New methodology for nucleophilic fluorination

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entitled

NEW METHODOLOGY FOR NUCLEOPHILIC FLUORINATION

Submitted by

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A candidate for the degree of Doctor of Philosophy

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Dedicated to the memory of Cyril Swarbrick (1918 – 2003), loving grandfather and an inspiration for many years

Those who cannot remember the past are condemned to repeat it.

George Santayana

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Memorandum

The work described in this thesis was carried out at the University of Durham between October 2000 and July 2003. This thesis is the work of the author, except where acknowledged by reference and has not been submitted for any other degree. The copyright of this thesis lies solely with the author and no quotation from it should be published without prior written consent and information derived from it should be acknowledged.

Part of this work has been the subject of the following:

- C.B. Murray, G. Sandford and S. R. Korn, *J. Fluorine Chem.*, **123**, 2003, 81.

and has been presented by the author at:

- Avecia Poster Session, University of Durham, January 2002.
- Avecia CASE Symposium, Grasmere, May 2003.
- 3rd RSC Fluorine Subject Group Postgraduate Meeting, University of St Andrews, September 2003.

Nomenclature and Abbreviations

Note that fluorine in the centre of a ring denotes that all positions not explicitly shown are bonded to fluorine.

The following abbreviations are used throughout this thesis:

AHF	Anhydrous hydrogen fluoride
BMIM	*N*-Butyl-*N*-methylimidazolium
DCM	Dichloromethane
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
HFP	Hexafluoropropene
MeCN	Acetonitrile
GC-MS	Gas liquid chromatography-mass spectrometry
MS	Mass Spectrometry
NMP	*N*-Methylpyrrolidinone
NMR	Nuclear Magnetic Resonance
PFIB	Perfluoroisobutene
PFP	Pentafluoropyridine
PTC	Phase transfer catalyst
TFE	Tetrafluoroethene
THF	Tetrahydrofuran
TFT	Trifluoro-*s*-triazine
TMS-OTf	Trimethylsilyl trifluoromethanesulfonate

Statement of Copyright

Abstract

NEW METHODOLOGY FOR NUCLEOPHILIC FLUORINATION

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This work describes the development of three methods for the fluorination of electrophilic substrates:

1.) The reaction of caesium fluoride with perfluoro(2-methylpent-2-ene) leads to the formation of perfluoro(2-methylpentan-2-yl)caesium. This perfluoroalkyl carbanion has been shown to undergo significant fluoride ion exchange at temperatures above 60°C. Thus, reaction of a solution of the carbanion with a suitable electrophile resulted in the selective formation of a carbon-fluorine bond or perfluoroalkylation of the electrophile.

2.) Caesium fluoride has been developed as a moderately effective nucleophilic fluorinating agent in the Room Temperature Ionic Liquid (RTIL) solvent [BMIM][PF_6]. The fluorination of a range of volatile substrates was studied, and fluorination in the absence of a conventional organic solvent was demonstrated. Recycling of the solvent has been investigated, as has the decomposition of [BMIM][PF_6] in the presence of caesium or potassium fluoride at elevated temperatures.

3.) Reaction of a highly fluorinated azaheterocycle with DMAP leads to the formation of a fluoride salt. This salt, formed *in situ*, was used as a source of nucleophilic fluoride ion for the fluorination of a range of electrophiles. Several of the fluoride salts were converted to their more stable tetrafluoroborate or triflate analogues and characterised.

Table of Contents

A Note on the Style of this Thesis

Although the majority of the work presented in this thesis is directed towards the selective nucleophilic fluorination of a range of substrates, each chapter is comprised of research on a separate area of chemistry. Accordingly, the thesis has a general introductory chapter reviewing classically important fluorination techniques and recent progress in methodology for the formation of carbon-fluorine bonds.

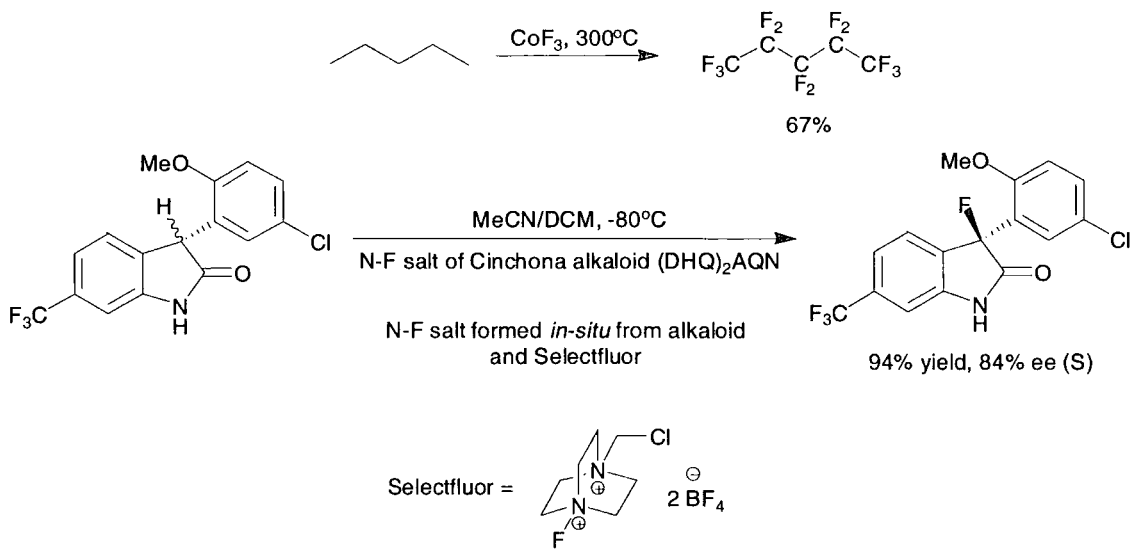
Each of the three results and discussion chapters are then presented with an individual introduction to outline the particular area of research (perfluoroalkyl carbanions, Room Temperature Ionic Liquids and the reactions of perfluorinated azaheterocycles). References are listed at the end of each chapter, rather than at the end of the thesis as a whole. Compounds are numbered consecutively throughout the thesis; tables, figures and schemes are numbered sequentially by chapter.

1. Introduction

1.1 Organofluorine Chemistry

The chemistry of fluorine-containing organic compounds is now well established, with the first fluorocarbons being isolated and characterised at the beginning of the 20th century.[1] The field remained relatively immature until the vastly important work of Swarts and the large volume of research carried out under the auspices of the Manhattan Project in the USA.[1] It was perhaps this, the desire to develop the first nuclear weapon, more than anything else, which transformed fluorine chemistry into a field of vital importance.

The last few decades have seen remarkable growth in both the scope and utility of organofluorine chemistry.[2] Much of the early research on organofluorine chemistry concentrated on techniques for the exhaustive fluorination of organic compounds – electrochemical fluorination, metal fluoride techniques (particularly those involving cobalt trifluoride) and fluorination with elemental fluorine were heavily studied.[1] The compounds produced by these techniques were usually highly fluorinated, for example, perfluorinated aromatic and heteroaromatic compounds and perfluoroalkanes. Although these materials have found many uses in speciality applications,[3] this type of research has, in some respects, been overtaken by selective fluorination, and this is where the main thrust of current research lies. The illustration below (Scheme 1.1) is illustrative of the change in research emphasis. The perfluoroalkane shown was synthesised using early cobalt trifluoride methodology, a fairly harsh technique that can lead to significant byproducts.[1] In contrast, enantioselective electrophilic fluorination of the complex heterocycle under very mild conditions led to the formation of the novel fluorooxindole (BMS-204352, Maxipost) shown below, currently in worldwide phase III clinical trials as a treatment for certain types of stroke.[4]



Scheme 1.1 Selective and unselective fluorination methodologies

Selective fluorination has grown in importance as the utility of fluorine-containing pharmaceuticals and speciality chemicals has increased.[2] The selective introduction of a single fluorine atom into a hydrocarbon skeleton has become one of the most studied problems in the field of fluorine chemistry. However, it also remains one of the most challenging, the common difficulties being competing side reactions due to forcing conditions and the required use of expensive or difficult to handle reagents.

1.1.1 Properties of the Fluorine Atom and of Carbon-Fluorine Bonds

The attractiveness of fluorinated compounds as targets for synthesis lies in the particular properties of the fluorine atom and the effects which it bestows upon molecular systems. Fluorine is a rather interesting atom to consider, despite its lack of d-orbitals ($1s^2$, $2s^2$, $2p^5$) or multiple oxidation states. On the Pauling scale it is the most electronegative atom and so it exerts a very large negative inductive (σ) effect when present in an organic molecule. Fluorine has three non-bonding electron pairs and, due to the relatively small size of the atom, these can provide significant electronic repulsion. They also allow fluorine to act as a π-donor atom, in addition to the very strong σ-withdrawing effect.

The carbon-fluorine bond is the strongest single bond to carbon, considerably stronger than the other carbon-halogen bonds (Table 1.1).[5] Because of this fact, many

highly fluorinated compounds are extremely inert when compared with the corresponding hydrocarbons. Perhaps the classic example of this is the comparison between PTFE (polytetrafluoroethene) and polythene, composed of repeating difluoromethylene and methylene units respectively. PTFE is extremely thermally stable up to 380°C, although significant decomposition does not occur until even higher temperatures. When the polymer begins to decompose, it "unzips" cleanly to tetrafluoroethene (TFE) monomer (and, potentially, other species depending on the reaction conditions). Polythene has rather lower thermal stability, and the depolymerisation reaction is less uniform, mostly due to the weaker carbon-hydrogen bonds.

Table 1.1 Bond energies of bonds to carbon

Single Bond	Average Energy/kJ mol^{-1}
C-H	418
C-O	351
C-N	289
C-C	339
C-F	***439***
C-Cl	331
C-Br	280
C-I	238

Of course all of these considerations are academic if the incorporation of fluorine into an organic structure is impossible. Fortunately, the relatively small size of fluorine allows it to be substituted, in principle, for any or all of the hydrogen atoms in a hydrocarbon skeleton, paving the way to an analogous fluorocarbon chemistry. Using bond lengths as a crude indication of atomic radius, we can see that although it is often erroneously stated that fluorine is similar in size to hydrogen, it is actually very much closer to oxygen (Table 1.2).[6] Even so, this infers that it is possible to place fluorine atoms within an organic structure with minimal effects on the geometry of the system.

Table 1.2 Bond lengths of bonds to carbon

Bond to sp^3 carbon	Average bond length/Å
C-C	1.53
C-H	1.09
C-O	1.43
C-F	***1.40***
C-Cl	1.79

1.2 Methodology for the Formation of Carbon-Fluorine Bonds

The numerous techniques that have been developed over the course of the last century or so provide access to a vast array of fluorinated molecules. Unfortunately, there is no one perfect fluorinating agent. Three main modes of fluorination are possible, with a wide array of reagents available for each. This allows some flexibility depending upon the chemistry of the particular substrate for fluorination. Specifically, the classes of fluorinating agent are radical ($F^{\cdot}$), electrophilic ("F^{+}") and nucleophilic (F^{-}). Radical and electrophilic fluorination will be considered briefly below. A separate section will be devoted to nucleophilic fluorination, owing to its direct relevance to this thesis. Several comprehensive books[1, 7-9] and review articles[10-12] have been published on the subject of fluorination, perhaps the most immediately helpful of which was written by Wilkinson in 1992.[12]

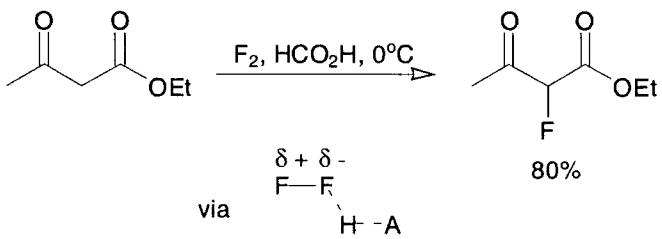
1.2.1 Radical Fluorination

Radical fluorination was the first fluorination technique to be widely developed, and the use of elemental fluorine in the gaseous phase to perfluorinate hydrocarbon substrates was one of the earliest methods for the formation of carbon-fluorine bonds.[1] Later refinements, including dilution with an inert gas (e.g. He) or the use of "catalytic" metal packing have increased the efficacy of this technique.[1] Radical fluorination is often quoted as being uncontrollable due to the highly exothermic nature of the reaction, caused in part by the very weak fluorine-fluorine

bond. In actual fact, under suitable conditions to moderate the reaction, the technique is applicable to many systems.[13]

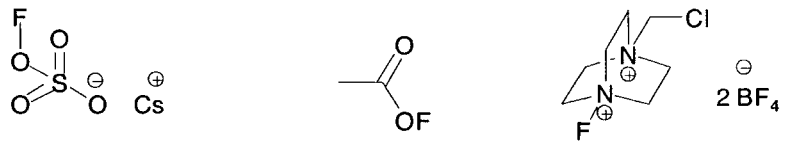
1.2.2 Electrophilic Fluorination

Electrophilic, or so-called "F^+", fluorinating agents are now well known. The general principle behind the generation of electrophilic fluorine is to place the fluorine atom adjacent to a powerful electron withdrawing group, a good leaving group or both. The original electrophilic reagent was fluorine, which when used in conjunction with a suitably polar solvent system gives rise to a polarised complex (Scheme 1.2). This complex is capable of reaction with sites of high electron density via transfer of electrophilic fluorine.



Scheme 1.2 Electrophilic fluorination with elemental fluorine

A significant advance in the field was made when Banks, in conjunction with Air Products, developed Selectfluor ® as a "shelf-stable," solid source of "F^+" in 1992 (Figure 1.2).[14-16] This reagent has been touted as a direct substitute for elemental fluorine (a slight exaggeration as the reactivities can differ significantly) and it is applicable to many of the transformations previously carried out with previous generations of electrophilic fluorinating agents. These compounds, such as acetyl hypofluorite and caesium fluoroxysulfate are generally effective fluorinating agents, but they tend to be expensive or very difficult to handle (Figure 1.1).[1, 11, 12]



caesium fluoroxysulfate acetyl hypofluorite Selectfluor

Figure 1.1 Electrophilic fluorinating agents

Since the introduction of Selectfluor ® a variety of other reagents has appeared, most notably some interesting chiral alkaloid based N-F systems, synthesised *in-situ* from Selectfluor ® and the corresponding alkaloid.[4, 17] These commercially available N-F reagents have been used for the fluorination of β-ketoesters and other carbonyl systems, amines, nitriles and aromatic compounds to name a few. The synthetic utility of electrophilic fluorinating agents is limited by their high cost or handling difficulties, although the N-F reagents are finding widespread use in the area of pharmaceutical chemistry in particular.[4, 17-19]

1.3 Nucleophilic Fluorination

Nucleophilic fluorination is arguably the most widely used technique for the selective introduction of a fluorine atom into an organic compound. The method is applicable to a significant range of substrates and there have been many different reagents or fluorination systems of this type developed. Although the work presented in this thesis is mostly concerned with so-called Halex (i.e. halogen exchange) fluorination, a slightly broader review will be given here to allow for a more general examination of the field of nucleophilic fluorination. This review is not intended to give a comprehensive coverage of the subject; rather it is designed to highlight interesting areas of progress or valuable widely used reagents.

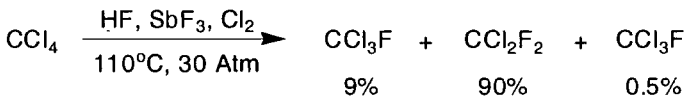
1.3.1 Anhydrous Hydrogen Fluoride and Onium Poly(hydrogen Fluoride) Complexes

Historically, the most well known nucleophilic fluorinating agent is anhydrous hydrogen fluoride (AHF). Systems containing AHF as the source of fluoride tend to

be very effective fluorinating agents and have the advantage that AHF is a powerful solvent for many organic materials. A vast body of work has been accumulated on the use of AHF for a variety of transformations, including the hydrofluorination of alkenes and alkynes, Halex fluorination and the fluorination of alcohols.

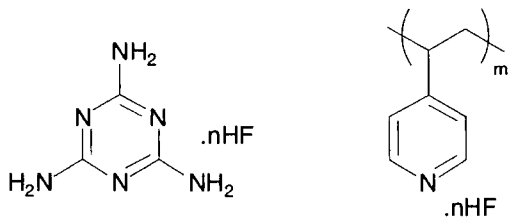
Although AHF is cheap and widely available, it has three very significant disadvantages: The pure compound boils at around 20°C, thus restricting work to either low temperatures or pressurised equipment. The resulting high vapour pressure of the substance under ambient conditions means that there is always likely to be a significant concentration of HF vapour in the surrounding atmosphere. AHF is extremely corrosive to glass in the presence of moisture, thus special laboratory apparatus (typically constructed from PTFE, polythene or certain metals) is often required. Such equipment can be very expensive and may be difficult to obtain. Finally, AHF is extremely toxic by all routes of exposure, although its dermal toxicity is perhaps the most infamous. Contact with even a small quantity of AHF (or solutions of HF) can cause serious injury and special precautions, including the provision of specific antidotes, are required for laboratory work with this material.[20] For these reasons AHF has found only limited use as a reagent for laboratory-scale fluorination, despite its excellent fluorinating ability. However, AHF is used on a huge scale in industry where the enclosed systems utilised for its handling mean that the risk of contact is extremely small.

Much of the original work carried out by Swarts utilised AHF, in combination with extremely powerful Lewis acids such as antimony (V) chlorofluorides, to produce fluorinated organic compounds via Halex processes.[21] The Lewis acid coordinates with the halogen (usually chlorine) on the precursor, thus facilitating the fluorination reaction. Such was the influence of Swarts on this field of work, that these processes are now commonly known as Swarts reactions (Scheme 1.3).[1, 22]



Scheme 1.3 Example of a Swarts' reaction

Work carried out by Olah and co-workers has allowed some of the safety issues surrounding AHF to be resolved. AHF will form stable complexes with many Lewis bases, in particular tertiary amines (Figure 1.2).[23, 24]

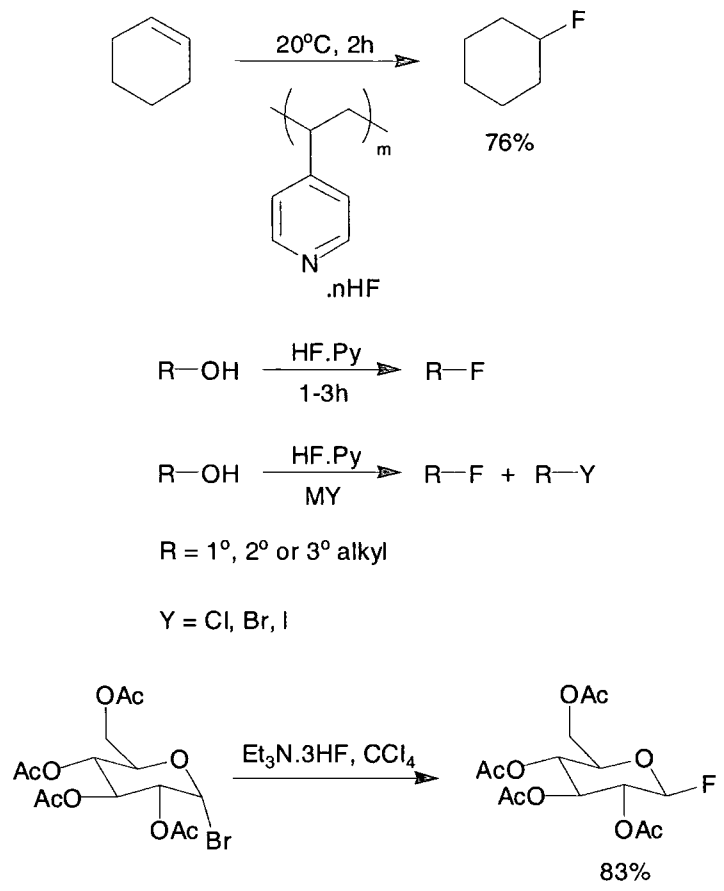


$(CH_3)_2O.5HF$ $Et_3N.3HF$ $C_5H_5N.nHF$

Figure 1.2 Onium poly(hydrofluoride) complexes

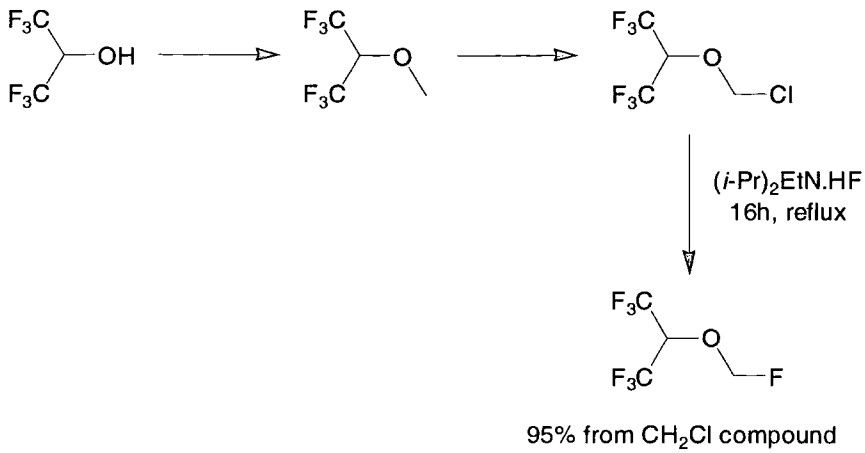
Although not commonly considered as such, these materials (e.g. pyridinium poly(hydrogen fluoride), commonly known as Olah's reagent) are room temperature ionic liquids, similar to the so-called "green" solvents which are currently generating a great deal of interest. These complexes tend to have elevated boiling points when compared with AHF and are thus considerably safer to use, although the toxicity issues still remain. A further advantage is that the systems often have significantly reduced acidity, allowing the use of glass apparatus in certain cases and minimising the side reactions (rearrangements etc.) so often seen with AHF.

A variety of such complexes are commercially available at reasonable prices, and in many procedures they can act as a direct replacement for AHF.[23, 24] Thus these reagents may be used for the hydrofluorination of alkenes and the fluorination of alcohols and haloalkanes (Scheme 1.4).[25-27]



Scheme 1.4 Fluorination with onium(polyhydrofluorides)

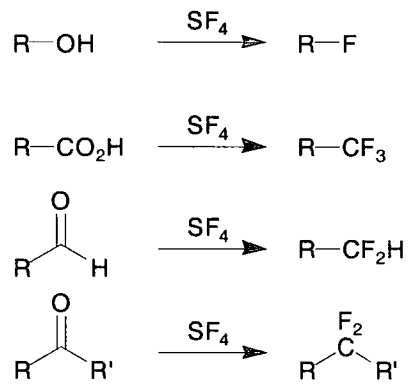
Such complexes may even be used on a larger scale, as a recent publication demonstrates. Ramig reported the use of diisopropylethylamine mono(hydrogen fluoride) to prepare the anaesthetic sevoflurane on a multi kilogram scale (Scheme 1.5).[28]



Scheme 1.5 Synthesis of sevofluorane

1.3.2 Sulfur Tetrafluoride and Related Compounds

Another well known "classical" fluorinating agent is sulfur tetrafluoride, a reagent which is capable of replacing oxygen by fluorine in a range of functional groups (Scheme 1.6).[11, 12] Although sulphur tetrafluoride is very widely applicable to a range of synthetic routes, it also has significant disadvantages: It is a colourless, highly toxic gas which hydrolyses readily to HF. The use of sulfur tetrafluoride requires the use of autoclaves constructed of resistant materials and it is not readily used in a normal laboratory environment.



