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Review

Elemental fluorine in organic chemistry (1997–2006)

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Abstract

The use of elemental fluorine as a reagent over the period 1997–2006 for carbon–fluorine bond formation in organic synthesis is reviewed. Recent advances in the exhaustive fluorination of ethers and esters to give perfluorinated systems, selective direct fluorination of aliphatic, aromatic, heterocyclic and carbonyl systems and the application of microreactor techniques to direct fluorination are discussed.

Keywords: Direct fluorination; Elemental fluorine; Gas liquid continuous flow microreactor; Fluoroarene; Selective fluorination

Contents

1. Introduction

Since very few naturally occurring compounds that possess a carbon–fluorine bond exist, the vast majority of organofluorine compounds must be prepared by synthesis [1,2]. Whatever strategy is adopted for the preparation of a particular target molecule, whether it is a biologically active derivative for the life science industry or a high molecular weight polymer for the materials sector [3], the key step is the synthesis of a carbon–fluorine bond at some stage of the synthetic sequence and many fluorinating agents have been developed over the years with the goal of solving this fundamental problem, with varying degrees of success [1–5]. Arguably the most direct method for the introduction of fluorine atoms into an organic system is the replacement of hydrogen, attached to sp^2 or sp^3 carbon, by fluorine which requires the use of an electrophilic fluorinating agent. The least expensive and most reactive electrophilic fluorinating agent is fluorine gas itself although other very useful reagents are now readily available for general laboratory use [6,7]. Elemental fluorine has now, it is perhaps fair to say, been accepted by many organofluorine chemists as a viable reagent for synthesis of carbon–fluorine bonds in a range of organic systems.

This review will cover published literature concerning the use of elemental fluorine for the synthesis of carbon–fluorine bonds in organic systems over the period 1997–2006, updating

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our earlier review [8] on this subject in a similar format and complementing other recent discussions in this area [9–11]. The fluorination of fullerenes has been reviewed [12,13] and will not be discussed here whilst the chemistry of reagents that are synthesised from fluorine, such as reagents of the N-F class [6,14] and HOF [15], is also beyond the scope of this review.

It is hoped that a discussion of the most recent developments in this field will help to persuade even the most sceptical non-fluorine chemist that fluorine, which is available commercially in cylinders as dilute mixtures in nitrogen, is a valuable reagent to the synthetic chemist for carbon–fluorine bond forming processes.

2. Perfluorination

Perfluorination is the exhaustive replacement of all hydrogen atoms in an organic system by fluorine, which is usually carried out using free radical conditions [16]. A summary of the strategies used and considerations regarding the thermodynamics of perfluorination processes that must be taken into account when planning a perfluorination reaction is included in our previous discussion [8]. The mechanism and the thermodynamics of perfluorination processes and brief details of the LaMar [16], Aerosol and Liquid Phase photofluorination methods were outlined previously [8]. Russian workers have reviewed their perfluorination studies for the synthesis of a range of perfluoroalkanes, ethers and tertiary amines [17].

LaMar perfluorination-type processes have been used by Lagow and co-workers to synthesise various perfluorinated *spiro*-fused crown ethers [18], large ring crown ethers [19], highly branched ethers [20], carbohydrates [21] and bicyclo[1,1,1]pentanes [22] by exhaustive fluorination of the corresponding hydrocarbon derivative (Scheme 1).

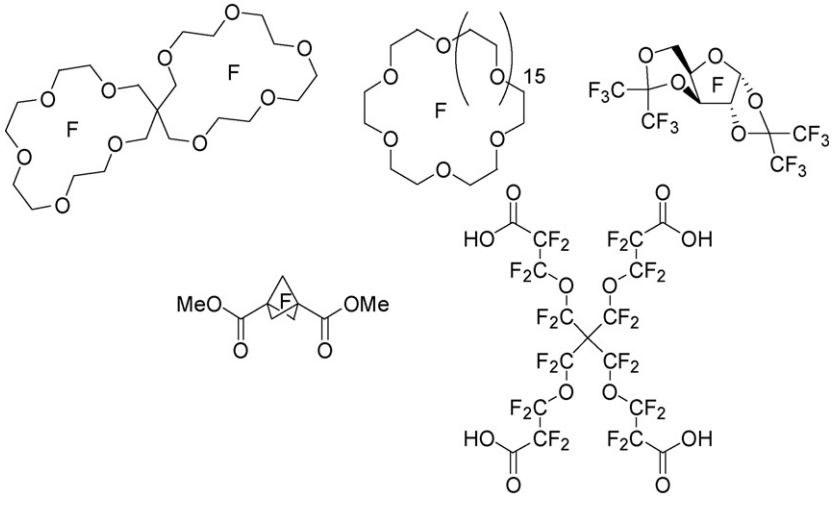
Perfluorination of methanesulfonyl fluoride, using a perfluorocarbon fluid as the reaction medium, gave good yields of trifluoromethanesulfonyl fluoride (Scheme 2) [23].

Partially fluorinated substrates are excellent starting materials for perfluorination because the presence of fluorine atoms in an organic molecule lowers the oxidation potential of the system, thereby enhancing the stability of the substrate towards the sometimes necessarily harsh perfluorination conditions [8,24]. Furthermore, the fluorinated groups render the substrate more soluble in the fluorinated solvents that are often used for such reactions. Using this strategy, perfluorination of a range of ethers and polyethers bearing hexafluoropropyl units has been achieved (Scheme 3) [24]. The use of small molecular weight polyfluoroethers **1**, which are themselves perfluorinated under the reaction conditions, as a solvent for perfluorination of high molecular weight polyether derivatives allows perfluorination reactions to be carried out in non-ozone depleting solvents.

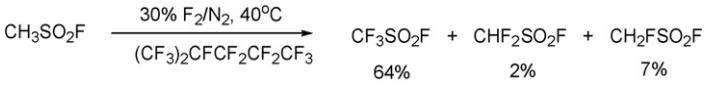
The use of partially fluorinated substrates for perfluorination has been used to great effect recently by Okazoe et al. at the Asahi Glass company [25–28]. Suitable partially fluorinated esters are synthesised by condensation of a perfluoroacid fluoride with an alcohol derivative (Scheme 4).

The partially fluorinated esters can be efficiently perfluorinated by direct fluorination in CFC solvents (Scheme 5) [27,28].

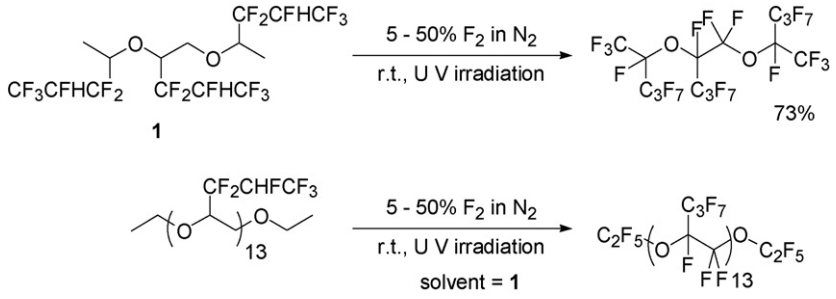
By similar procedures, chlorine containing esters gave the corresponding perfluorinated derivative although some product arising from chlorine migration was observed [28] and diesters gave appropriate perfluorinated derivatives when a perfluorocarbon fluid was used as the reaction medium (Scheme 6) [26]. In addition, perfluoroalkane sulfonyl fluorides could also be synthesised by this general strategy (Scheme 6) [25].



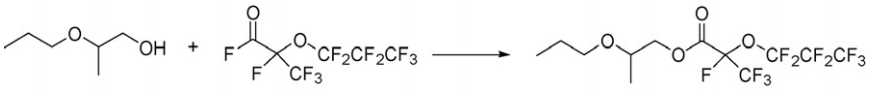
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

Heating the perfluorinated esters with sodium fluoride leads to the synthesis of perfluorinated acid fluoride derivatives which are useful building blocks for a range of perfluoroalkylated systems and this has been termed the 'PERFECT' process [27] (PERFluorination of an Esterified Compound then Thermal Elimination). The 'PERFECT' cycle for the synthesis of a perfluorinated acid fluoride, which is a precursor of perfluoro(propyl vinyl ether) (PPVE), an important commercial monomer, utilising the chemistry described above is shown in Scheme 7. Reaction of the alcohol with the perfluorinated acid fluoride gives the partially fluorinated ester that is subjected to perfluorination. Heating this substrate gives 2 mol of the acid fluoride target molecule, one of which is recycled and the other collected as product [27].

3. Selective direct fluorination

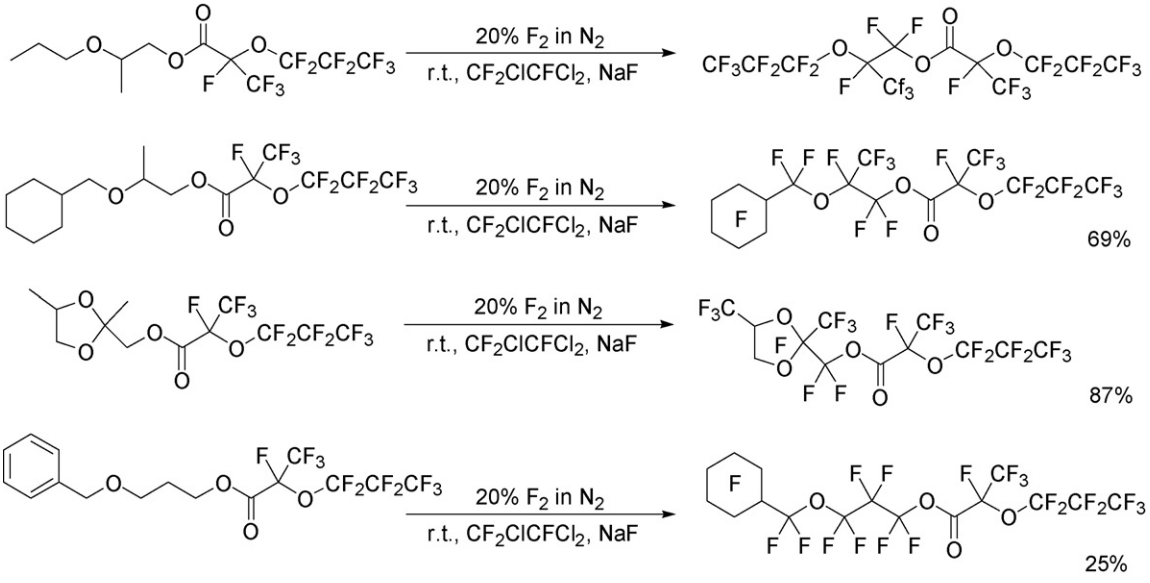
Selective direct fluorination (SDF), the replacement of one or two hydrogen atoms by fluorine, is usually carried out in conditions that favour nucleophilic attack by the substrate on electrophilic fluorine whilst limiting competing free radical processes. Consequently, the reaction media of choice for SDF reactions are either high dielectric aprotic solvents such as acetonitrile [29] or strong protonic acids [30] such as formic or sulfuric acids, both of which make fluorine more susceptible towards nucleophilic attack (Scheme 8).

