-Alder reaction with 1,3-diphenylisobenzofuran. A single fluorine atom in the β-position lowered the rate of the [4 + 2] reaction by a factor of ten; when the fluorine atom occupied the α-position (Eq. 142), the reaction was over 30 times slower than that of the unsubstituted styrene.



(142)

This effect cannot be explained by simply considering differences in frontier orbital energies. A useful monofluorinated dienophile has been prepared [364] using metallated difluoroenol carbamate chemistry (Eq. 143); cycloaddition occurred smoothly with a range of dienes, and desulfination could be achieved under mild conditions without loss of the fluorine atom. Wakselman and co-workers [365] synthesised a rare competent difluorinated dienophile. Lewis acid catalysed Diels-Alder reaction with furan afforded an acceptable yield of (unfortunately) unstable cycloadduct which decomposed to a phenolic product via a dehydrofluorination reaction, circumscribing its utility (Eq. 144).

More recently, a more stable α-(*N*,*N*-diethylcarbamoyloxy) analogue was prepared (Eq. 145) [366]; heating this material with cyclopentadiene afforded a high yield of cycloadduct. A furan adduct was also prepared but in lower yield



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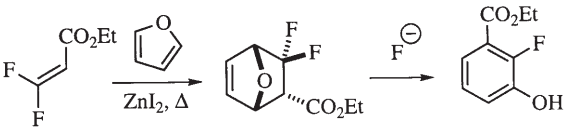

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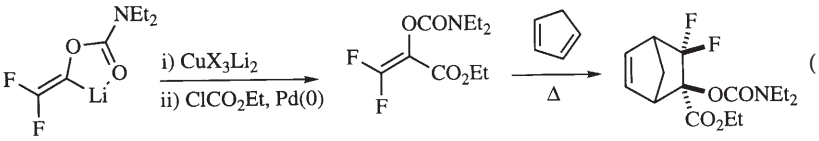


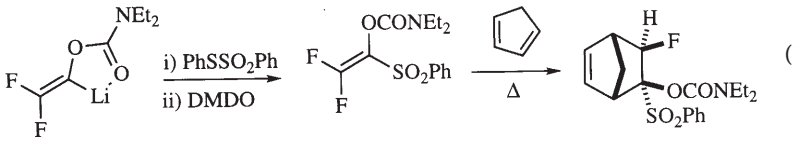
(145)

(though the reaction has not been optimised). Related enones were shown to react with cyclopentadiene alone; hydrofluorination competed and the reaction with other dienes was not sufficiently rapid for cycloadducts to be formed. Indeed, the high Michael reactivity of activated alkenes in which two fluorine atoms are located β- to the electron-withdrawing group is extremely high; a most unusual in situ reduction was observed [367] when a difluorovinylsulfone was heated with cyclopentadiene (Eq. 146).

The reviewer found only a single example [368] of a [3+2] dipolar cycloaddition involving a fluoroalkene component (Eq. 147) in the literature.

Fluorinated dienes have been described, though again, the incidence is rare. Treatment of an α,β-unsaturated-α-fluoroaldehyde with chlorotrimethyl silane afforded [369] the 1-trimethylsilyloxy-2-fluorobutadiene which underwent [4+2] cycloadditions with dienophiles, though more slowly than its non-fluorinated counterpart, and with lower regioselectivity (Eq. 148).

Taguchi described a difluorodiene (Eq. 149) which underwent smooth hetero Diels-Alder reaction with aldehydes, but was extremely unreactive towards



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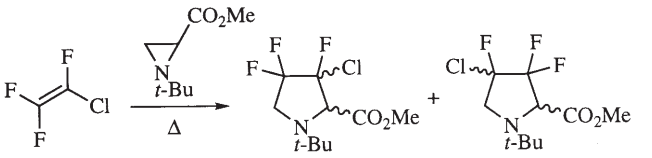
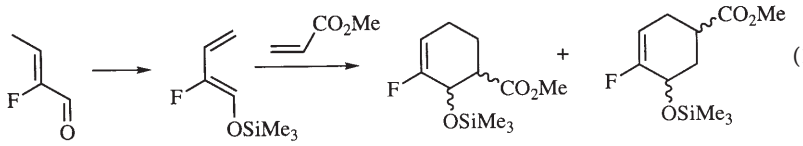
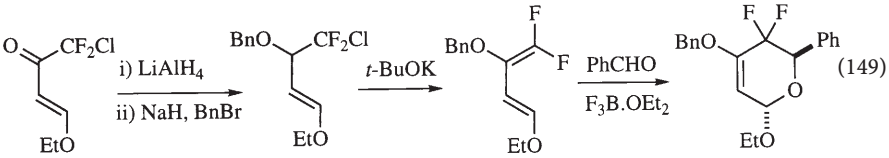


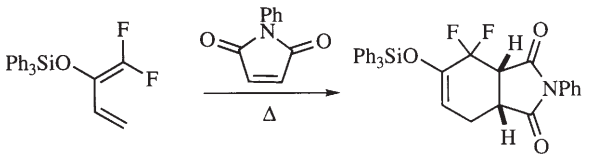
(147)



(148)



(149)

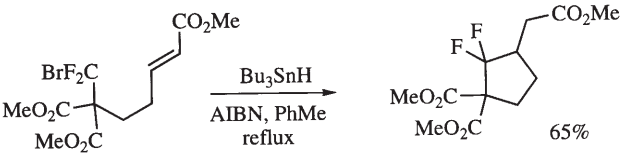


(150)

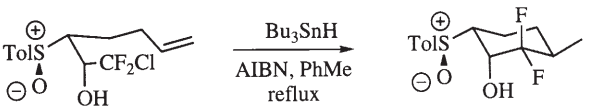
carba-dienes [370] while a related compound [371] underwent [4+2] and [2+2] (Eq. 150).

7.4
Free Radical Reactions involving Fluorinated Centres

The high strength of the C-F bond renders it virtually inert under the conditions used to trap and generate free radicals, though fluorine atoms may exert a significant effect on the course of free radical reactions. However, the magnitude and direction of the effects remain far from clear. Recent physical organic studies have demonstrated the highly electrophilic σ-nature of perfluoroalkyl radicals. The SOMO energy is relatively low because of delocalisation of the unpaired spin into the β C-F σ^* orbitals, and the inductive electron-withdrawal exerted by the perfluoroalkyl group. Set against this effect is the SOMO raising interaction with the non-bonding electron pairs on the fluorine atoms borne on the radical centre. The trifluoromethyl radical therefore has π-character [372–374]. Recent work allows an assessment of the effects of one or two fluorine atoms at different locations relative to the radical centre to be made [375]. Buttle and Motherwell demonstrated that difluoromethyl radicals displayed some nucleophilic character [376]. Higher yields of cyclisation products were obtained when an electrophilic alkene was present to trap the difluoromethyl radical. Equation 151 shows a successful cyclisation. The precursor was constructed by bromodifluoromethylation of a malonate carbanion in moderate yield. According to Bravo and co-workers, difluoromethyl radicals are electrophilic and highly reactive though their studies do not provide evidence either in support of or against this view [377]. The cyclisation in Eq. (152) afforded product as a single stereoisomer in moderate yield.

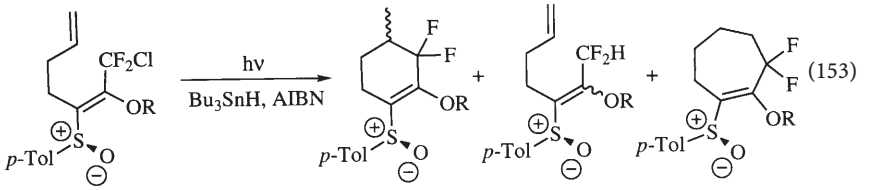


(151)

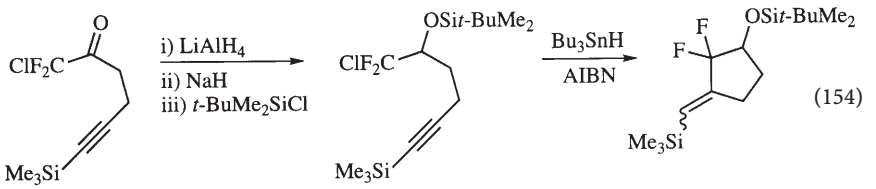


(152)

The preference for the methyl group to assume an equatorial orientation is presumably reinforced by the necessity to avoid a 1,3-diaxial repulsion with the axial hydroxyl group. Similar routes to monofluorocyclohexanes [378] and difluorocyclopentanes [379] have been described by these authors. Recently, difluoroallylic radicals were investigated (Eq. 153); products from 6-*exo* and 7-*endo* cyclisations were obtained along with reduction products [380]. Carbon-chlorine bond cleavage was used to initiate radical formation in all these cases; the effect of a ketonic carbonyl group next to the incipient radical centre is most interesting. Barth and Oyang [381] showed that only products of radical reduction were formed when the chlorodifluoromethyl ketone in Eq. (154) was exposed to tin hydride conditions. However, reduction of the carbonyl group and protection of the hydroxyl allowed a radical cyclisation to be performed. This suggests that the fluorine atoms and π-donor carbonyl group provide excessive stabilisation of the free radical, lowering the rate of cyclisation below a viable level (consistent with the observations of Itoh and co-workers [200]).

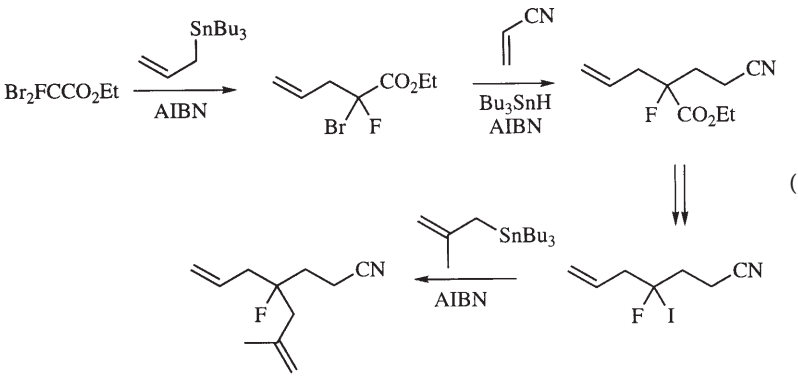


(153)



(154)

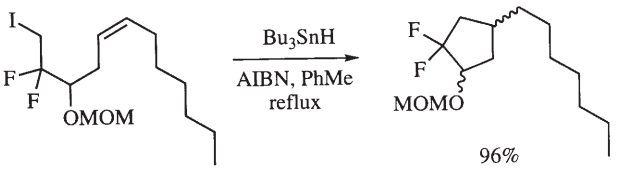
Takeuchi has described a general free radical route to tertiary alkyl fluorides from esters of dibromofluoroacetic acid [175]. The allylstannane fragmentation method was used to prepare an adduct which underwent free radical addition to acrylonitrile (Eq. 155), or Reformatsky reaction with aldehydes. A high yielding bromodecarboxylation was achieved using Barton methodology; iodide/bromide exchange set the stage for a second radical allylation affording the tertiary product. Recent ab initio calculations show that the SOMO energy is indeed lowered still further by the presence of a fluorine atom at the radical centre [382].



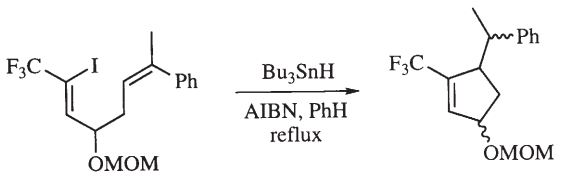
(155)

Radicals generated at the position β to C-F bonds are expected to be more electrophilic than analogous alkyl radicals. Taguchi et al. have explored the scope of cyclisations involving primary and secondary β,β-difluoroalkyl radicals [383]. Difluorotetrahydropyrans and cyclohexanes were prepared; Eq. 156 shows an efficient cyclisation.

The precursor was prepared via a lengthy sequence involving the elaboration of a Reformatsky adduct. The cyclic product was obtained as a 1.2:1 mixture of *cis* and *trans* isomers.The presence of the fluorine atoms had no effect on the efficiency of the cyclisation reaction. A subsequent study [384] extended the range of cyclisations to include trifluoromethyl alkyl and alkenyl radicals (Eq. 157). Free radical cyclisation reactions therefore show considerable promise for the rational synthesis of fluorinated carbocycles.



(156)



(157)

8
Conclusions and Perspectives

When compared with the breadth and depth of non-fluorinated building block chemistry, the subject of this review remains in its infancy. Progress has been made to the stage where one-bond disconnections, for which reliable synthetic equivalent chemistry exists, can be made from fluorinated target molecules. A growing number of methods allow the transformation of readily-available motifs into more complex arrays. However, the repertoire is weaker in the area of processes in which multiple C-C bonds are formed, particularly in Diels-Alder chemistry, an area where significant progress is required, and in useful photochemical transformations. Organofluorine chemists interested in the building block approach are also confronted with the issues presented by the Montreal protocol which restricts the availablility of chlorofluorocarbon carbon starting materials, and with the increasing demands for clean synthesis bringing pressures for atom economy (particularly, presumably, of fluorine atoms!) and mild processing conditions. The key future developments in this area may involve a judicious use of large-scale fluorination methodology combined with sophisticated multiple carbon-carbon bond forming methods.

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Electrofluorination of Organic Compounds

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The three principal electrochemical methods are described by which fluorine can be directly introduced into organic compounds, namely electrolysis in molten salts or fluoride ion solutions, electrolysis in molten potassium fluoride/hydrogen fluoride melts at porous anodes, and electrolysis in anhydrous hydrogen fluoride at nickel anodes. Using examples from the past decade, it is aimed to demonstrate that electrofluorination in its various forms has proved to be an increasingly versatile tool in the repertoire of the synthetic chemist. Each method is described in terms of its essential characteristics, reaction parameters, synthetic utility, advantages and disadvantages, patent protection, and potential for commercial exploitation. The different mechanisms proposed to explain each process are critically reviewed.