Scheme 1.6 Fluorination with sulfur tetrafluoride

The mechanism of reaction is of interest, because sulfur tetrafluoride appears to become rather less reactive if rigorously purified. The key to the observed high reactivity of impure sulfur tetrafluoride is the presence of trace quantities of HF in the gas. This allows for an equilibrium process to occur, generating small quantities of SF_3^+ HF_2^-. Addition of catalytic quantities of AHF or other Lewis acids to pure sulfur tetrafluoride also results in this process. The fluorination reaction generally proceeds by attack of nucleophilic oxygen on SF_3^+, followed by loss of SOF_2 and attack of fluoride ion, although the exact mechanism is of course dependent on the type of substrate.[29-31]

Due to the problems highlighted above, a range of related sulfur-based fluorinating agents have been developed (Figure 1.3).[32, 33] These are significantly easier to use, being liquids under ambient conditions, although they are still extremely reactive (indeed heating these materials can cause an explosion)[34] and require rigorously anhydrous conditions. Diethylamino sulfur trifluoride (DAST), developed by Middleton, remains the most well known of these compounds, although it is beginning to be superseded by more thermally stable alternatives such as Deoxofluor ®.[35]

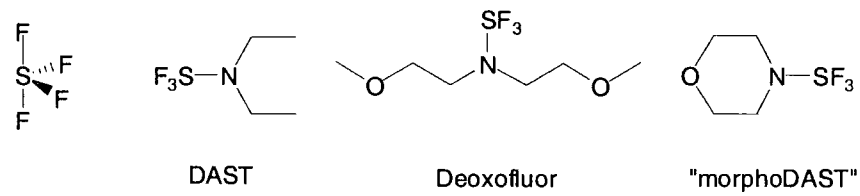
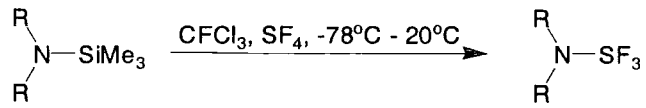


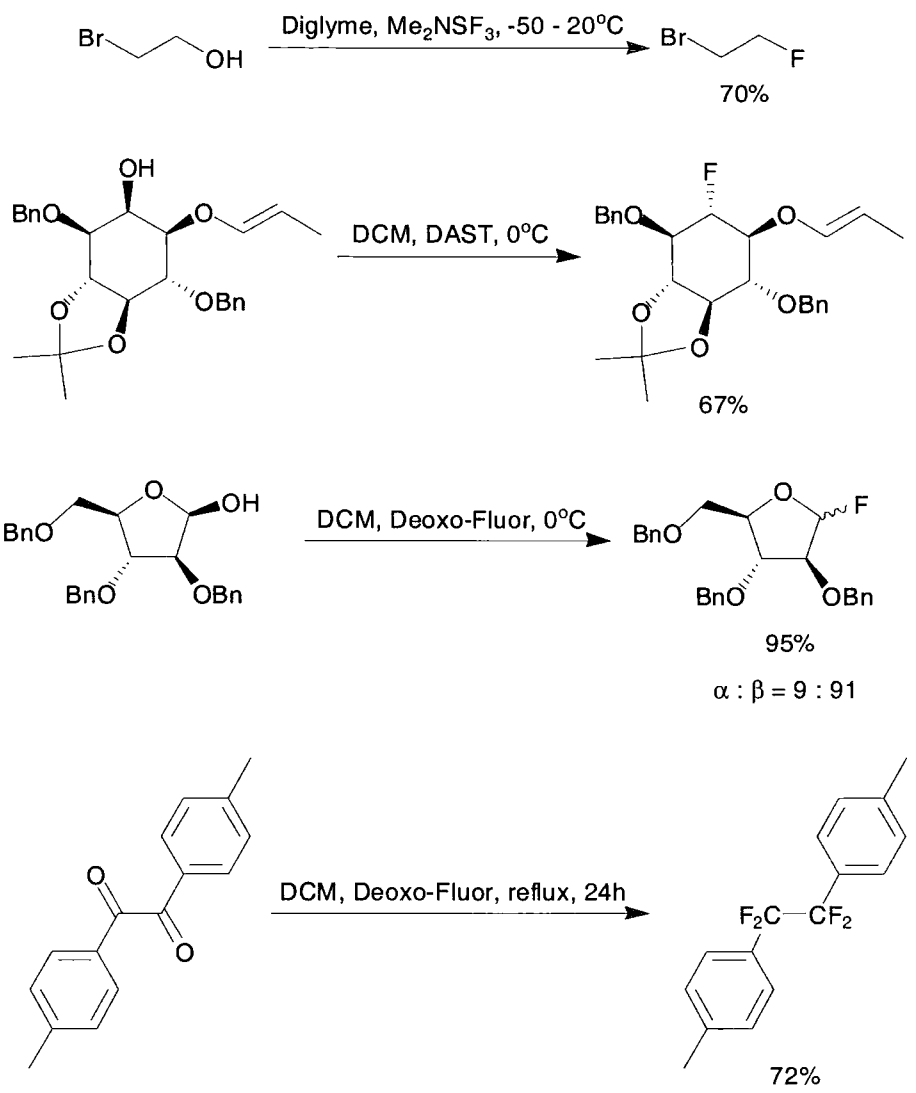
Figure 1.3 Sulfur tetrafluoride and analogues

These materials are generally synthesised from sulfur tetrafluoride and the corresponding silylated amine (Scheme1.7). Fortunately, given the use of sulfur tetrafluoride in their synthesis, many of these materials are commercially available.



Scheme 1.7 Synthesis of amine sulphur trifluoride compounds

As with sulfur tetrafluoride, these amine sulphur trifluoride reagents react with oxygen-containing functionalities. The main use for DAST in recent years has been the conversion of alcohols to fluoromethylene groups, although many other transformations are possible (Scheme 1.8). Alcohols can be fluorinated selectively by DAST in the presence of aldehydes. Aldehydes can in turn be fluorinated in the presence of ketones using the same reagent. DAST has therefore found particular utility in the fluorination of sensitive substrates such as sugars and nucleosides.[33, 35-38]



Scheme 1.8 Fluorination with amine sulphur trifluorides

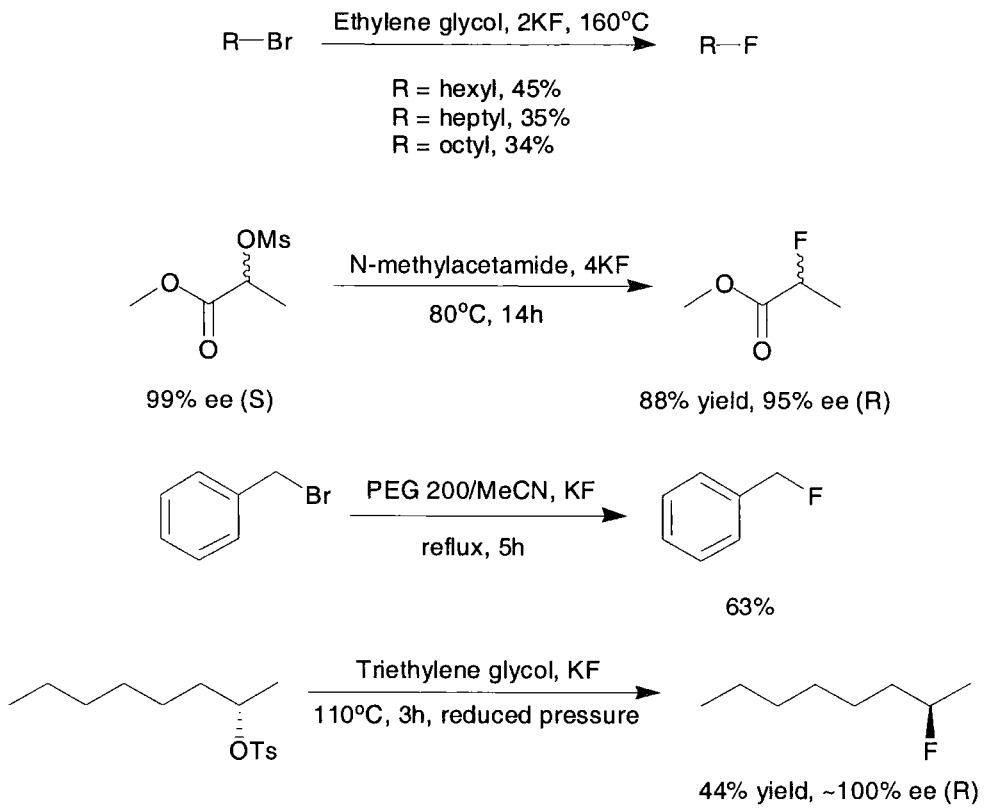
1.3.3 Metal Fluorides and Related Fluoride Ion Sources

Metal fluorides are often seen as one of the oldest classes of fluorinating agents. Fluorination of a molecule via nucleophilic displacement of a suitable leaving group with fluoride ion is an obvious way to make a carbon-fluorine bond. The most widely used metal fluorides are those in Group I of the periodic table, particularly potassium and caesium, although sodium fluoride has been used occasionally.[39] Many other metal fluoride systems have been developed, and they will be mentioned only in passing.

To increase the reactivity of fluoride ion, it is necessary to generate a reasonable concentration of fluoride in the reaction solvent. This problem is approached by the use a solvent with an ability to coordinate to the metal cation. Such solvents can be either dipolar aprotic materials (e.g. DMF, sulfolane, NMP) or oxygenated (i.e. donor) chains (glymes, polyethylene glycols). In almost all cases, these solvents have high boiling points to allow the use of high temperature reactions. Clearly it is desirable to use anhydrous solvents to minimise the solvation of fluoride ion by water. Fluoride ion will strongly hydrogen bond to any suitable donor atoms, forming a tightly bound solvation shell, shielding it from reaction with electrophilic species. One problem with this approach is that as the fluoride becomes less solvated and hence more nucleophilic, it also behaves as a considerably stronger base.[40] Indeed, Christe recently prepared truly anhydrous tetramethylammonium fluoride and found it to be so strongly basic that it deprotonated acetonitrile.[41]

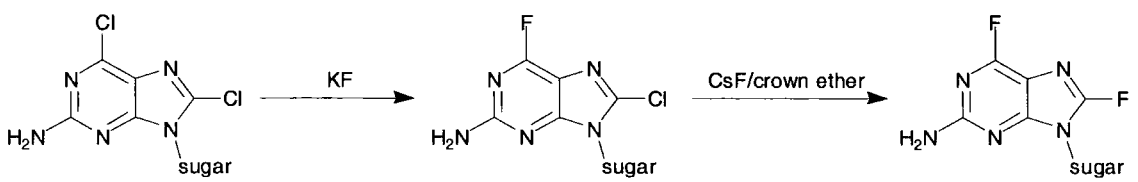
A. Group I Metal Fluorides

Potassium fluoride is by far the most widely used group I metal fluoride. It has various advantages over the other metal fluorides in that it is reasonably cheap, fairly reactive and only moderately hygroscopic. KF has been used for many different nucleophilic fluorination processes with a variety of leaving groups (Scheme 1.9). In almost all reported syntheses, KF is carefully dried before use.[42-45]



Scheme 1.9 Fluorination with potassium fluoride

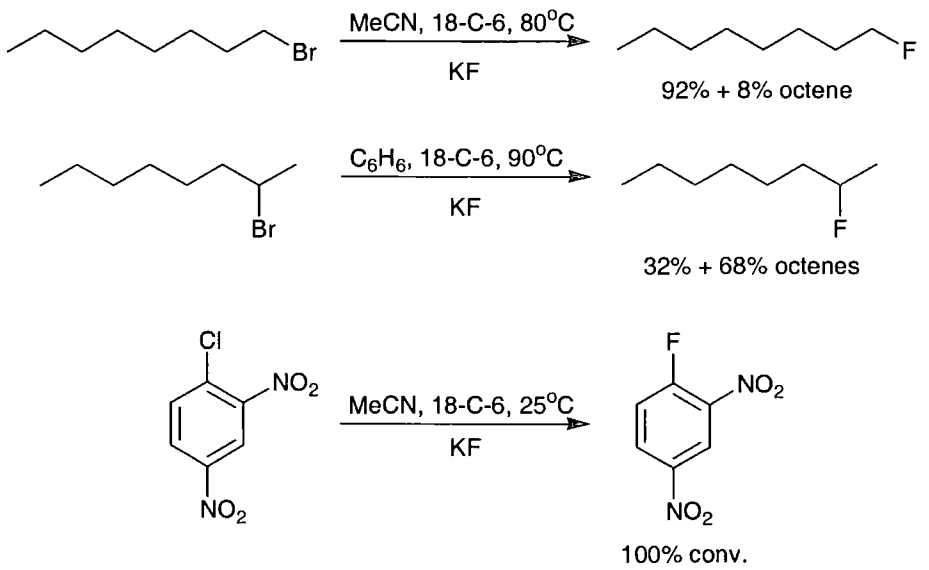
Caesium fluoride has also been used extensively, but usually only when KF is not sufficiently reactive (Scheme 1.10).[46] CsF has significantly lower lattice energy than KF (dissimilar sized ions, hence less effective packing) and is therefore correspondingly more reactive. Unfortunately, it is difficult to work with, as it must be laboriously dried and preferably manipulated in a moisture-free environment. Also, it is extremely hygroscopic and rather expensive.



Scheme 1.10 Fluorination with caesium fluoride

B. Group I Metal Fluorides with Crown Ethers as a Source of "Naked" Fluoride

In order to increase the reactivity of potassium and caesium fluoride, crown ethers can be used to aid in the dissolution of ionic species in the reaction solvent. These materials function by complexing the cation, resulting in a significant increase in the lipophilicity of the metal ion. Liotta reported the use of 18-crown-6 (18-c-6) and KF to produce increased concentrations of fluoride ion in acetonitrile and benzene. The system was highly effective as a fluorinating agent for a range of electrophilic substrates (Scheme 1.11).[47] As can be seen from the results with 2-bromooctane, however, the so-called "naked" fluoride ion exhibits significant competing basicity.



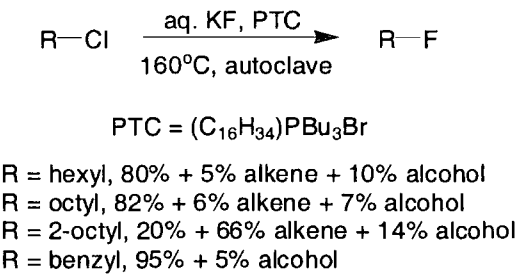
Scheme 1.11 Fluorination with potassium fluoride/crown ether

C. Phase Transfer Catalysed Fluorination with Group I Metal Fluorides

Another process which has been used to good effect is that of phase transfer catalysis. The metal fluoride can either be a suspension in an organic solvent (biphasic solid-liquid catalysis) or as an aqueous solution in contact with an organic solution of the substrate (biphasic liquid-liquid catalysis). Other combinations are possible, but these are the most frequently encountered. The phase transfer catalyst employed is

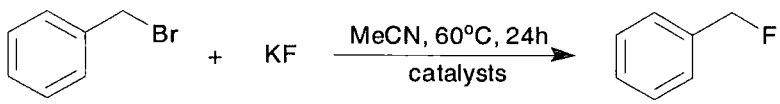
generally a salt with a highly lipophilic cation such as tetrabutylammonium bromide. Performing a biphasic reaction with a fluoride ion source in the presence of this material results in the *in situ* formation of the more soluble tetrabutylammonium fluoride. This then becomes the active species in the reaction phase.

A limitation of certain catalytic species, particularly the quaternary ammonium salts, is that they will decompose in the presence of fluoride ion under harsh conditions (via Hoffman elimination, or straightforward S_N2 attack on an alkyl group). Different catalytic systems have been developed to avoid this problem. Montanari demonstrated the phase transfer fluorination of a range of organic halides and mesylates using aqueous KF in the absence of other solvents.[48] The reactions were run at high temperature under pressure with a more stable quaternary phosphonium bromide as the catalyst. Yields were generally moderate to good, although the corresponding alcohol was formed as a byproduct in almost all cases due to attack of water on the substrate (Scheme 1.12).



Scheme 1.12 Fluorination with aqueous potassium fluoride under PTC conditions

Recently, Makosza has published several papers on the use of triorganotin halides as phase transfer catalysts for fluorination.[49] The catalytic activity is attributed to the formation of highly soluble hypervalent triorganodifluorostannate ions (Scheme 1.13).



Yield with catalyst

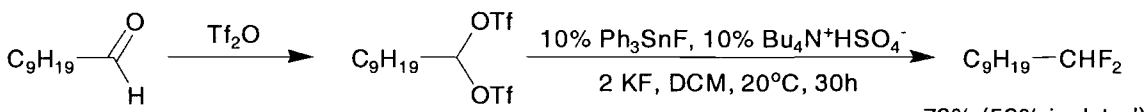
No catalyst = 0%
$Bu_4N^+HSO_4^-$ = 6%
$Bu_4N^+HSO_4^-$ + Ph_3SnF = 42%

Reaction proceeds via formation of hypervalent tin fluorides:

$$Ph_3SnF + KF + Bu_4N^+HSO_4^- \longrightarrow Bu_4N^+Ph_3SnF_2^- + KHSO_4$$

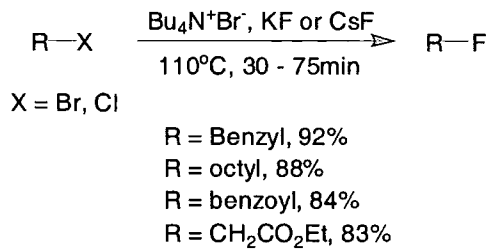
Scheme 1.13 Fluorination with hypervalent organotin compounds

Similarly, the same author reported an efficient synthesis of difluoroalkanes from *bis*-triflates using KF with a catalytic quantity of triphenyltin fluoride (Scheme 1.14).[50] This route is preferable to the corresponding non-catalytic fluorination of these substrates with tetrabutylammonium difluorotriphenylstannate, as this requires three molar equivalents of the expensive, high molecular weight reagent.[51]



Scheme 1.14 Synthesis of 1,1-difluoroalkanes with triphenyltin fluoride

A related technique, developed by Jaiswal, seeks to combine the fields of phase transfer catalysis and ionic liquid chemistry by using a semi-molten mixture of KF or CsF and tetrabutylammonium bromide at 110°C.[52] Exothermic reactions were observed on addition of electrophilic bromides and the corresponding fluorides were isolated in high yields (Scheme 1.15). The yields were higher than the quoted literature values for the same reactions with TBAF (tetrabutylammonium fluoride) in all cases.

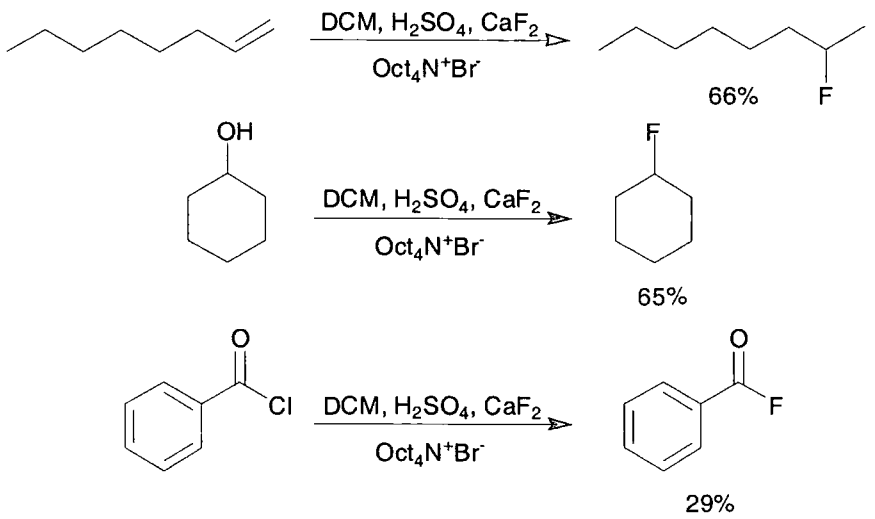


Scheme 1.15 Fluorination with molten tetrabutylammonium bromide and potassium or caesium fluoride

D. Fluorination with Calcium Fluoride

One of the frustrations of nucleophilic fluorination methodology is the inability to use calcium fluoride. This very cheap, readily available material is the mineral from which fluorine is extracted commercially. To use this fluoride directly, thus avoiding the need for energy-intensive chemical extraction of AHF, would be a huge advantage. Several papers have appeared regarding the use of KF/CaF_2 mixtures, which appear to have activity greater than either of the component metal fluorides. These have been used for the fluorination of a range of alkyl and acyl halides and sulfonates.[53, 54]

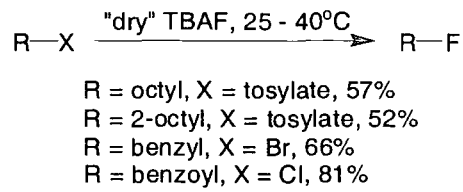
A further interesting paper on the use of CaF_2 appeared recently. The approach taken here differs somewhat from the other metal fluoride-based techniques in that the salt is used as an *in situ* source of AHF.[55] Reaction of an equimolar mixture of CaF_2 and sulfuric acid in DCM for five minutes in a PTFE vessel gave a solution of AHF in DCM. Addition of oct-1-ene and tetraoctylammonium bromide to this solution gave 66% of isolated 2-fluorooctane after 30 hours at ambient temperature. Similarly, alcohols and alkyl or acyl halides could be fluorinated under the same conditions (Scheme 1.16).