The use of these solvents has allowed SDF of several classes of aliphatic, aromatic and heterocyclic systems to be effectively realised.

3.1. Replacement of hydrogen by fluorine

3.1.1. Aliphatic derivatives

A relatively uncommon aliphatic electrophilic substitution process [31] is considered to be the mechanism for the transformation of an sp^3 hybridised C–H to a C–F bond (Scheme 9) [31] and this has been supported by theoretical work [32].



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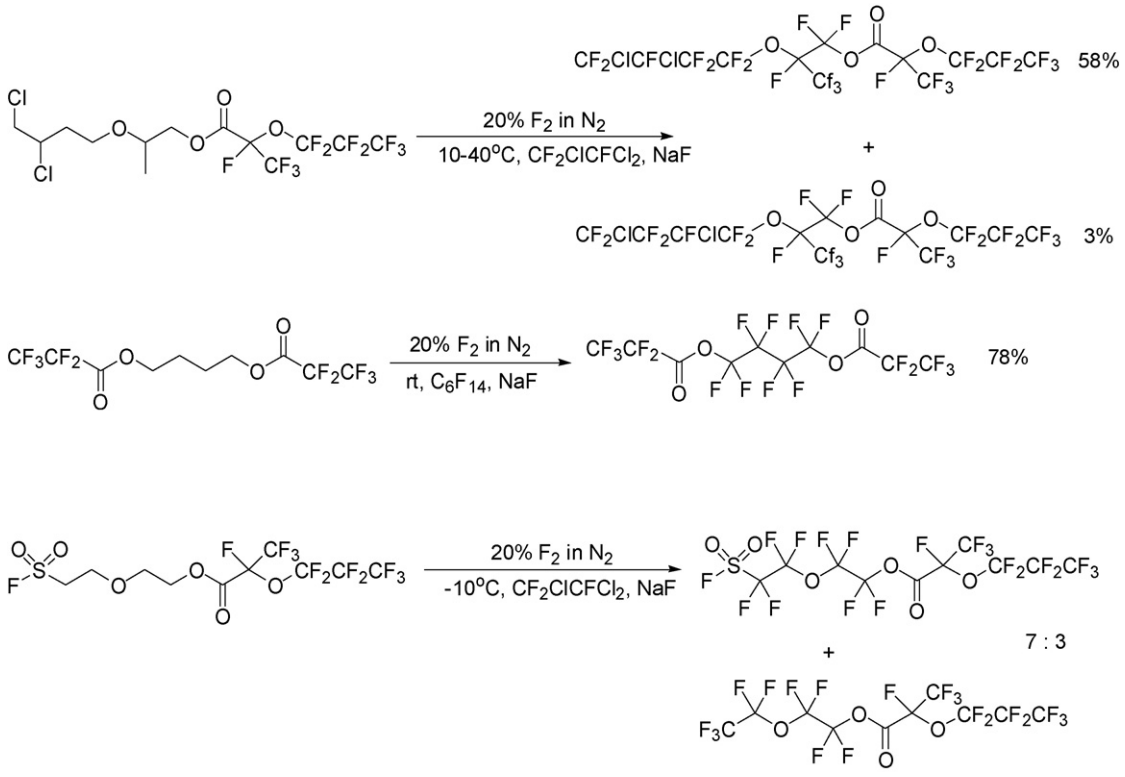
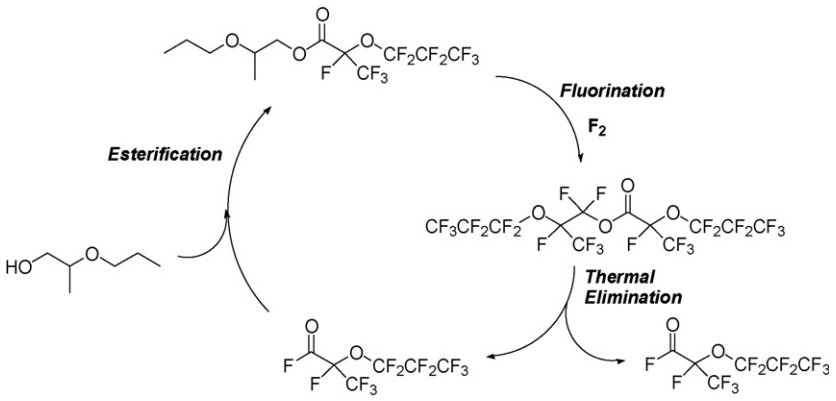
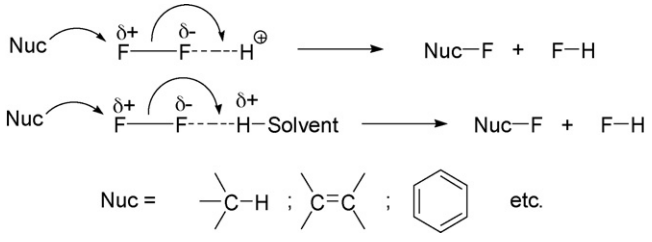


Scheme 6.

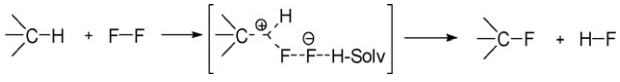


Scheme 7.

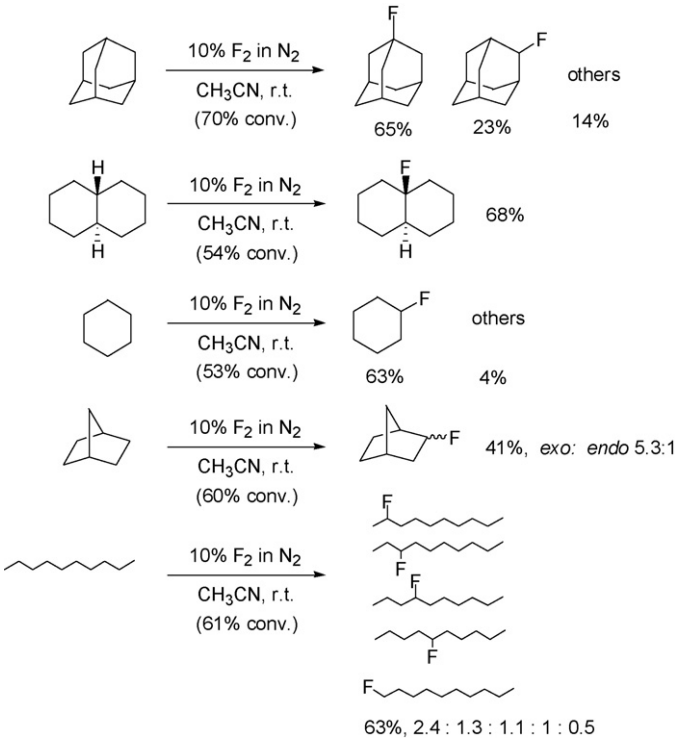
The polar solvent (Solv-H) not only encourages polarisation of the fluorine molecule and makes it more susceptible to nucleophilic attack, but more importantly, acts as an acceptor for the counterion (fluoride ion) in the transition state. Pioneering work in this area was carried out by Rozen and Gal [33] who used a mixture of $CFCl_3$ and chloroform as the reaction medium, the polar chloroform molecules acting as depicted in Scheme 9. More recently, acetonitrile was used as the reaction medium in attempts to carry out fluorination reactions of saturated hydrocarbons in non-ozone depleting solvents (Scheme 10) [29,34]. The polar acetonitrile is thought either to enhance fluorination by acting as a polar solvent as depicted in Scheme 8 or by reaction with fluorine to form a transient electrophilic N-F derivative that acts as the fluorinating agent [29]. In these cases, hydrogen atoms attached to



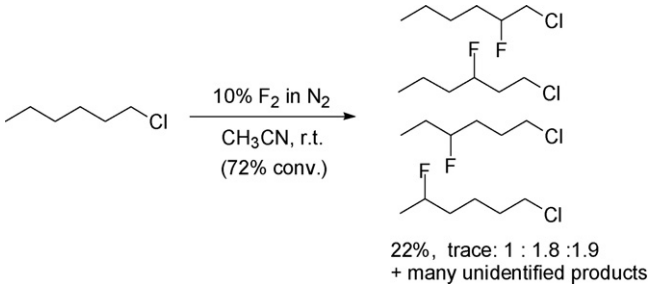
Scheme 8.