Keywords: Electro-; Simons; Anodic; Fluroination; Electron-transfer.

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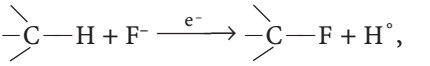
1 Introduction

This chapter covers the three principal methods by which fluorine is introduced into organic compounds via the formation of new carbon to fluorine bonds using electrochemical techniques, a process which, in principle, can be represented as



with the electrode acting as the simple, but effective, reagent.

The three methods are

- electrolysis in molten fluoride salts or solutions containing fluoride ions, at noble metal or graphite anodes,
- electrolysis in molten potassium/hydrogen fluoride at a porous carbon anode (the Phillips or CAVE Process),
- electrolysis in anhydrous hydrogen fluoride at nickel anodes (the Simons or ECF Process).

Although, confusingly, all three of these methods have been termed electrochemical fluorination in the literature, it will be seen that each has its own peculiar characteristics, operational parameters, synthetic utilities and mechanistic explanations.

This chapter does not attempt to cover electrochemical processes which involve the insertion of a group already containing carbon-fluorine bonds into an existing molecule (the building block approach), e. g., perfluoroalkyl group insertion via the Kolbe reaction, or fluoroacyloxylations or fluoroalkoxylations via electro-oxidation, or fluoroalkylation via electro-reduction. These have been reviewed elsewhere [1, 2].

The purpose of the chapter is to highlight the increasing range of possibilities open to the chemist by including new techniques of electrochemical fluorination into his synthetic repertoire as a result of advances in the field over the past five to ten years.

Electrochemical techniques, in general, bring a number of advantages to the synthetic and industrial chemist.

i) They allow the preparation of complex molecules, often difficult to obtain by other methods, in a single stage, single "pot" operation.
ii) The processes require relatively simple equipment, operating at moderate temperatures and pressures, compared with other types of chemical hardware, e.g. autoclaves or furnaces, resulting in lower capital costs.
iii) The processes often use relatively cheap raw material to generate high added-value products.
iv) The reaction parameters of electrochemical processes, e.g., voltages or current, are controllable with precision, and therefore, theoretically at least, so should be product formation.
v) Electrical power is a cheap " reagent", e.g., an electrochemical transformation involving a two electron transfer, operating at, say, 5 V would require only 268 kWh/mole, i.e., for a product of molecular weight 200, the cost of electrical "reagent" would be around £0.10/kg.

2 Electrolysis in Molten Fluoride Salts or Fluoride Ion Solutions

The principal characteristics of this method are the electrolysis of solutions of organic compounds using electrodes of platinum or graphite at anode potentials below those which could give rise to the evolution of elemental fluorine.

Typically, these reactions yield only partially fluorinated products, introducing one, two, or a maximum of four fluorine atoms into the organic substrate. This is in stark contrast to the other methods described later, which readily yield perfluorinated products.

It is generally agreed that the mechanism describing this process can be explained by a sequence of direct electrochemical oxidations of the organic substrate, followed by addition/elimination reactions of fluoride and hydrogen ions, respectively:

$$RH \xrightarrow{-e} RH^{+\circ} \xrightarrow{+F^-} RHF^{\circ} \xrightarrow{-e} RHF^{+} \xrightarrow{-H^+} RF \longrightarrow \text{etc.}$$

A range of experimental conditions, in terms of supporting electrolyte and fluoride source, have been explored in which reactions of this type have been studied [3]. Typical of such systems are:

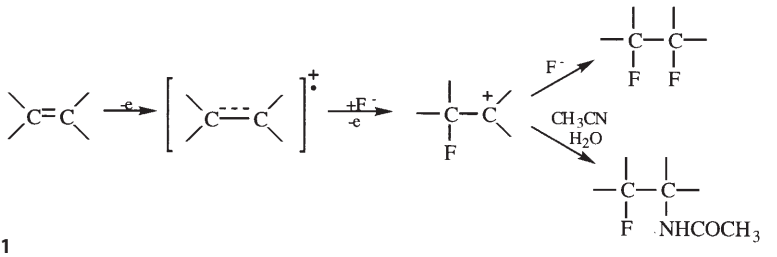
Electrolyte/Solvent:
$R_4NF \cdot nHF / CH_3CN$; $R_3N \cdot mHF$ (neat); $CH_3COOH/KF \cdot HF$; HF / BF_3; Pyridine $\cdot$ 9HF; KOH/KF(NaF)

Whereas in earlier work it was usual to conduct synthetic reactions of this nature under constant current conditions, in recent years greater control and understanding of the systems have been achieved by employing potentiostatic techniques in which the potential of the working electrode (anode) is regulated precisely with respect to a third, reference electrode (e.g., Ag/Ag^+ or saturated calomel, SCE).

The extent and versatility of this methodology can be illustrated by the examples set out below.

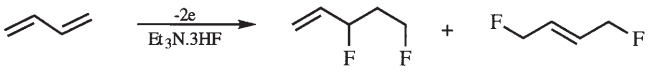
2.1 Alkene Derivatives

Electrofluorination of carbon-carbon double bonds using the versatile $Et_3N \cdot 3HF/CH_3CN$ system [4] produces mixtures of *cis-/trans*-isomeric vicinal difluorides, often together, however, with products resulting from solvent incorporation.



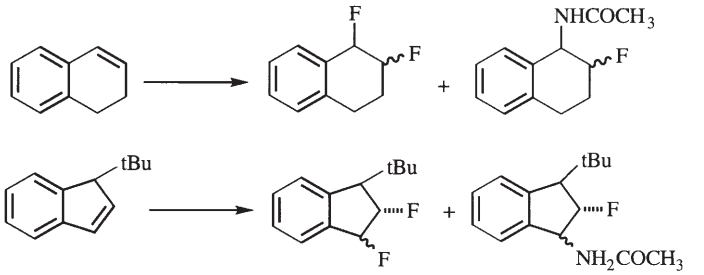
Scheme 1

In the absence of an organic solvent, electrofluorination in neat $Et_3N \cdot 3HF$ of alkenes like styrene, stilbene, 2,3-dimethylbut-2-ene, or 2-methyl-2-butene yield the corresponding vicinal difluorides in 22–55% yield. Butadiene produces a 1:2 mixture of 1,2- and 1,4- difluorides [5].



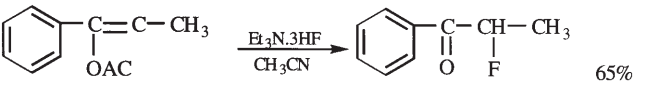
Scheme 2

1,2-Dihydronaphthalene, indene, and 3-*tert*-butyl-indene in acetonitrile solution of $Et_3N \cdot 3HF$ gave mixtures of diastereomeric difluorides, and the respective *N*-(*β*-fluoroalkyl)acetamides. In methylene dichloride solution the difluorides were formed in 67 % yield [6].



Scheme 3

Studies by Laurent et al. have shown the a number of α-fluoroketones can be produced by the electrochemical oxidation of enol esters in $Et_3N \cdot 3HF$ as electrolyte, following basic work-up [7].

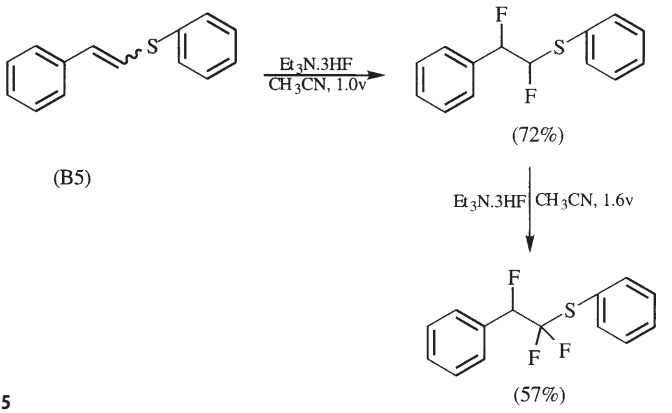


Scheme 4

The enol acetates from acetophenone, benzylphenyl ketone, isopropylphenyl ketone, benzylmethyl ketone, and tetralone gave the corresponding α-fluoroketones, in a similar fashion.

The technique has been developed to include the fluorination of vinyl sulphides to give vicinal difluorides in good yields [8].

At higher anode potentials a trifluoro-sulphide was reported.



Scheme 5

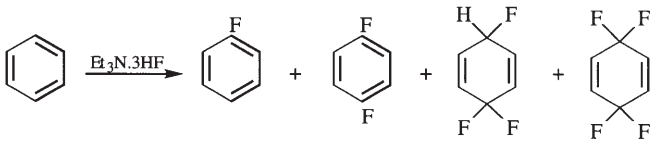
2.2 Aromatic Compounds

The electrochemical oxidations of aromatic compounds in the presence of a fluoride ion sources have been widely studied by a number of workers to produce a range of partially fluorinated compounds [9–12].

However, because of the very similar ionisation potentials (and electrochemical oxidation potentials) of the precursors and products (e.g., benzene, 9.25 eV; fluorobenzene, 9.21 eV; *p*-difluorobenzene, 9.15 eV) selective monofluorination is often difficult to achieve.

Further problems can exist in the electrofluorination of aromatics arising from polymer formation on the anode surface, causing increased cell impedance and low current efficiencies.

Thus, electrofluorination of benzene in neat $Et_3N \cdot 3HF$ yields a mixture of fluorobenzene, *p*-difluorobenzene, trifluorocyclohexadiene, and tetrafluorocyclohexadiene [13].



Scheme 6

In more recent work, Momota et al. [14] have shown that by using acetonitrile as a co-solvent greater selectivity can be achieved in the fluorination of benzene.

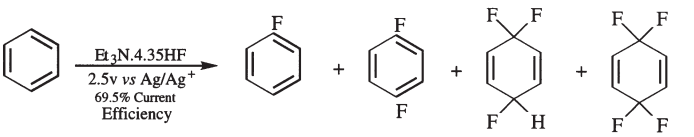
This study also explored in detail the effects of variation of electrolyte composition including $(C_2H_5)_3N \cdot 3HF$ and $R_4NF \cdot nHF$, (where $R = CH_3$, C_2H_5, n-C_3H_7, n-C_4H_9, and $n = 2,3,4$) in acetonitrile solution during potentiostatic electrolysis at 2.5 V (vs Ag/Ag^+), and during cyclic voltammetry.

In comparison with reaction in neat $Et_3N \cdot 3HF$, benzene in a 1 mol/l solution of $Et_3N \cdot 2.9HF$ in acetonitrile, electrolysed at 2.5 V (vs Ag/Ag^+) produced 35% fluorobenzene, together with 4.8% difluorobenzene and 0.6% 3,3,6-trifluoro-1,4-cyclohexadiene.

Asahi Chemical Industries KK have patented this process as being an advantageous and high yield route to fluorobenzene [15].

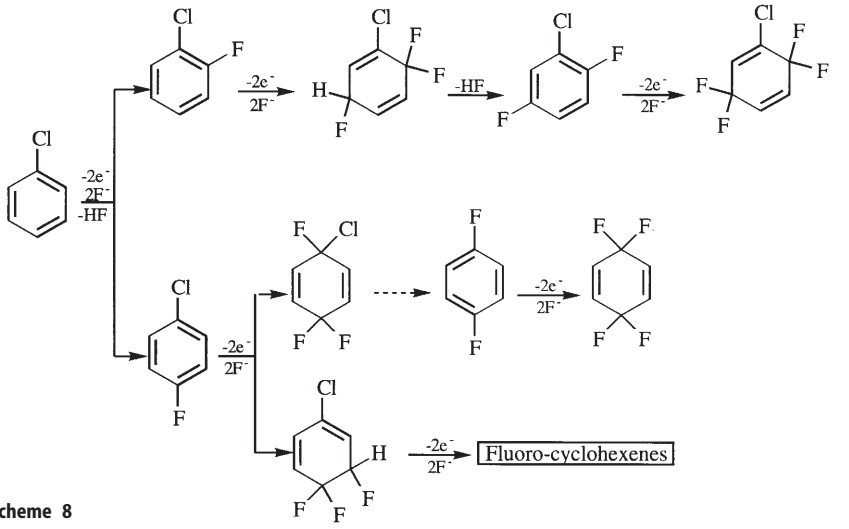
In further studies [16], using a group of new electrolytes, $R_4NF \cdot mHF$ (where $R = CH_3$, C_2H_5, n-C_3H_7, and $m > 3.5$), said to have beneficial properties in terms of viscosity, electrolytic conductivity, and electrochemical stability, the same workers have published a series of papers in which they have studied the electrofluorination of benzene, fluorobenzene, and 1,4-difluorobenzene, (Part I) [16], at high current densities, and high current efficiencies without any film formation at the anode.

Thus, typically, they achieved the following reactions:



Scheme 7

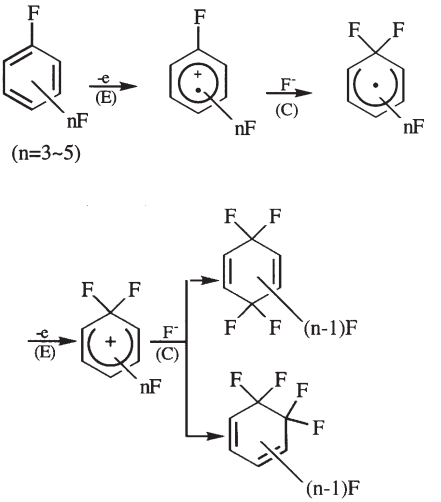
Subsequent papers in this series have reported the electrochemical fluorination of di- and tri-fluorobenzenes, (Part II) [17]; trifluoromethyl-benzenes, (Part III) [18]; chlorobenzene, (Part IV) [19]; as well as side reactions during the fluorination of halobenzenes, (Part V) [20].