Scheme 1.16 Fluorination with calcium fluoride/sulphuric acid

1.3.4 Non-metal Fluoride Ion Reagents

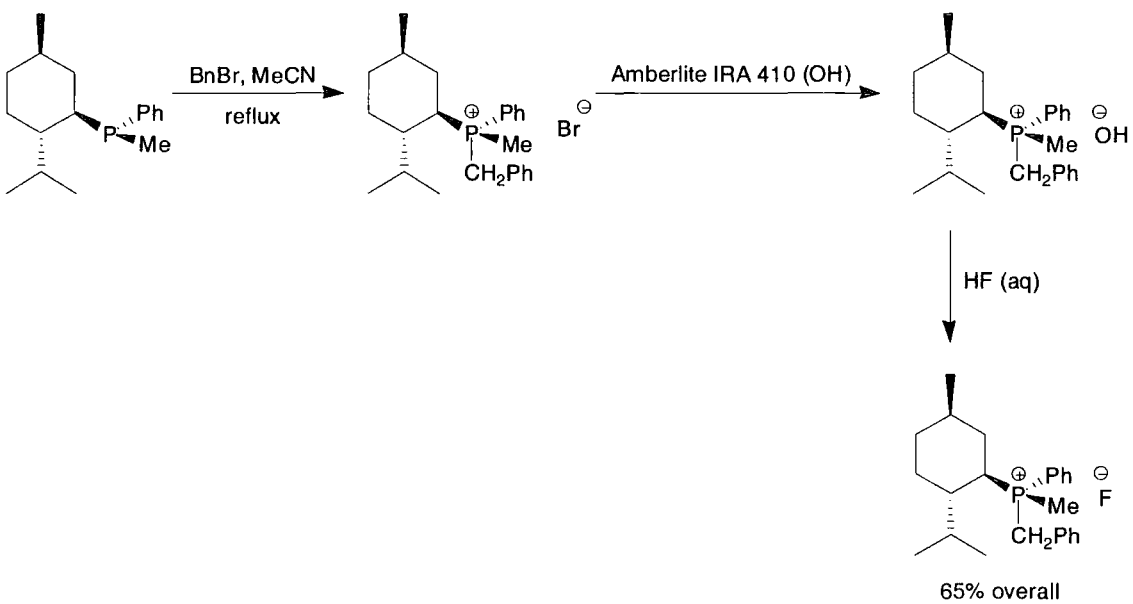
As the major problem with metal fluoride reagents is their solubility in common organic solvents, there has been a concerted effort to develop more soluble sources of fluoride ion. A variety of approaches have been taken, yielding a range of effective heteroatom based fluorinating agents. Perhaps the most well known of these is tetrabutylammonium fluoride, or TBAF.[56] This material is a fluoride salt which is soluble in many organic solvents. It is extremely difficult, if not impossible, to obtain in anhydrous form as the basicity of fluoride increases with decreasing water content, leading to Hoffman degradation of the quaternary amine group (a problem which also occurs spontaneously at elevated temperatures). Procedures to dry the material to even moderate water content lead to the formation of a sticky viscous mass which is still an effective fluorinating agent. Fortunately, for reasons still not fully understood, TBAF is a useful reagent even when present as the pentahydrate. Reaction under such conditions also appears to reduce the basicity of the system without reducing the fluorinating ability (Scheme1.17).[56, 57]



Scheme 1.17 Fluorination with tetrabutylammonium fluoride

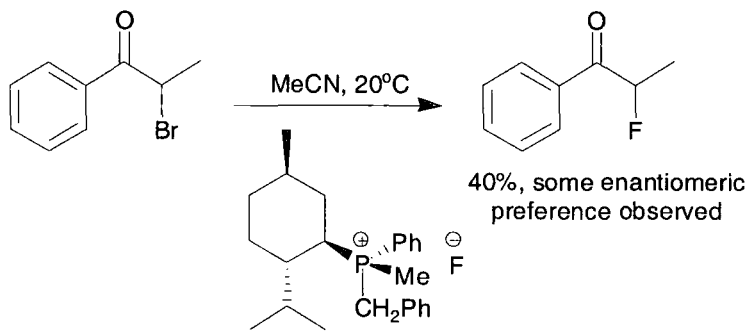
A similar, although perhaps more stable, reagent is tetrabutylammonium bifluoride, $Bu_4N^+HF_2^-$, TBABF, which give similar yields to TBAF.[58]

In order to avoid the complications seen with quaternary ammonium-based reagents (i.e. instability due to elimination processes), phosphonium systems have been suggested as these are more stable. Yoshioka prepared anhydrous tetrabutylphosphonium fluoride from the hydroxide and aqueous HF,[59] and showed it to be a useful reagent for the nucleophilic fluorination of epoxides, alkyl halides, alkyl sulfonates and steroidal sulfonates. A potential direction for this field is the possibility of synthesising chiral phosphonium fluorides for asymmetric fluorination of racemic precursors. This was demonstrated in a preliminary paper by Beaumont in 2001 (Scheme 1.18).[60]



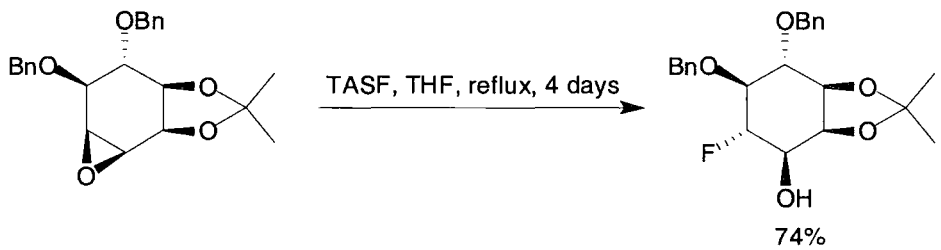
Scheme 1.18 Synthesis of a chiral phosphonium fluoride

The chiral phosphonium fluoride was used to fluorinate an α-bromoketone, and some enantioselectivity was observed based on the specific rotation of the product (Scheme 1.19). Exact figures were not given.



Scheme 1.19 Fluorination with a chiral phosphonium fluoride

Another well established fluoride ion source is TASF, or tris(dimethylamino)sulfonium difluorotrimethylsilicate.[61, 62] This material, prepared from sulfur tetrafluoride, is a very active source of fluoride ion. Its only major drawback is that it is expensive, and it has been used recently with a variety of sensitive substrates (Scheme 1.20).[63, 64]



Scheme 1.20 Fluorination with TASF

Further silicon based reagents have been developed,[65] including tetrabutylammonium butyldifluorodimethylsilicate and difluorodimethylphenylsilicate.[66] These were reported by Kvicala in 2001 and they have been shown to be highly effective fluorinating agents, generally giving higher yields than TBAF with alkyl halides and sulfonates. Similar hypervalent tin reagents

have already been mentioned (see section **1.3.3.C**) and shown to be effective sources of nucleophilic fluoride.[67] Tin is now perceived as a rather hazardous element, and its continued large-scale use in chemistry is in doubt.

Another source of fluoride ions that has received significant attention are the anion exchange resins. Amberlyst-A 26 is a quaternary ammonium resin containing hydroxyl groups which may be easily replaced by fluoride with dilute aqueous HF. Reaction of the resin with a range of electrophiles in boiling pentane, hexane or THF led to the formation of the corresponding fluorides in high yields.[68] Product isolation was very simple as the resin was filtered off and the product purified by distillation following removal of solvent. Yields were generally higher than those with TBAF as reported above.

1.4 Conclusion

Although there is clearly a very wide range of fluorinating agents (of which only a selection of the most important reagents has been presented above), each has its own advantages and disadvantages. Many of the more active reagents are expensive or difficult to handle, whilst some are rather unstable. There is still a need for new fluorinating agents to further broaden the area and provide advantages over current methodology in terms of cost, efficiency and safety.

New perceptions of "green" chemistry are creating a desire for new types of reagent. These should be effective, preferably non-hazardous and have minimal effect on the environment. Many of the current fluorination systems will struggle to fit into this arena of chemistry, and it is worth bearing in mind that fluorine chemistry has traditionally been viewed as a particularly hazardous undertaking. Of course, things have moved on somewhat since the days of Moissan and Dewar:[69]

"Oil of turpentine, in the solid state, is attacked by liquid fluorine. To perform this experiment a little oil of turpentine was placed at the bottom of a glass tube surrounded with boiling liquid air. As soon as a small quantity of fluorine was liquefied on the surface of the solid, combination took place with explosive force. After each explosion, the current of fluorine gas was kept up slowly, a fresh quantity of liquid fluorine was formed, and the detonations succeeded each other at intervals of

6 – 7 minutes. Finally, after a longer interval of about 9 minutes, the quantity of fluorine formed was sufficient to cause, at the moment of reaction, the complete destruction of the apparatus. In several of these experiments a little liquid fluorine accidentally fell on the floor; the wood instantly took fire."

In stark contrast to this, as can be seen from the first figure in the chapter, it is now possible to selectively place a fluorine atom into a relatively sensitive molecule under extremely mild conditions. To be able to do this in total safety (with regard to the environment, as well as the experimentalist!) under ambient conditions is the goal of much of the current research on fluorination methodology, and it is hoped that the work presented in this thesis has gone some small way towards achieving that aim. Further developments involving safer, more selective reagents and ultimately fully enantioselective fluorination are awaited with interest.

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2. Perfluoro(2-methylpentan-2-yl)caesium as a Source of Soluble Fluoride Ion

It has been known for several decades that highly fluorinated alkenes can react with fluoride ion sources to produce carbanionic species of varying stability.[1] This type of reaction forms the backbone of much of organofluorine chemistry and it has been studied extensively. Within the last 20 years, the isolation of stable perfluorinated carbanions was reported, and it was this work which inspired the current research. The reaction of a fluoride ion source, such as CsF, with a perfluoroalkene to form a soluble perfluoroalkyl caesium salt is a reversible process. The aim of the current research was to synthesise a carbanion species known to undergo fluoride ion exchange at moderate temperatures and investigate whether this material could be used as an *in situ* source of soluble fluoride ion.

2.1 Perfluoroalkenes and Derived Carbanions

2.1.1 Perfluoroalkenes[2]

Perfluoroalkenes are an interesting class of compounds, being composed entirely of carbon and fluorine with at least one carbon-carbon double bond. They have a distinctive reactivity and exhibit a varied and sometimes surprising range of reactions. In common with many highly fluorinated compounds, they possess so-called "mirror image" chemistry when compared to their hydrocarbon counterparts. In other words, whereas an alkene is nucleophilic due to the localised high electron density of the π-bond, a perfluoroalkene behaves as an electrophile.[3]

Although there are many different perfluoroalkenes, the experimental work in this chapter is only concerned with one, namely perfluoro(2-methylpent-2-ene), more commonly known as hexafluoropropene (HFP) dimer (Figure 2.1) and synthesised by fluoride induced oligomerisation of HFP.

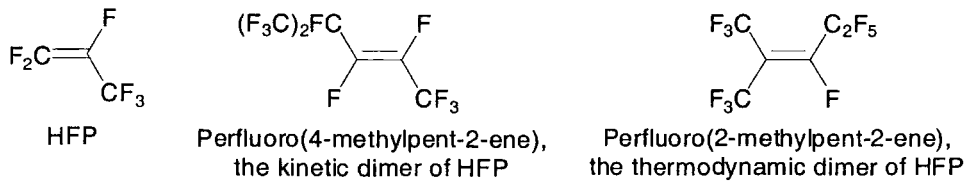
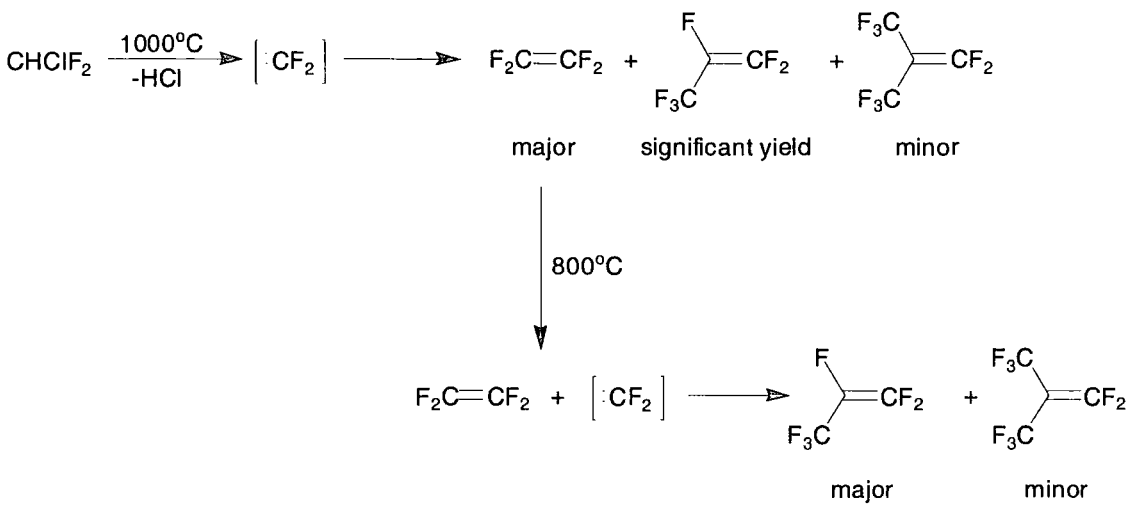


Figure 2.1 Fluoroalkenes of interest

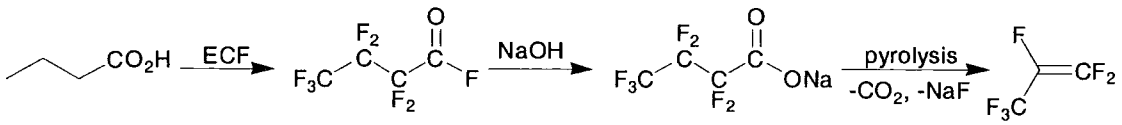
2.1.2 Synthesis of Perfluoroalkenes

HFP itself is synthesised industrially as a byproduct of PTFE manufacture and is a colourless gas (b.p. -28°C). During the synthesis of TFE monomer, chlorodifluoromethane (R22) is pyrolysed at approximately 1000°C.[4] This causes elimination of HCl and the formation of difluorocarbene. The conditions of the process are carefully controlled so as to minimise the formation of higher CF_2 homologues, but appreciable quantities of HFP are formed during the reaction (Scheme 2.1). The C_3 alkene can then be fractionated during the distillation of TFE monomer. Alternatively, HFP can be made via the direct pyrolysis of TFE under slightly milder conditions and this process is the source of much of the HFP produced today (Scheme 2.1).[5]



Scheme 2.1 Synthesis of TFE, HFP and PFIB

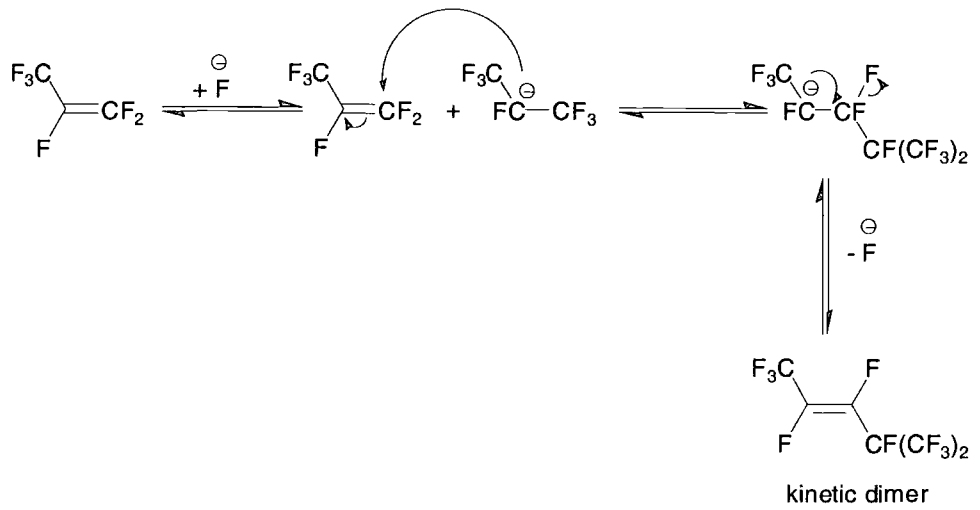
Laboratory synthesis of HFP can be accomplished by pyrolysis of PTFE or a range of highly fluorinated halocarbons. In many of the pyrolysis reactions listed, care must be taken to guard against the formation of the branched C_4 alkene, perfluoroisobutene (PFIB) as this is extremely toxic.[6] A further synthesis is the treatment of butyric acid with AHF in an electrochemical cell, leading to the formation of perfluorobutanoyl fluoride via electrochemical fluorination (ECF). Formation of the sodium salt of this material followed by pyrolysis at moderate temperature gives hexafluoropropene (Scheme 2.2).[7]



Scheme 2.2 Laboratory synthesis of HFP

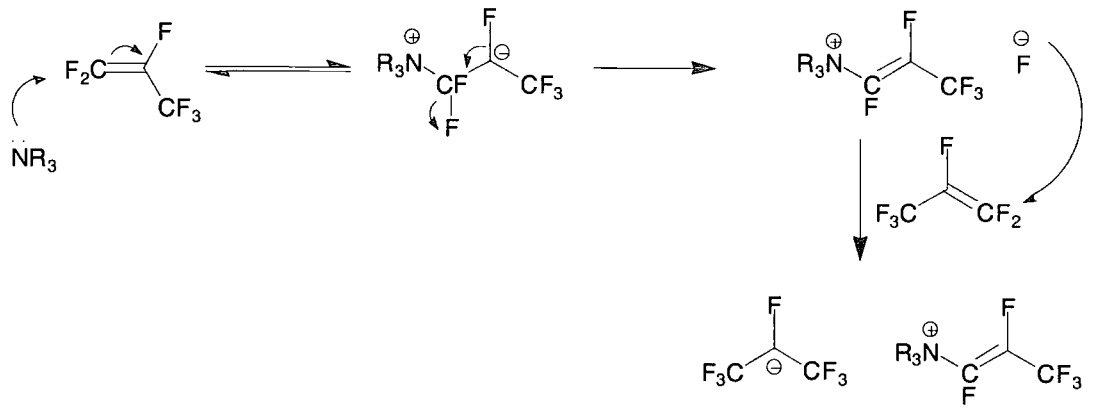
2.1.3 Dimerisation of HFP

Dimerisation of HFP can be initiated in a variety of ways, although all methods rely on the generation of a fluoride ion which reacts with HFP to form the perfluoroisopropyl carbanion. This carbanion is rather reactive and it attacks another molecule of HFP at the CF_2 terminus to yield a further carbanion, which then eliminates fluoride ion to give the kinetic dimer of HFP (Scheme 2.3).



Scheme 2.3 Fluoride catalysed dimerisation of HFP

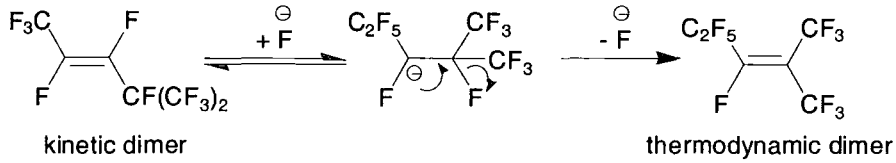
Amine initiators have been used to good effect under solvent free conditions,[8] via nucleophilic attack on HFP followed by fluoride ion release to form a salt (Scheme 2.4).



Scheme 2.4 Amine initiated formation of a carbanion from HFP

The addition of a metal fluoride,[2] TASF[9] or other suitable fluoride ion source to HFP in an appropriate solvent is also a useful synthetic route. Reaction at ambient temperature tends to produce the kinetic dimer, perfluoro(4-methylpent-2-ene). However, performing the reaction at higher temperature or distilling the reaction

products over CsF causes equilibration via fluoride ion exchange to the more stable thermodynamic dimer, perfluoro(2-methylpent-2-ene) (Scheme 2.5).[2]



Scheme 2.5 Fluoride catalysed isomerisation of HFP dimer

2.1.4 Factors Affecting Perfluoroalkene Reactivity

Although perfluoroalkene chemistry is dominated by nucleophilic attack at the alkene functionality,[3] radical reactions[2] of such systems are also well known and there are even some rare examples of electrophilic attack[2] under very specific conditions. The two latter modes of reaction will not be considered further in this chapter. The factors that affect the reactions of perfluoroalkenes with nucleophiles can be split into several distinct effects, comprising the reasons for reaction in the first place and the orientation of attack of the nucleophilic species on the double bond. These factors will be discussed below:

2.1.4.1 Why Do Perfluoroalkenes React With Nucleophiles?

- Electrophilicity of carbon centres within the double bond

The main influence on the reactivity of a perfluoroalkene is the very high electronegativity of the fluorine atoms bonded directly to the carbon atoms of the double bond. Compared with chlorine, with its larger atomic radius and more diffuse orbitals, a fluorine atom causes much greater polarisation of the carbon-halogen bond (Figure 2.2). This results in the carbon atoms of the π-bond becoming much more electrophilic and consequently much more reactive than those in a perchloroalkene system.

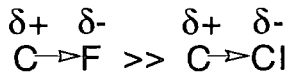


Figure 2.2 Polarisation of carbon-halogen bonds

A terminal difluoromethylene group is the extreme case of this effect, as it is the most reactive of all the conceivable perfluoroalkene moieties. The high reactivity is due to the two fluorine atoms possessing a higher electronegativity than any perfluoroalkyl group. This causes the terminal carbon to become more electrophilic than in other perfluoroalkene systems.

Theoretical work conducted by Russian researchers reinforces this argument (Table 2.1).[10] Calculations to predict the electron density of the carbon atoms in the double bond showed the expected trend in which the perfluoroalkene carbon atoms with the highest degree of positive charge in the ground state coincided with those that were found experimentally to be the most reactive towards nucleophilic species.

Table 2.1 Charge distribution in perfluoroalkenes

Alkene	TFE	HFP	PFIB
Terminus	Charge distribution on carbon atom of π-bond terminus		
CF_2	+0.317	+0.419	+0.520
CR_FR_F'	+0.317	+0.026	-0.208

R_F, R_F' = F, CF_3

2.1.4.2 Prediction and Rationalisation of the Orientation of Attack of a Nucleophile on a Perfluoroalkene

From the information shown above, it is clear that perfluoroalkenes are highly electron deficient species. However, when reactions with nucleophiles are performed, the regioselectivity of the reaction is often very pronounced. For example, addition of a nucleophile to perfluoroisobutene occurs exclusively at the difluoromethylene terminus of the double bond. No attack is seen at the carbon bearing two trifluoromethyl groups (Figure 2.3). This selectivity can be rationalised using several

different arguments, and these are critical to our understanding of the reactivity of such systems.

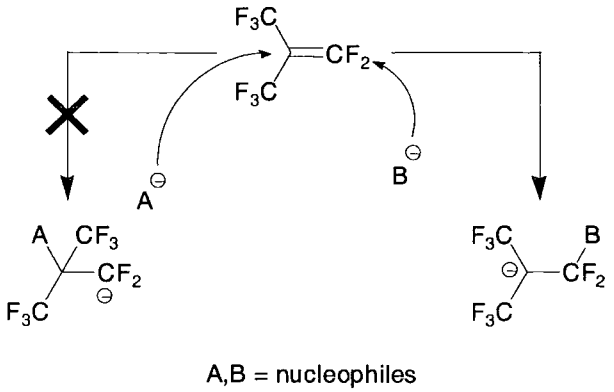


Figure 2.3 Possible sites of nucleophilic attack on PFIB

- Steric requirement of the perfluoroalkene

A basic argument regarding reactivity may be made on the basis of the steric requirements of any perfluoroalkyl groups that are present. Perfluoroalkyl groups are considerably bulkier than their hydrocarbon counterparts and it is conceivable that these may interfere with the approach of a nucleophile in certain situations. For example, the extreme difficulty observed in homopolymerising HFP is attributed to the steric requirements of the trifluoromethyl group.[11]

- Stability of intermediate perfluoroalkyl carbanion species

Perfluoroalkyl carbanions occur as intermediates in reactions of highly fluorinated alkenes, and so understanding the properties and behaviour of these species is vital if we are to predict the chemistry of such fluorinated systems. The subject of perfluoroalkyl carbanion chemistry has been reviewed recently by Farnham,[12] and an older review by Young[1] is still useful. The effect of carbanion stability on the orientation of attack of a nucleophile (fluoride ion) on a perfluoroalkene will be discussed below; for the corresponding treatment with regard to fluorinated aromatic compounds see section **4.1.3**.

- Perfluoroalkyl carbanion stability: Inductive effects and lone pair repulsion

Once a nucleophile has reacted with a perfluoroalkene, resulting in an anionic species, the electron withdrawing fluorine or perfluoroalkyl substituents exert a stabilising influence on the negative charge. This "mirrors" the stabilising effect of an alkyl group adjacent to the centre of positive charge in the intermediate formed by electrophilic attack on an alkene (Figure 2.4).

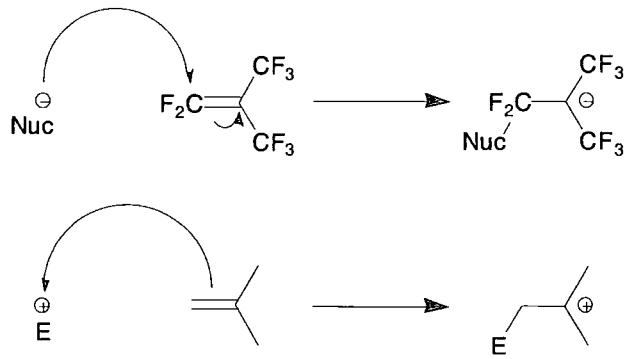


Figure 2.4 "Mirror image" chemistry: Formation of a perfluorinated carbanion and hydrocarbon carbocation

A carbanion centre bearing a fluorine substituent experiences some stabilisation due to the inductive effect of the fluorine atom but in an sp^2 system the carbanion may actually be destabilised due to lone pair repulsion. A carbanion centre on an sp^3 hybridised carbon is only marginally destabilised relative to hydrogen due to the more favourable geometry of the system (Figure 2.5).

sp^2 system - significant repulsion, causes carbanion destabilisation

sp^3 system - more open geometry reduces repulsion

Figure 2.5 π-repulsion effects on perfluorocarbanion stability

A carbanion centre bearing a β-fluorine (for example $^{-}$C-C-F) is strongly stabilised as the fluorine is too distant for lone pair repulsion to be a major factor. The inductive effect is very much apparent even over two sigma bonds and so the system is capable of reducing the degree of localisation of the negative charge on the carbanion centre, thereby significantly stabilising the carbanion (Figure 2.6).