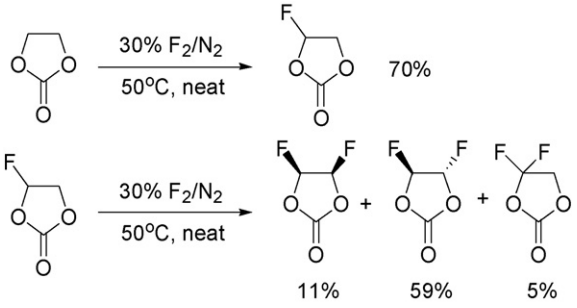
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

tertiary sp^3 carbon are selectively replaced with retention of configuration, over primary and secondary sites, upon reaction with fluorine, consistent with an electrophilic process and in agreement with Rozen's results [33]. Secondary hydrogen may also be displaced by fluorine if no tertiary sites are present [29] or if the tertiary C–H bond has a lower p orbital contribution, and is therefore less nucleophilic, than the available secondary sites. Reactions of fluorine with non-cyclic hydrocarbon derivatives in acetonitrile give mixtures of monofluorinated products. For example, *n*-decane gave predominantly four products, in essentially equal amounts, arising from unselective fluorination of all available secondary C–H sites. Similarly, reaction of dodecane absorbed on aluminium fluoride with fluorine in the gas phase also gave predominantly a mixture of monofluorinated dodecane products [35]. Presumably, interaction of fluorine with the strong Lewis acid renders the fluorine more susceptible towards attack by nucleophiles.

Reactions of model halohexane derivatives of the form C_6H_{13}-X (X = Cl, Br, I) with elemental fluorine were studied in order to assess the impact of halogen substituents upon fluorination of an alkyl chain [36] (Scheme 11).

Fluorination of 1-chlorohexane occurs at secondary sites, with a slight preference for those that are furthest removed from the electron withdrawing group, consistent with an electrophilic process and in agreement with earlier work involving the fluorination of various functional steroid derivatives by Rozen and Ben-Scushan [37], although mixtures of fluorinated products are obtained in most cases. In contrast, bromo- and iodohexane give many unidentified products and tar formation, probably arising from oxidative fluorination processes. These studies give some indication of both the opportunities and the problems that may be encountered when performing direct fluorination reactions of saturated, functional systems.

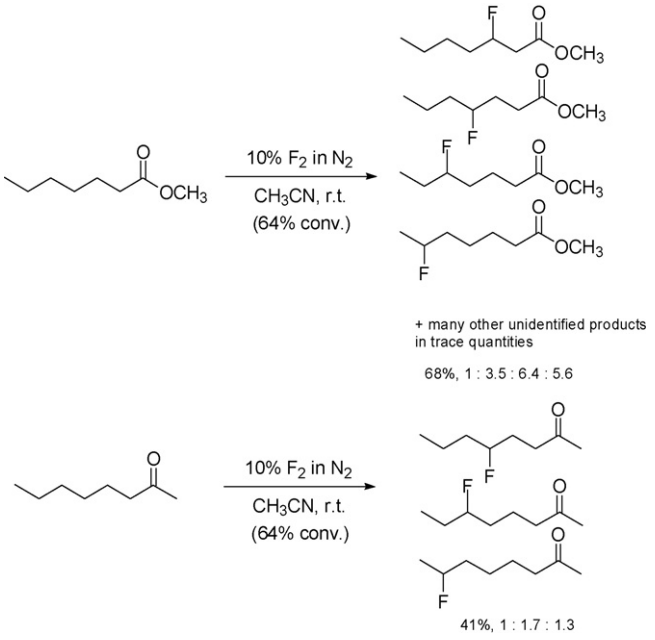
1,3-Dioxolan-2-one, essentially a protected diol, reacts with fluorine to give high yields of the 4-fluoro derivative in the absence of any other solvent (Scheme 12) [23]. Further fluorination was also carried out to give a mixture of difluorinated products. In both reactions, the O–C=O groups can be considered to be electron withdrawing substituents that lower the reactivity of the adjacent carbon–hydrogen bonds towards electrophilic attack and, therefore, more forcing conditions are required to permit fluorination.

3.1.2. Carbonyl compounds

The carbonyl group is, of course, of fundamental importance in organic synthesis since carbon–carbon bonds may be formed by either reaction directly with the carbonyl group (e.g. Grignard reagents, Wittig reactions, etc.) or by reaction with the corresponding enolates (e.g. alkylation, aldol condensations, etc.) and many of these transformation can be achieved enantioselectively. Consequently, much attention has been focussed on developing realistic synthetic methodology for the synthesis of fluorocarbonyl derivatives, which can be used subsequently as building blocks for the preparation of more structurally sophisticated systems.

Reactions of various carbonyl containing derivatives of the form C_6H_{13}-X (X = CO_2Et, COMe, CHO) with elemental fluorine have been reported [36] to establish the functional group compatibility towards fluorination and the effect of a carbonyl functionality on the fluorination of saturated carbon chain (Scheme 13).

Fluorination of the ester and ketone derivatives preferably occur at secondary sites that are furthest removed from the



Scheme 13.

electron withdrawing group, consistent with the fluorination of chlorohexane described above.

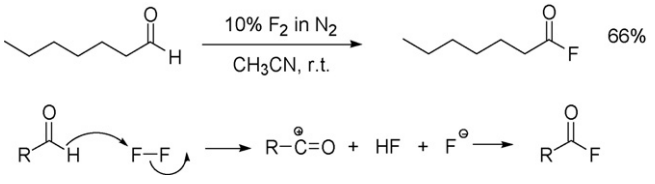
In contrast, an aldehyde substrate [36], heptanal, gave the corresponding acid fluoride selectively by an oxidative process outlined in Scheme 14.

These model studies confirm that, in general, selective fluorination of carbonyl derivatives is very difficult.

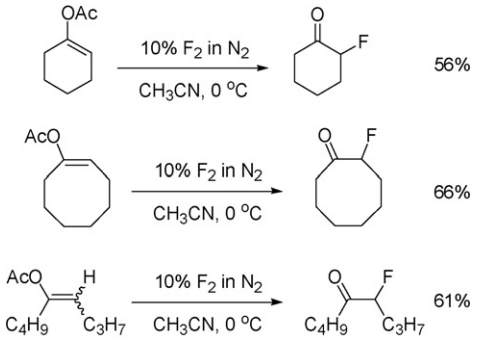
However, the synthesis of carbonyl derivatives bearing fluorine at sites adjacent to the carbonyl functionality (α-fluorocarbonyl derivatives) is possible because, in these cases, selective fluorination of the enol form of the carbonyl system can be achieved and processes involving the fluorination of various enol derivatives have been described [38]. Despite previous observations [39], fluorination of enol acetates using either acetonitrile or formic acid as the reaction media has been shown to be a very effective method for the synthesis of various α-fluoroketones (Scheme 15) [38].

In the case of nonan-2-one, acylation gave a mixture of three enol acetate derivatives and so subsequent fluorination gave a mixture of α-fluoroketone systems. Fluorination of corresponding trimethylsilyl enol ethers was, however, found to be very unselective, primarily due to the instability of these substrates to the acidic reaction media.

These studies [38] and previous work concerning the fluorination of 1,3-dicarbonyl derivatives [9] show that



Scheme 14.



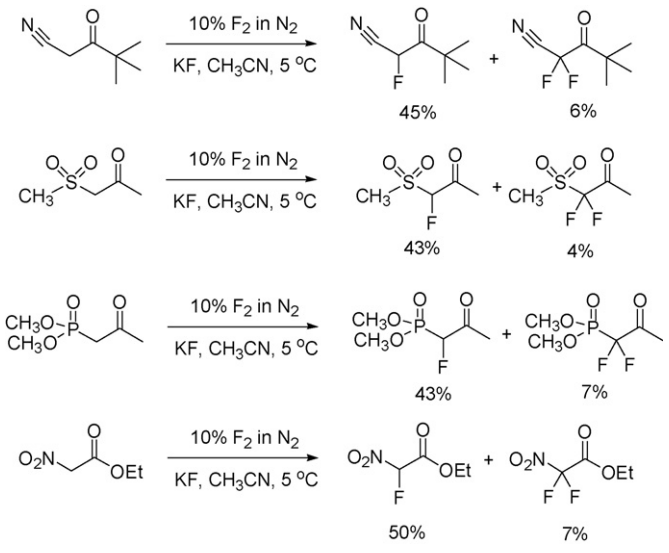
Scheme 15.

α-fluorination of carbonyl derivatives occurs very selectively if the substrates are either present predominantly in their enol form, for example, as an enol acetate, and/or enolise rapidly in the reaction medium. For substrates that enolise at reasonable rates, then higher conversion of starting material to product may be achieved by varying the flow rate of fluorine into the reaction mixture. Thus, a slower rate of addition of fluorine to ethyl acetoacetate, thus allowing enolisation to occur, allows efficient use of fluorine [40].

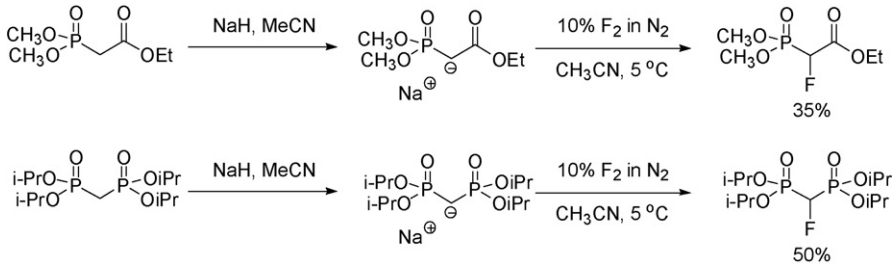
For carbonyl systems that do not fall into either of these categories, fluorination must be carried out in conditions that enhance enol formation by either base catalysis, metal catalysis or deprotonation of α-hydrogen atoms [41]. For example, fluorination of carbonyl systems bearing strong electron withdrawing groups (CN, SO_2CH_3, NO_2, etc.) at the α-position and, hence, possessing relatively acidic α-hydrogen atoms, occurs when an excess of basic potassium fluoride is present as a suspension in acetonitrile solution (Scheme 16) [41].

As an alternative strategy, carbanion derivatives formed by proton abstraction by sodium hydride, may be efficiently fluorinated to provide access to various fluoroester and diphosphonate systems (Scheme 17) [41].