Scheme 8

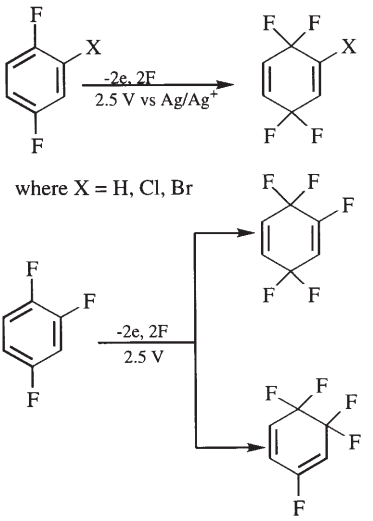
In parallel studies, this group has also studied the electrofluorination of bromobenzene [21] under similar conditions.

They have likewise synthesised a series of polyfluorinated cyclohexadienes by the electrochemical fluorination of polyfluorobenzenes [22].



Scheme 9

The development of these electrochemical techniques to preparative scale, using constant-current methodology, for the fluorination of *p*-difluorobenzenes has produced a number of fluorohexadienes, not previously isolated, in pure states, in very high yields and current efficiencies [23].

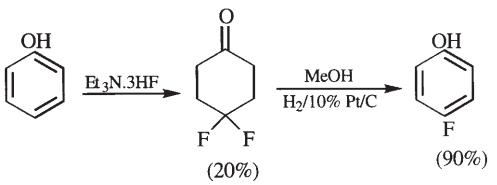


Scheme 10

The authors of this work are obviously mindful of the potential commercial exploitation of these techniques as is evidenced by the filing of patent protection by Morita et al. [24], in which they claim the route towards organic compounds containing fluorine useful as intermediate raw material of drugs, pesticides, and liquid crystals.

Asahi Chemical Industries KK have patented [25] a process for the fluorination of benzene using a nitrile solvent, a base salt, typically $(n\text{-}C_4H_9)_4NF \cdot 3HF$, at a rhodium anode, said to be superior to platinum in corrosion resistance and performance.

Meurs et al. have also studied the electrofluorination of phenol [13] to produce 4,4-difluorocyclohexadienone in 20% yield; this was then hydrogenated to give 4-fluorophenol (90%).

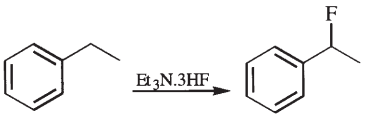


Scheme 11

Patent protection for this and related work has been filed by Shell Research B.V. [26].

2.3
Benzylic Compounds

Meurs et al. have shown the electrofluorination of ethylbenzene in neat $Et_3N \cdot 3HF$ gives 1-fluoro-1-phenylethane in 42% yield [13].



(42%)

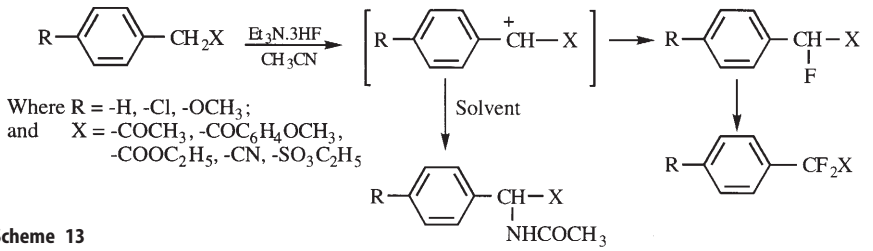
Scheme 12

Further, by using $Et_3N.3HF$ in acetonitrile as solvent, they have demonstrated that electrolysis of benzyl nitriles, carboxylic acid esters, sulphonic acid esters and ketones give the corresponding monofluoro- or difluoro-compounds, depending on anode potential in yields of 30–70%.

The best results are reported using p-substituted aromatics, e.g., *p*-chloro, or *p*-methoxy-derivatives, which stabilise the intermediates [27, 28].

The formation of minor quantities of acetamide by-products can be avoided by using sulpholane as solvent; however, concomitant fluorination of the aromatic ring is said to occur under these conditions [27, 29].

Diastereoselective fluorination of the benzylic position has also been studied by these same workers [30].

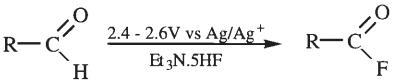


Scheme 13

Patent cover for this and related work has been filed by Rhone Poulenc Research for the preparation of compounds of pharmacological interest. It is claimed that the process is simpler and shorter than prior art methods [31].

2.4
Aldehydic Compounds

A recent report by Yoneda et al. describes the selective displacement of formyl hydrogen with fluorine in aliphatic aldehydes by electrolysis in base · nHF (base = pyridine, Et_3N; n = 3–6) systems, both neat and in acetonitrile and sulpholane solutions [32], e.g.



RCOH	AV(vs. Ag/Ag^+)	Conversion	Yield of RCOF
Where R =		%	%
n - pentyl	2.6	93	70
3 - heptyl	2.55	96	89
cyclohexyl	2.40	98	84
t - butyl	2.40	97	60

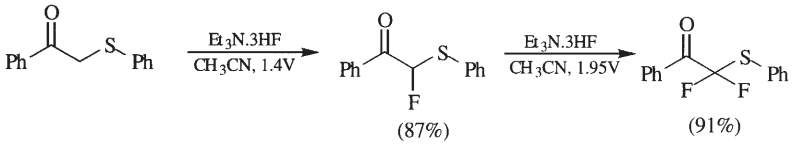
Scheme 14

Patent protection for this and related work has been filed by the Mitsubishi Chemical Corporation as a route to compounds used for medical or agricultural chemicals or liquid crystals [33].

2.5 Compounds Containing Hetero-Atoms

Selective electrofluorinations of activated a-positions in thioethers, sulphides, selenides and heterocycles have been reported by a number of workers [34–38].

The activated sulphur compound $PhCOCH_2SPh$ has been shown to react in a two stage process to produce, firstly, at lower potential, the monofluoro- derivative, and then, at higher potential, the difluoro-compound, both in good yields [39].



Scheme 15

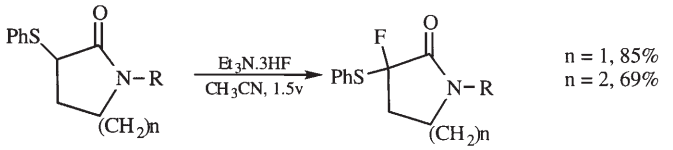
Using similar methodology, constant potential electrolysis, $Et_3N \cdot 3HF/CH_3CN$ electrolyte, platinum anode, Fuchigami prepared the α-fluorinated derivatives of a series of different aryl 2,2,2-trifluoroethyl sulphides.

$$ArSCH_2CF_3 \xrightarrow{Et_3N \cdot 3HF/CH_3CN} ArSCFHCF_3$$

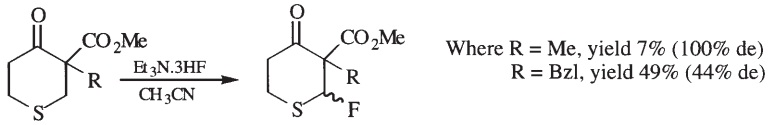
where Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, $PhCH_2$.

Fuchigami et al. have also studied the anodic fluorination of sulphur-containing heterocycles.

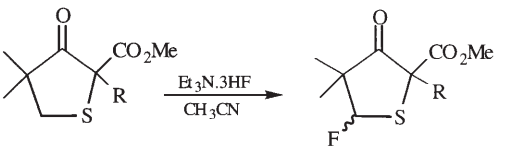
A series of *α*-sulphenyl lactams, thiacyclohexanones, thiolanones, and thiazolidinones have been fluorinated to produce the corresponding diastereomers, some of which have been shown to possess biological activity [35, 36, 40–42].



Scheme 16

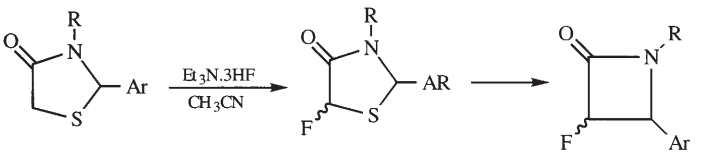


Scheme 17



Where R = Me. at 2.1v, 5.1 $Fmol^{-1}$, yield 74% (48% de)
R = Bzl, at 2.4v, 8.2 $Fmol^{-1}$, yield 71% (22% de)

Scheme 18



Ar = Ph, naphthyl; R = H, Me, i-Pr, Ph.

Scheme 19

Sono and co-workers have electrofluorinated a number of complex nitrogen-containing compounds in the presence of $Et_3N \cdot 3HF/CH_3CN$ [43]. Caffeine afforded 8-fluorocaffeine as the sole product in 40.3% yield.

Guanosine tetraacetate and uridine triacetate gave the monofluoro- derivatives 8-fluoroguanosine tetraacetate (17.5%), and 5-fluorouridine triacetate (4.6%), respectively [44].

Using similar techniques, Suda et al. have fluorinated a series of 4-trimethylsilylazetidin-2-ones in an efficient and regioselective preparation of 4-fluoroazetidin-2-ones [45].

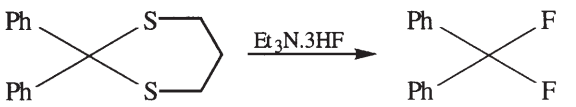
Where R = Ph, yield 49-80%
R = Pr, yield 78%

Scheme 20

The preparation of new fluorine containing pyridazinones, prepared by electrofluorination in various base. HF systems has been patented by Rikagaku Kenkyusho as a route to herbicidal, insecticidal or bactericidal compounds [46].

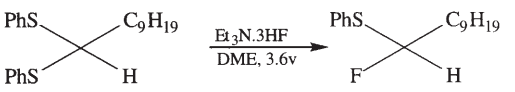
2.6 Thioacetal Compounds

Laurent et al. have shown that 2,2-diphenyl-1,3-dithiane is electrofluorinated in $Et_3N \cdot 3HF$ to the gem difluoride in good yield [47].



Scheme 21

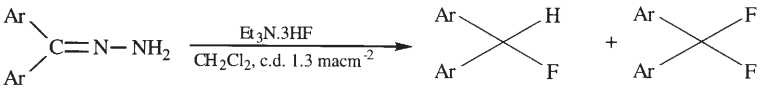
Yoshigama and Fuchigami have also reported that several dithioacetals of aliphatic and alicyclic ketones can be converted to their gem difluoroderivatives in a similar manner. However, they found that with diphenyl dithioacetals only one C – S bond is cleaved to give the monofluoro- compound [48].



(54%)

Scheme 22

Likewise, in a later publication, the same workers found that electrofluorination of a series of diarylketone hydrazones in $Et_3N \cdot 3HF/CH_2Cl_2$ electrolyte produced almost solely the monofluoro-derivative [49].



Where Ar	Monofluoride	Difluoride
Ph	95	3
p-ClC_6H_4	40	0
p-FC_6H_4	63	8
p-MeC_6H_4	16	1

Scheme 23

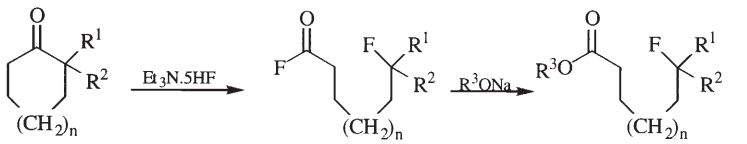
2.7 Lignins

In a somewhat unusual example of electrochemical fluorination, a group of Russian workers have reported [50] the modification of lignins by fluorination of the organic substrate in aqueous alkaline solutions of sodium and potassium fluorides, at platinum or platinised titanium anodes. The fluorine content in the product was said to reach 20%.

Patent protection for this work [51] describes the use of such products as anti-friction additives in powder metallurgy.

2.8 Cyclic Ketones

Recently, Yoneda et al. [52] have reported an interesting electrochemical fluorinative α-cleavage reaction of cyclic ketones as a route to fluorocarboxylic acid esters. The reaction is carried out in the presence of $Et_3N \cdot 5HF$ as electrolyte, when the 2,2-disubstituted cyclic ketone is subject to selective cleavage of the C–C bond between the carbonyl carbon and the substituted α-carbon.



Scheme 24

3
Electrolysis in Molten Potassium Fluoride/Hydrogen Fluoride at a Porous Anode

The so-called Phillips Process was, as its name implies, devised in the laboratories of the Phillips Petroleum Company during the 1970s [53].

Since that time the process has been acquired by the 3 M Company, the technology developed, and given the additional name of the CAVE (Carbon Anode Vapor phase Electrochemical fluorination) Process [54].

The process is characterised by the electrofluorination of volatile organic substrates within the matrix of pores of a carbon anode immersed in molten $KF \cdot 2HF$ as electrolyte (as in a mid-temperature fluorine generator cell), and depends on the phenomenon that the anodically charged porous carbon is not wetted by the electrolyte. The fluorination probably takes place at the three phase interface of organic vapour, solid carbon, and liquid electrolyte in close proximity to, or at the sites where fluorine is being evolved.

Products from this process range from partially fluorinated through to fully fluorinated materials. Certain functional groups, e.g., acyl fluorides, esters, and some cyclic structures, are retained after fluorination.

The mechanism of the process can be explained by established free-radical reactions involving elemental fluorine (see below in Sect. 3.3).

A number of original papers and reviews covering this process have been published in recent years in which the synthetic utility, methodology, and operational problems are described in some detail [55].

3.1
Equipment

A diagrammatic representation of a laboratory CAVE cell is shown in the figure below.