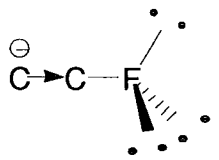


Figure 2.6 Stabilisation of β-carbanion by the inductive effect of fluorine

This argument is the one which is most often used to understand the regioselectivity of attack of a nucleophile on a perfluoroalkene. For example, considering PFIB below, we can now explain the observed regioselectivity of attack of the nucleophilic species. The observed reaction at the terminal difluoromethylene group is rationalised by the relative stability of the carbanions generated from the two different routes (Figure 2.3, Table 2.2).

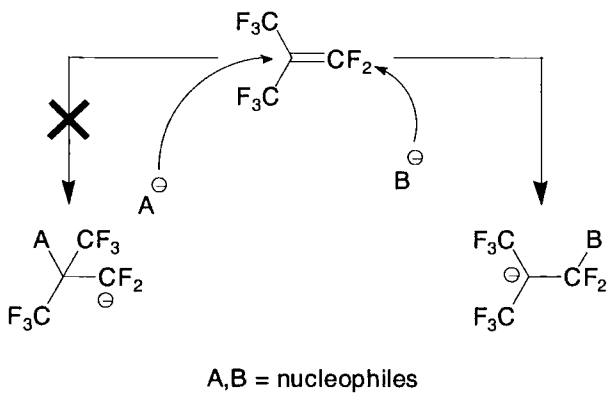


Figure 2.3 Possible sites of nucleophilic attack on PFIB

Table 2.2 Summary of carbanion-fluorine interactions in the carbanion derived from PFIB

Route	A	B
Number of potentially destabilising $^{-}$C-F interactions	2	0
Number of stabilising $^{-}$C-C-F interactions	0	8
	(1 if A = F)	(9 if B = F)

- Molecular Orbital theory as applied to perfluoroalkene reactivity

As an addition to the above arguments, the use of frontier molecular orbital (FMO) theory has been proposed as a way to explain some of the remaining issues which are not explicitly resolved when invoking the stability of the intermediate carbanion species.[13] Essentially, the presence of a trifluoromethyl group raises the LUMO coefficient on the opposite carbon atom (see Figure 2.7), thus increasing the reactivity of the system towards nucleophilic attack. This argument has been used to explain the unexpected trend in reactivities of certain perfluoroalkenes which cannot be explained using the carbanion stability arguments detailed above. For example, perfluoroisobutene is significantly more reactive then perfluorobut-2-ene despite the fact that they both possess two allylic fluorine atoms and similar carbanion intermediates following nucleophilic attack.

Using this approach, it becomes possible to rationalise the reactivities of perfluorobut-2-ene and PFIB. In the case of perfluorobut-2-ene, there is a trifluoromethyl group at either end of the double bond, thus no major perturbation of the double bond electron density occurs. As PFIB has two trifluoromethyl groups attached to one carbon atom this causes a distinct polarisation of the bond, leading to greater ground state reactivity (Figure 2.7). The nucleophile reacts correspondingly at the difluoromethylene terminus.

Effects of CF_3 groups cancel

Effect of CF_3 groups additive

Figure 2.7 Illustration of the effect of trifluoromethyl groups on the LUMO of a perfluoroalkene

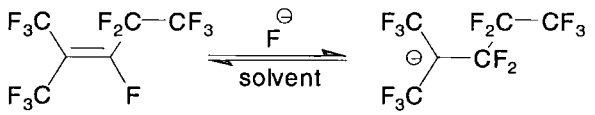
Primary and secondary carbanions thus have fewer stabilising factors capable of reducing the degree of localisation of the negative charge and also have considerably less steric hindrance around the reactive carbanion centre. The observed reactivity trend, which is rationalised by the above arguments is that tertiary carbanions are considerably more stable than secondary carbanions and these in turn are more stable than primary carbanions. Primary and secondary carbanions therefore tend to be unstable with respect to oligomerisation (e.g. TFE can be oligomerised to relatively high molecular weight species using anionic initiation) whereas tertiary carbanions are more likely to be stable, although even PFIB can be dimerised under suitable conditions.[14] Indeed, several tertiary perfluorinated carbanions have been observed by NMR spectroscopy[15, 16] or even isolated as solids,[9, 16] a feat that has so far proved extremely unusual with primary or secondary systems. The mono-acetonitrile solvate of perfluoro(isopropyl)silver has been isolated, although the unsolvated material was not accessible via the techniques employed. Metathesis with a tetraalkylammonium salt afforded the complex ion $Ag[CF(CF_3)_2]_2^-$ as an isolable solid.[17]

2.2 Literature Review

There are three main topics to discuss here, namely the formation of carbanions, their isolation where possible and the nature of subsequent reactions.

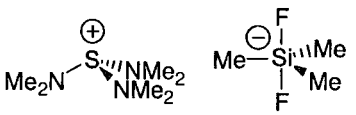
2.2.1 Synthesis of Perfluoroalkyl Carbanions

Perhaps the most well-known methodology for carbanion formation is the reaction of a suitable fluoride ion source with a perfluoroalkene (Scheme 2.6) and this route has been investigated extensively by many workers.



Scheme 2.6 Representative formation of a perfluoroalkyl carbanion

Suitable sources include metal fluorides such as caesium or silver(I) fluoride[17] as well as other more exotic species such as TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate) (Figure 2.8).[9]



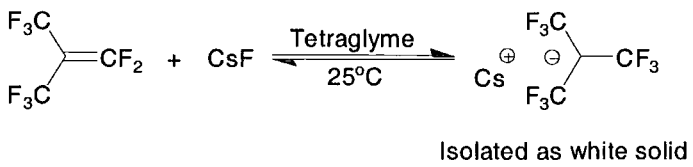
TASF

Figure 2.8 TASF

The choice of solvent in such procedures is often critical, as the solvent must be capable of dissolving a sufficient quantity of the fluoride ion source without solvating the fluoride ion itself to a high degree. The solvent must also be aprotic due to the high basicity of perfluoroalkyl carbanions. Dipolar aprotic solvents such as DMF, NMP, sulfolane, MeCN, THF and various glymes have therefore been used for carbanion generation.[16, 18-23] However, MeCN and THF are unfortunately ill-suited to the generation of carbanions with many of the metal fluorides, perhaps due to the limited solubility of such fluorides in these solvents. TAS carbanions (synthesised from perfluoroalkenes and TASF) have been prepared in THF and MeCN[20] as TASF is rather more soluble in these solvents than e.g. CsF.

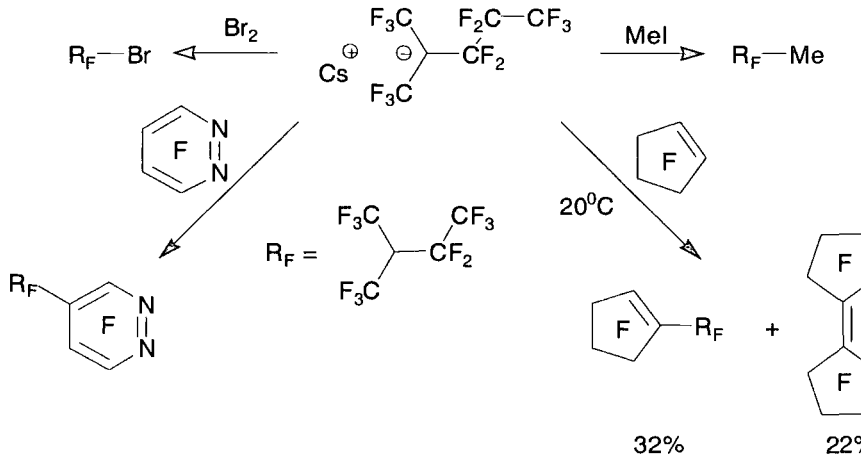
The first observation of stable cyclic perfluoroalkyl[22] and isolation of aliphatic perfluoroalkyl[15] carbanion salts were reported by Chambers in 1980 and 1985 respectively, shortly followed by Farnham and Smart[9] and a further publication by the Chambers group in 1986.[16] In each of these papers, the synthetic route taken was the reaction of a perfluoroalkene with either a metal fluoride or TASF.

Chambers demonstrated the isolation of solid perfluoro(2-methylpropyl)caesium (the caesium salt of the carbanion formed from PFIB) as large needle-like crystals (Scheme 2.7). These could be redissolved to give the carbanion spectrum with little or no decomposition but, unfortunately, the crystals decomposed before an X-ray study could be carried out.

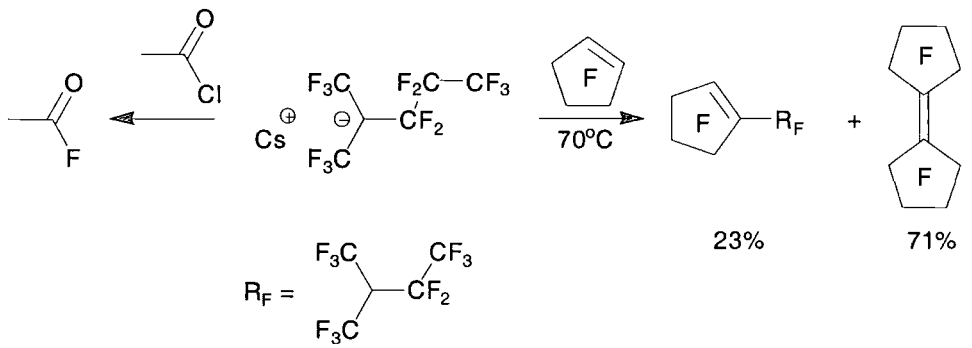


Scheme 2.7 Synthesis of perfluoro(2-methylpropyl)caesium

Several other carbanions were prepared as both TAS and caesium salts, although these were not isolated. In general, trapping experiments were performed demonstrating the utility of these materials as perfluoralkylating agents (for example with iodomethane, elemental halogens and perfluorinated aromatic compounds, Scheme 2.8) or as fluoride ion sources (with acetyl chloride, and in the dimerisation of perfluorocyclopentene, Scheme 2.9).



Scheme 2.8 Perfluoroalkyl carbanions as perfluoroalkylating agents

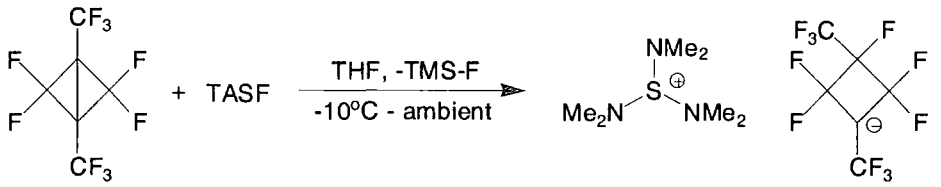


Scheme 2.9 Perfluoroalkyl carbanions as fluorinating agents

A key point to note is the effect of temperature on the reaction between the perfluoroalkyl carbanion and perfluorocyclopentene. At low temperatures, the carbanion is the main species present and so perfluoroalkylation occurs predominantly. As the temperature is raised, the carbanion begins to undergo rapid fluoride ion exchange and the bicyclic perfluoroalkene, produced by fluoride ion induced dimerisation of perfluorocyclopentene, predominates.

It was not until a further three years had elapsed that an isolated perfluoroalkyl carbanion was obtained in a form suitable for study by X-ray diffraction by Farnham and Dixon.[20] The carbanion generated from perfluoro(1,3-dimethylbicyclo[1.1.0]butane) was isolated by reaction with TASF (Scheme 2.10). The preparation is interesting in itself, as the pair of electrons that form the

carbanionic centre come from a σ-bond rather than a π-system. This takes advantage of the extremely strained bonds of the bicyclobutane moiety, made even weaker by the adjacent trifluoromethyl groups. Interestingly, the carbanion structure provides significant evidence for negative hyperconjugation. The ring carbon-carbon bonds attached to the carbanion centre are significantly shortened, whilst the two difluoromethylene groups possess unusually long carbon-fluorine bonds.



Scheme 2.10 Synthesis of a perfluoroalkyl carbanions suitable for X-ray diffraction

The process is shown below, along with the more usual hydrocarbon case for comparison (Figure 2.9). Although the effect has been much debated, this paper provided the first direct evidence for negative hyperconjugation in a perfluoroalkyl carbanion system.

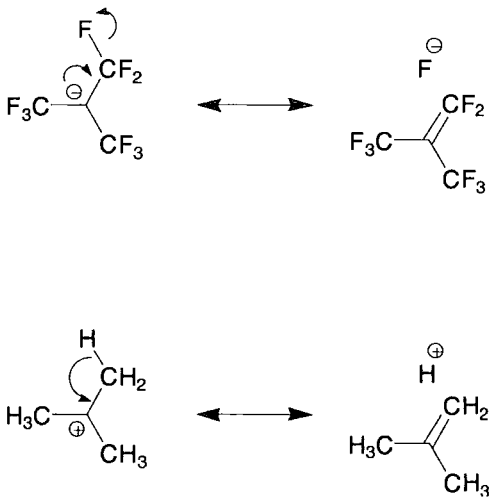
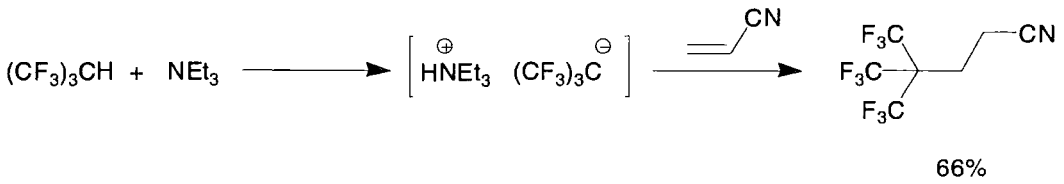


Figure 2.9 Negative and positive hyperconjugation

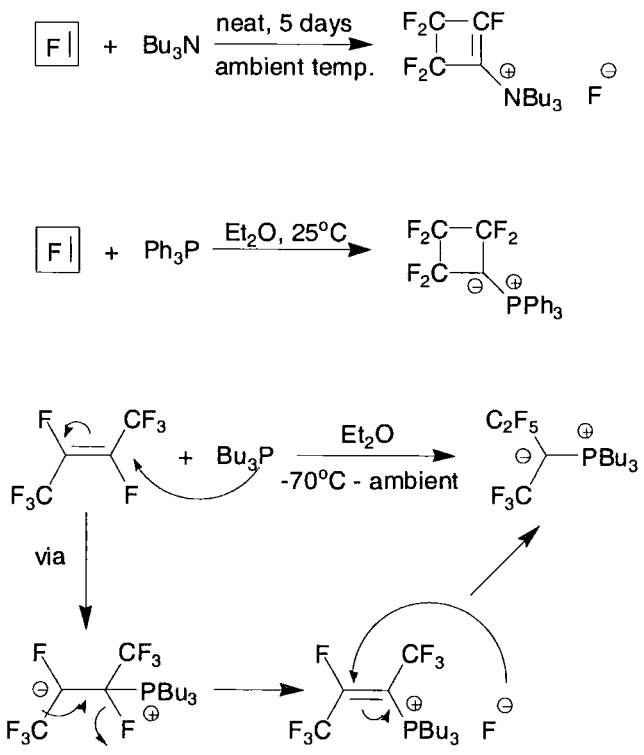
Further synthetic methodology involves deprotonation of a monohydroperfluoroalkene to produce a carbanion (Scheme 2.11), although these

tend to be unstable with respect to elimination of fluoride ion. The methodology has been applied to generate carbanions *in-situ* for use in Michael addition reactions, as shown below.[24]



Scheme 2.11 Deprotonation of a monohydroperfluoroalkane

Fluorocarbon heteroatom ylids have been claimed for several decades, and a few of these have also been isolated, generally via reaction of a reactive perfluoroalkene with a tertiary amine or phosphine (Scheme 2.12). Note that the structure of the tributylammonium adduct below was confirmed only by elemental analysis and dissociation of the product to the starting materials on heating.[25, 26]



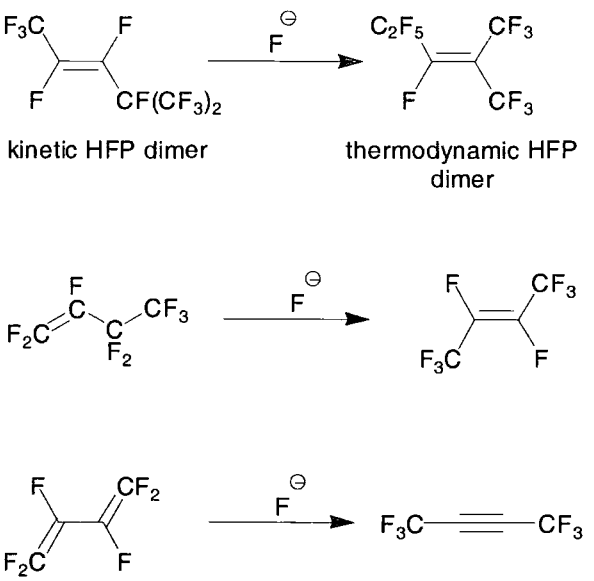
Scheme 2.12 Synthesis of fluorocarbon heteroatom ylids

2.2.2 Reactions of Perfluoroalkyl Carbanions

Once formed, a carbanion has several possible reaction pathways available. These can result in rearrangement, regeneration of the initial perfluoroalkene or trapping of the anion as a perfluoroalkyl group.

2.2.2.1 Loss of Fluoride Ion

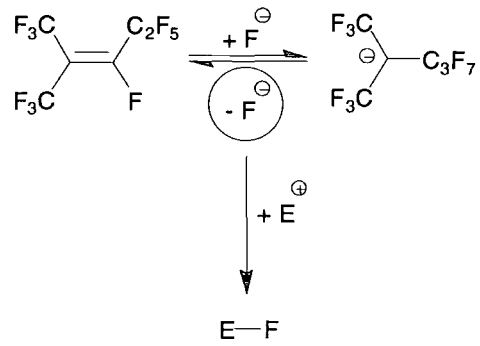
A β-fluorine may be lost as fluoride ion, yielding a substituted alkene which may then undergo further nucleophilic attack. This route, essentially an S_N2' substitution, is the mechanism by which a less thermodynamically stable perfluoroalkene can isomerise to a more stable one in the presence of fluoride ion (Scheme 2.13).



Scheme 2.13 Isomerisation processes catalysed by fluoride ion

The fluoride ion released in the elimination can undergo further reaction, either reacting with more perfluoroalkene to maintain the equilibrium or with any other electrophile in the system (Scheme 2.14). The exploitation of this side-reaction,

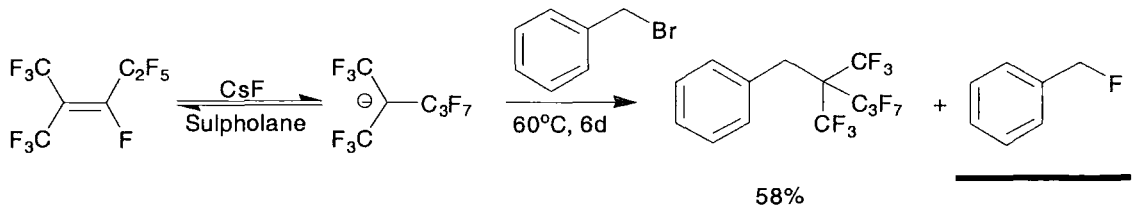
undergone by the anion of HFP dimer, is the foundation for this chapter of work.[16, 27]



Scheme 2.14 The fate of fluoride ion from a perfluoroalkyl carbanion

Following earlier work in the Chambers group, it was determined from variable temperature (VT) NMR studies that the carbanion formed from HFP dimer underwent significant fluoride ion exchange at particularly low temperatures (around 50°C) compared to the other carbanions studied.[16] A variety of reactions was performed with electrophilic species demonstrating the utility of the carbanion both for perfluoroalkylation and fluorination processes. It was established that with the exception of carbonyl centres, at which fluorination was preferred, perfluoroalkylation was the major reaction observed. However, as the focus of the paper was on a variety of carbanions, the reactivity of the particular carbanion derived from HFP dimer was not investigated in detail.

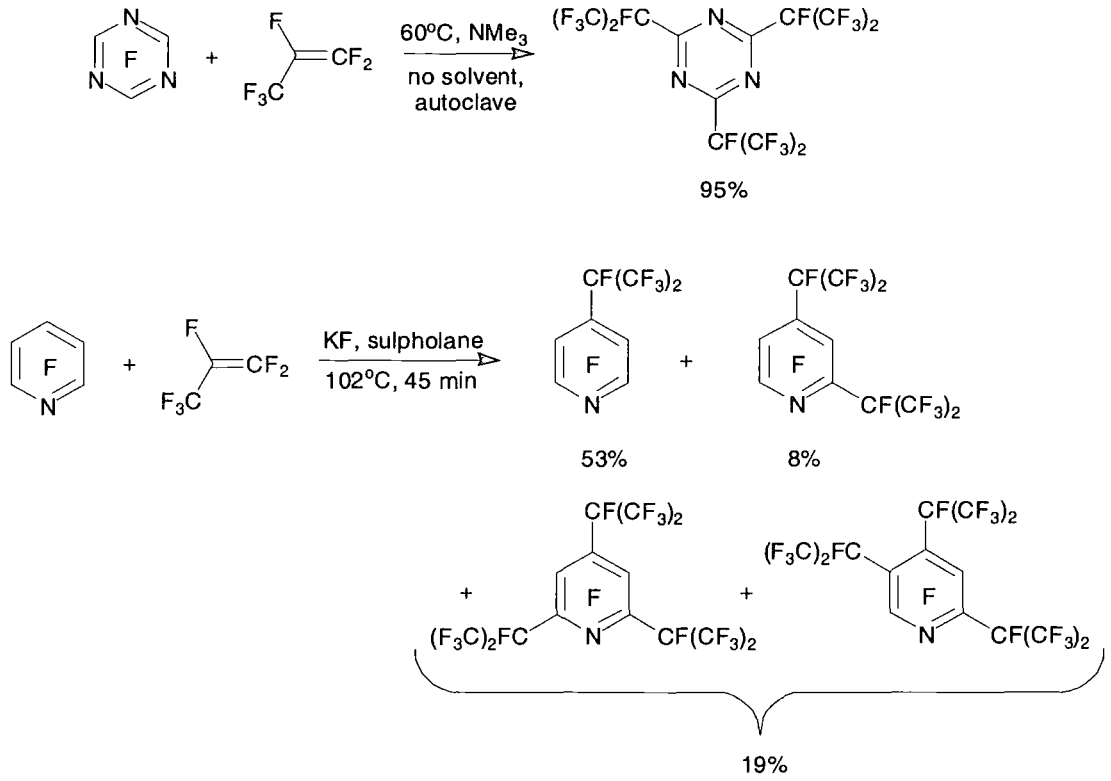
As shown below, a further publication reported the optimisation of a process for the perfluoroalkylation of various benzylic bromides (Scheme 2.15).[27] Interestingly, the formation of benzyl fluoride, in unknown yield, was also reported. As this perfluoroalkyl carbanion system is capable of fluorination, the possibility of encouraging the fluoride ion exchange process, thereby increasing the yields of selectively fluorinated products, is rather appealing.