Furthermore, fluorination of various malonate and β-carbonyl systems is very efficiently catalysed by the addition



Scheme 16.



Scheme 17.

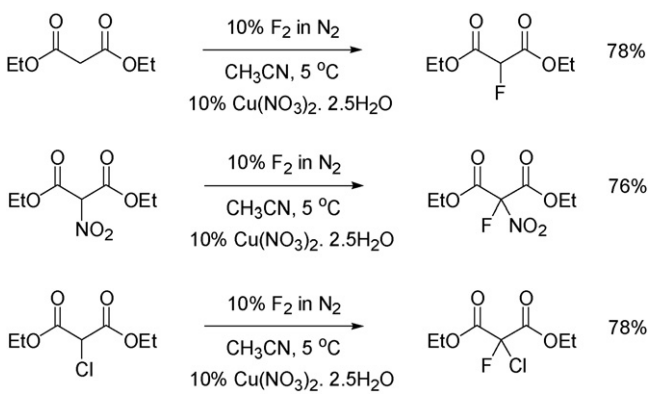
of copper(II) nitrate hydrate ($Cu(NO_3)_2{\cdot}2.5H_2O$) which must be involved in promoting the enolisation rate of the dicarbonyl substrate by complexation processes (Scheme 18) [41].

In summary, a wide range of α-fluorocarbonyl systems is now accessible by direct fluorination methodology and their use as building blocks in organic synthesis can now be further explored. For example, the Pfizer herbicide, Veroconazole, requires the use of an α fluoro-ketoester building block which is itself synthesised on the manufacturing scale by direct fluorination [42].

3.1.3. Benzenoid compounds

Protonic acids (formic [30,43], sulfuric [43] and triflic [44] acids and hydrogen fluoride) have been shown to be effective media for promoting selective fluorination of aromatic systems, yielding products that are consistent with an electrophilic aromatic substitution process. Fluorine is considered to be made more susceptible towards nucleophilic attack by an aromatic system due to polarisation in the acid (Scheme 19) whilst competing unselective free radical processes are minimised.

Fluorination of 1,4-disubstituted substrates in acidic reaction media, in which only one position is activated towards electrophilic attack by the presence of appropriately situated electron releasing (OH, OMe, NHAc, Me) and withdrawing (NO_2, CN) groups *para* to one another, allows the synthesis of a range of monofluorinated aromatic systems (Table 1) [43]. Purification by column chromatography or distillation is required as difluorinated products may also be formed.



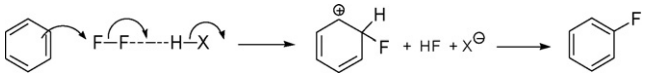
Scheme 18.

However, if both substituents are strongly deactivating (NO_2, CN), fluorination is very difficult under these reaction conditions and when both groups are activating, complex product mixtures are obtained.

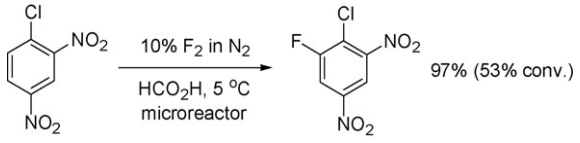
In general, for deactivated substrates, a stronger acid medium such as conc. sulfuric acid can lead to higher conversions and yields of fluorinated aromatic products. However, aromatic substrates bearing groups that may be protonated in such strongly acidic media (OH, OMe) are deactivated towards electrophilic attack and are more favourably fluorinated in formic acid. Cyanobenzene derivatives are hydrolysed to acetophenones in sulfuric acid and so, again, formic acid is a more effective reaction medium for direct fluorination in this case. Thus, the reaction medium must be tailored to suit the structure of the substrate.

Even aromatic systems that bear two strong electron withdrawing groups that are in positions *meta* to one another and are, of course, very deactivated towards electrophilic attack, can be fluorinated using acidic reaction media (Scheme 20) using microreactor techniques [45].

Similarly, mixtures of triflic acid in $CFCl_3$ (5%, v/v) have been used as the reaction medium in studies concerning the direct fluorination of fluorobenzene and the difluorobenzenes [44,46]. Fluorobenzene and 1,2- and 1,3-difluorobenzene gave fluorinated products as would be expected for an electrophilic substitution process (Scheme 21), although several other fluorinated derivatives are obtained, whilst 1,4-difluorobenzene led to a number of non-aromatic products. Reaction of 4-fluorophenyltrimethyl silane in a triflic acid/$CFCl_3$ solvent system led to a mixture of products arising from *ipso* substitution and/or desilylation [46].

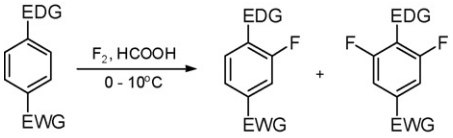


Scheme 19.

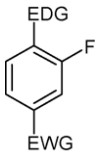
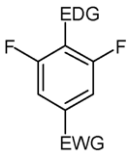


Scheme 20.

Table 1

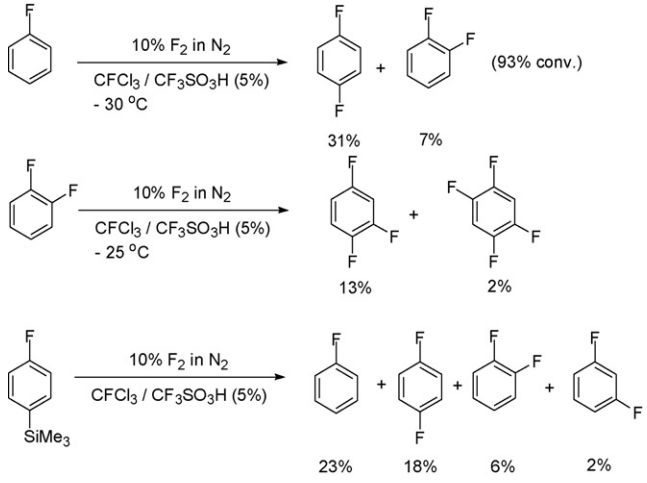


EDG = electron donating group
EWG = electron withdrawing group

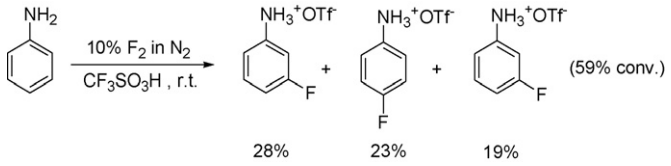
EDG		Conv. (%)	Yield (%)	
				
OH	NO_2	75	70	8
OMe	NO_2	100	50	20
NHAc	NO_2	100	60	8
Me	NO_2	63	50	Trace
F	NO_2	36	53	Trace
Cl	NO_2	47	44	Trace
OH	CN	84	64	10
OMe	CN	90	35	10
NHAc	CN	86	66	10
Me	CN	86	60	5
F	CN	67	40	Trace
OH	CF_3	100	12	22
OH	COMe	83	41	7
OH	CO_2H	50	55	20
OH	CO_2Me	100	28	17
OH	Br	90	22	4
OH	Cl	100	18	13
OMe	CO_2Me	92	51	9
OMe	Br	92	43	15
OMe	Cl	80	49	7
OMe	Me	48	53	5

EDG: electron donating group, EWG: electron withdrawing group.

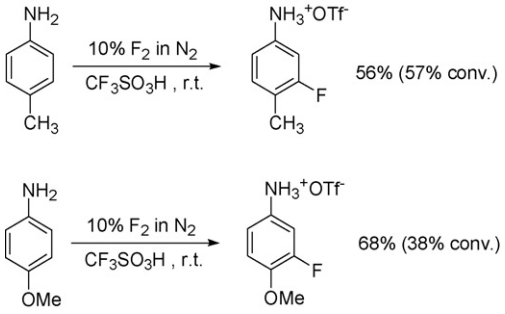
In triflic acid, anilines gave mixtures of fluorinated isomers including significant amounts of product that is fluorinated at the *meta* position (Scheme 22) indicating that substitution of the protonated aniline, where NH_3^+ acts as an electron withdrawing group, is occurring [47].



Scheme 21.



Scheme 22.



Scheme 23.

The presence of an electron releasing group at the 4-position allowed selective fluorination of various aniline derivatives giving products consistent with an electrophilic process (Scheme 23) in which the protonated amino group may be considered as an electron withdrawing substituent [47].

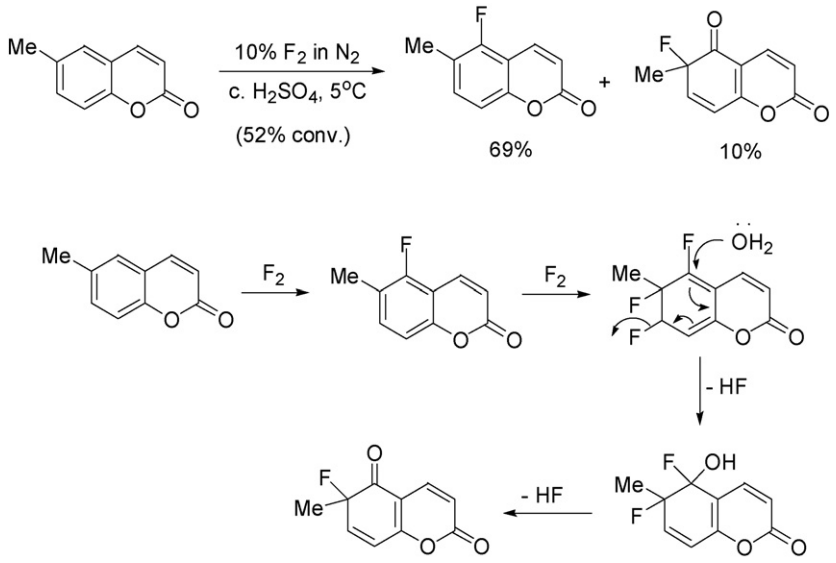
The use of acidic reaction media has, therefore, allowed the ready synthesis of a range of fluoroarene derivatives and, in some cases, direct fluorination methodology provides a viable alternative synthetic strategy to the well established and industrially important Balz-Schiemann fluorodediazonization and halogen exchange methods [48].