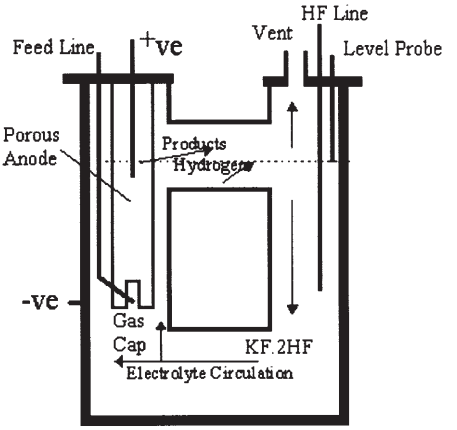


Fig. 1

The heated cell case, which also acts as cathode, is usually constructed of mild steel, with the head fabricated from either poly(chlorotrifluoroethylene) of unfilled poly(tetrafluoroethylene).

Much effort has gone into the study of suitable types of porous amorphous carbons for use as anode material. Union Carbide products PC 25, PC 45, and PC 60 are said to be suitable, with the more friable PC 25 having the best performance in respect of the "polarisation" problem.

A typical laboratory cell, having an anode 3.5 cm in diameter, 35 cm long, and immersed to a depth of 28 cm, will run at two faradays per hour (53.6 A) at a constant current density of 200 mA cm^{-2}.

The volatile organic substrate is fed into the gas cap at the base of the anode where, after formation of a non-wetting layer of so-called graphite fluoride "CF_x", the organic vapour begins to percolate upwards through the pores of the carbon where it makes contact with electrochemically generated fluorine and reacts to form the range of fluorinated products which emerge from the electrode above the electrolyte level and exit the cell head for collection.

Hydrogen generation at the cathode provides electrolyte lift and circulation within the cell.

3.2 Operational Complexities

As mentioned above, before proper fluorination of the substrate can begin it is necessary to "condition" the anode. This step, which occurs on start-up with voltages commencing at ~3 V rising to ~5 V (at a current density of 25 mA cm^{-2}) over a period of a few minutes, produces, irreversibly, the non-wetting film which allows the organic to enter the porous structure of the anode following the displacement of the electrolyte.

Fluorination of the substrate then proceeds smoothly at a constant anode current density of around 200 mA cm^{-2}, with a cell voltage of ~7 V for a period of time (which may last longer than 100 h with anodes of carbon PC 25, but perhaps as short as a few hours with carbon PC 60) until the phenomenon of "polarisation" set in. This results in erratic swings and dramatic increases in cell voltages. The exact nature of the phenomenon is not fully understood but it is believed to be due to the formation of a gas film over the anode surface causing a significant impedance to current flow though the electrode – electrolyte interface.

This problem of "polarisation" is solved operationally by imposing a high voltage (60–80 V) across the cell for approximately 90 s, switching off, then back on . After this "depolarisation" process the cell will resume normal operation for several hundred hours with PC 25 anodes.

Again, the process of "depolarisation" is not clear, but it is thought that the high energy input (12–16 W cm^{-2}) may partially remove the build-up of excessively non-wetting material on the electrode surface, or un-block the porous structure in some way.

3.3
Synthetic Utility and Mechanism

Where the organic substrate is sufficiently volatile, and not very soluble in hydrogen fluoride, the process can be highly efficient for many fluorinations, with current efficiencies between 80–100%.

Examples of these include 1,2-dichloroethane (80% retention of the 1,2-dichloro structure); acetyl fluoride (85% yield of fluorinated acetyl fluorides); tetrafluorocyclobutane (90% retention of cyclic structure); isopropyl trifluoroacetate (to the perfluoroester and subsequently hexafluoroacetone).

A detailed analysis of the products from the CAVE fluorination of ethane gives fluoroethanes (96%), fluorobutanes (4%), with traces of fluoromethanes and olefins.

All the fluoroethanes are produced, but no butane is found, although fluorobutanes, ranging from butyl fluoride to perfluorobutane, have been identified.

The magnitude of current and substrate feed rate determine the degree of hydrogen replacement per pass, typically 20–50% per pass, but partially fluorinated materials may be recycled to give higher fluorinated products.

Childs and Fall state that products in CAVE fluorinations appear to arise from the statistical replacement of hydrogen in the substrate in a typical radical process [56], as illustrated below:

Principal Substitution Process

$$CH_3CH_3 + F_2 \longrightarrow CH_3CH_2^{\circ} + F^{\circ} + HF$$
$$CH_3CH_2^{\circ} + F^{\circ} \longrightarrow CH_3CH_2F$$

Radical Disproportionation

$$2\,CH_3CH_2^{\circ} \longrightarrow CH_2{=}CH_2 + CH_3CH_3$$

Dimerisation

$$CH_3CH_2^{\circ} + CH2{=}CH2 \longrightarrow CH_3CH_2CH_2CH_2^{\circ}$$
$$CH_3CH_2CH_2CH_2^{\circ} + F^{\circ} \longrightarrow CH_3CH_2CH_2CH_2F$$

N.B.

$$CH_3CH_2^{\circ} + CH_3CH_2^{\circ} \longrightarrow \text{as no butane is formed}$$

It is interesting to note that little work on this process has been conducted outside the laboratories of Phillips Petroleum Company and 3 M Company; however, related studies on the fluorinations of formamide and acetamide in molten KH_2F_3 on amorphous carbon anodes at 120 °C have been reported by Tasaka and co-workers [57]. The amides were said to react with atomic fluorine produced on the $(C_xF)_n$ [x > 2] film by discharge of fluoride ion, according to the scheme below.

$$CH_3CONH_2 \xrightarrow{[F^{\circ}]} \underline{CH_3COF + NH_2^{\circ}} \xrightarrow{[F^{\circ}]} N_2 + NF_3 + CF_4 + CHF_3 + C_2F_6 + COF_2$$
$$\underline{\phantom{CH_3COF + NH_2^{\circ}}} \xrightarrow{[F^{\circ}/H_2O]} N_2 + N_2O + CO_2$$

Thus, although the CAVE process has definite value in its ability to fluorinate smoothly certain organic compounds which are not particularly amenable to other methods of fluorination, for example, by the ECF Simons process, its general application is obviously severely limited by the combined requirements that substrates be only slightly soluble in hydrogen fluoride and sufficiently volatile at the temperature of the cell (~100 °C) to permit diffusion though the porous carbon matrix of the anode.

It is not generally known to what extent this process will, or can, be commercialised even though it is reported that cells carrying 4000 A were operated at the Phillips Petroleum Company.

4
Electrolysis in Anhydrous Hydrogen Fluoride at Nickel Anodes

The Simons Process or Electrochemical Fluorination (ECF) was devised during the 1940s, as part of the Manhattan Project, with a view to synthesising perfluorinated materials capable of tolerating the aggressive conditions encountered in the uranium hexafluoride diffusion process for the preparation and separation of uranium isotopes.

ECF is characterised by the electrolysis of organic compounds, dissolved or dispersed in anhydrous hydrogen fluoride, at nickel anodes (no other material appears to be as effective), under voltage conditions where the evolution of gaseous fluorine does not normally occur.

The process usually yields fully fluorinated products, with the great benefit that certain important functional groups are retained in the products.

The process licence was acquired by the 3 M Company in 1946 [54] and has been investigated and, to varying extents, commercially exploited by this [58] and other companies (e.g., Air Products Inc., Asahi Glass Co., BASF AG, Borax Research Inc., Bayer AG, Daikin Industries, Dainippon Inc., EA Technology Ltd., Green Cross Corp., ICI plc, Kanto Denka Kogyo Co., Miteni S.p.A., Mitsubishi Metal Corp., Rimar S.p.A., Tokuyama Soda KK) during the intervening years, with the expansion of its synthetic utility, production and power efficiencies.

However, despite being studied for more than fifty years, not only by the above companies, but also by a number of academic institutions world-wide, several aspects of the process remain enigmatic. Nonetheless, because of its many advantages, interest in the process remains high with several groups continuing to study, utilise, and contemplate further commercialisations.

Over the years the subject has been reviewed at regular intervals [54, 59–69].

Contained within these reviews are descriptions of the state-of-the-art (at the time) regarding equipment and techniques employed, as well as the scope and limitations of the method as a synthetic tool. It is not proposed to repeat here the very adequate coverage of specific pieces of equipment or reactions detailed therein.

During the last decade or so, primary publications can be defined broadly as falling into three main categories, namely, those describing work in which the objectives have been to:

1) expand the synthetic scope of ECF, or
2) develop techniques to improve the performance of ECF, or
3) elucidate the fundamental mechanisms which operate in ECF.

Obviously, considerable overlap exists between these arbitrary divisions, for example, a piece of work setting out to synthesise new compounds can also shed light on the mechanism [70], and similarly, a study designed to investigate the mechanism can result in modifications to operational procedures [71].

4.1 Chemistry to Expand the Synthetic Scope of ECF

The synthetic utility of ECF, developed over the years, has been described in considerable detail in a number of review articles [54, 59–69].

The range of organic compounds which have been subject to the Simons process is wide and includes aliphatic and aromatic hydrocarbons, halocarbons, ethers, aliphatic and aromatic amines, heterocyclics, thiols, alkyl sulphonic and carboxylic acids, and their derivatives, among others.

The degree of success achieved in these fluorinations is often determined by the ability of the substrate to dissolve in hydrogen fluoride to produce stable, conducting electrolytic solutions.

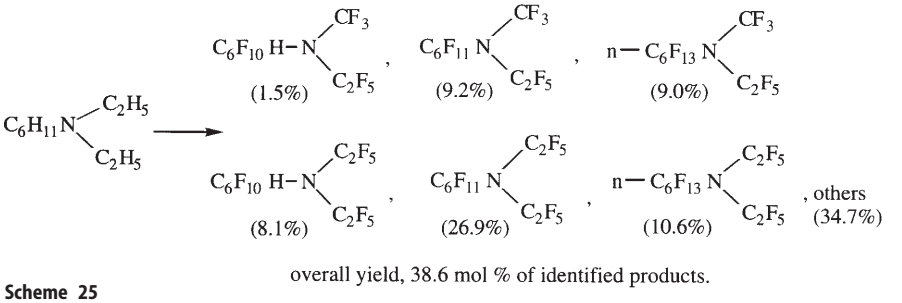
Thus, precursors such as hydrocarbon ethers, amines, carbonyl compounds which are readily protonated tend to be more amenable to ECF than, say, hydrocarbons or halocarbons whose solubilities and conductivities are low. A number of techniques have been developed in the past decade, however, to overcome such problems (see Sect. 4.2). Similarly, advances in methodology of ECF now allow the fluorination of gaseous, liquid, solid, and even polymeric materials [72–77].

Whereas previously it had been customary to describe the process as producing exhaustive (i.e., complete) fluorination [78] (which indeed it does!) recent studies have demonstrated that it is possible to control the degree of fluorination [79], and, moreover, analysis of partially fluorinated products has cast new light on possible mechanisms in the process [70].

Latterly, a high proportion of published work has been targeted at the synthesis of inert, new materials of improved performance for application in the fields of biomechanics, medicine, electronic and electrical engineering, hydraulics, as well as in the more established fields of surfactants, strong acids, and synthetic building blocks.

4.1.1 *Amines*

In the course of their work on suitable materials for use as blood substitutes the group at the University of Padua have studied the electrochemical fluorination of cyclic tertiary amines [80]. The ECF of *N,N*-diethylcyclohexylamine and *N*-ethyldicyclohexylamine gave the corresponding perfluoroamines together with several other compounds arising from incomplete fluorination and fragmentation reactions.

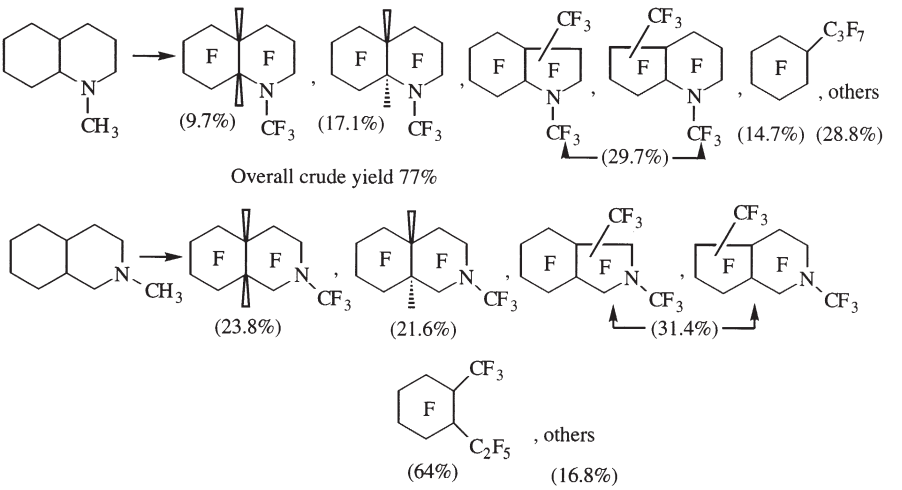


Scheme 25

With *N*-ethyldicyclohexylamine the product yield was lower (16%) and the resultant mixture too complex for complete identification.

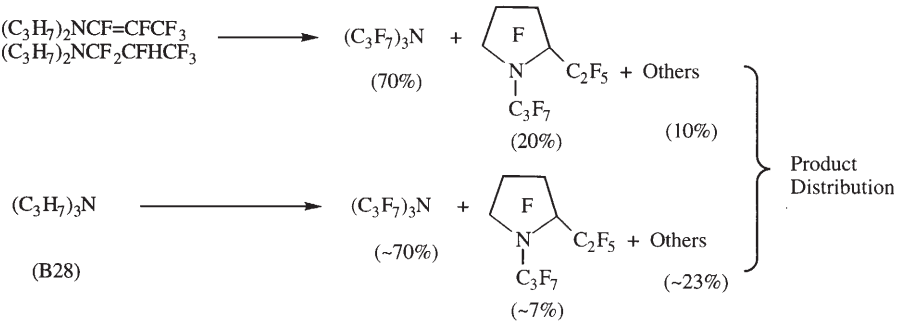
The Green Cross Corporation, who have also been very active in the field of artificial blood substitutes, have synthesised a wide range of potential materials stemming from their first practical product Fluosol-DA, a mixture of perfluorodecalin and perfluorotripropylamine.