Scheme 2.15 Reaction of perfluoro(2-methylpentan-2-yl)caesium with benzyl bromide

2.2.2.2 Trapping of the Perfluoroalkyl Carbanion with Electrophiles

The carbanion may also react with an electrophilic species to yield a saturated 1,2-disubstituted system. In the case of perfluoroalkenes which form primary or secondary carbanions, oligomerisation in the presence of a suitable nucleophilic initiator (fluoride ion, amine etc.) is possible although this is less likely for highly substituted systems due to the steric requirements of the alkene. The generation of a relatively stable perfluorinated carbanion followed by attack of an electrophile is a general method for the introduction of a perfluoroalkyl group into a variety of molecules. The technique has been applied to both aromatic (so called negative Friedel-Crafts reactions in the case where fluoride is the leaving group) and aliphatic substrates (Scheme 2.16).[8, 27, 28]



Scheme 2.16 "Negative Friedel-Crafts" reactions

Perfluorinated carbanions are also rather strong bases,[16] and as they are not particularly strong nucleophiles, this can cause problems with the perfluoroalkylation or fluorination of less reactive substrates that are prone to elimination (see section **2.4.2.A** for example).

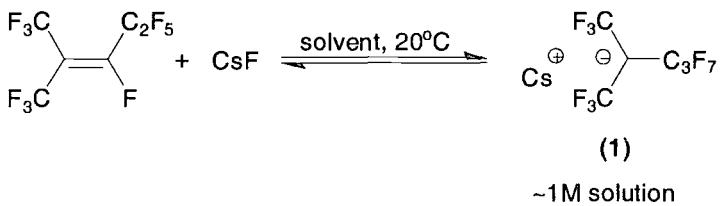
2.3 Results and Discussion

The aim of this project was to try and optimise reaction conditions so that fluorination (see scheme 2.15) was the major reaction pathway, as the VT NMR studies conducted previously[16] had demonstrated the lability of the fluorine atom at the 3-position of the carbanion. The hope with the project was that as the fluoride ion would be formed *in-situ*, it would be essentially solubilised when compared to the highly crystalline CsF which is only sparingly soluble in many dipolar aprotic solvents. This would mean that the fluoride produced would be highly nucleophilic and fluorination should therefore occur readily.

The perfluoroalkyl carbanion was synthesised and the VT NMR experiments were repeated to check the accuracy of the data. Following confirmation of the exchange temperature, the carbanion was reacted with a range of electrophilic species and its reactivity pattern was studied. Factors potentially affecting the yield of fluorination (or extent of fluoride exchange) were examined, including:

- Solvent
- Temperature
- Concentration
- Leaving group of electrophile

2.3.1 Synthesis of Perfluoro(2-methylpentan-2-yl)caesium



(1)

~1M solution

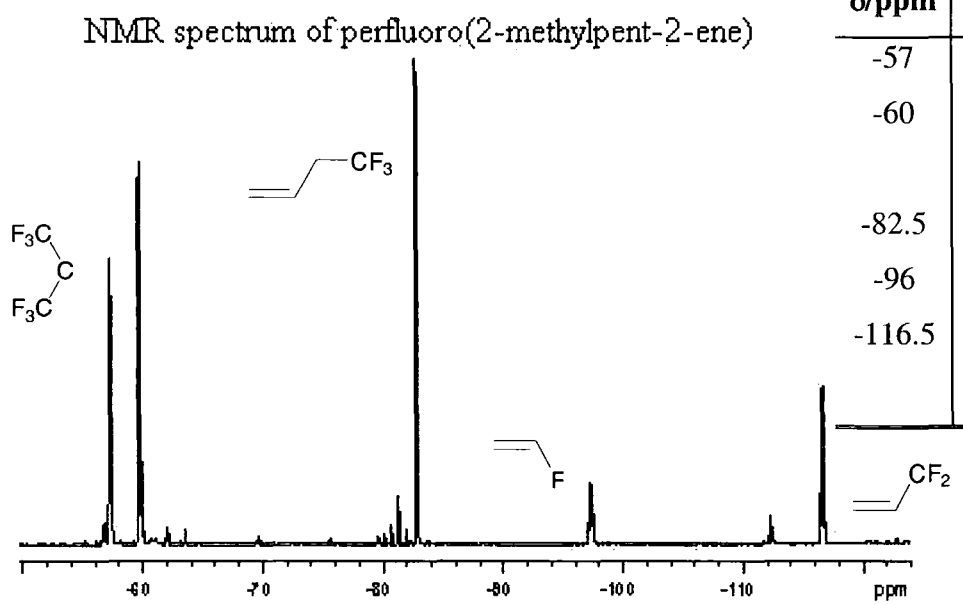
Scheme 2.17 Synthesis of **(1)**

The carbanion **(1)** was synthesised by reaction of perfluoro-2-methylpent-2-ene with anhydrous CsF in a dipolar aprotic solvent. Previous work in this research group used sulfolane or tetraglyme[16, 27] but, due to ease of handling, DMF and NMP were used most frequently in this project. The perfluoroalkene was injected into a specially designed apparatus that had been charged with CsF and the solvent, essentially a variation on a double schlenk flask fitted with a frit. This allowed formation, filtration and isolation of the pure perfluoro(2-methylpentan-2-yl)caesium solution within a single vessel under an inert atmosphere.

Over the course of several days, the solvent would change from colourless to bright yellow and finally to a deep red colour. After this colour change, **(1)** was the only fluorinated material detectable by ^{19}F NMR. The solution, once formed, was almost entirely stable for several months provided that air and particularly moisture

were rigorously excluded. Accordingly, all transfer operations were conducted using syringe or cannula techniques.

2.3.2 NMR Studies of Perfluoro(2-methylpentan-2-yl)caesium



δ/ppm	J/Hz
-57	m
-60	dq $^4J_{FF}$ 31
	$^4J_{FF}$ 10
-82.5	m
-96	m
-116.5	qd $^3J_{FF}$ 19
	$^3J_{FF}$ 6

Figure 2.10 ^{19}F NMR spectrum of perfluoro(2-methylpent-2-ene)

The ^{19}F NMR spectrum of perfluoro(2-methylpent-2-ene) is very distinctive (Figure 2.10). There is a multiplet at δ -57ppm, corresponding to one of the geminal CF_3 groups. The remaining geminal CF_3 appears at δ -60ppm as a doublet of quartets. The final CF_3 group manifests itself as a multiplet δ -82.5. The vinylic fluorine appears as a very complex broad multiplet at δ -96 and the CF_2 group as a quartet of doublets at δ -116.5, $^3J_{FF}$ 19Hz, $^3J_{FF}$ 6.4Hz.

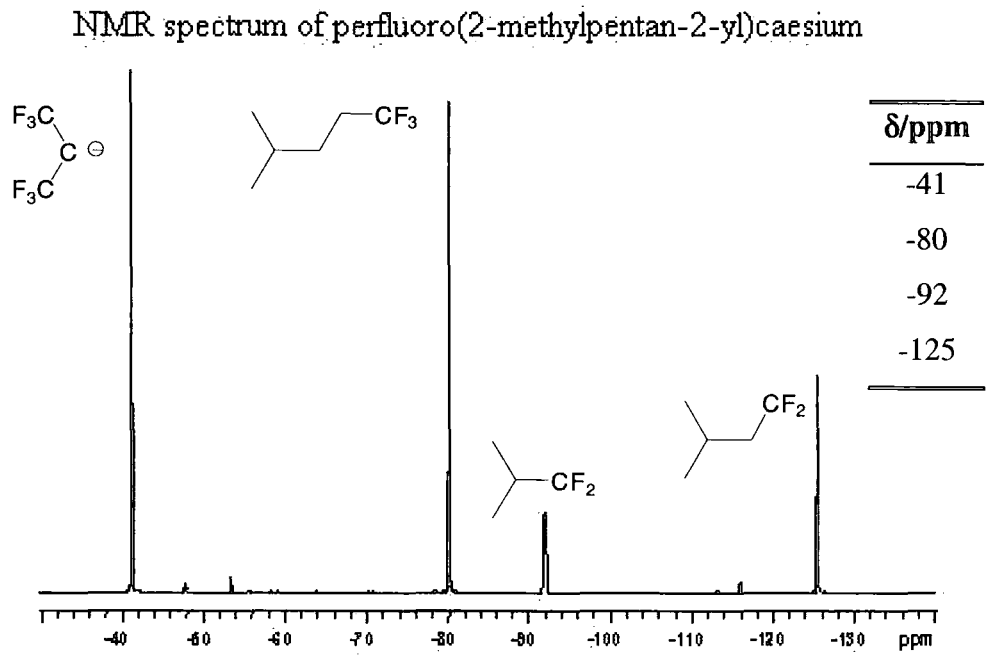


Figure 2.11 ^{19}F NMR spectrum of **(1)**

Formation of (1) results in a marked change in the spectrum (Figure 2.11) due to the appearance of the negative charge and the removal of the vinylic fluorine atom and double bond. The system is now more simplistic in nature, containing two equivalent CF_3 groups (δ -41ppm) bonded to the carbanion centre and a perfluoropropyl group attached likewise (CF_2CF_3 δ -125ppm, CF_3 δ -80ppm). Significant peak broadening of the peaks (all appear as broad singlets) is seen due to fluoride ion exchange even at ambient temperature, and this effect may be significantly increased by heating the carbanion solution as seen above.

Earlier work by Chambers had shown that heating perfluoroalkyl carbanion solutions causes fluoride ion exchange to occur.[16] Various species were studied with respect to their NMR line widths on the carbon bearing the exchanging fluorine atom during heating (see section **2.2.2.1**). As previous work had been carried out in tetraglyme, it was decided that a repeat of the study should be carried out for **(1)** in DMF to see if the exchange profile differed.

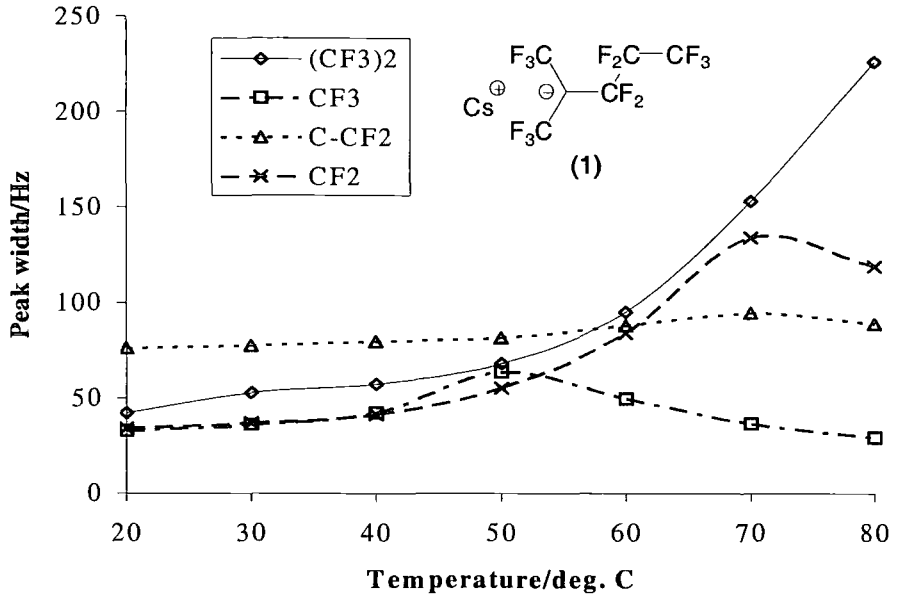


Figure 2.12 ^{19}F NMR line widths of **(1)** in DMF at various temperatures

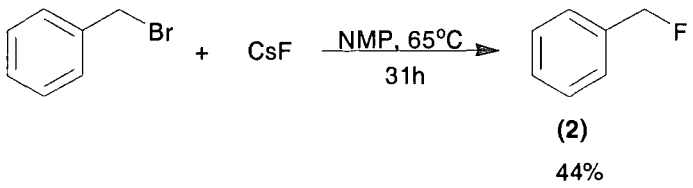
The graph above (Figure 2.12) shows the peak widths of **(1)** during a ^{19}F VT NMR experiment run in DMF-d_7. As the carbanion approaches the temperature where fluorine exchange becomes significant on the NMR timescale, the peaks broaden and shift. The broadening is indicative of the amount of exchange which is taking place. The rate of exchange is extremely low until the temperature rises to around 50°C, although the difluoromethylene peak bearing the exchanging fluorine is significantly broad even at 20°C, indicating that the fluorine atoms on this group are somewhat labile. The graph indicates that exchange of fluoride ion increases as the temperature is raised; the peaks shift toward a value between the resonances of the carbanion and the perfluoroalkene.

From this study, it is clear that reactions should be carried out at elevated temperature for there to be any likelihood of fluorination occurring as the major reaction pathway. At lower temperatures, the concentration of fluoride ion is likely to be too low, and perfluoroalkylation would be expected as the preferred reaction. A temperature of 65°C was therefore chosen as a compromise between increasing the

quantity of available fluoride ion and minimising the loss of highly volatile perfluoro(2-methylpent-2-ene) due to evaporation.

2.3.3 Reactions of Perfluoro(2-methylpentan-2-yl)caesium

A. Reaction at Primary sp^3 Carbon Sites

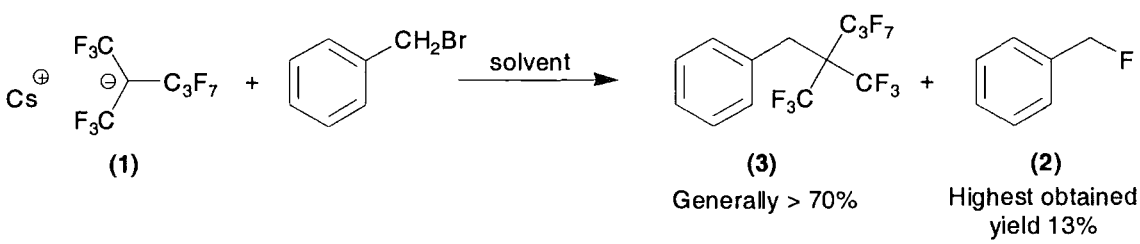


Scheme 2.18 Control reaction: Fluorination of benzyl bromide with caesium fluoride

Table 2.3 Yield of **(2)** in control reaction

Yield of (2)	
System	**Yield/%**
CsF	44

A control reaction was run for comparison purposes, with CsF in NMP as the fluorination system (Scheme 2.18, Table 2.3). Benzyl fluoride **(2)** was synthesised in 44% (NMR) yield, and this was used as the target figure for the carbanion system (Scheme 2.19).



Scheme 2.19 Fluorination of benzyl bromide with **(1)**

As previous work had been carried out with benzyl bromide (with the aim of optimising the reaction for perfluoroalkylation), it was decided to attempt to optimise the reaction conditions for the fluorination of this substrate. A solution of the carbanion **(1)** was prepared and transferred then to an appropriate reaction apparatus. The substrate was then added and after an appropriate time the reaction products were determined by quantitative ^{19}F NMR in relation to a known mass of reference material. Previous work had shown that the predominant species formed was the perfluoroalkylated product, [(perfluoro-2-methylpentan-2-yl)methyl]benzene **(3)** and that this could be extracted in moderate yield by the use of an aqueous work up followed by continuous extraction with a suitable perfluorocarbon solvent (e.g. PP2, perfluoro(methylcyclohexane)). Reactions were run overnight with the reactive benzyl bromide, ^{19}F NMR measurements confirming the consumption of the carbanion. The perfluoroalkylated product was identified by comparison of the ^{19}F and ^{1}H NMR and MS spectra with literature data.[27]

- Effect of Temperature on Yield of Fluorination

Table 2.4 Effect of temperature on the yield of **(2)**

Effect of temperature on yield of (2)	
Temperature of reaction/°C	**Yield/%**
25	1.5
65	3
Carbanion solution preheated to 65°C prior to addition of electrophile	13

Increasing the reaction temperature from 25°C to 65°C caused a minor increase in the yield of **(2)** (from 1.5% to 3%), but a significant increase was noted when the carbanion solution was preheated to 65°C prior to addition of the substrate (Table 2.4). In this case, the yield of **(2)** rose to 13%, the highest obtained yield in this work. Unfortunately, the major product was always the perfluoroalkylated benzyl compound, **(3)**. These results agree with the VT NMR study shown above, in that there is clearly a higher concentration of fluoride ion available in solution when the

reaction is run at a higher temperature, producing an increased yield of the selectively fluorinated product.

- Effect of Concentration on the Yield of Fluorination

Table 2.5 Effect of concentration on the yield of **(2)**

Effect of concentration on yield of (2) with carbanion solution preheated to 65°C	
Concentration/M	**Yield/%**
1	13
0.06	trace

The concentration of the reaction was varied from 0.06M to 1.00M. At the lower concentration, benzyl bromide was added slowly to the preheated carbanion solution at 65°C, the aim being to allow the equilibrium for the production of free fluoride ion to establish itself at the higher temperature. Only a very low yield of the fluoride **(2)** was produced under these conditions with the perfluoroalkylated compound **(3)** being the major product (Table 2.5). This indicates that the rate of production of fluoride ion and therefore the effective concentration at any one time was very low, thus the only nucleophile present in any quantity was the carbanion.

- Effect of Solvent on the Yield of Fluorination

The effect of the reaction solvent on the yield of **(2)** synthesised was assessed for various aprotic solvents (DMF, NMP, sulfolane, tetraglyme). In all cases, the yields were essentially the same within experimental error. No solvent effect was observed, even with tetraglyme, a reaction medium which is rather different to the three dipolar aprotic solvents also studied.

Conclusion after Attempted Optimisation of Benzyl Bromide Reaction

In all cases, the major product formed was the perfluoroalkylated methylbenzene **(3)**. NMR yields for this material varied but were generally above

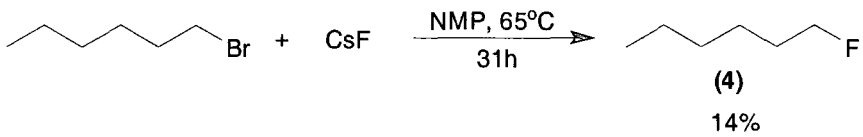
70%, whilst isolated yields were between 30% and 50%, mostly depending upon the length of time that the continuous extraction was run for.

Table 2.6 Comparison of optimised yield of (2) with control reaction

Yield of (2)	
System	**Yield/%**
CsF	44
Perfluoro(2-methylpentan-2-l)caesium	13 (highest obtained)

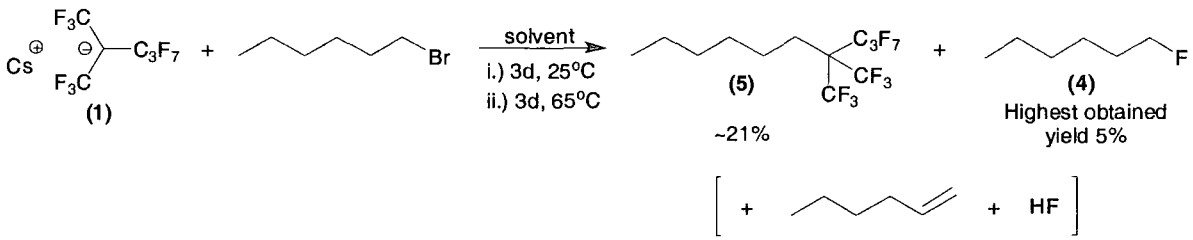
It would appear that due to association with the carbanion, the fluoride ion produced from carbanion (**1**) is significantly less reactive than that from CsF, despite the predicted enhanced solubility. For benzyl bromide at least, anhydrous CsF is a considerably more effective fluorinating agent than (**1**) (Table 2.6).

After the optimised conditions had been set, the reaction was repeated with a much less reactive substrate, 1-bromohexane.



Scheme 2.20 Control reaction: Fluorination of 1-bromohexane with caesium fluoride

Once again, a control reaction with CsF in NMP was run for comparison purposes (Scheme 2.20). As predicted, the yield of 1-fluorohexane (**4**) was significantly lower than with benzyl bromide due to the nature of the substrate.



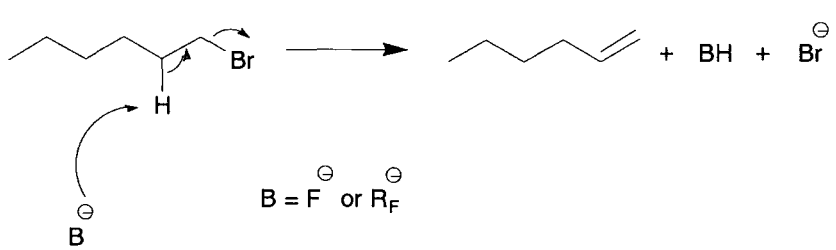
Scheme 2.21 Fluorination of 1-bromohexane with (**1**)

Table 2.7 Effect of temperature on the yield of (4)

Effect of temperature on yield of (4)	
Temperature/°C	**Yield/%**
25	0
65	5

As a minor change in product distribution occurred with a change in temperature for the reaction with benzyl bromide, the optimised reaction conditions was tested by performing reactions at both 25°C and 65°C (Scheme 2.21, Table 2.7). Little reaction was observed at 25°C, even over an extended period (two weeks). Reaction at 65°C did proceed quite readily, although longer reaction times of a few days were needed for complete consumption of the carbanion (**1**). On examination of the ^{19}F NMR spectrum of the reaction mixture, it became evident that the reaction was rather complex. Thus after three days at 25°C and three days at 65°C, the reaction gave a 48% yield of HF, a 21% yield of 4,4-di(trifluoromethyl)-1,1,1,2,2,3,3-heptafluorodecane (**5**) and a 5% yield of the desired product (**4**). Other unidentified fluorinated products were present in small quantities. Reaction proceeded equally well in DMF and NMP, with little change in product distribution being observed.

The reaction was subjected to aqueous work-up as before and extracted into PP2. Removal of the perfluorocarbon solvent yielded a dark brown oil with a complex NMR spectrum. Preparative scale GC allowed the isolation of the major product as the perfluoroalkylated material (**5**).



Scheme 2.22 Possible elimination pathway for 1-bromohexane

Once again, the carbanion system was unable to fluorinate the substrate to a high degree and even perfluoroalkylation presented considerable difficulties. The most likely explanation for the more complex reaction is attack at one of the 2-H positions by either fluoride or carbanion acting as a base, leading to elimination of bromide and formation of hex-1-ene (Scheme 2.22). Although the difference was not as pronounced as with benzyl bromide, it is clear that in this case also, CsF is a more effective fluorinating agent than the carbanion **(1)**.

- Effect of Leaving Group on the Yield of Fluorination

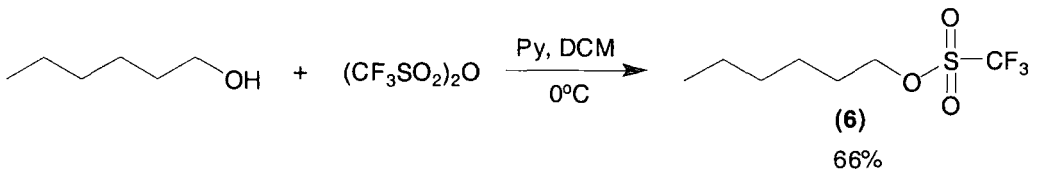
Following the initial paper by Chambers detailing the use of perfluoroalkyl carbanions as fluorinating and perfluoroalkylating agents,[16] attempts were made to discern the effect of the leaving group on the electrophile. The paper reported that fluorination was the preferred reaction pathway at carbonyl halide centres, whereas, under the conditions employed, perfluoroalkylation reactions predominated with alkyl halides. This effect can be attributed to the fact that the sp^2 hybridised electrophilic centre of the carbonyl halide is considerably harder than that at, for example, methyl iodide.