3.1.4. Heterocyclic aromatic compounds

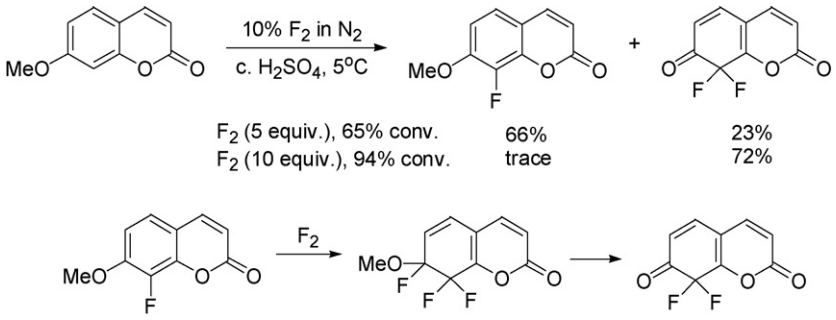
The Durham group has extended their studies on the fluorination of aromatic substrates to include related systems where aromatic rings are fused to heterocycles, such as the coumarin [49] and quinoline [50] series.

Direct fluorination of coumarin in acid media led to complex mixtures of products arising from electrophilic substitution processes [49]. In contrast, however, fluorination of 6-methyl- and 7-alkoxy-coumarins was more selective and preparatively useful quantities of various fluorinated systems were obtained. 6-Methyl-coumarin gives the corresponding 5-fluoro derivative as the major product, arising from fluorination of the site that is activated by the methyl group and is formed via the most stable carbocationic intermediate. Small quantities of a fluoroketone derivative are also obtained, formed by fluorination of the 5-fluoro derivative and subsequent hydrolysis during aqueous work-up as depicted in Scheme 24.

Fluorination of 7-methoxycoumarin also occurs *ortho* to the methoxy group at the site adjacent to the heterocyclic ring and a product arising from further fluorination and hydrolysis is also obtained (Scheme 25). The relative quantities of mono and difluorinated products that are isolated depend on the amount of



Scheme 24.

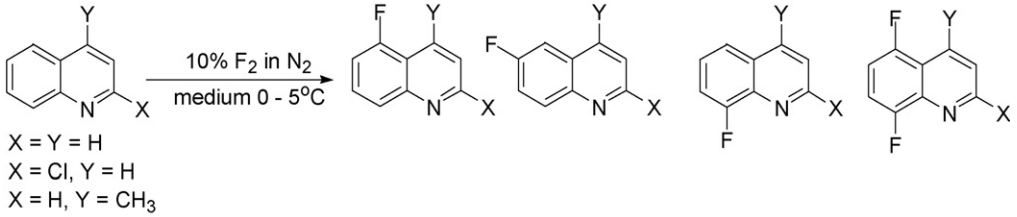


Scheme 25.

fluorine that is passed through the reaction mixture. An excess of fluorine (10 equivalents) gives the difluoroketone product exclusively in a remarkably effective process [50].

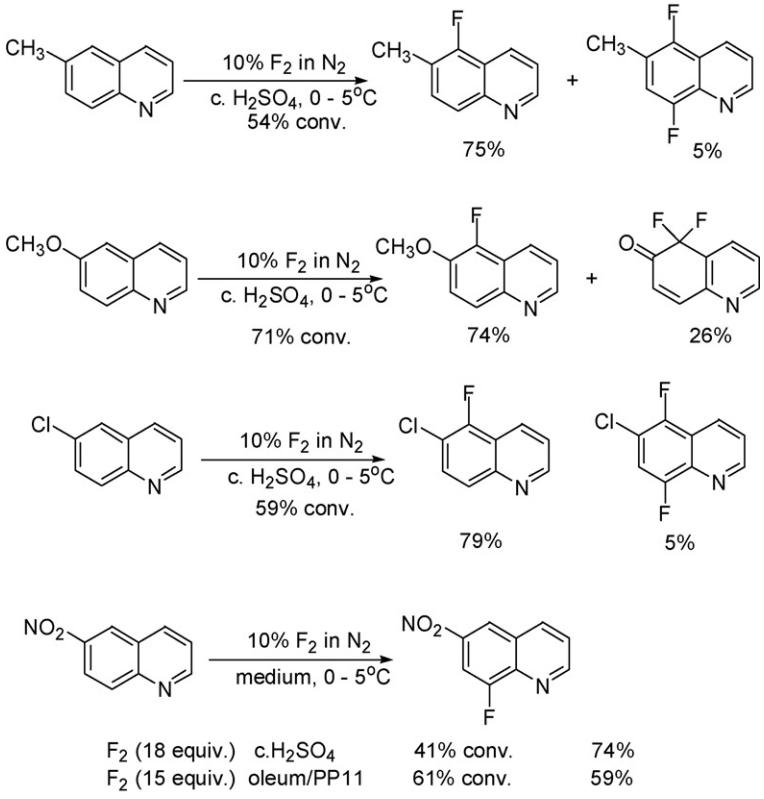
Fluorination of various quinoline derivatives using either conc. sulfuric acid or oleum/perfluorocarbon fluid mixtures as the reaction medium was also realised [50,51] and, in these cases, the heteraryl ring is deactivated towards electrophilic attack by interaction with the acid medium. Quinoline and derivatives bearing substituents (Cl or CH_3) on the heteraryl ring gave mixtures of products arising from fluorination at the 5-, 6- and 8-positions (Scheme 26).

Fluorination of quinoline systems bearing substituents at the 6-position gave products consistent with an electrophilic substitution process (Scheme 27). *Ortho* and *para* directing groups (Cl, CH_3, CH_3O) gave the 5-fluoro derivative whilst *meta* directing groups (NO_2) gave the 8-fluoro derivative. In each case, the hydrogen attached to carbon that is adjacent to the heteraryl ring is selectively replaced when there is a choice.



F_2	medium	conversion (%)		Yield (%)		
12 equiv.	c. H_2SO_4	67	27	8	14	32
12 equiv.	oleum/PP11	68	25	11	16	21
3 equiv.	c. H_2SO_4	26	48	14	23	6

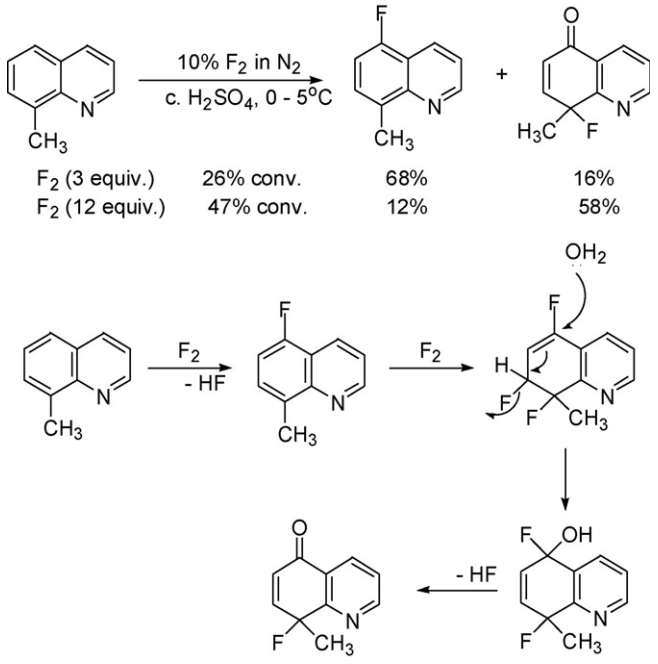
Scheme 26.



Scheme 27.

A difluoroketone derivative is obtained as a by-product upon fluorination of 6-methoxyquinoline in a process similar to the fluorination of the corresponding methoxy coumarin system.

In addition, fluorination of 8-methylquinoline gives a fluoroketone system upon fluorination and subsequent hydrolysis (Scheme 28).



Scheme 28.

These results demonstrate that, whilst relatively unreactive towards fluorine, selective fluorination of ring-fused heterocyclic systems is possible given a judicious choice of substituent.

The use of fluorine in combination with iodine in an inert solvent allows the fluorination of pyridine, quinoline and quinoxaline derivatives at positions that are adjacent to ring nitrogen only (Scheme 29) [52]. An addition elimination mechanism of the iodine monofluoride which is generated *in situ* is suggested to account for the regiochemistry (Scheme 29).

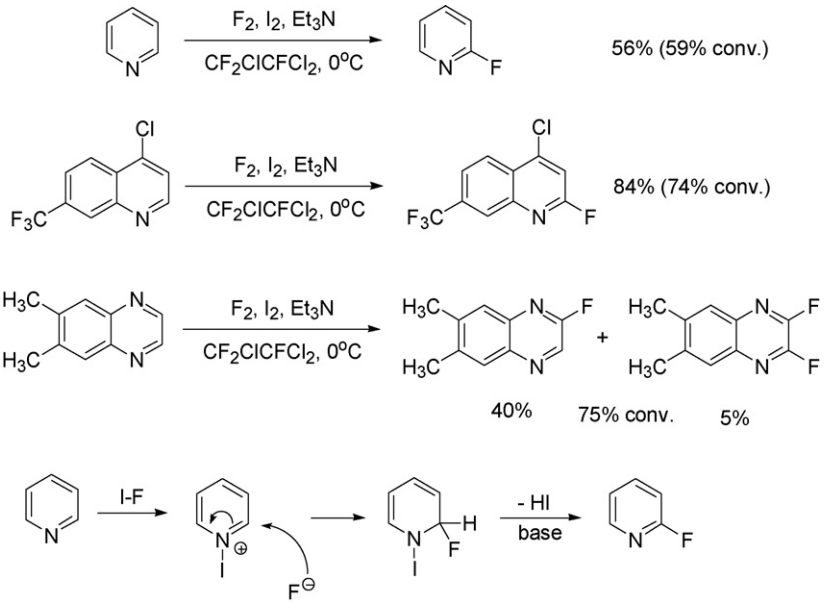
3.2. Addition to carbon–carbon double bonds

Addition of fluorine to carbon–carbon double bonds is a well established process and generally proceeds by *syn* addition. Several examples of fluorination of both very nucleophilic and very electrophilic alkenes have been reported in the past decade, demonstrating the range of systems that react efficiently with fluorine.