With the objective of preparing a single material which possessed the desired combined properties of this emulsion, they set out to fluorinate *N*-methyldecahydroquinoline and *N*-methyldecahydroisoquinoline [81].



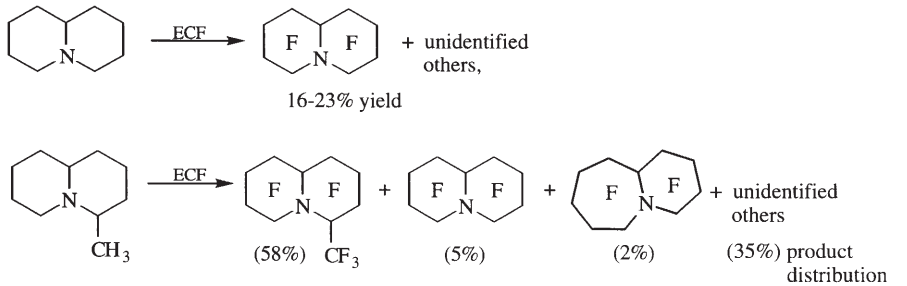
Scheme 26

Their attempts to increase the yields of perfluorotripropylamine by starting with partially fluorinated precursors, which may reasonably have been expected, were, however, thwarted by the formation of large amounts of undesired by-products [82].



Scheme 27

In their search for oxygen carrying agents with favourable characteristics in terms of emulsifiability and pharmacodynamic properties, the same group reported [83] the first electrochemical synthesis of the bridge-head nitrogen compounds perfluoroquinolizidine and 4-(trifluoromethyl)-perfluoroquinolizidine.



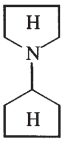
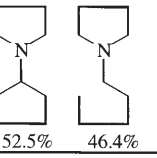
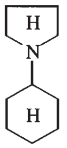
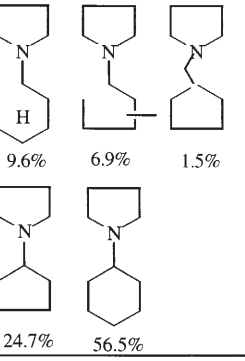
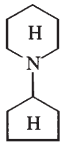
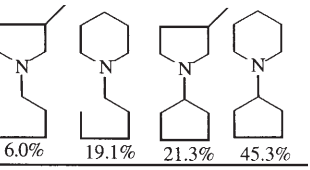
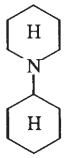
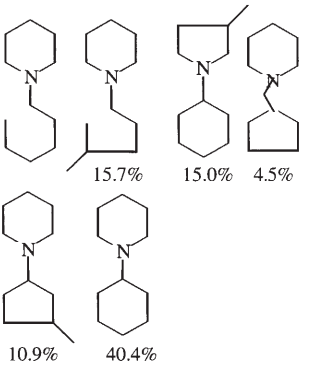
Scheme 28

Because of the expected superior excretion rates of bicyclic perfluorotertiary amines as oxygen carrying emulsions, they studied the ECF of several *N*-cycloalkyl-pyrrolidines and -piperidines, from which they reported crude yields of 74 – 78 % for the fluorinated products [84] (see Scheme 29).

Interestingly, from these results they were able to make a number of observations concerning the mechanisms of these transformations, namely:

a) ring opening reactions occur only at cycloalkane rings,
b) bond scission occurred predominantly at a tertiary carbon,
c) products were explainable by either a ring contraction, or ring opening, reaction,
d) ring contracted products arise from six-membered rings but not from five-membered rings, and
e) the over-riding factor which operated in these processes appeared to be that of steric hindrance.

Product distribution of F-*tert*-amines obtained by the electrochemical fluorination

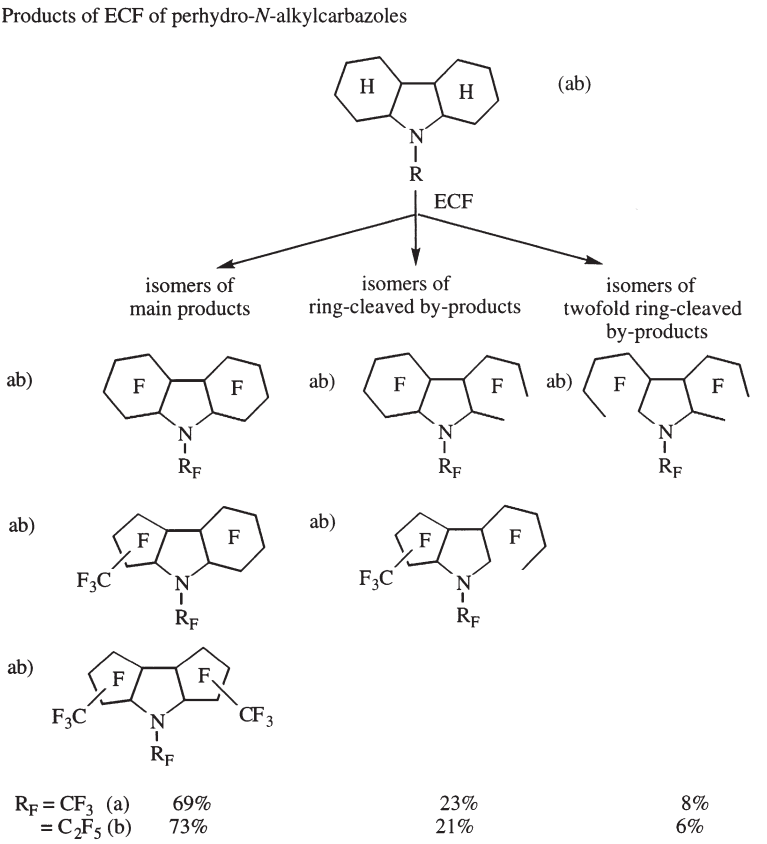
Substrate	Yield		Product Distribution (%)
	Crude	After Treatment	
	76	55	 52.5% 46.4%
	76	53	 9.6% 6.9% 1.5% 24.7% 56.5%
	78	51	 6.0% 19.1% 21.3% 45.3%
	74	52	 15.7% 15.0% 4.5% 10.9% 40.4%

Product distribution was calculated by glc peak areas. All unmarked positions are bonds to fluorine

Scheme 29

Meinert et al. have also studied the electrochemical fluorination of piperidine-, carbazole-, and morpholine-derivatives [85, 86]. The perfluoro-derivatives were said to be produced in yields up to 45%, with the fluorination of *N*-carbazoles representing a new class of compounds.

The importance of ring contractions, fragmentations, and rearrangements in these types of reactions was again emphasised, and inferences were drawn from this work as to the mechanism of the reaction, based on steric modelling of the compounds. (See Sect. 4.3).



Scheme 30

Patent cover for this, and related work [87, 88], has claimed these products as useful in oxygen-transporting aqueous emulsions for organ perfusion and storage in transplant surgery, and as diagnostic agents for ultrasonography and ^{19}F NMR tomography.

Tokuyama Soda KK have claimed the production of perfluorotripentylamine by ECF as a route to material suitable for use in vapour phase soldering for small electronic components [89].

Furin et al. [90] have conducted the electrochemical fluorination of a series of amines, tripropylamine, tributylamine and triamylamine, and a series of enamines formed by the reaction of hexafluoropropene, its dimers and trimers with the secondary amines dipropylamine, dibutylamine and diallylamine. As well as the anticipated saturated perfluoroanalogues of the starting materials by-products resulting from structural breakdown were also produced.

This work again confirmed the advantage of using a starting material which is already partially fluorinated in terms of enhanced yields and greater current efficiencies, as can be seen in the table below.

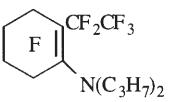
ECF data for partially fluorinated enamines and trialkylamines

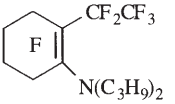
Starting Material	Desired Product	Strenth of Current (A/cm^2)	Mass per cent Substrate (%)	Voltage (V)	Quantity of Electricity Passed ($A\ h\ l^{-1}$)	Yield per 1 $A\ h^{-1}$ (g)	Yield of Crude Product (%)
$(C_3H_7)_3N$	$(C_3F_7)_3N$	5/0.02	6.4	5.4-6.1	1030	71	12
14	$(C_3F_7)_3N$	8.4/0.02	10	4.6-61.	1000	154	34
$(C_4H_9)_3N$	$(C_4F_9)_3N$	12.6/0.03	6.5	5.1-6.1	1640	194	37
3	8	4.6/0.02	10	4.5-5.1	1640	262	62
$(C_5H_{11})_3N$	$(C_5F_{11})_3N$	7.0/0.03	8	5.7-6.3	1390	352	23
4	12	12/0.03	15	4.8-6.2	1310	256	32
1	9	8.4/0.02	8	4.6-6.1	2200	512	54
5	10	8.4/0.02	6.5	6.0-6.6	1500		70
6	11	8.6/0.02	6.8	6.0-6.6	1670		75

Where 1 = $(C_4H_9)_2NCF = C(CF_3)CF_2CF_2CF_3$

3 = $(H_2C{=}CHCH_2)_2NCF{=}C(CF_3)CF_2CF_2CF_3$

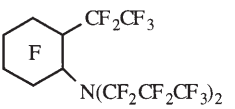
4 = $(H_2C{=}CHCH_2)_2NCF{=}CFCF[CF(CF_3)_2]_2$

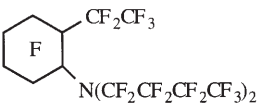
5 = 

6 = 

8 = $CF_3CF_2CF_2CF(CF_3)CF_2N(CF_2CF_2CF_3)_2$

9 = $CF_3CF_2CF_2CF(CF_3)CF_2N(CF_2CF_2CF_2CF_3)_2$

10 = 

11 = 

12 = $(C_3F_7)_2NCF_2CF_2CF.[CF(CF_3)_2]_2$

14 = $(C_3H_7)_2NCF{=}CFCF_3$

Scheme 31

In a related piece of work, chemists at the Akad. Wissenschaft DDR claimed the preparation of perfluorodicyclicamines by the ECF of enamines incorporating alicyclic and heterocyclic rings [91].

This same group has demonstrated, and patented [92–94], a series of schemes by which potential blood substitutes may be synthesised via the

production of perfluoroamines, including new perfluoro *N*-cyclohexylmethyl derivatives formed by the fluorination of the corresponding benzyl derivatives of cyclic amines [95].

The preparation of new tertiary perfluoroamines and thioamides are reported by Richman of 3 M Co. [96] by the fluorination of a tertiary thioamide to give materials said to be of use as hydraulic, heat transfer and pump fluids for corrosive environments.

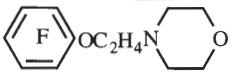
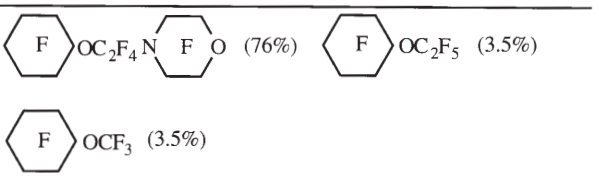
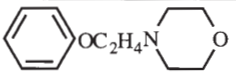
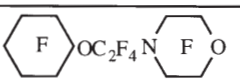
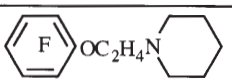
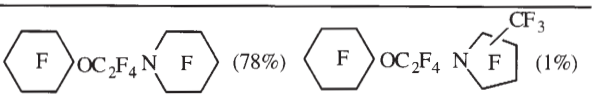
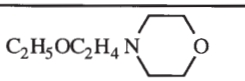
Asahi Chemical Industries KK claim the unique compound 2-fluoro-4,4′-diaminodiphenyl methane, used as a monomer of very high heat resisting resins, is easily obtained by the ECF of 4,4′-diaminodiphenyl methane [97].

4.1.2 *Amino-Ethers*

Following the demonstration by Moore et al. at the 3 M Co. [98] that ECF was a successful method for the fluorination of aminoalkyl ethers, of interest to them mainly for their low temperature properties and chemical and thermal stabilities [99–101], Rüdiger et al. explored a series of cyclic aminoethers with a view to preparing possible candidates for blood substitutes [102].

A synopsis of these results is shown below.

Liquid perfluorination products from ECF of aminoethers

Aminoether	Perfluoro products (relative amounts according to GLC
	 (76%) (3.5%) (3.5%)
	 (74%)
	 (78%) (1%)
	 (35%)

Scheme 32

It is said that one of these products, perfluoro-4-(2-cyclohexyloxyethyl) morpholine, has promising properties as a blood substitute.

An interesting insight into the possible mechanism of ECF from this work is the observation that concentrations of starting compounds containing the pentafluorophenyl moiety were undetectable in the electrolyte after as little as 30% of the theoretical total current had passed, a fact inconsistent with the "zipper" mechanism which requires individual molecules to remain attached to the anode until fluorination is complete. The presence of partially fluorinated, HF-soluble products would almost certainly account for this observation, which was again reported by the same workers in a later publication describing the electrochemical fluorination of 2-phenyl-3,4-dimethylmorpholine [103]. The significance of these findings will be discussed in Sect. 4.3.

Patent cover for this work has been sought [104].