The hard and soft acids and bases principle (HSAB) defines hard and soft Lewis acids (i.e. electrophiles) and bases (i.e. nucleophiles) as follows:[29-32] A hard acid generally has a small acceptor atom, tightly bound electrons and a significant degree of positive charge. A soft acid centre will tend to be of a larger size with more diffuse, less tightly bound electron density. For bases, hardness is equated with highly electronegative donor atoms of low polarisability, whereas a soft base tends to be rather polarisable and less electronegative. The theory goes on to state that hard acids will react preferentially with hard bases, and soft acids with soft bases.

Applying this theory to the reaction of the perfluorinated carbanion with the carbonyl halide, we can see that the carbanion is a relatively soft nucleophile, whilst the carbonyl halide electrophilic centre is distinctly harder in character. Thus, the reaction does not appear to be particularly favourable. However, fluoride is a hard nucleophile and can react readily with the carbonyl system. To mimic these effects to some extent in an aliphatic system, the leaving group employed was changed to triflate. Alkyl triflates possess hard electrophilic centres and are extremely reactive

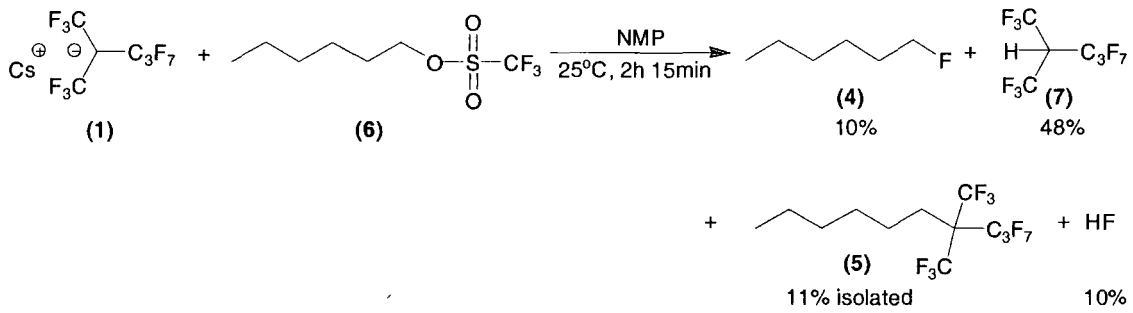
towards nucleophiles. Reaction of such a compound with **(1)** should allow the effect, if any, of a harder leaving group to be assessed. Clearly, the desired and predicted outcome is that the yield of fluorination will increase relative to the bromoalkane case.

Thus, 1-triflatohexane **(6)** was synthesised by a literature procedure[33] in 66% yield from the parent alcohol (Scheme 2.23).



Scheme 2.23 Synthesis of **(6)**

The product was stored briefly at –20°C and then used in the next reaction.



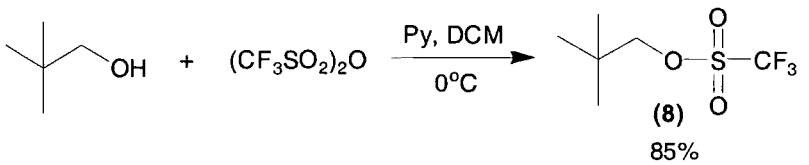
Scheme 2.24 Fluorination of **(6)** with **(1)**

Reaction of the triflate **(6)** with **(1)** yielded roughly 10% of 1-fluorohexane **(4)** in 2 ¼ hours (Scheme 2.24), essentially double the highest yield achieved with 1-bromooctane in a much shorter period of time, but, as observed with the bromoalkane system, elimination products predominated. The 2-H-perfluoroalkane, 1,1,1,2,2,3,3,5,5,5-decafluoro-4-trifluoromethyl-pentane **(7)**, was present in 48%

yield, identified by comparison with literature data,[9] and a 10% yield of HF was detected.

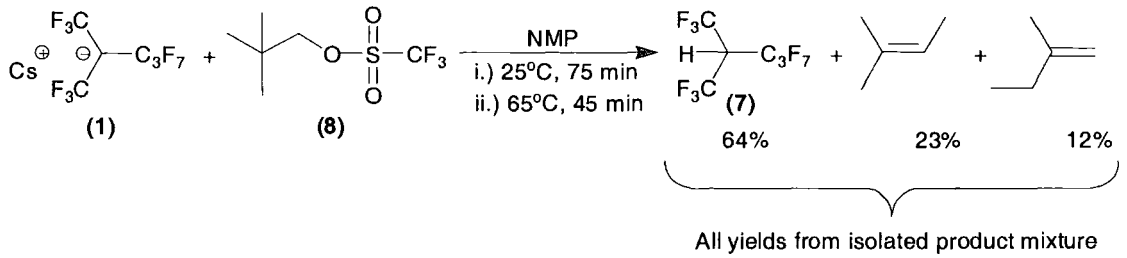
To some extent, this result bears out the prediction made by HSAB theory that the harder electrophilic carbon centre of the triflate will react preferentially with fluoride as the hardest nucleophile present in the reaction system. However, the distinction was nowhere near as large as was hoped for, and the favoured reaction pathway was that of elimination. The massively more labile triflate leaving group, when compared with bromide, will favour an elimination mechanism that will be someway towards E_1 rather than E_2-like in nature. Given that this would increase the acidity of the beta-proton on the triflate, it would allow deprotonation to occur via attack of the perfluoroalkyl carbanion **(1)** as this would be present in much higher concentration than fluoride. A slower deprotonation step would allow more fluoride to be generated from the equilibrium between the carbanion and the alkene/fluoride ion, thus forming more HF in the product mixture.

A further primary system that was studied was 1-triflato-2,2-dimethylpropane **(8)**, synthesised as below by a literature procedure (Scheme 2.25),[33] where β-elimination is not possible.



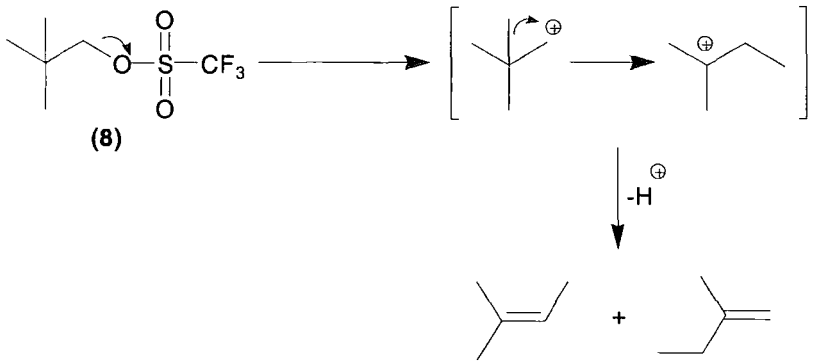
Scheme 2.25 Synthesis of **(8)**

The product was stored briefly at –20°C and then used in the next reaction.



Scheme 2.26 Attempted fluorination of **(8)** with **(1)**

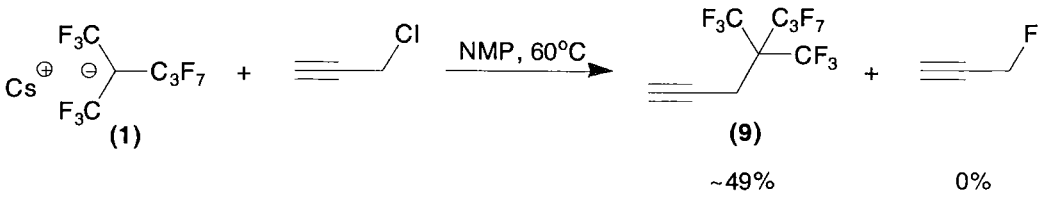
Again, this is a primary substrate, but it is one with a very high steric hindrance to S_N2 attack and a notable propensity for elimination-rearrangement processes due to the lack of protons β to the leaving group. Surprisingly, after 1¼h at 25°C, no reaction was observed. The reaction was then heated to 65°C for a further 45 minutes after which time the carbanion had been consumed (Scheme 2.26). No nucleophilic substitution products or HF were detected and the only fluorinated product was the 2-H-perfluoroalkane.



Scheme 2.27 Elimination-rearrangement pathway for the synthesis of alkene products from **(8)**

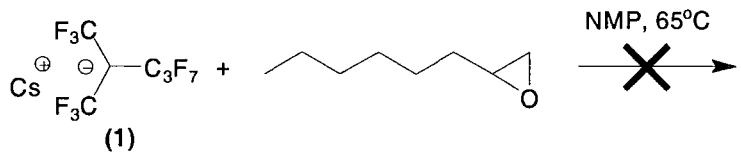
Vacuum transfer of the volatile materials gave a colourless liquid which contained compound **(7)** (64%), 2-methylbut-2-ene (23%) and 2-methylbut-1-ene (12%). The formation of the alkene products is rationalised above (Scheme 2.27). Unfortunately, some of the 2-H perfluoroalkene **(7)** appeared to have been lost during vacuum transfer as no other fluorinated materials were detected in the residue.

Chambers reported the reaction of carbanion (**1**) with 1-iodoprop-2-ene to produce the perfluoroalkylated product.[16] The reaction was repeated with 1-chloroprop-2-yne to see if any fluorination could be detected with this extremely reactive system (Scheme 2.28).



Scheme 2.28 Attempted fluorination of 1-chloroprop-2-yne with (**1**)

Little reaction occurred after 24h at 25°C, and only after a further 18h at 65°C was appreciable consumption of the carbanion (**1**) observed. Analysis of the reaction mixture and subsequent product isolation by vacuum transfer and preparative scale GC showed the major product to be 5,5,6,6,7,7,7-heptafluoro-4,4-bis(trifluoromethyl)hept-1-yne (**9**) with a yield of approximately 49%. It is surprising that the propargyl system did not show higher reactivity as it was expected to undergo an almost S_N1 type process due to the resonance stabilised cation generated during reaction. Although the monofluorinated product, 1-fluoroprop-2-yne, would have been extremely volatile, one would still expect to see a trace of its rather distinctive ^{19}F NMR peak in the reaction mixture had it been formed.



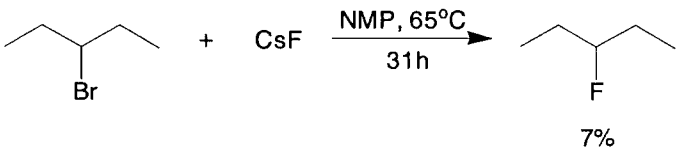
Scheme 2.29 Attempted reaction of (**1**) with 1,2-epoxyoctane

Several attempts were made to ring-open an epoxide, namely 1,2-epoxyoctane, with (**1**). It was hoped that either a fluoroalcohol or a perfluoroalkylated alcohol (or rather their caesium salts prior to acidic work-up) would be produced. Unfortunately, no reaction was observed even under forcing conditions (Scheme 2.29). The lack of

reactivity is perhaps attributable to steric factors, but the inactivity of fluoride ion is surprising. It may be that, as above, the activity of the fluoride ion is reduced due to association with the carbanion.

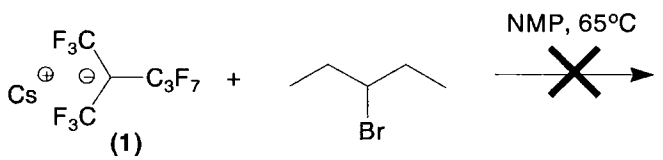
B. Reaction at Secondary sp^3 Carbon Sites

In order to test the applicability of the fluorination system to a range of substrates, an attempt was made to fluorinate a secondary alkyl bromide, 3-bromopentane.



Scheme 2.30 Control reaction: Fluorination of 3-bromopentane with caesium fluoride

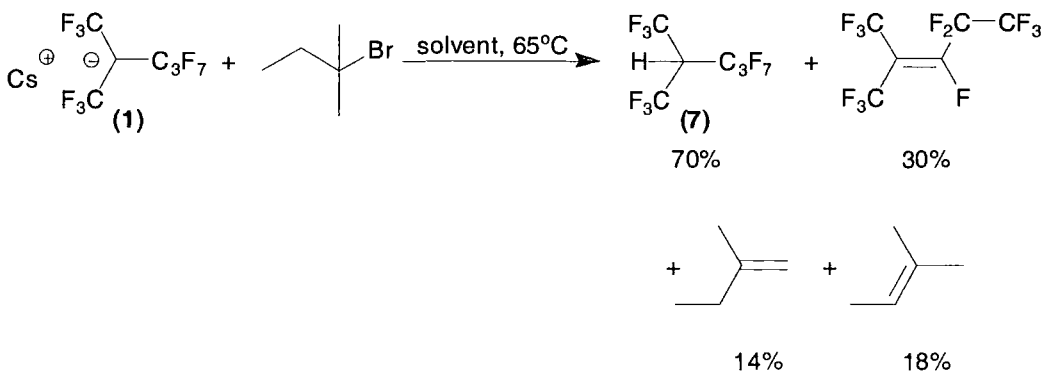
A control reaction with CsF in NMP was run for comparison purposes (Scheme 2.30). The less reactive secondary system produced only a low yield of the fluorinated product.



Scheme 2.31 Attempted fluorination of 3-bromopentane with **(1)**

Reaction with a secondary bromide was attempted with 3-bromopentane as the substrate (Scheme 2.31). Unfortunately, no reaction was detected even after extended periods at elevated temperatures, nor was there any sign of the 2-H-perfluoroalkane **(7)** or HF that would indicate an elimination process. The carbanion ^{19}F NMR spectrum remained essentially unchanged. Again, the carbanion **(1)** was shown to be less reactive than the reference CsF/NMP system.

C. Reaction at Tertiary sp^3 Carbon Sites



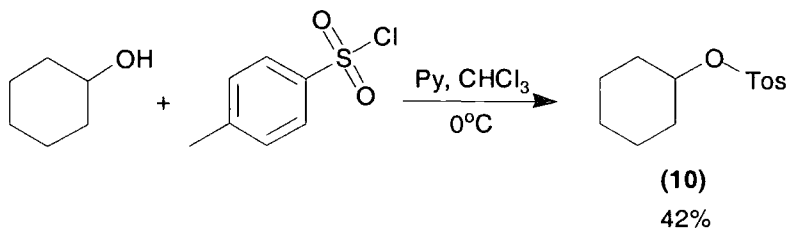
Scheme 2.32 Attempted fluorination of 2-bromo-2-methylbutane with **(1)**

The reaction of **(1)** with a tertiary bromide, 2-bromo-2-methylbutane was also studied (Scheme 2.32). Freshly double-distilled material (to eliminate HBr contamination) was used with the following results: No reaction occurred at 25°C, although reaction at 65°C for 24 hours resulted intotal consumption of the carbanion. Vacuum transfer of the volatile fractions gave a colourless liquid which contained perfluoro(2-methylpent-2-ene) and 2-H-perfluoroalkene **(7)** as the only fluorinated products, together with 2-methylbut-2-ene and 2-methylbut-1-ene.

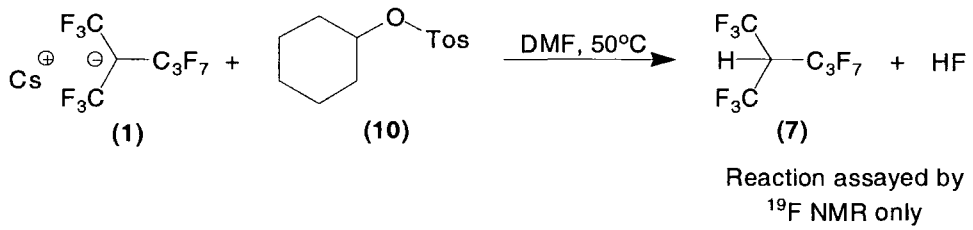
The steric requirements imposed by this electrophile are significant and both the lack of access to the electrophilic carbon and the relief of steric crowding during bromide elimination contribute to the observed preference for elimination over substitution of any sort. It would appear that decomposition followed the expected E_1-like pathway as a significant quantity of 2-H-perfluoroalkane **(7)** was formed, indicating that proton loss was not rate limiting. As proton loss was rapid there would have been very little time between the available fluoride ion forming HF and the reaction of the rest of the protons with the carbanion. Slow proton loss, i.e. rate limiting and hence E_2-like would have allowed the generation of a higher equilibrium concentration of fluoride ion during deprotonation with a consequently higher yield of HF.

D. Reaction at Alicyclic sp^3 Carbon Sites

1-Cyclohexyl-*p*-toluenesulfonate **(10)** was synthesised using a literature procedure as shown below (Scheme 2.33),[34] and purified by column chromatography before being used in the next reaction.



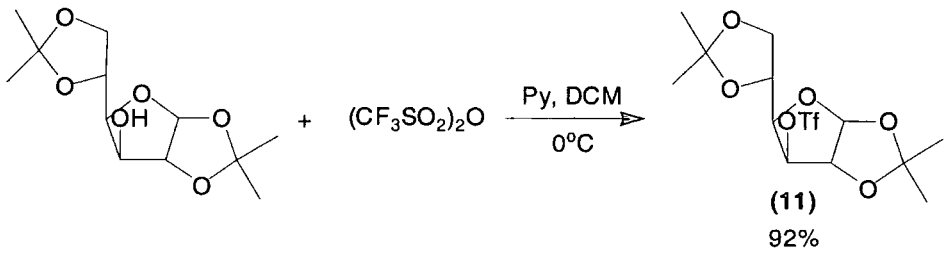
Scheme 2.33 Synthesis of **(10)**



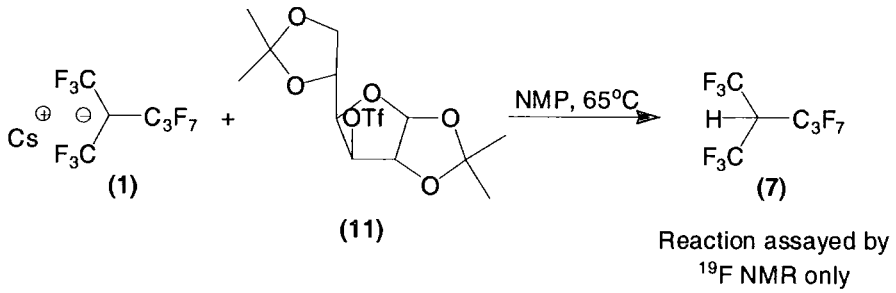
Scheme 2.34 Attempted fluorination of **(10)** with **(1)**

The tosylate **(10)** was reacted with carbanion **(1)** at 25°C (Scheme 2.34), but following aqueous work-up the reaction yielded unreacted tosylate and *p*-toluenesulfonic acid as the only identifiable products. When the reaction was repeated at 50°C, there were no peaks attributable to a perfluoroalkylated cyclohexane or fluorocyclohexane and the only identifiable fluorinated product in the reaction mixture was HF. The volatile materials were removed by vacuum transfer to yield a colourless liquid, containing the 2-H-perfluoroalkane **(7)** as the only fluorinated product. Clearly, the substrate is not as reactive as expected towards the carbanion system. Elimination seems to predominate at higher temperatures, which is not surprising given the good leaving group on the secondary site and the basic nature of the carbanion and fluoride present.

Diacetone-d-glucose triflate (11) was synthesised by a literature procedure in high yield as shown below (Scheme 2.35):[35]



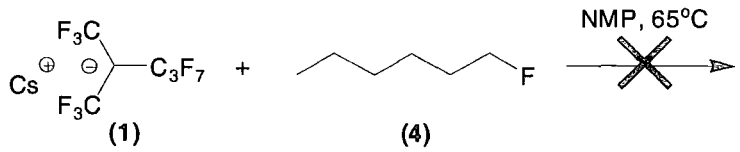
Scheme 2.35 Synthesis of **(11)**



Scheme 2.36 Attempted fluorination of **(11)** with **(1)**

The triflate **(11)** was reacted with **(1)** at 20°C for one hour (Scheme 2.36), but in distinct contrast to the other triflate systems that had been investigated, no reaction was detected. Heating to 65°C for a further hour produced a decrease in the concentration of carbanion **(1)**, although a considerable quantity was still present in the reaction mixture. Following vacuum transfer of the volatile fractions, the only identifiable fluorinated products were the 2-H-perfluoroalkane **(7)** (34%) and perfluoro(2-methylpent-2-ene) (62%). A very small peak at δ -133 ppm, possibly a fluorinated sugar, was not isolated. Again, it would appear that the steric requirements of the electrophile were too restrictive to allow anything other than deprotonation as the major reaction pathway.

E. Control Reaction with 1-Fluorohexane

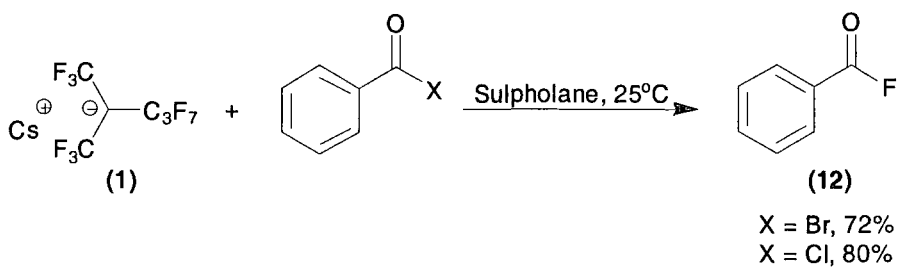


Scheme 2.37 Control reaction: Attempted reaction of 1-fluorohexane with **(1)**

The final reaction carried out with an sp^3 substrate was a control reaction on 1-fluorohexane **(4)** (Scheme 2.37). It was postulated that the monofluorinated products (e.g. **(4)** from 1-bromohexane) might be reacting with the carbanion **(1)** or fluoride ion to yield elimination products. This would explain the low yields of monofluorinated products versus elimination products. As expected however, no reaction occurred with the somewhat unreactive compound **(4)**. This indicates that the low yield of monofluorinated products is a characteristic of the system, rather than due to decomposition of product material.

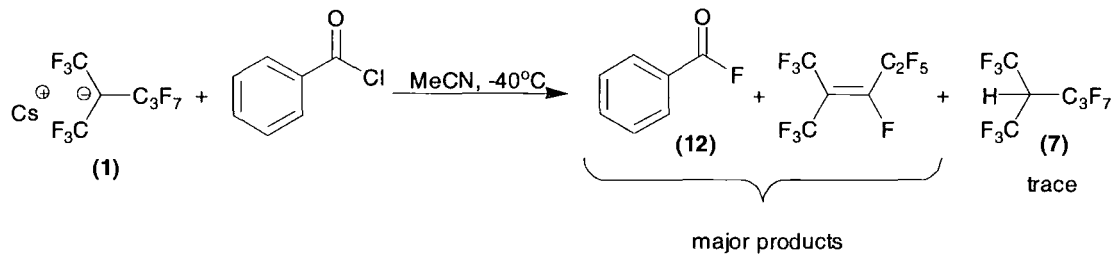
F. Reaction at sp^2 Carbon Sites

The reaction of carbanion **(1)** with ethanoyl chloride has been reported previously as producing ethanoyl fluoride as the only substitution product, although the yield was not reported.[16] This is one of the only examples of fluorination occurring in preference to perfluoroalkylation with this system and is attributed to the hardness of the carbonyl centre.