Reaction of the very electron rich alkene, tetrakis(dimethylamino) ethylene (TDAE) gives a fluoride salt (Scheme 30) which may be used as a source of fluoride ion in various carbon–fluorine bond forming processes [53].

2,5-Dihydrothiophene-1,1-dioxide gave a mixture of products (Scheme 31) upon reaction with fluorine arising from addition to the carbon–carbon double bond [54].

Relatively electron deficient fluoro vinyl ethers were fluorinated (Scheme 32) to give the appropriate saturated systems using the chloroform/$CFCl_3$/ethanol solvent system [55].

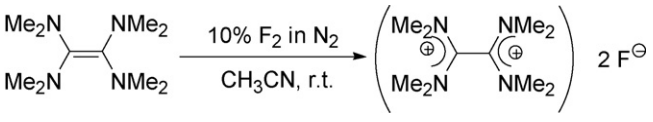


Scheme 29.

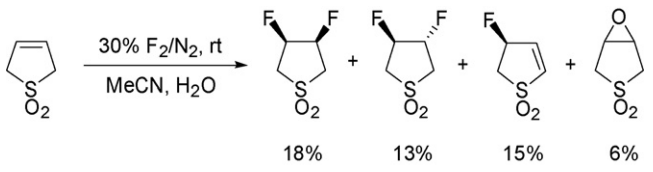
4. Microreactor techniques

Although industry prefers to use continuous flow processes for larger scale chemical synthesis, chemists working in the laboratory tend to avoid such an approach. There are a number of reasons that contribute to this situation when considering gas/liquid reactions but scale, convenient control and monitoring of gas and liquid flow are the main factors. Consequently, there is frequently a large technology gap between bench-scale development of a chemical process and even the most modest scale-up.

In the last few years, microreactor devices [56–58] have been developed that could bridge this gap with simple equipment that may be used for laboratory, pilot and manufacturing scale. The use of continuous flow, microreactor devices has many advantages for applications in synthetic organic chemistry over standard batch-wise processes because of the greater possibilities for high throughput, the use of very small quantities of material when appropriate, reduced waste streams, low manufacturing, operation and maintenance costs, low power consumption, increased precision and accuracy and disposability, amongst other features [56–58]. Most importantly for gas/liquid reactions such as direct fluorination, the contact between the reagents is increased tremendously because of the large surface area that exists between phases when present in a microchannel, leading to improved control, heating or cooling and overall performance of the reactor system.



Scheme 30.

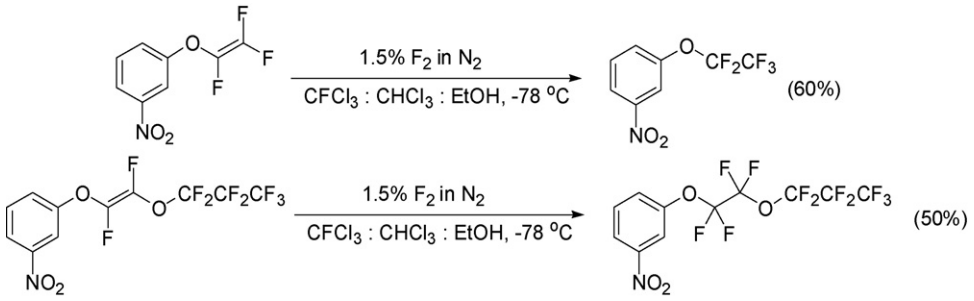


Scheme 31.

Microreactors could be used in *series*, where different stages in a process could be carried out in stepwise fashion, but also in *parallel*. In this situation, scale is achieved by *scale-out* by using several identical microreactors in parallel, rather than a classical *scale-up* which is achieved by using a larger reaction vessel. Consequently, all of the information garnered from laboratory experiments using a single channel microreactor is immediately applicable to a large scale process that uses many microreactors in parallel. Therefore, in principle, research work would exactly mirror the manufacturing situation making good manufacturing procedures (GMP) achievable in shorter time scales and, consequently, requiring far less capital expenditure. Also, since the quantities of each reagent that are in contact in one reaction channel at any given time is very small indeed, safer direct fluorination procedures can be achieved because of the lower possibility of forming aerosols between organic matter and fluorine in a confined small microreactor channel.

Novel reactor design for the miniaturisation of many chemical processes is, therefore, growing in importance [56–60] and, although there are relatively few gas/liquid microreactors that have been described in the literature, several microreactor devices have been used for various direct fluorinations of organic compounds [59,61,62] and this research theme has been reviewed [59,60,63].

Two groups independently studied the reaction of fluorine with toluene using microreactor technology [59,60,64] using either a micro-bubble column or a falling film microreactor device (Fig. 1).



Scheme 32.

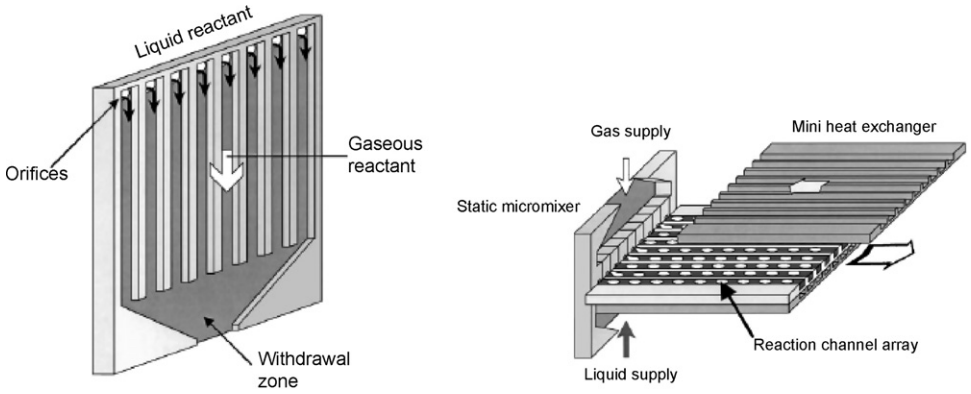


Fig. 1. Falling film (l) and micro-bubble (r) column microreactor devices [60]. Reprinted with permission from Elsevier.

The micro-bubble column consisted of a mixing and a reaction unit which allows a continuous stream of small gas bubbles to flow through the liquid whereas the falling film microreactor includes a platelet comprising a large number of microchannels that allows a thin falling film of several 10 μm thickness to flow down the channels and the fluorine/nitrogen mixture to pass over the thin film surface. Direct fluorination of toluene, giving a mixture of products, using a nickel coated silicon wafer microreactor was also reported by Jensen and co-workers [64].

The Durham group developed a basic microreactor (Fig. 2) consisting of a solid piece of nickel metal which has a 0.5 mm wide groove etched into its surface [65]. Controlled delivery of fluorine to one end of the reaction chamber (the shallow groove) is by an accurate electronic mass-flow controller and reagents are delivered a short distance downstream via a syringe pump. The gas and liquid mixtures flow down the microchannel without turbulence and such laminar or 'pipe flow' (Fig. 3) is a major advantage for reactivity because, in these cases, surface area contact between phases is maximised making mixing is extremely rapid and reactions diffusion controlled. An alternative flow regime, 'slug' or 'plug flow' (Fig. 3), where alternate 'slugs' of gas and liquid follow each other down the reactor channel is not as effective for phase mixing and is not observed when this microreactor design is used.

Given the dimensions of the device, a surprisingly large volume of material can be passed through the microchannels in a short period of time and, typically, volumes of 0.5 ml h^{-1} of substrate solution and 20 ml min^{-1} of a 10% mixture of fluorine in nitrogen were used for each reaction. This simple nickel microreactor has successfully been used to conduct a variety of selective and perfluorination reactions including the synthesis of representative examples of fluorinated dicarbonyl and aromatic derivatives, SF_5 substituted aromatics and perfluorinated saturated systems (Scheme 33) [66].

Whilst the prototype reactors described above demonstrated that gas/liquid fluorination reactions could, indeed, be carried

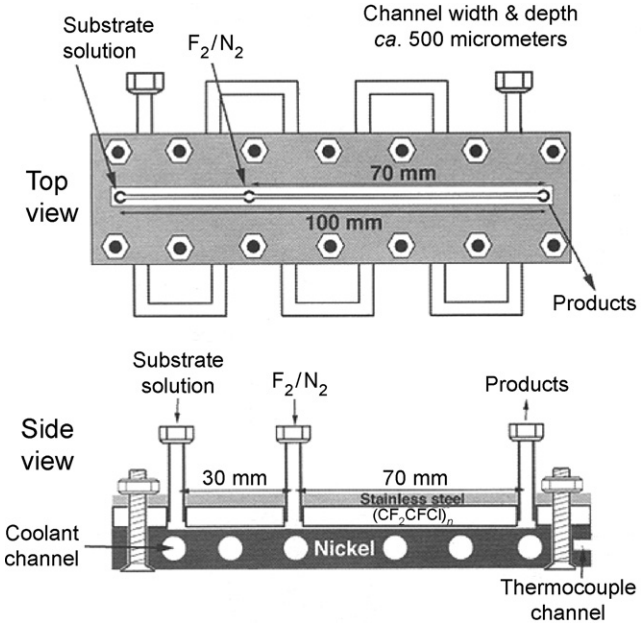


Fig. 2. Single channel microreactor [65]. Reproduced by permission of The Royal Society of Chemistry.