4.1.3
Nitrogen-Containing Carboxylic Acids

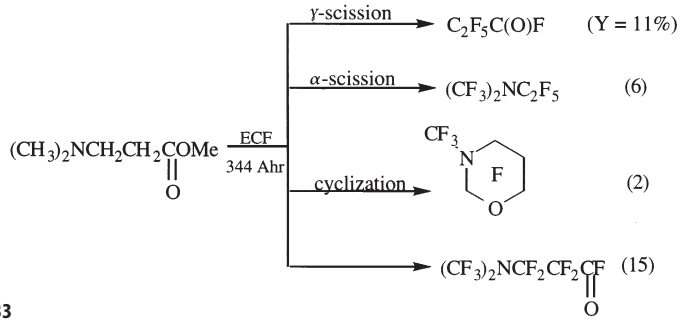
With a view to accessing perfluoro nitrogen-containing carboxylic acids for use as building blocks in biodegradable surfactants and chiral syntheses of biologically active compounds, workers at the National Industrial Research Institute of Nagoya, Japan have studied the ECF reactions of a series of dialkylaminoacetic, propionic and butyric acid methyl esters, where the dialkylamino- groups included dimethyl-, diethyl-, pyrrolino-, morpholino-, piperidino-, and *N*-methylpiperazino as substituents [105–109].

Typical of the reactions studied are those shown below:

$(R)_2NCH_2CH_2C(O)OMe \longrightarrow (R_f)_2NCF_2CF_2C(O)F$

where	R =	R_f =	yield
	CH_3	CF_3	11%
	C_2H_5	C_2F_5	30%
	C_3H_7	C_3F_7	26%
	C_4H_9	C_4F_9	14%

Generally, the fluorination products obtained could be classified into three groups – i) degradation products, ii) cyclisation products, iii) expected products – with the yields of the desired compounds ranging from fair to good, depending upon the structure of the acid skeleton, and the nature and position of the substituent (e.g., to block cyclisation by-product formation).



Scheme 33

4.1.4
Sulphur Compounds

The interest in fluorinated organic sulphur compounds has continued unabated throughout the current period by virtue of their potential applications in such diverse fields as fuel cells, ion-exchange resins, insecticides, as well as the established surfactants.

Liu et al. have prepared difluoromethyldisulphonyl fluoride by the electrochemical fluorination of methyldisulphonyl fluoride, followed by its conversion to the disulphonic acid form. The chemical yield of the ECF stage was around 70% with a current efficiency of 44% [110].

$$CH_2(SO_2F)_2 \xrightarrow[5.5v,\,0.5adm^{-2}]{ECF} CF_2(SO_2F)_2$$

In a similar fashion, Sartori and Jüschke also fluorinated methyldisulphonyl fluoride to produce not only the difluoromethyldisulphonyl fluoride in similar yield (75%), but also reported the formation of fluoromethyldisulphonyl fluoride as a minor product (2%) [111].

Likewise, the electrochemical fluorination of the partially fluorinated ether containing disulphonyl fluoride, $CH_2(OCF_2CF_2SO_2F)_2$ has been shown to produce a mixture of both the difluoromethane- (19% yield) and the fluoromethane- (20% yield) sulphonyl fluorides. New fluorinated ether salt derivatives of these products, e.g. $Ca[CF_2(OCF_2CF_2SO_3)_2]$ were prepared and characterised [112].

Rüdiger et al. [113] have reported the electrochemical fluorination of a number of *N,N*-dialkylamidosulphonyl halides (and compared this with cobalt trifluoride fluorination) with a view towards testing the products for their biological activity.

A synopsis of their results is shown below:

Educt	Products	Yield (%)		
		By ECF	By CoF_3 at 200–250 °C	By CoF_3 at 300–350 °C
$(CH_3)_2NSO_2F$	$(CF_3)_2NSO_2F$	31	5.9	44
	$CF_3(CHF_2)NSO_2F$	8	6.6	12
	$(CHF_2)_2NSO_2F$	4	38.5	4
	$CHF_2(CH_2F)NSO_2F$	-	11.9	-
$(C_2H_5)_2NSO_2F$	$(C_2F_5)_2NSO_2F$	10	-	

Scheme 34. Products from ECF and CoF_3 fluorination of N,N-dialkylamidosulphonyl halides

It can be seen that ECF tended to produce a higher proportion of fully fluorinated compounds in the product mixture compared with cobalt trifluoride, particularly at lower temperatures. The partially fluorinated products were found to have greater toxicities.

The 3M Co. have maintained their high interest in this area as is evidenced by the number of patents filed covering a range of new and improved derivatives of sulphonic acids [114–116], e.g., $SF_5C_3F_6COF$, $SF_5C_4F_8COOLi$ said to be used for oil and water repellancy in textiles and other substrates, in reducing surface tension of liquids, evaporation and flammability of volatile organic compounds, and improving levelling of organic polymer coatings.

Bayer AG have reported the preparation of the sulphonyl fluorides $C_3F_7CHFSO_2F$ and $C_3F_7CH_2SO_2F$ as minor products in the ECF of sulpholene [117], and patented the preparation of perfluorobutylsulphonyl fluoride by the electrochemical fluorination of butylsulphonyl fluoride, sulpholane and/or sulpholene in the presence of octylsulphonyl fluoride, in mole ratios ranging from 86:14 to 99:1 [118].

4.1.5
Ethers

Thermally stable fluorinated ethers have been considered for use as replacing CFCs and HCFCs in such applications as cleaning of engineering and electronic components, and working fluids and heat transfer agents.

Thus 3 M Co. have patented a process for the production of 2-hydrofluorinated ethers by the electrofluorination of perfluoroisobutene – alcohol adducts. The products range, depending upon operating conditions, from mixtures of the 2-hydrofluorinated ether and the fully fluorinated ether, to compositions comprising perfluorethyl- and perfluoroalkyl-pentafluoro-2-(perfluoromethyl)-propyl ether [119]. One advantage of this process is said to be that it makes use of toxic and highly volatile perfluoroisobutene from waste gas streams to produce valuable materials in high yield and purity.

4.1.6
Volatile Fluorocarbons

The fluorination of gases continues to attract interest but, because of the physical properties and low solubilities of the starting materials, technical modifications to the standard Simons cell or operational changes to the method are usually required.

However, the preparation of octafluorocyclobutane by ECF of 1,1,2,3-tetrafluorocyclobutane in a Simons cell is claimed by 3 M Co. [120].

Similarly, ICI plc. has reported the fluorination of 1,1,1,2-tetrafluoroethane (HFC134a) to pentafluoroethane (higher partially fluorinated products being obtained in preference to the perfluorocompound) in a cell designed specifically for the treatment of volatile starting materials [79].

4.2
Techniques to Improve the Performance of ECF

As Dresdner and Young remarked in one of their early papers [121], ECF is still an art in many respects, often with each different electrochemical fluorination requiring its own specific optimal reaction conditions.

Typical of the problems encountered in operating the process have been the following.

a) Poor reproducibility. Yields and ratios of products often vary from experiment to experiment for no obvious reason. For example, Kazukov et al. [122] described 500 fluorinations they had performed and concluded "in practically none of the series of experiments was an acceptable reproducibility of results obtained".
b) Variable chemical yields and current efficiencies.
c) Poor selectivity. The degree of fluorination of the substrate is not easily controlled, usually total fluorination occurs.
d) The process only operates at low current densities (typically $< 2\ \mathrm{adm}^{-2}$, as compared with $> 100\ \mathrm{adm}^{-2}$ in a fluorine cell). Commercially this means that, for production of the same quantity of fluorine, in one case for reaction in situ, and in the other for separation and collection, a larger cell would normally be required in ECF, with the attendant greater capital costs.

Thus, with these shortcomings in mind, much work over the past decade has been targeted towards investigating the various reaction parameters which might influence the course of electrochemical fluorination reactions with the view to maximising the yield of products, minimising by-product formation (often caused through rupture of the carbon skeleton), optimising current and power efficiencies, and space-time yields.

4.2.1
Reaction Parameters and Cell Design

Gambaretto et al. have studied [123] the fluorination of tripropylamine in order to correlate the operating conditions of temperature, voltage, initial concentration of amine, constant concentration of amine, and stirring effect, with the yield of the corresponding perfluorotripropylamine. Experimental data showed that temperature is the parameter exerting the most remarkable influence over perfluoramine yield and by-product formation. Also, low temperature (−4 °C) operation resulted in a cleaner, less coloured system, presumed to be due to less tar formation than at higher temperature (19 °C).

Other studies by Drakesmith and Hughes [124] have used the fluorination of propene and octanoyl chloride as model compounds to investigate the effects of anode potential, current density, reactant concentration, temperature, etc. on reproducibility, product structure, distribution and yield in novel cell designs ranging in scale from 100 ml to 100 l cell capacities.

In this work two distinct stages in the process were identified:

i) the "conditioning" of the anode, and
ii) the fluorination of the organic substrate.

It was concluded from the work that

a) proper "conditioning" of anodes was essential for reproducible results,
b) control over anode potential (and therefore current density) during fluori-

nation can be used to moderate the reaction, and so prevents breakdown of the carbon skeleton, and

c) the process is controllable within certain limits to give optimum yields of either perfluorooctanoyl fluoride (8–47%), or perfluorocyclic ethers.

The use of porous nickel and nickel foam anodes in these experiments was shown to be advantageous in terms of providing very high specific surface areas (and therefore low current densities), excellent heat dissipation, and thorough mixing.

Later, almost identical results were claimed in a Japanese patent by Mitsubishi Metal KK [125].

The application of a very similar system using foam electrodes has been patented by ICI plc [79] for the controlled fluorination of partially fluorinated volatile materials to give excellent yields of more highly fluorinated products.

In the quest for a greater understanding of the controlling factors in ECF, Liu et al. have designed a novel microprocessor-aided modified Simons reactor system. The reactor employs batch mixer design criteria to enhance and enable the characterisation of the mass transfer in the reaction. The electrode packs were arranged to give a more uniform anode current density distribution, and to act as baffles for the mixed flow field. The microprocessor system in conjunction with other accessories were used for monitoring, control, and data acquisition of the process [126].

Using this equipment, the group studied the fluorination of methanedisulphonyl fluoride [127] at constant anodic potential (vs Cu/CuF_2 reference electrode) and report product yields of difluoromethanedisulphonyl fluoride of 75–82%, current efficiencies in excess of 66%, and electrical energy efficiencies of at least 33%. They also observed, in common with others, that after the reactant was added, an induction period, typically accounting for 30% of the theoretical total charge, occurred, suggesting that interaction between the organic substrate and the anodic film of nickel fluoride was necessary for the fluorination to proceed; this, together with the zero-order behaviour of the organic, were consistent with the potential dependent adsorption mechanism previously suggested by Comninellis et al. [128].

Corrosion of the anodes was approximately forty times greater than corrosion of the cathodes, and the amount of this corrosion was directly proportional to the anodic potential applied.

4.2.2 *Electrolyte Additives*

In a later publication [129], using the same equipment, Liu et al. describe process improvements in the electrochemical fluorination of octanoyl chloride in which formation of polymeric tar at the anode surface was limited by addition of a mercaptan (1-methyl-1-propanethiol), and by constant current density operation (7 mA cm^{-2}). Continuous operation was achieved by frequent additions of a solution of reactant in hydrogen fluoride. Conversion of reactant to perfluorinated products was increased to 80%, with good selectivity.

In a similar vein, patents by both Dainippon Ink Chem. KK [130] and Daikin Kogyo KK [131] claim the addition of dimethylsulphoxide to the electrolyte prevents adhesion of polymeric tar to the anode, lowers the rise in cell voltage, and assists long term fluorination of *n*-octanecarbonyl fluoride.

In a somewhat different approach, Asahi Glass KK have claimed [132] that the addition of a transition metal salt (e.g., cobalt-, copper-, lead-, cerium-, bismuth-, manganese-, chromium-, iron- chloride, or cobalt fluoride, etc.) greatly improves the ECF production of perfluorobicyclic compounds, derived from naphthalene, indene, benzofuran, phthalimide, indole, quinolizine, benzotriazole, and quinoline.

Likewise, Bayer AG have patented [133] an improvement process which entails the addition of fluoride salts to the HF electrolyte enabling the ECF of alkylsulphonyl fluorides to be run for many months, giving high yields and using less energy than usual. Examples of the additives are alkaline earth fluorides, alkali tetrafluoroborates, alkali hexafluorophosphates, HPF_6, HBF_4 and BF_3.

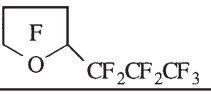
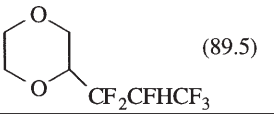
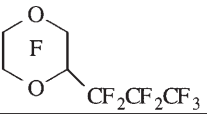
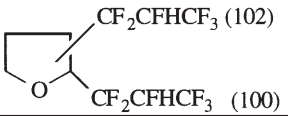
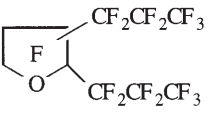
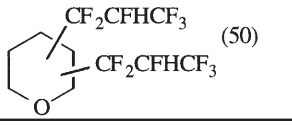
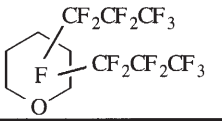
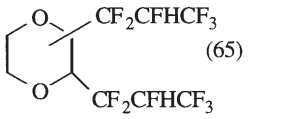
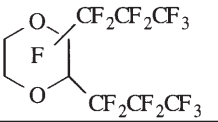
4.2.3 *Choice of Starting Material*

The technique of incorporating fluorine in the starting material prior to further fluorination as a means of stabilising the structure against skeletal breakdown is well known [134] and has again been demonstrated by Sartori et al. [135] in the case of electrochemical fluorination of adducts of hexafluoropropene to cyclic ethers to give the corresponding perfluoroethers with, in some cases, surprising efficiency.