Scheme 2.38 Fluorination of benzoyl halides with **(1)**

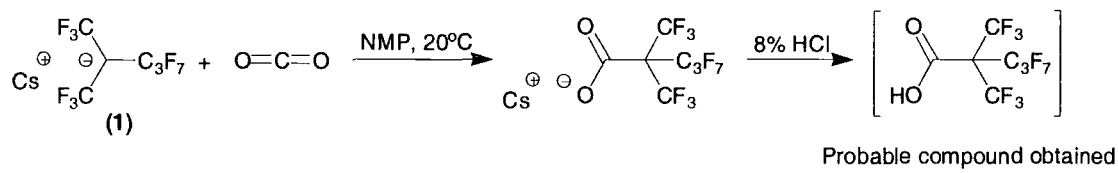
With the exception of benzyl bromide, the benzoyl halides were the only halide substrates which did not require heating as the reactions proceeded rapidly at 25°C (Scheme 2.38). This can be attributed to the operation of a tetrahedral mechanism, as opposed to S_N1 or S_N2; here the electron shift in the rate determining step occurs in the π rather than the σ system and so requires less energy. There are also rate enhancements from the more electrophilic carbon and the trigonal geometry of the system (less steric hindrance to an attacking nucleophile). Reaction of either halide with the carbanion **(1)** at 25°C gave benzoyl fluoride **(12)** in high yield: 80% for benzoyl chloride and 72% for benzoyl bromide by ^{19}F NMR. No perfluoroalkylation was observed.



Scheme 2.39 Attempted perfluoroalkylation of benzoyl chloride with **(1)**

Even at -40°C, fluorination predominated with no competing perfluoroalkylation (Scheme 2.39). The influence of the carbonyl group was pronounced as reaction was still rapid at low temperature. This again appears to lend weight to the arguments predicted by HSAB theory for this system. The harder centre in this case caused fluorination to occur exclusively.

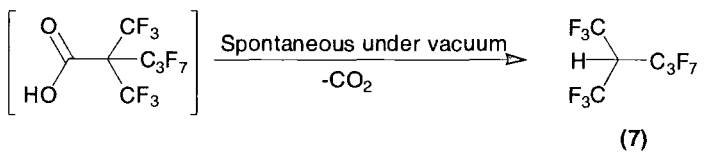
G. Attempted Reaction with Carbon Dioxide



Scheme 2.40 Attempted reaction of **(1)** with carbon dioxide

Attempts were made to synthesise 3,3,4,4,5,5,5-Heptafluoro-2,2-bis-trifluoromethyl-pentanoic acid by reaction of carbanion (**1**) with carbon dioxide (Scheme 2.40). Similar reactions have been reported previously.[36] Carbon dioxide was passed through a solution of (**1**) for several hours, resulting in the formation of a white precipitate. After removal of the volatile material under vacuum, the residual off-white solid was dissolved in water and acidified with 8% HCl to decompose the caesium salt. The aqueous components were then carefully removed under vacuum to yield a pale green solid, suggesting possible metal ion contamination from the needle used to bubble the CO_2 into the reaction.

On vacuum sublimation, a small quantity of pale orange crystals was isolated and these gave a pH of less than one with universal indicator paper. The crystals were volatile and extremely deliquescent, short exposure to the atmosphere (seconds) led to the crystals appearing to become visibly moist. Even careful drying under vacuum resulted in almost complete loss of product within one minute.



(7)

Postulated decomposition pathway

Scheme 2.41 Postulated decomposition pathway for perfluorinated careboxylic acid

The product appeared to be unstable, probably losing carbon dioxide to form the 2-H compound (**7**) (Scheme 2.41) and unfortunately no analytical data could be obtained. The highly acidic indication shown by the indicator paper would suggest that the perfluoroalkyl carboxylic acid was obtained, as this would have a very low pH. It is highly likely that the failure to produce an isolable compound was due to the steric requirements of the system.

2.4 Conclusions

Following the work carried out in this chapter, it has been conclusively shown that perfluoro(2-methylpentan-2-yl)caesium (**1**) is not an effective fluorinating agent.

There are exceptions to the rule, as with the carbonyl centred electrophiles, but they are few and far between and can be accomplished with cheaper and easier synthetic methodologies. It is unlikely that other perfluoroalkyl carbanions will be useful as **(1)** is one of the less stable species[16] and yet it does not undergo fluoride exchange readily enough to be synthetically useful.

The system does have some use as a perfluoralkylating agent for electrophiles lacking acidic protons however. Reactions performed with haloalkanes, and the corresponding triflates, gave elimination or perfluoroalkylation as the major reaction pathways. This is attributed to several factors: The basicity of the fluoride ion and the perfluoroalkyl carbanion system, the low availability of fluoride ion in the system and the softness of the electrophile in the case of the halide systems. Unfortunately, it was demonstrated beyond any doubt that the carbanion **(1)** is a less active source of fluoride ion than CsF when used in a conventional dipolar aprotic solvent, such as NMP.

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3. Room Temperature Ionic Liquids as a Medium for Fluorination with Caesium Fluoride

3.1 Green Chemistry

There has been a recent surge of interest in so-called "green chemistry", that is to say chemistry which is environmentally benign. The 1999 launch of an RSC journal, Green Chemistry, dedicated to the subject serves to underline the profound influence of this field of chemistry. Steps taken to minimise environmental impact have included the generation of hazardous reagents *in-situ*, the use of alternative less hazardous materials and the use of inert, environmentally acceptable solvents. Perhaps the three best known examples of this last methodology are fluorous solvents, super critical carbon dioxide and Room Temperature Ionic Liquids (RTILs).

Fluorous solvent chemistry has made some impact on the laboratory scale (Figure 3.1), particularly in the fields of combinatorial chemistry and fluorous-phase synthesis (essentially derived from phase-transfer chemistry). A recent issue of Tetrahedron was dedicated to this relatively new field of work, and the lead[1] and following articles provide a brief introduction to the area and the technique is illustrated schematically below.

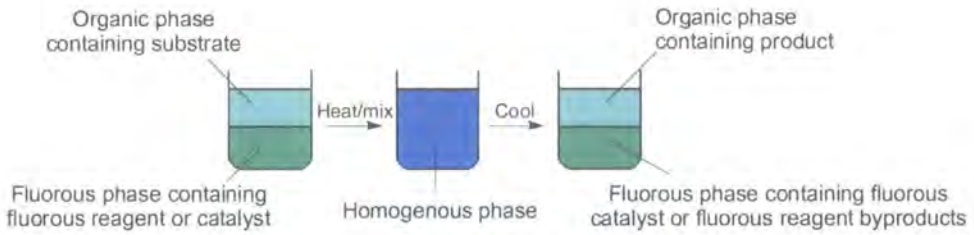


Figure 3.1 Fluorous biphasic chemistry

The advantage of this technique lies in the easy separation of products and reagents due to the peculiar solubility characteristics of fluorocarbon materials. Disadvantages are the requirement for the synthesis of special "fluorous" reagents (generally similar to conventional reagents, but with perfluoroalkyl chains attached to confer solubility in the fluorous phase) and catalysts, and the very high cost of such

solvent systems. This, coupled with their often significant vapour pressure has led to a lack of interest on the industrial scale. The perfluorocarbon materials used as solvents are generally small molecules with significant global warming potential, so their environmental impact may, in fact, be significant after all.

Supercritical carbon dioxide chemistry[2] has conversely made more of an impact in industry, for example, processes to produce PTFE[3] and to extract caffeine from coffee[4] are already running at plant scale. Laboratory scale chemistry with this solvent is possible, but is limited by the high pressures required to generate the super critical phase. Biphasic reactions, where the carbon dioxide is present as a supercritical phase and then vented to leave the products in the other phase are becoming popular. The technique shares many principles with the fluorous-phase chemistry outlined above. The supercritical solvent itself is of course safe to release into the environment.

3.2 Introduction to Room Temperature Ionic Liquids

Ionic Liquids were initially developed in the 1940s as fluids for electroplating baths and battery electrolytes, amongst other uses.[5] They are salts, comprised of an organic cation and an inorganic or organic anion, which are liquid at or around room temperature (although some systems still considered to be a part of this class of materials have melting points that are significantly above room temperature). In general, these materials are polar,[6] moderately viscous liquids with almost no measurable vapour pressure.[7, 8]

The early work was often carried out with chloroaluminate based materials, i.e. those containing $AlCl_4^-$ anions but the resulting RTILs were highly moisture sensitive and exhibited strong Lewis acid behaviour. These systems were often difficult to handle, frequently requiring manipulation in the inert atmosphere of a glove box or Schlenk apparatus. However, more recent RTILs have used more stable anions such as BF_4^- or PF_6^- (Figure 3.2),[9] whilst very new work has resulted in RTILs with organic acid anions, for example lactate, or cations derived from amino acids thus allowing the synthesis of chiral ionic liquids (Figure 3.3).[10]

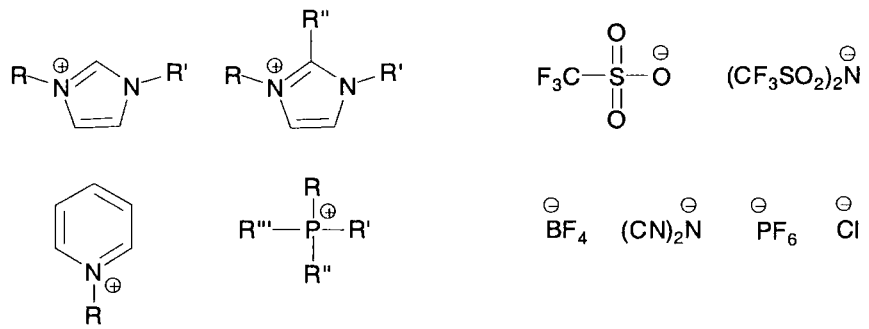


Figure 3.2 Common RTIL cations and anions

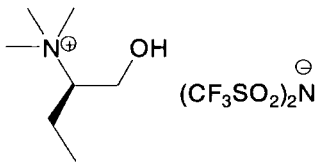


Figure 3.3 Chiral RTIL, mp ~ 18°C

The cations most frequently encountered are based on imidazolium or pyridinium moieties although other heterocyclic systems, alkylammonium and phosphonium salts are becoming more widespread (Figure 3.2). A major advantage of these systems is the ability to tune the properties of the RTIL by varying the pendant groups on the cation, as well as by changing the anion.[8]

A simple example of this is shown below – it is possible to tune the hydrophilicity of the N-alkyl-N-methylimidazolium RTILs, where alkyl varies between butyl and octyl, by changing the anion (Figure 3.4). The PF_6^- RTILs are fairly hydrophobic and immiscible with water, whilst the Cl^- derivatives are completely miscible. The BF_4^- analogues exhibit behaviour between these two extremes, solubility depending upon the alkyl chain length.[11]

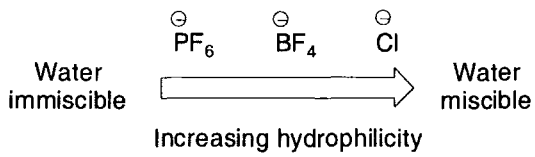
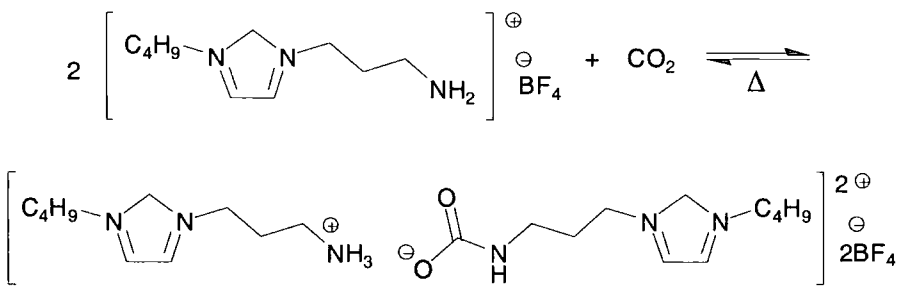


Figure 3.4 Hydrophilicity of BMIM RTILs

The ability to tailor the properties of the RTIL is also reflected by a trend of melting point depression with increasing hydrocarbon chain length, although the situation is more complex than it at first appears. For the N-alkyl-N'-methylimidazolium chlorides, the melting point decreases markedly from R = methyl (~126°C) to R = propyl (~62°C). This can be attributed to the longer alkyl chains causing difficulty in crystal packing and thereby introducing disorder into the system. However, for R = butyl, the melting point increases slightly to 67°C. For considerably longer alkyl chains (R = octyl in the case of the N-alkyl-N'-methylimidazolium hexafluorophosphates) the melting points begin to rise significantly. It is likely that distinct hydrocarbon domains are formed by the alkyl chains, thus leading to a more ordered layer-type structure.[12, 13]

A wide range of systems has now been synthesised with many combinations of cations and anions possible. This highlights the interesting possibility of theoretical modelling to produce task specific RTILs. Indeed, the concept of RTILs tailored for a specific application has already been proven at a basic level.



Scheme 3.1 RTIL tailored for reversible carbon dioxide capture

The above scheme illustrates the use of an RTIL designed specifically to reversibly capture CO_2 (Scheme 3.1). The reaction cycle was demonstrated over several cycles with no loss of activity up to a level close to the theoretical maximum uptake.[14] Other tailored systems, e.g. for metal ion extraction[15] or fluorous synthesis[16] have also been developed.

3.3 RTILs as "Green Solvents"

RTILs have received a sudden resurgence of interest due to their possible use as "green solvents." This has occurred because their almost negligible vapour pressure, non-flammability and probable low toxicity[17] mean that they are likely to have a low environmental burden. A large body of work has already been carried out demonstrating the suitability of these materials as solvents for a wide range of reactions.[8, 18] A significant factor in the applicability of these materials to everyday synthesis is that it is claimed to be possible to recycle the RTIL in many of the reaction processes.

As RTILs are currently rather expensive (although this situation should change with increasing use, particularly from an industrial standpoint), recycling is necessary for any process to be cost-effective. The uses of RTILs as solvents are many and varied. They have been employed as solvents for synthetic procedures (see below), to enhance separation methods and even for techniques such as enzymatic chiral resolution.[19]

3.4 Literature Survey of Reactions in RTILs

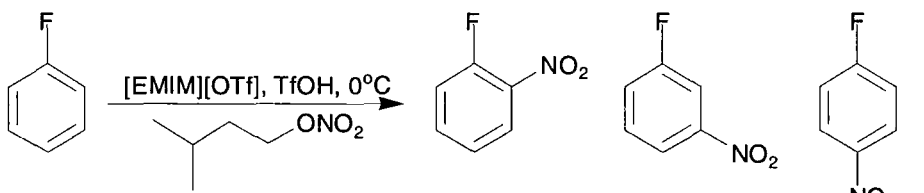
As has been alluded to, the range of reactions carried out in RTIL solvent systems is large and ever increasing. For the sake of brevity, this section will not aim to give a comprehensive coverage and the reader is directed to several of the more important reviews in this area.[5, 8, 18] A range of core synthetic techniques has now been demonstrated for RTIL systems, often with comparable or better results than with conventional solvent systems. A representative selection of papers is summarised below:

Much work has been carried out on the use of Lewis acidic chloroaluminate(III) ionic liquids as solvent-reagents for Friedel-Crafts type reactions,[18] i.e. Lewis acid catalysed electrophilic aromatic substitution. In simple alkylation processes, polyalkylation occurs readily, for example, reaction of benzene with chloroethane led to a mixture of mono- through to hexa-substituted alkylbenzenes. That the chloroaluminate(III) RTILs are significantly Lewis acidic is

demonstrated by the fact that it is possible to isolate solid $[CH_3CO]^+[AlCl_4]^-$ from the reaction of acetyl chloride with an *N*-ethyl-*N*-methylimidazolium RTIL, $[EMIM][AlCl_4]$.[20]

Wasserscheid and Gordon developed the first oligomerisation of ethene in a moisture stable ionic liquid.[21] Using a nickel catalyst in a range of N,*N*-methylalkylimidazolium hexafluorophosphate ionic liquids, they achieved the efficient conversion of ethene to higher alkenes with a higher efficiency and selectivity than in conventional solvents. Several papers describing the hydroformylation of alkenes and alkenones with a range of rhodium catalysts have also been published.[22-24]

With respect to this thesis, displacement reactions are of particular interest and several relevant papers have now been published covering both electrophilic and nucleophilic substitution processes. Laali reported the use of RTIL solvents in aromatic electrophilic nitrations with a range of nitrating agents (Scheme 3.2).[25] Generally high yields were reported and attempts were made to enable the effective re-use of the solvent, although in some cases the RTIL itself was nitrated. An important feature of such reactions was that only a stoichiometric equivalent of strong acid was needed, a requirement which can differ considerably from the traditional "mixed acid" HNO_3/H_2SO_4 system.



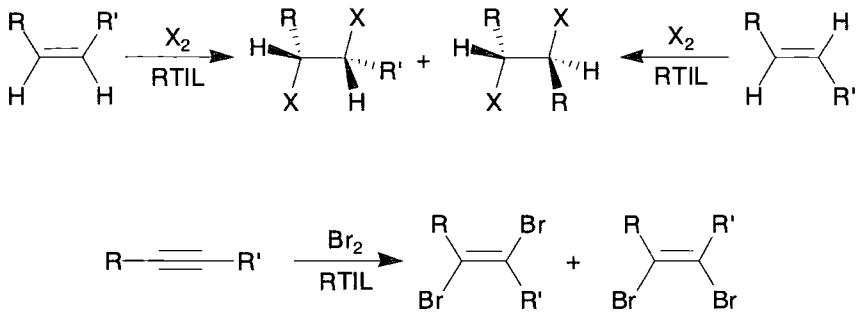
Isomer distribution *o* : *m* : p = *9.4 : 3.2 : 87.4*

Total GC yield 90%

Scheme 3.2 Nitration in RTIL solvent

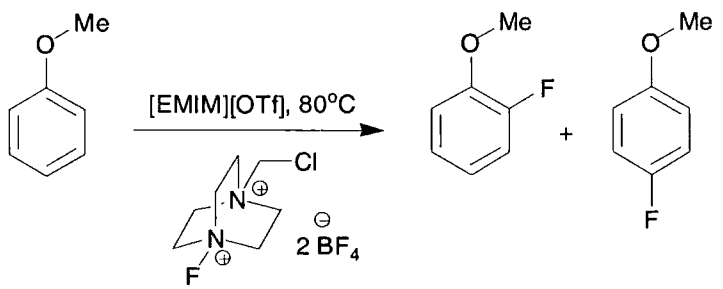
Both Chiappe[26] and Seddon[27] have reported electrophilic bromination and chlorination of alkenes with elemental halogens in RTIL systems although, again, some attack on the RTIL was observed (Scheme 3.3). High yields were observed

under mild conditions and a high degree of *anti*-stereoselectivity was noted in almost all cases. Interestingly, 1,2-bromochloro-substituted products were produced during chlorination with Cl_2 in [BMIM][Br]. The suggested reason for this was the formation of $BrCl_2^-$, which acts as a source of both electrophilic bromine and nucleophilic chlorine in reaction with the double bond.



Scheme 3.3 Electrophilic halogenation in RTIL solvent

Electrophilic fluorination has been reported by Laali[28] using Selectfluor ® in a range of imidazolium RTILs (Scheme 3.4). The substrates were aromatic systems ranging from electron rich (4-methylanisole) to electron deficient (nitrotoluene). Fluorination was observed in moderate yield for all but the electron deficient systems.



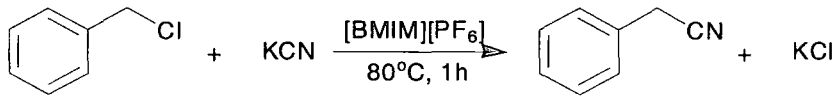
Isomer distribution *o* : *p* = 4.7 : 5.3

Total NMR yield 53%

Scheme 3.4 Electrophilic fluorination in RTIL solvent

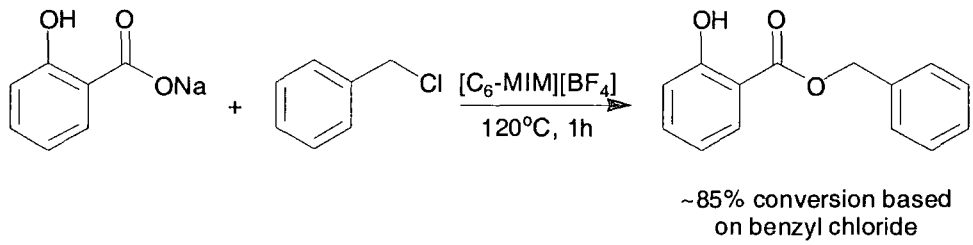
The paper that prompted the current research on RTILs was published in 2001 by Eckert and co-workers on the nucleophilic attack of cyanide ion on benzyl chloride (Scheme 3.5).[29] Under moderate conditions (80°C in [BMIM][PF_6], three fold excess

of KCN) the displacement reaction achieved complete conversion in under one hour. This paper indicated the suitability of [BMIM][PF_6] as a solvent system for reactions involving strong nucleophiles.



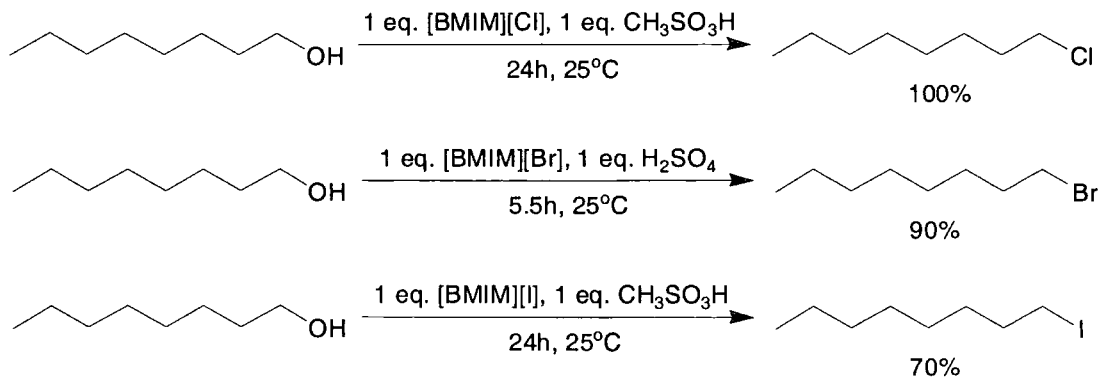
Scheme 3.5 Nucleophilic displacement by cyanide in RTIL solvent

A second paper involving non-halide nucleophilic substitution was published in 2002 by Judeh, involving the use of sodium salicylate as a nucleophilic species in an esterification reaction (Scheme 3.6).[30] The solvent in the example shown below was an RTIL bearing an N-hexyl group, [C_6-MIM][BF_4], and high conversion was attained rapidly.



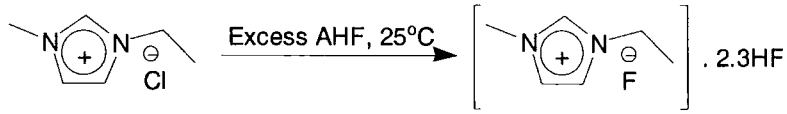
Scheme 3.6 Nucleophilic displacement by salicylate in RTIL solvent

Nucleophilic halogenation has received little attention until recently; the facile conversion of alcohols to alkyl halides was reported in 2001 by Ren, utilising [BMIM] halides under acidic conditions (one equivalent of hydrochloric, methanesulfonic or sulfuric acid added) to activate the hydroxyl group (Scheme 3.7).[31] Halogenation (Cl, Br and I) of octan-1-ol and a range of isomeric butanols was achieved in generally good yield.