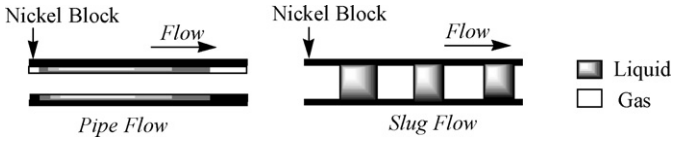
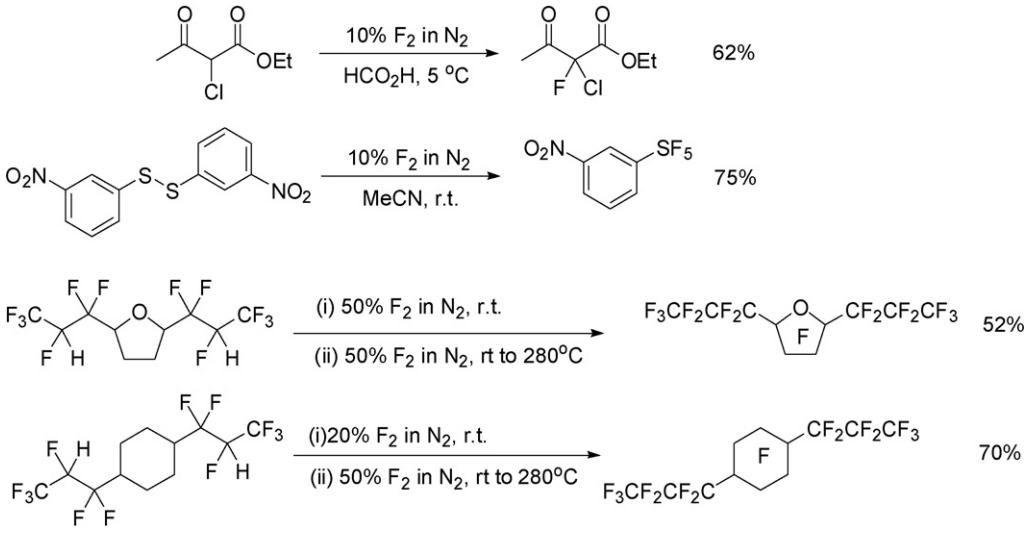


Fig. 3. Pipe and slug flow [65]. Reproduced by permission of The Royal Society of Chemistry.

out in microchannels, the devices could not be conveniently 'scaled-out' beyond a very limited number of parallel microchannels. A more versatile and efficient multi-channel microreactor system (Fig. 4) was designed that can be realistically used for larger scale syntheses [63,67]. The substrate and fluorine are fed into separate cooled reservoirs that are located within a stainless steel base unit before entering the many microchannels which allow the introduction of fluorine and substrate into many channels from one source. Construction and maintenance are simple and the number of channels used can be easily varied by using an appropriate channel plate (Fig. 5).

Fluorination of a range of 1,3-ketoesters and 1,3-diketones gave the corresponding 2-fluoro derivatives in high conversions and yields in cases where the dicarbonyl substrate is either present predominantly in its enol form and/or enolises rapidly in the reaction medium [68]. For systems that do not enolise rapidly, much slower flow rates of substrate through the reactor channels are required to achieve high conversions, although this is still difficult in some cases.

Direct fluorination of malonate esters using microreactor techniques gave a mixture of products arising from substitution of hydrogen atoms attached to carbon adjacent to the ester oxygen as well as the desired methylene site [69]. However,



Scheme 33.

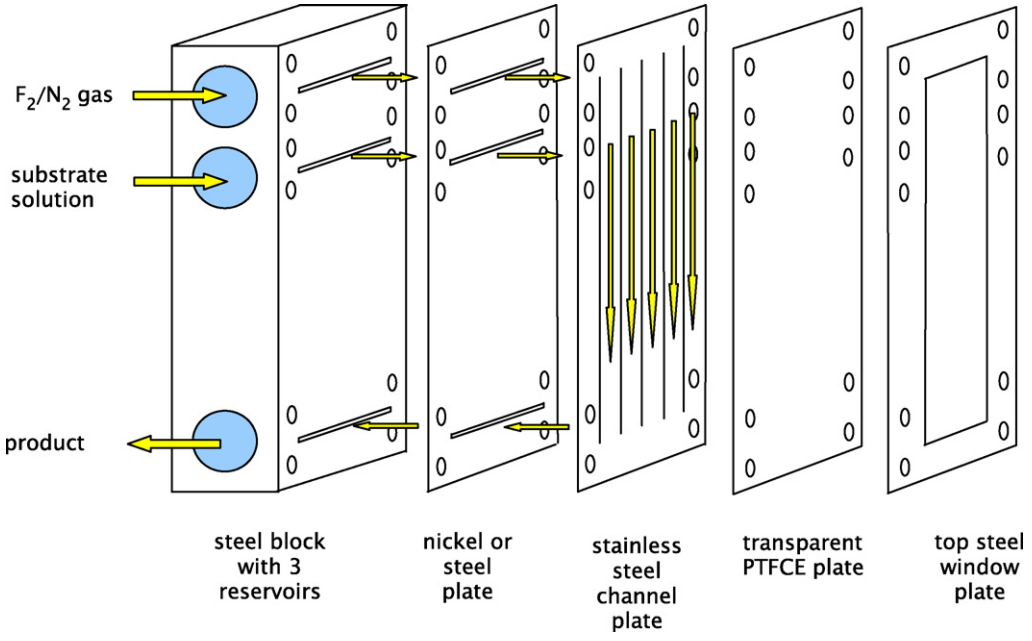


Fig. 4. Schematic representation of modular microreactor device [67]. Reproduced by permission of The Royal Society of Chemistry.

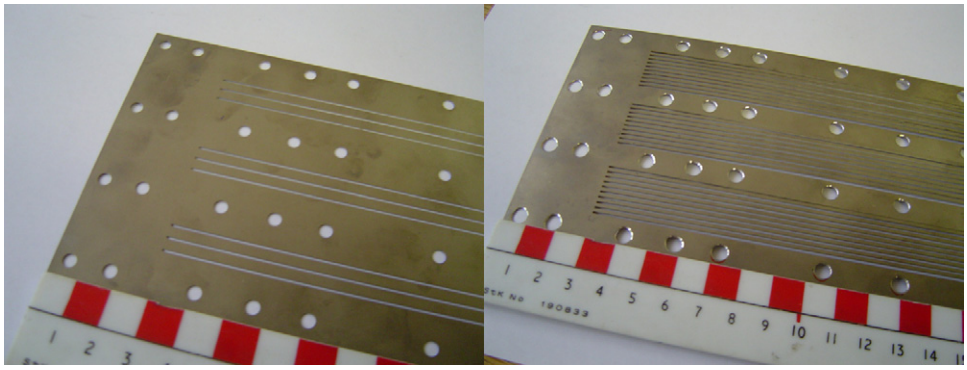
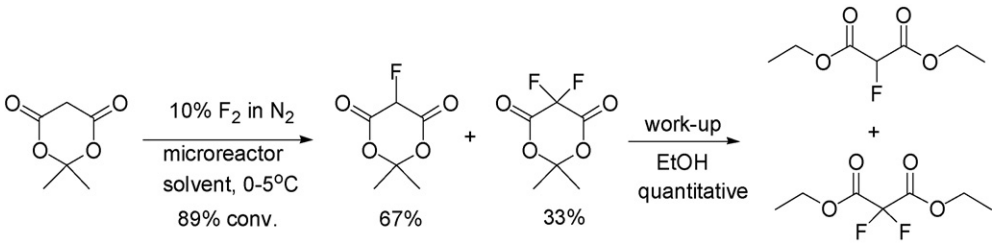


Fig. 5. Channel plates with 9 (left) and 30 channels (right) respectively [67]. Reproduced by permission of The Royal Society of Chemistry.



Scheme 34.

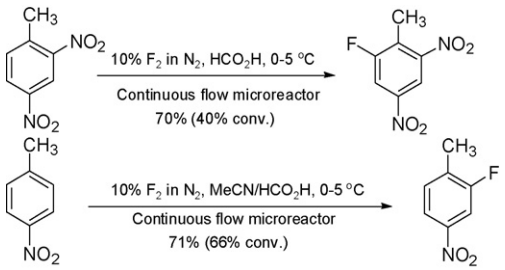
successful synthesis of 2-fluoromalonate derivatives can be achieved by using a cyclic diester substrate that does not possess carbon–hydrogen bonds at positions adjacent to ether oxygen. Selective direct fluorinations of Meldrum's acid (Scheme 34) gave high conversions and yields of mono- and difluorinated products which could be isolated as the diethyl malonate esters after work-up using ethanol.

Successful fluorination of malonate ester derivatives provides an example of where improved reaction performance is achieved using microreactor techniques because conventional 'bulk' fluorination reactions require the use of added transition metal catalysts or malonate salts as substrates.

Fluorination of aromatic systems can also be readily achieved using microreactor devices (Scheme 35) [67].

5. Summary

Direct fluorination has become a viable method for carbon–fluorine bond formation for both pefluorination and selective fluorination processes in both laboratory and large scale syntheses. Perfluorination methods are now efficient procedures that can give rise to a potentially unlimited number of perfluorinated structures and non-ozone deleting solvents are now used routinely as reaction media providing viable effective, methodology. Selective direct fluorination methods have benefited from the recent use of acidic or polar aprotic reaction media which allow syntheses of fluorinated chemical intermediates to be achieved at reasonable operating temperatures with limited waste streams. The number of potentially very versatile aliphatic, aromatic and heterocyclic fluorinated building blocks that may be accessed very easily by direct fluorination has grown significantly in the past decade, extending the number of polyfunctional fluorinated systems available to discovery chemists whilst microreactor techniques show great promise as efficient and effective reactor devices for both academia and industry. Organofluorine chemistry arises from chemists' ability to synthesise carbon–fluorine bonds and elemental fluorine is now a reagent that synthetic chemists should not be reluctant to consider using.