The possibility of obtaining real improvements in the industrial production of perfluorooctanoic acid by using perfluorohexyl acetyl chloride in place of octanoyl chloride as starting material has been investigated [136]. In particular, the effect of blocking the formation of cyclic ethers on the yield of the perfluoroacid was examined; this was, however, less than expected due to the increased formation of perfluoro-*n*-heptane.

$$\underset{}{n\text{-}C_6F_{13}CH_2COCl} \longrightarrow \underset{33.1\,\%}{C_7F_{15}COF} + \underset{55.1\,\%}{C_7F_{16}} + \underset{8.5\,\%}{C_7F_{15}H} + \underset{3.3\,\%}{C_7F_{14}}$$

Likewise, the same group investigated the use of 4-(perfluoro-*n*-butyl)-*n*-butanoyl chloride as starting material for the production of perfluorooctanoic acid [137]. Here again, the cyclisation process was inhibited and formation of cyclic ethers prevented, and, although a larger amount of perfluoro-*n*-heptane was produced, the molar yield of perfluorooctanoyl fluoride and its weight percentage in the reaction mixture increased. Furthermore, by using this technique, it was reported that the electrochemical process was shorter, the current consumption lower, and did not yield tar or degradation products.

Starting Material (g)	Product	Total Recovered Organic Mat'l (g)	Yield (%)
Mono-adduct			
 (101)		83.5	50
 (89.5)		34.9	16
Di-adducts			
$(CF_3CFHCF_2CH\text{-})_2O$ (89.6)	$(CF_3CF_2CF_2CF)_2O$	32.5	8
		70.0 82.7	45
 (50)		30.5	36
 (65)		36.5	27

Scheme 35

Expt.	n-$C_7F_{15}COF$	Unidentified isomers (uii[a])	Unidentified isomers (uii[a])	FP[b]	FF[c]	n-C_7F_{16}	Others	Tar
1	37.8	-	1.5	-	14.9	29.3	16.5	no
2	38.3	-	1.3	-	15.6	28.9	15.9	no
3	39.1	-	1.2	-	14.8	29.8	15.1	no
4	37.4	-	1.6	-	15.1	29.5	16.4	no
5	12.7	1.7	1.2	11.8	27.9	18.1	26.6	yes
6	11.1	2.1	1.7	12.2	27.1	18.7	27.1	yes

[a] = unidentified perfluorooctanoyl fluoride isomers.
[b] = perfluoro-2-propyl-tetrahydropyran.
[c] = perfluoro-2-butyl-tetrahydrofuran.

Scheme 36. Composition of reaction mixtures in the ECF of 4-(perfluoro-*n*-butyl)-*n*-butanoyl chloride (Expts.1–4) and *n*-octanoyl chloride (Expts.5–6)

4.2.4
Electrochemical Engineering and Operational Procedures

An improvement to the electrochemical engineering of ECF is that described by 3 M Co. [138] using a bipolar electrode stack capable of channelling the flow of electrolyte, an example of which is tripropylamine in hydrogen fluoride. The bipolar electrode assembly has low resistive heating in the electrical connection from bus bar to electrode stack, and the nature of the cell enables the construction and use of large, high capacity cells which run on low currents. Additionally, the power costs are low as transformer and rectifier systems are more efficient when direct current is provided at high voltage.

Another novel type of electrochemical fluorination unit, incorporation a metal electrolyser lined with teflon, capable of both bipolar and monopolar function is claimed in a Russian patent [139] to have advantages in simplicity of assembly and operation.

A filter press arrangement incorporating perforated bipolar electrodes to allow flow channels is described in another Russian patent [140].

A recent patent from 3 M Co. [141] describes an improved operational technique obviating the need for expensive equipment which enables the safe fluorination of volatile compounds which are not very soluble in HF. This is achieved by the simultaneous fluorination in a Simons cell of a mixture of a higher boiling component together with the more volatile compound precursor.

Using a similar, mixed component technique, Tokuyama Soda KK claim [142] to have increased the yield of perfluorooctane to greater than 45% by the simultaneous fluorination of *n*-octane and a nitrogenous organic compound.

In a series of patents [143–146] the same company describes the advantages of a circulatory system for ECF in which they report the efficient, long and stable electrolytic production of, for example, perfluoro(*N,N*-dialkyl hexylamines). They have also explored the beneficial effects of stop-flow techniques to this type of system [147].

In an earlier patent [148] they claim that a two-stage fluorination at different specific voltages and current densities (0.1–1.0 A dm^{-2}, and 2–4 A dm^{-2}) significantly increases the yield of fluorinated products.

Because the overall economics of a commercial ECF process is dominated by usage and loss of HF, a number of companies have addressed methods of ameliorating this particular problem.

Thus, Tokuyama Soda KK have patented [149] a piece of technology for the combustion of the hydrogen gas with the fluorocarbons produced in the ECF reaction with the objective of recovering HF which would otherwise be lost.

Towards the same end, Dainippon Ink Institute of Chemical Research has patented [150] a technique in which exhaust gases from the electrolytic cell are returned to the base of the electrode assembly thereby enhancing convection and stirring without increasing HF loss.

A further technique said to be useful on an industrial scale for the ECF conversion of alkanesulphonyl fluoride and tetramethyl sulphone to form perfluoroalkane sulphonyl fluorides involves the continuous extraction of products from the electrolyte and hydrogen gas stream. The method claims high yields (93%) without recovery problems of prior art [151].

4.2.5
Anode Construction and Corrosion Management

A further persistent problem in commercial operations is that of anode corrosion, both because of detrimental metal loss and the deleterious effects of metal concentration build-up in the electrolyte.

Bayer AG has addressed this problem by patenting [152] electrodes fabricated from nickel or coated with nickel [153] having a columnar structure. Since these electrodes are said not to corrode, they allow long-term, continuous fluorination and require lower voltages, making the process more economical.

A further advantageous modification of electrodes is claimed by Watanabe [154] for the Central Glass Co. Ltd. which uses anodes coated with a composite layer of nickel containing a dispersed eutectoid of PTFE particles or fluorinated graphite particles. The low surface energy nickel based composite is said to improve the yield of perfluorooctanesulphonyl fluoride to 40.5% in ECF.

The complications arising from corroded metal ion build-up have been studied by Tokuyama Soda and removal of these by electrolysis has been reported; nickel removal [155] and iron removal [156] results in longer run times and greater voltage stabilities.

4.3
Attempts to Elucidate the Mechanism of ECF

The precise mechanism of the Simons process remains a matter of debate despite the considerable efforts since its invention to gain a proper understanding of the fundamentals involved [157–163].

What is certain is that any explanation must be consistent with the following significant observations reported by various workers from their experiments.

a) The process only functions with nickel as the anode material. (Hackerman et al. have screened 23 materials as possible alternatives [164]).
b) There is an induction period with new anodes, during which time a film of nickel fluoride(s) builds up.
c) No free fluorine is produced during reaction of the organic substrate, even though the preferred working voltage (5–6 V) is higher than that of the voltage of a fluorine cell (~2.8 V) [165], although fluorine is reported to be formed at the beginning and end of runs, when organics are absent.
d) Organics which are protonated by hydrogen fluoride and dissolve in the electrolyte are more amenable to the process.
e) Cell voltages appear to be largely independent of substrate structure and concentration.
f) Perfluorinated products tend to be produced, but the formation of partially fluorinated products also takes place.
g) Rearrangements, dimerisations, isomerisations, cyclisations, etc. which are characteristic of ECF.

Simons himself, suggested [166] a radical mechanism in which fluoride ions, oxidised at the anode to produce fluorine atoms, underwent homolytic sub-

stitutions with hydrogen in the organic substrate. This cannot be the full story, however, as it does not explain many other aspects of the process identified later, nor does it differentiate its unique characteristics from other fluorinations, e. g. the Phillips process (see Sect. 3).

Obviously, the role of the film produced on the anode surface is crucial to the mechanism [167].

A number of workers have studied this phenomenon [124, 168 – 170] and have concluded that the proper formation of this film determines the efficacy and reproducibility of the system, and that experimental data are consistent with a reaction controlled by the amount of surface area available on the anode film [171]. Also, the corrosion rate of nickel anodes is much lower in the presence of the organic reactant than the rate of corrosion in pure hydrogen fluoride, indicating that the anode reaction is modified by the presence of the organic.

Thus, it is beyond doubt that the fluorination reaction proceeds via an association between the organic substrate (or its protonated derivative) and the electrochemically generated nickel fluoride(s) on the anode surface. However, since the precise nature of this association, and the exact species involved, are not known, the next stage in the mechanism of fluorine substitution is not apparent and it has generally been the practice to make inferences from studies of product analyses.

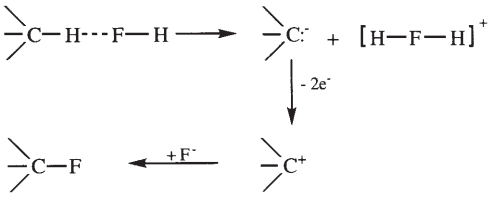
As a result of this scope for interpretation, two separate hypotheses appear to have emerged, differentiated by what is essentially the first electron transfer, and whether this is from

1. the organic substrate to form a radical cation, to produce the Carbocation Mechanism, or,
2. a fluoride ion to form a fluorine atom, producing the Radical Mechanism.

4.3.1
The Carbocation Mechanism

Protagonists of this first group argue that the substitution reaction proceeds via a series of alternate electrochemical and chemical steps, initiated by the direct oxidation of the organic substrate.

Meinert and others [85] have stated that their concept for the electrochemical fluorination of organic compounds is based on the assumption that the first step is the anodic oxidation of the organic molecule. The electrochemical process is promoted by weakening of the C – H bonds due to hydrogen-fluorine bridges. After anodic withdrawal, the C – F bond is formed by insertion of a fluoride ion, present in the Helmholtz-double-layer at the electrode surface.

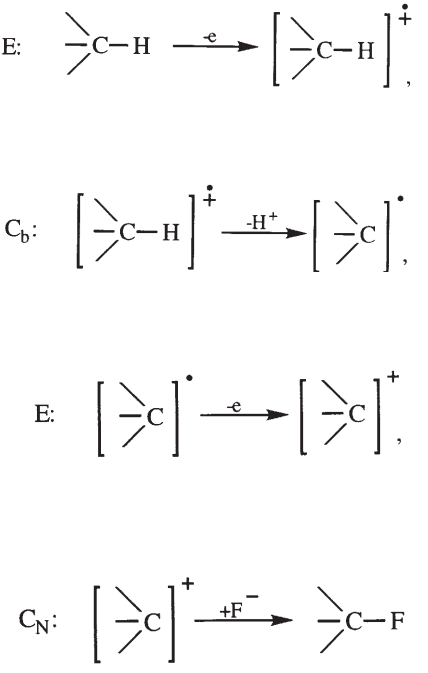


Scheme 37

Electrofugal leaving of further hydrogen atoms linked at this carbon atom is promoted by insertion of the strongly electronegative fluoride ion and the formation of the C–F bond. Repetition of this mechanism leads to perfluorination. In these molecules the reaction proceeds until there is complete substitution of hydrogen atoms. After this, the perfluorinated molecule leaves the adsorption layer at the anode and moves into the bath.

Subsequent development of this hypothesis by Burdon et al. [159], Rozhkov [9] and Gambaretto et al. [172] produced the EC_bEC_N mechanism.

In this, the adsorbed organic substrate is electrochemically oxidised to form a radical cation, a proton is eliminated in a chemical step to form a radical, which is then further electrochemically oxidised to a carbocation, which reacts with a fluoride ion in the double layer to produce the fluoroorganic compound.



Scheme 38

Repetition of this process, whilst the organic remains on the anode surface, leads to perfluorination [69], at which point the molecule is desorbed.

It should be noted that the early stages of this proposed mechanism for ECF, as stated, are not dissimilar to those used to describe other systems (see Sect. 2), and begs the question why perfluorination does not occur in these earlier reactions, but does so readily in the Simons process, particularly in those where the electrochemical conditions are not so very different, (e.g., R_4NBF_4 + KF in CH_3CN) [173]. Moreover, it is difficult to reconcile the established fact that oxidation potentials of compounds dramatically increase as a function of

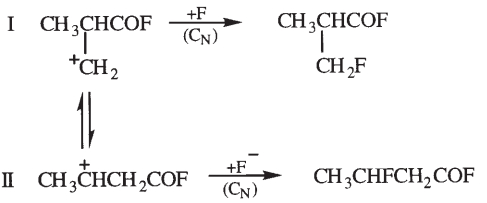
increasing fluorine content with a mechanism which requires the repeated facile oxidation of intermediate, increasingly fluorinated, species to generate the ultimately perfluorinated products.

However, support for this mechanism is claimed by the results from a number of reactions.

Gambaretto and co-workers [172] showed that the ECF of benzoyl chloride occurred at voltages below those at which fluorine was evolved in the absence of the organic (using a "blank" solution of KF in HF of the same conductivity), and claimed this meant that fluorination may have occurred without anodic formation of fluorine atoms, i.e., by implication, it did occur via the discharge of the organic compound.

This position does not, however, take account of the possible effects of adsorbed species on lowering the fluorine overpotential of the system.

Other reactions studied in this paper, the fluorination of *iso*- and *n*-butyryl chlorides demonstrated that isomerisations took place during the course of ECF, with the formation of fluorinated *normal* structures from *iso*- starting materials being preferred over the formation of fluorinated *iso*-structures from *n*-starting materials. This was said to be consistent with a cationic mechanism and was explained by a rearrangement involving carbocations (I and II), and the relative stabilities of the species concerned. However, this is contrary to normal expectation, where *iso*- structures in carbocationic species are generally more the thermodynamically stable, and can therefore only be explained by virtue of the strongly de-stabilising effect of perfluoroalkyl groups.



Scheme 39

Moreover, as has been pointed out [174], the carbocation II must have arisen from COF group migration rather than the more conventional methyl migration, which would have produced the less stable carbocation $CH_3CH_2C^+HCOF$.

Similarly, both Meinert and Gambaretto, with their respective co-workers [80, 172, 175], have invoked this mechanism to explain the formation of partially fluorinated products in ECF reactions of the amines, tripropylamine, *N*-methylmorpholine, and a series of α,ω-dimorpholino- and dipiperidino-alkanes. The selective order in which the hydrogens were substituted in these molecules was said to be consistent with that expected for the mechanism in that carbon atoms nearest to oxygen (in the morpholine rings), where the electron density is greatest, were the first to react, and those nearest to the quaternised nitrogen the last, not in a random order as might be expected in a radical mechanism.

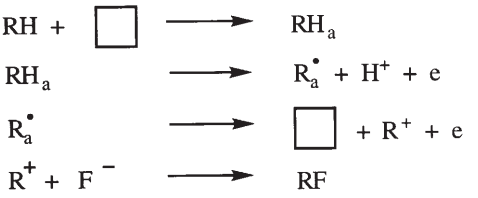
The order of substitution was also affected by the manner in which the organics were supposed to lie on the surface of the anode, i. e., with the positively charged protonated nitrogen atoms being furthest away from the positive electrode.

This, of course, may well be the case, however, even with a radical mechanism in which the adsorbed species took up these same orientations one would expect the hydrogen atoms furthest away from the nitrogen, and therefore closest to the electrode, to be replaced first simply by virtue of their proximity to the source of fluorination.

The difficulty in proving any theory of the ECF mechanism is that of identifying precisely and directly the intermediate species involved, rather than trying to infer these indirectly by product analysis.

Where this direct approach has been attempted, the difficulties are self-evident.

Novak and Boa [176], using ring-disc electrode techniques, studied intermediates and transients in the fluorination of acetyl fluoride and methanesulphonyl fluoride and concluded that the initial step was the discharge of the organic substrate in the adsorbed state, according to the following scheme:



Scheme 40

Unfortunately, the exact nature of the intermediate species detected by the ring electrode is not clear, and whether these are from different stages in the "zipper" process, or why they should have left the disc electrode part way through the fluorination, is not explained.

4.3.2
The Radical Mechanism

The essence of this theory on the mechanism of ECF is that reaction occurs via inorganic fluorinating agents generated at the anode; these include "nascent" fluorine, molecular fluorine, or its loose complexes with nickel fluorides, and simple or complex forms of high valence nickel fluorides [62, 65, 169, 178, 179]. However, until the precise nature and structure of the active nickel anode surface is characterised the position remains a matter for conjecture.

Nonetheless, much evidence has accumulated which is considered to support this proposition, not least the observation that the formation of this anodic layer is fundamental to proper operation of the Simons process, with its development

being studied by Watanabe [169] and others prompting the conclusion that a great deal of fluorine is absorbed in the film.

In a series of publications on the fluorination of amines and quaternary ammonium salts Rüdiger and co-workers have reported their findings on the analyses of the three product containing phases from the reactions, the "perfluorinated" liquid phase, the gaseous phase, and the so-called HF-phase, which was shown to contain significant quantities of partially fluorinated material, some of which were considered as intermediates in the fluorination process, but also others which remained inert to further reaction [180, 181].

The observation of large amounts of polyfluorinated compounds dissolved in the HF-phase was claimed not to be peculiar to these reactions but was said to be a normal part of all ECF reactions, and as such, said to contradict the "zipper mechanism" production of perfluorinated compounds, a pathway regarded as a support of the EC_bEC_N process [62, 172].

Of course this need not necessarily be the case, as in any mechanism where species are attached to an anode, changes in their electronic make-up, resulting from hydrogen replacement by fluorine, might be expected to cause variations in the adsorption forces with possible desorption into the electrolyte as a consequence.

However, the same workers performed a series of interesting voltammetric measurements [182] on dibutylmethylamine (DBMA), fluorinated dibutylmethylamine (F-DBMA), HF-phase (protonated and unprotonated) in acetonitrile, with $(Bu)_4NBF_4$ as supporting electrolyte, both on platinum and nickel anodes. Their results are set out in the table below.

Expt	Electrode	Electrolyte	Oxidation Potential vs. Hg/Hg_2Cl_2(sat.)
1	Pt, rotat.	$AN/(Bu)_4NBF_4$ + DBMA	0.94 v
2	Pt, rotat.	$AN/(Bu)_4NBF_4$ + HF-phase	1.81 v[a]
3	Pt, rotat.	$AN/(Bu)_4NBF_4$ + F-DBMA	2.3 v[b]
4	Pt, rotat.	$AN/(Bu)_4NBF_4$ + DBMA+HBF_4(1:1.5)	2.3 v[b]
5	Pt, rotat.	$AN/(Bu)_4NBF_4$ + HF-phase+HBF_4(1:1.5)	2.3 v[b]
6	Ni	$AN/(Bu)_4NBF_4$	0.1 v[c]
7	Ni, pre-electrolysed in HF	$AN/(Bu)_4NBF_4$	1.5 v[c]
8	Ni, pre-electrolysed in HF	$AN/(Bu)_4NBF_4$ + DBMA	1.5 v[c]

[a] The value will be somewhat lower, if the HF-phase comes from an ECF experiment with still running PFC-production.
[b] above 2.3 v the electrolyte becomes oxidised.
[c] oxidation of Ni.

Scheme 41. Voltammetric investigations in acetonitrile (AN)

The oxidation potentials show that, whereas unprotonated DBMA and unprotonated HF-phase were oxidised on Pt under these conditions (at 0.94 V and 1.81 V vs Hg/Hg_2Cl_2 sat., respectively), the protonated species, i.e., the form in which they would exist in ECF, were not, at least up to the limits of stability of the electrolyte. The authors cite this as evidence against the EC_bEC_N mechanism, where the electrochemical properties of the organic compound to be fluorinated, particularly its ability to be oxidised, are stated to be decisive.

Two important caveats, however, must be borne in mind in extrapolating these results into ECF; these are, firstly, that anode potentials are normally higher than 2.3 V, so it may still be possible for the protonated species to be oxidised at the actual potentials encountered, and, secondly, that the anode material in ECF is nickel not platinum. (In the systems studied, meaningful measurements of oxidation potentials of the organics were not possible because of oxidation of the nickel anode itself.)

Later studies on the ECF of tetraalkyl ammonium salts, known to be very stable towards electrochemical oxidation, showed that these reactions proceeded similarly to tertiary amines, but with increased formation of gaseous cleavage products [183].

A detailed analysis of the partially fluorinated products formed by the ECF of triethylamine (TEA) [184], in particular the fluorine distribution throughout the TEA skeleton during the course of the reaction, has led the authors to compare the striking similarity to the product distribution known for free radical halogenations.

In a very recent publication [70] Rüdiger has summed up these preceding results to propose a persuasive mechanism in which fluorination proceeds stepwise via partially fluorinated intermediates which are repeatedly adsorbed on the anode, fluorinated, and desorbed.

As the fluorination proceeds, solubilities, basicities, oxidation potentials, etc. of the successive products will alter such that new molecules formed will become competitors in the dynamic equilibrium between electrolyte and anode surface. It is supposed that this process continues until perfluorination takes place, unless, in the case of partially fluorinated compounds which are resistant to further fluorination by virtue of there structure, they remain in the HF-phase or in the "perfluorinated" phase depending upon the number and positions of remaining hydrogen atoms and the properties which this imparts.

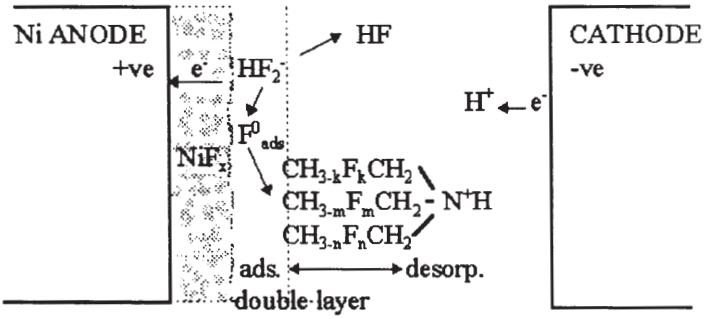
Thus, it is stated, in this model of the ECF process, the physico-chemical properties of the partially fluorinated intermediates – or more precisely, the course of these properties with progressive fluorination – provide the clue to a better understanding of the mechanisms involved.

Regarding the anode process, Rüdiger comes down firmly on the side of those supporting the argument that the fluorinating agent is electrochemically generated fluorine atoms adsorbed on the Ni/NiF_2 surface of the electrode, on the basis that

a) ECF occurs only at potentials which are high enough for the oxidation of fluoride ions,

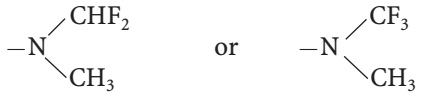
b) the minimum potential necessary for ECF is not influenced by varying amounts of substrate,
c) there is a great similarity between products from ECF and direct fluorinations, including the formation of stable free radicals [185].

The mechanism is illustrated schematically below.



Scheme 42. Electrode processes in an ECF cell

Further evidence against the EC_bEC_N carbocation mechanism is claimed by Sartori and co-workers [186] from their work on the fluorination of *N,N*-dimethyltrifluoromethanesulphonamides at different temperatures (–15 °C and +5 °C). According to the carbocation mechanism, it is stated, introduction of fluorine atoms into the sulphonamide should take place stepwise, first in one methyl group and then into the other; however, detailed examination of the reaction mixture by ^{19}F NMR spectroscopy showed no trace of compounds containing the moieties



whereas compounds with fluorine substitution in both methyl groups do occur. This, and the strong dependence of the process on temperature are said to indicate that direct electrochemical oxidation of the starting organic material is not a key step in the process.

Instead, the authors suggest that the reaction takes place firstly by the formation of higher valence nickel fluoride(s) on the surface of the anode, and secondly, by specific adsorption of the organic on that surface.

Support for the mechanism involving high valence nickel fluorides as the fluorinating agent was said to be provided by an independent experiment in which the anode surface was generated (at 5.0 – 5.3 V for 48 h) in HF, the current turned off, and then *N,N*-dimethyltrifluoromethane sulphonamide added and left for 18 h. Analysis of the reaction mixture by 19F NMR again showed the presence of the same range of partially and perfluorinated compounds as previously observed, demonstrating the chemical nature of the reaction rather than an electrochemically driven one.

The potency of such nickel fluorides as fluorinating agents has been provided by Zemva and co-workers [187] who have recently described the rapid conversion of Xe to XeF_2, and C_3F_6 to C_3F_8 using NiF_3 and NiF_4.

A very significant recent contribution to the debate on the possible nature of the fluorinating agent in ECF is the report [188] that hydrogen has been replaced by fluorine in a variety of organic compounds smoothly and efficiently in liquid HF, to yield products similar to those from ECF, using thermodynamically unstable fluorides R-NiF_3 and NiF_4, the latter being prepared in situ from K_2NiF_6 with BF_3. This is the first time a reagent has been shown to perform the same type of fluorination reactions, at low temperature, in hydrogen fluoride, as those achieved in ECF, and could provide a crucial piece of evidence as to the reactive species on the surface of the anode in the Simons process.

Thus, an assessment of the present situation would suggest, on balance, that experimental evidence appears to support the Radical Mechanism over the Carbocation Mechanism, although a number of important questions remain far from being resolved.

In the argument against the EC_bEC_N concept, much, perhaps too much, store has been placed by critics on observations which seem to undermine the "zipper mechanism" in the apparent belief that this mechanism is axiomatic with the EC_bEC_N as a whole. However, as has been shown, changing physico-chemical properties of progressively fluorinated products inevitably result in different adsorptive forces for these compounds, with possible desorption from the electrode as a consequence; this situation could apply equally well with products formed via a carbocation mechanism as with radically generated compounds, even though, as originally stated, the implication is otherwise.

Detailed analyses of partially fluorinated compounds from the ECF of amines, and relatively simple sulphonic acid derivatives have been performed with interesting and illuminating results; but do these observations translate into other complex systems, e. g., long chain carboxylic acid derivatives? The experiments have yet to be done.

Additional crucial data still to be gathered experimentally are the actual values of oxidation potentials of organic substrates under ECF conditions; e. g. is it really possible to remove an electron from, say, a protonated amine salt under the electrochemical conditions which prevail in the cell?

If so, is it then not likely that both mechanisms could operate, possibly with cross-over routes between one another, during the course of a reaction? Such a concept would go a long way towards explaining the many rearrangements, cyclisations, etc. characteristic of the process.

As to what, exactly, might be the fluorinating agent in the proposed Radical Mechanism; we have seen how some workers favour that of fluorine absorbed on or in the nickel fluoride layer, whereas others prefer that of high valence fluorides. In this respect, it is interesting to note how different workers interpret what are apparently very similar phenomena upon opening the electrical circuit of a previously "conditioned" ECF anode, e. g., Watanabe [169], and the decay of electrode potential, as an example of the first, and Sartori et al. [186], and the persistence of chemical activity, as an example of the second. Perhaps, in reality, the dynamic equilibrium which relates fluoride ion, nickel fluorides, and atomic

fluorine at the surface of the ECF anode means there is little difference between the two.

However, the proponents of the Radical Mechanism would argue that, whatever the actual agent, the fact remains that the process provides a means of generating fluorine at a rate, and in a form which is conducive to controlled reaction with organic compounds, probably constrained on a favourable, possibly catalytic [189] heat-sink surface, in such a way as to overcome the two principal problems inherent in all elemental fluorinations [190], namely

i) the low equilibrium concentration at ambient temperature of fluorine atoms in molecular fluorine gas,

$$F_2 \rightleftharpoons 2F^{\circ} \text{ where } K \sim 10^{-20};$$

even though the bond dissociation energy for this process is so low, $\Delta H = 38.8$ kcal mole^{-1}, and

ii) the highly exothermic nature of fluorine substitution of hydrogen bonded to carbon,

$$\text{C–H} \longrightarrow \text{C–F} \qquad \Delta H = 104 \text{ kcal mole}^{-1}.$$

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