Scheme 35.

References

[1] R.D. Chambers, Fluorine in Organic Chemistry, Blackwell, Oxford, 2004.
[2] B. Baasner, H. Hagemann, J.C. Tatlow (Eds.), Houben-Weyl Organofluorine Compounds, Thieme, Stuttgart, 2000.
[3] R.E. Banks, B.E. Smart, J.C. Tatlow (Eds.), Organofluorine Chemistry. Principles and Commercial Applications, Plenum, New York, 1994.
[4] G. Resnati, Tetrahedron 49 (1993) 9385–9445.
[5] M. Shimizu, T. Hiyama, Angew. Chem. Int. Ed. Engl. 44 (2005) 214–231.
[6] G.S. Lal, G.P. Pez, R.G. Syvret, Chem. Rev. 96 (1996) 1737–1756.
[7] S.D. Taylor, C.C. Kotoris, Tetrahedron 55 (1999) 12431–12477.
[8] J. Hutchinson, G. Sandford, Top. Curr. Chem. 193 (1997) 1–43.

[9] R.D. Chambers, J. Hutchinson, G. Sandford, J. Fluorine Chem. 100 (1999) 63–73.
[10] J.S. Moilliet, J. Fluorine Chem. 109 (2001) 13–17.
[11] G. Sandford, Spec. Chem. 22 (2002) 35–37.
[12] R. Taylor, Chem. Eur. J. 7 (2001) 4074–4083.
[13] R. Taylor, J. Fluorine Chem. 125 (2004) 359–368.
[14] R.P. Singh, J.M. Shreeve, Acc. Chem. Res. 37 (2004) 31–44.
[15] S. Rozen, Eur. J. Org. Chem. 12 (2005) 2433–2447.
[16] R.J. Lagow, J.L. Margrave, Prog. Inorg. Chem. 26 (1979) 161–210.
[17] D.D. Moldavskii, T.A. Bispen, G.I. Kaurova, G.G. Furin, J. Fluorine Chem. 94 (1999) 157–167.
[18] H.C. Wei, V.M. Lynch, R.J. Lagow, J. Org. Chem. 62 (1997) 1527–1528.
[19] H.C. Wei, R.J. Lagow, Chem. Commun. (2000) 2139–2140.
[20] K.W. Felling, C.R. Youngstrom, R.J. Lagow, J. Fluorine Chem. 125 (2004) 749–754.
[21] T.Y. Lin, H.C. Chang, R.J. Lagow, J. Org. Chem. 64 (1999) 8127–8129.
[22] M.D. Levin, S.J. Hamrock, P. Kaszynski, A.B. Shtarev, G.A. Levina, B.C. Noll, M.E. Ashley, R. Newmark, G.G.I. Moore, J. Michl, J. Am. Chem. Soc. 119 (1997) 12750–12761.
[23] M. Kobayashi, T. Inoguchi, T. Iida, T. Tanioka, H. Kumase, Y. Fukai, J. Fluorine Chem. 120 (2005) 105–110.
[24] R.D. Chambers, A.K. Joel, A.J. Rees, J. Fluorine Chem. 101 (2000) 97–105.
[25] T. Okazoe, E. Murotani, K. Watanabe, M. Itoh, D. Shirakawa, K. Kawahara, I. Kaneko, S. Tatematsu, J. Fluorine Chem. 125 (2004) 1695–1701.
[26] T. Okazoe, K. Watanabe, M. Itoh, D. Shirakawa, K. Kawahara, S. Tatematsu, J. Fluorine Chem. 126 (2005) 521–527.
[27] T. Okazoe, K. Watanabe, M. Itoh, D. Shirakawa, H. Murofushi, H. Okamoto, S. Tatematsu, Adv. Synth. Catal. 343 (2001) 215–219.
[28] T. Okazoe, K. Watanabe, M. Itoh, D. Shirakawa, S. Tatematsu, J. Fluorine Chem. 112 (2001) 109–116.
[29] R.D. Chambers, M. Parsons, G. Sandford, J.S. Moilliet, J. Chem. Soc., Perkin Trans. 1 (2002) 2190–2197.
[30] R.D. Chambers, C.J. Skinner, J. Hutchinson, J. Thomson, J. Chem. Soc., Perkin Trans. I (1996) 605–609.
[31] G.A. Olah, G.K.S. Prakash, K. Wade, Hypercarbon Chemistry, Wiley, New York, 1987.
[32] H. Fukaya, K. Morokuma, J. Org. Chem. 68 (2003) 8170–8178.
[33] S. Rozen, C. Gal, J. Org. Chem. 52 (1987) 4928–4933.
[34] R.D. Chambers, M. Parsons, G. Sandford, R. Bowden, Chem. Commun. (2000) 959–960.
[35] H.D. Quan, M. Tamura, T. Takagi, A. Sekiya, J. Fluorine Chem. 99 (1999) 167–170.
[36] R.D. Chambers, M. Parsons, G. Sandford, E. Thomas, J. Trmcic, J.S. Moilliet, Tetrahedron 62 (2006) 7162–7167.
[37] S. Rozen, G. Ben-Scushan, J. Org. Chem. 51 (1986) 3522–3527.
[38] R.D. Chambers, J. Hutchinson, J. Fluorine Chem. 89 (1998) 229–232.
[39] S. Rozen, Y. Menachem, J. Fluorine Chem. 16 (1980) 19–31.
[40] K. Adachi, Y. Ohira, G. Tomizawa, S. Ishihara, S. Oishi, J. Fluorine Chem. 120 (2003) 173–183.
[41] R.D. Chambers, J. Hutchinson, J. Fluorine Chem. 92 (1998) 45–52.
[42] M. Butters, J. Ebbs, S.P. Green, J. MacRae, M.C. Morland, C.W. Murtiashaw, A.J. Pettman, Org. Proc. Res. Dev. 5 (2001) 28.
[43] R.D. Chambers, J. Hutchinson, M.E. Sparrowhawk, G. Sandford, J.S. Moilliet, J. Thomson, J. Fluorine Chem. 102 (2000) 169–173.
[44] P.L. Coe, A.M. Stuart, D.J. Moody, J. Chem. Soc. Perkin Trans. 1 (1998) 1807–1812.
[45] R.D. Chambers, M.A. Fox, G. Sandford, J. Trmcic, A. Goeta, J. Fluorine Chem. (2006).
[46] A.M. Stuart, P.L. Coe, D.J. Moody, J. Fluorine Chem. 88 (1998) 179–184.
[47] J.P. Alric, B. Marquet, T. Billard, B.R. Langlois, J. Fluorine Chem. 126 (2005) 661–667.
[48] J.S. Moilliet, in: R.E. Banks, B.E. Smart, J.C. Tatlow (Eds.), Organofluorine Chemistry. Principles and Commercial Applications, Plenum Press, New York, 1994, p. 195.
[49] D. Holling, G. Sandford, A.S. Batsanov, D.S. Yufit, J.A.K. Howard, J. Fluorine Chem. 126 (2005) 1377–1383.
[50] R.D. Chambers, D. Holling, G. Sandford, A.S. Batsanov, J.A.K. Howard, J. Fluorine Chem. 125 (2004) 661–671.
[51] R.D. Chambers, D. Holling, G. Sandford, H. Puschmann, J.A.K. Howard, J. Fluorine Chem. 117 (2002) 99–101.
[52] R.D. Chambers, M. Parsons, G. Sandford, C.J. Skinner, M.J. Atherton, J.S. Moilliet, J. Chem. Soc., Perkin Trans. I (1999) 803–810.
[53] R.D. Chambers, W.K. Gray, G. Sandford, J.F.S. Vaughan, J. Fluorine Chem. 94 (1999) 213–215.
[54] I. Nowak, L.M. Rogers, R.D. Rogers, J.S. Thrasher, J. Fluorine Chem. 93 (1999) 27–31.
[55] A.E. Feiring, S. Rozen, E.R. Wonchoba, J. Fluorine Chem. 89 (1998) 31–34.
[56] W. Ehrfeld, V. Hessel, H. Lowe, New Technology for Modern Chemistry, Wiley-VCH, New York, 2000.
[57] S.J. Haswell, R.J. Middleton, B. O'Sullivan, V. Skelton, P. Watts, P. Styring, Chem. Commun. (2001) 391–398.
[58] O. Worz, K.P. Jackel, T. Richter, A. Wolf, Chem. Eng. Sci. 56 (2001) 1029–1033.
[59] V. Hessel, P. Lob, H. Lowe, Chim. Oggi 22 (2004) 10–15.
[60] P. Lob, H. Lowe, V. Hessel, J. Fluorine Chem. 125 (2004) 1677–1694.
[61] K. Jahnisch, M. Baerns, V. Hessel, W. Ehrfeld, V. Haverkamp, H. Lowe, C. Wille, A. Guber, J. Fluorine Chem. 105 (2000) 117–128.
[62] M.D. Turnbull, N.B. Carter, S. Dennison, J. Deacon, R. Holley, Chimia 58 (2004) 159–163.
[63] R.D. Chambers, G. Sandford, Chim. Oggi (2004) 13–15.
[64] N.D. Mas, A. Gunther, M.A. Schmidt, K.F. Jensen, Ind. Eng. Chem. Res. 42 (2003) 698–705.
[65] R.D. Chambers, D. Holling, R.C.H. Spink, G. Sandford, Lab on a Chip 1 (2001) 132–137.
[66] R.D. Chambers, R.C.H. Spink, Chem. Commun. (1999) 883–884.
[67] R.D. Chambers, M.A. Fox, D. Holling, T. Nakano, T. Okazoe, G. Sandford, Lab on a Chip 5 (2005) 191–198.
[68] R.D. Chambers, M.A. Fox, G. Sandford, Lab on a Chip 5 (2005) 1132–1139.
[69] R.D. Chambers, M.A. Fox, D. Holling, T. Nakano, T. Okazoe, G. Sandford, Chem. Eng. Technol. 28 (2005) 344–352.