Scheme 3.7 Use of halide RTILs as solvent-reagents for nucleophilic halogenation

It is interesting to note that fluorination was not considered here, and given the results and method employed, an earlier publication may be of interest: Hagiwara and co-workers reported the synthesis of N,*N*-ethylmethylimidazolium hydrofluoride with a formula of [EMIM].2.3HF (Scheme 3.8).[32]

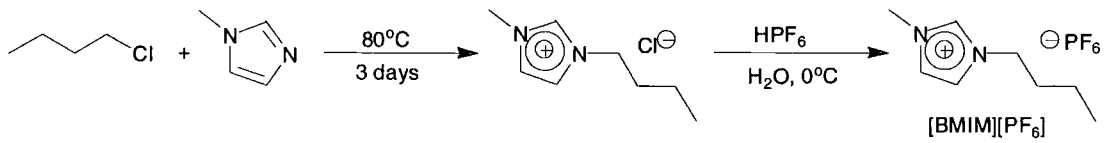


Scheme 3.8 Synthesis of an RTIL hydrofluoride

The liquid is acidic and apparently stable to air and it does not attack glass appreciably under ambient conditions. Considering the results detailed above, it would seem entirely possible that this system, in combination with aliphatic alcohols, would yield fluorinated products. The only downside to this potential stable fluorinating agent/solvent is the use of anhydrous HF for its synthesis. At this point it may be worth noting that the well known amine-HF fluorinating agents, for example $Et_3N.3HF$ and pyridine.$(HF)_x$, may be considered as RTILs. Although they were first developed long before the recognisable emergence of "green chemistry," they are ionic in nature, rather stable and comparable to the system described above.

3.5 RTIL Synthesis

In general, a two step approach is taken to the synthesis of ionic liquids:[33-35] Firstly a precursor material (usually a halide) is synthesised. This is then converted by metathesis of the counter ion or simple addition to give the RTIL. Generally the precursor is synthesised from the appropriate heterocyclic compound and an alkyl halide to yield an alkylated heterocyclic cation with a halide counter ion, for example in the synthesis of *N*,*N*-butylmethylimidazolium chloride (Scheme 3.9).

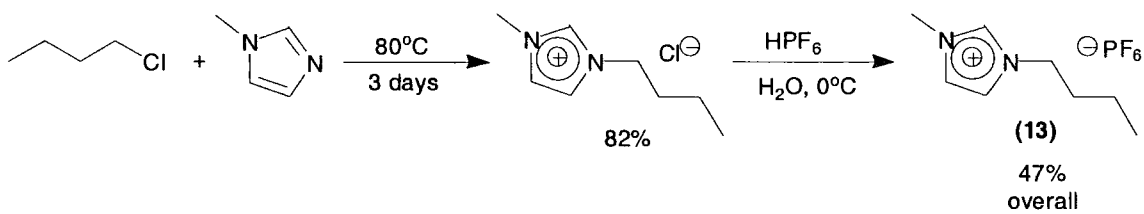


Scheme 3.9 Literature synthesis of [BMIM][PF_6]

This approach is used for the majority of known RTIL systems. The halide, after suitable purification, is dissolved in water and reacted with an appropriate source of the desired anion, for example hexafluorophosphoric acid to yield *N*,*N*-butylmethylimidazolium hexafluorophosphate, [BMIM][PF_6].

3.6 Results and Discussion

3.6.1 Synthesis of [BMIM][PF_6]



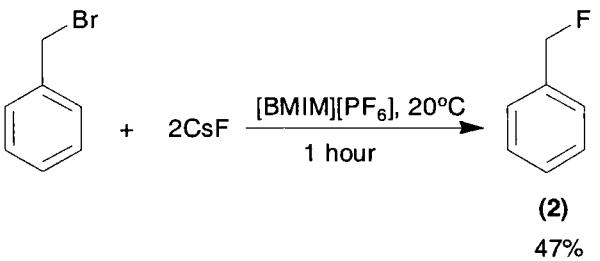
Scheme 3.10 Results of synthesis of **(13)**

Out of the wide variety of possible RTILs, [BMIM][PF_6] **(13)** was chosen for this study for several reasons: At the time of the project it was one of the few RTILs

widely available and its synthesis was relatively trivial, it had demonstrated suitability for nucleophilic displacement processes with a strong nucleophile[29] (cyanide ion) and it is hydrophobic (a factor considered beneficial for nucleophilic fluorination studies due to the desire for anhydrous conditions).

RTIL **(13)** was synthesised according to the method of Rogers *et al*,[34] whereby the precursor chloride salt was prepared by the reaction of neat 1-chlorobutane with 1-methylimidazole. The resulting low-melting solid was washed and then dissolved in water for metathesis with hexafluorophosphoric acid which was conducted in PTFE apparatus to avoid any contamination due to attack on glassware by liberated HF. Analytically pure **(13)** was prepared as a pale straw coloured liquid in 47% overall yield (Scheme 3.10). The synthesis was conducted several times over the course of the work with similar results.

3.6.2 Trial Fluorination of Benzyl Bromide



Scheme 3.11 Fluorination of benzyl bromide with caesium fluoride

Benzyl bromide was utilised as a test substrate as it is known to be extremely reactive to nucleophilic displacement due to resonance stabilisation of the intermediate cation. Forcing conditions were unlikely to be needed and if fluorination did not occur with this substrate then it was doubtful that it would proceed with any of the less reactive electrophiles planned for the study.

The CsF was rigorously dried by grinding and heating under vacuum prior to use. Pre-dried RTIL (**13**) and CsF were mixed and the whole mixture degassed under vacuum to facilitate mixing, but the CsF did not dissolve appreciably in the RTIL. After replenishing the argon atmosphere, benzyl bromide was added and the reaction was stirred for 1 hour at 20°C. After this time, the volatile materials were vacuum transferred into a cold trap. A colourless liquid was obtained, and this was analysed by ^{19}F and ^{1}H NMR, using a known mass of 1,4-difluorobenzene as a quantitative reference. The analysis showed that the reaction had produced benzyl fluoride (**2**) in 47% yield (66% conversion) under very mild conditions (Scheme 3.11). The product was obtained in pure form following distillation of the isolated product mixture on a Spaltrohr column.

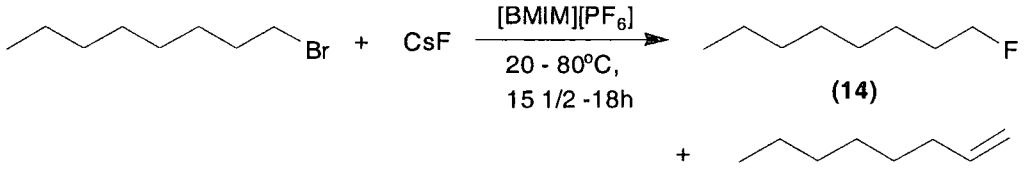
This reaction clearly demonstrated the potential of [BMIM][PF_6] (**13**) as a solvent system for nucleophilic fluorination with CsF. In addition a considerable portion of the unreacted starting material was also recovered, thus allowing the possibility of a relatively high efficiency process. Following this result, a decision was made to set out to develop a method for the fluorination of organic bromides and other electrophiles without the use of conventional organic solvents.

3.6.3 Fluorination Reactions Using Metal Fluorides in [BMIM][PF_6]

Following the successful test reaction with benzyl bromide, a study of the reaction of the CsF/(**13**) system was undertaken with a variety of electrophilic species.

A. Fluorination at sp^3 Carbon Sites

Due to ease of handling and stability of the desired fluorinated products, 1-bromooctane was chosen as the primary substrate on which reaction optimisation would be based (Scheme 3.12). The system allowed a study of the variation in nucleophilic displacement and elimination processes that may occur under a variety of conditions. 1-Triflatooctane was also used to enable the study of a structurally similar substrate with considerably higher reactivity. Note that CsF indicates anhydrous CsF, CsF* is used throughout this thesis to refer to "wet" CsF, indicating that the material has been used as received from the suppliers without further purification.



Scheme 3.12 Fluorination of 1-bromooctane with caesium fluoride

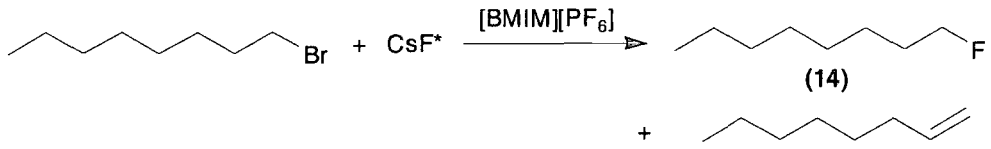
Table 3.1 Results of fluorination of 1-bromooctane with caesium fluoride under various conditions

Eq. CsF	T/°C	Time/h	(14)/%	Alkenes/%	Conversion/%	Recovery[a]/%
1	20	16 ½	12	3	17	93
1	70	18	19	5	26	~100
2	20	16	23	8	29	~100
2	80	15 ½	55	7	98	63

a.) Recovery is defined as the total quantity of transferred volatile materials.

From the table above, we can clearly see the effects of raising the temperature and increasing the quantity of CsF (Table 3.1). Reaction under ambient conditions with one equivalent of CsF produced a small yield of 1-fluorooctane **(14)**, along with some elimination products. In general, reactions in **(13)** produced a similar quantity of elimination products to their counterparts in conventional dipolar aprotic solvents.[36] Unsurprisingly, the harsher conditions lead to higher yields of the desired product, although the yields of alkene byproducts remain at a reasonable level and recovery is generally very good.

Late in the course of the work, it was discovered that the use of RTIL **(13)** removed the need to rigorously dry the CsF (Scheme 3.13). Indeed, from the results below it can be seen that the presence of small quantities of moisture is in fact beneficial!



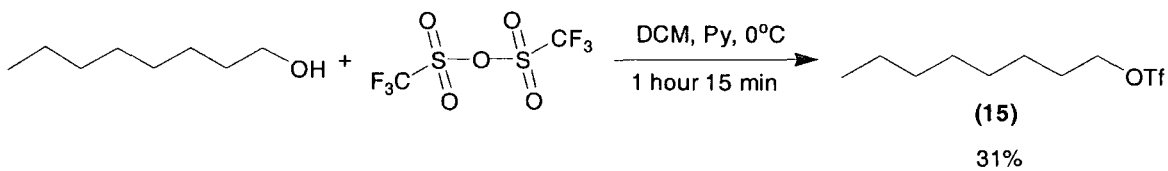
Scheme 3.13 Fluorination of 1-bromooctane with "wet" caesium fluoride

Table 3.2 Results of fluorination of 1-bromooctane with "wet" caesium fluoride under various conditions

Eq. CsF*	T/°C	Time/h	(14)/%	Alkenes/%	Conversion/%	Recovery/%
2	80	14 ½	65	11	76	100
2	80	1.5	35	10	46	98

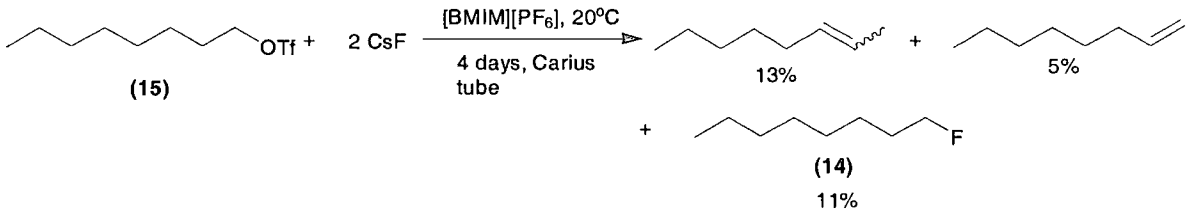
The use of "wet" CsF results in a significant increase in the yield of fluoroalkane and a minor increase in the yield of alkene (Table 3.2). It is possible that the water is allowing the formation of micelles of saturated CsF solution, thus increasing the contact between the fluorine source and the substrate.

To determine the behaviour of the fluorinating system with a more reactive substrate, 1-triflatooctane **(15)** was synthesised by a standard procedure and the product triflate was isolated in 31% yield (Scheme 3.14).



Scheme 3.14 Synthesis of **(15)**

Characterisation was effected by multinuclear NMR only, because the product was unstable. The product was stored briefly at –20°C and then used in the fluorination reaction shown below.



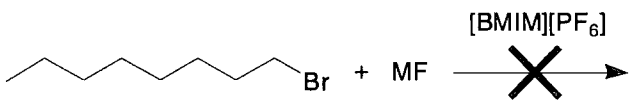
Scheme 3.15 Fluorination of **(15)** with caesium fluoride

Table 3.3 Results of fluorination of **(15)** with caesium fluoride

Eq. CsF	T/°C	Time/h	(14)/%	Alkenes/%	Conversion/%	Recovery/%
2	20/Carius tube	4 days	11	18	78	39

The fluorination of triflate **(15)** was carried out in a Carius tube to contain the expected high concentration of volatile octenes and to minimise potential exposure to the highly electrophilic triflate (Scheme 3.15, Table 3.3). The reaction of this substrate with CsF is somewhat surprising. The system shows low conversion to the desired products and a low recovery indicating that the starting material has been consumed. Clearly a different process is occurring here resulting in the trapping of the substrate material within the RTIL.

Following these results, attempts were made to fluorinate 1-bromooctane using the less expensive metal fluorides shown below. These have the disadvantage of being significantly less reactive than CsF as can be seen from the results.



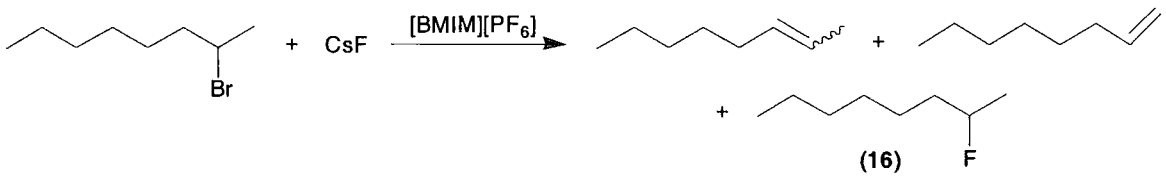
Scheme 3.16 Attempted fluorination of 1-bromooctane with various metal fluorides

Table 3.4 Results of attempted fluorination of 1-bromooctane with various metal fluorides

MF	T/°C	Time/h	(14)/%	Alkenes/%	Conversion/%	Recovery/%
KF	80	19 ½	0	0	0	77
KF*	80	19 ½	0	0	0	83
KHF_2	80	14 ½	0	0	0	71
CaF_2	80	15 ½	0	0	0	65

The use of two equivalents of dry KF, "wet" KF, KHF_2 and CaF_2 at 80°C resulted in no detectable substitution or elimination products when reaction with 1-bromooctane was attempted (Scheme 3.16, Table 3.4). The less than quantitative recovery seen with these reactions may, perhaps, be due to reaction of the substrate with the RTIL, trapping the substrate in the reaction mixture.

Attempts were also made to fluorinate a secondary substrate with CsF, although this was viewed as a more difficult process from the outset.



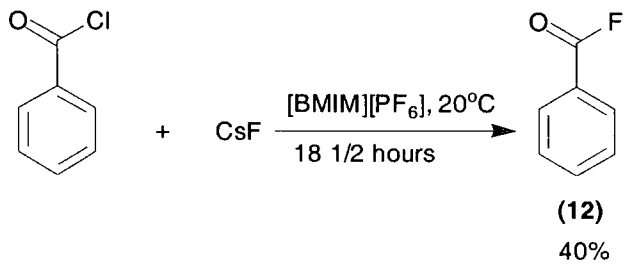
Scheme 3.17 Fluorination of 2-bromooctane with caesium fluoride

Table 3.5 Results of fluorination of 2-bromooctane with caesium fluoride under various conditions

Eq. CsF	T/°C	Time/h	(16)/%	Alkenes/%	Conversion/%	Recovery/%
1	20	18	0	10	11	92
1	70	16	0	4.5	5	76
2	20	18	<1	7	17	44
2	80	18 ½	3	16	38	49

2-Bromooctane was chosen as the test substrate, allowing direct comparisons to be drawn with the primary case shown above and, unsurprisingly, the system proved to be very much less reactive than the primary bromide (Scheme 3.17, Table 3.5). The predominant products were from elimination processes and fluorination to 2-fluorooctane **(16)** was clearly not the favoured reaction pathway regardless of the conditions employed. It is interesting to note that the use of excess CsF seemed to cause serious problems with the recovery of the substrate, presumably due to a similar decomposition reaction to that noted above. These reactions are clearly not efficient fluorination processes when compared to some recent publications on the fluorination of the same substrate under different conditions.[37]

B. Fluorination at an sp^2 Carbon Site



Scheme 3.18 Fluorination of benzoyl chloride with caesium fluoride

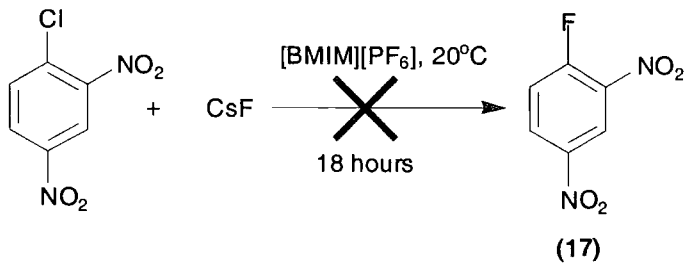
Table 3.6 Results of fluorination of benzoyl chloride with caesium fluoride

Eq. CsF	T/°C	Time/h	(12)/%	Conversion/%	Recovery/%
1	20	18 ½	40	74	54

Fluorination proceeded in moderate yield and with moderate recovery under ambient conditions (Scheme 3.18, Table 3.6). The yield of benzoyl fluoride **(12)** was lower than expected, although the low recovery hints at decomposition as above. This yield is appreciably lower than that achievable with many other Halex type methods.

C. Fluorination of Aromatic Substrates

Two aromatic substrates were chosen for fluorination; the highly reactive 2,4-dinitrochlorobenzene and trichloro-*s*-triazine, a reactive heterocycle which may be fully fluorinated.

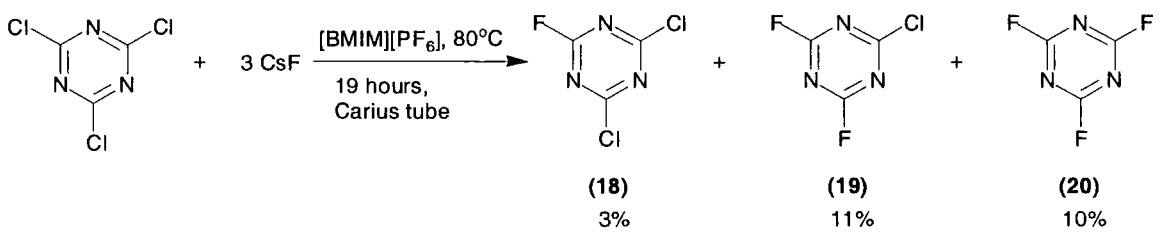


Scheme 3.19 Attempted fluorination of 2,4-dinitrochlorobenzene with caesium fluoride

Table 3.7 Results of attempted fluorination of 2,4-dinitrochlorobenzene with caesium fluoride

Eq. CsF	T/°C	Time/h	(17)/%	Conversion/%	Recovery/%
1	20	18	0	?	0

On addition of the 2,4-dinitrochlorobenzene to the RTIL/CsF mixture, an immediate deep bottle-green colouration developed. No volatile material was collected during vacuum transfer so it was impossible to assess the yield of 2,4-dinitrofluorobenzene (**17**), or the conversion of the reaction (Scheme 3.19, Table 3.7). It is possible that the green colouration was indicative of the formation of a charge transfer complex between the substrate and the imidazolium cation.



Scheme 3.20 Fluorination of trichloro-*s*-triazine with caesium fluoride

Table 3.8 Results of fluorination of trichloro-*s*-triazine with caesium fluoride

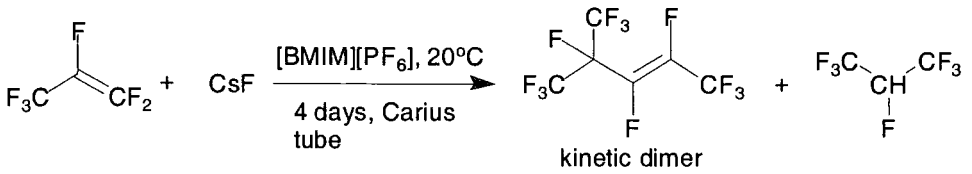
Eq. CsF	T/°C	Time/h	R-F/%			Conv./%	Rec./%
			(18)	(19)	(20)		
1	80/Carius tube	19	3	11	10	?	25

Using a stoichiometric quantity of CsF, the fluorination of trichloro-*s*-triazine proceeded to give a mixture of dichloro-*s*-triazine **(18)**, chlorodifluoro-*s*-triazine **(19)** and TFT **(20)** in low yield (Scheme 3.20, Table 3.8). These were easily identified by their characteristic ^{19}F NMR and GC-MS spectra. The corresponding preparative reaction with KF under solvent free conditions uses an excess of KF to give TFT in ~80% yield (see section **4.3.2.2**). The conditions of the reaction are much harsher, however, with the fluorination being conducted at 310°C under moderate pressure. The conversion could not be accurately calculated as the solid materials present in the reaction mixture sublimed on to the inside of the Carius tube and were impossible to remove. The appearance of the RTIL after reaction was consistent with moderate decomposition. A light brown mobile liquid layer was observed as compared to the pale straw-coloured RTIL before reaction.

It is likely that any free amine produced by decomposition of RTIL **(13)** would react with the highly electrophilic halogenated triazine moiety to give an intractable, possibly polymeric material. It is interesting that even with a stoichiometric quantity of CsF, considerable quantities of chloro-fluoro-triazines were isolated. This indicates a deficiency of fluoride during the reaction, suggesting the likelihood of significant reaction between RTIL **(13)** and CsF and possible coating or inerting of the solid fluoride ion source by a surface layer of CsCl.

D. Reactions of Hexafluoropropene in [BMIM][PF_6]

D.1 Reactions of HFP with CsF in [BMIM][PF_6]

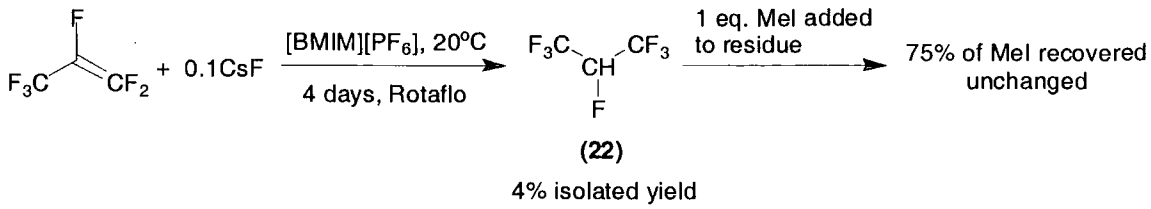


Scheme 3.21 Reaction of HFP with caesiuum fluoride

Reaction of hexafluoropropene with CsF in RTIL **(13)** was attempted as a demonstration of the fluoride-ion catalysed formation of a carbon-carbon bond (Scheme 3.21). In the presence of a fluoride ion catalyst (e.g. CsF), rapid dimerisation reaction occurs at room temperature to yield the kinetic form of the dimer (perfluoro-4-methylpent-2-ene) **(21)** with the thermodynamic form of the dimer (perfluoro-2-methylpent-2-ene) being formed as the major product at elevated temperatures.[38]

The reaction was conducted in a Rotaflo vessel at ambient temperature. After the reaction was completed the liquid phase had turned into a dark red/brown solid, although a white crystalline material collected on the walls of the tube during freezing with liquid nitrogen. NMR of the gaseous/volatile liquid product in a sealed tube revealed the presence of the kinetic dimer of HFP **(21)** as well as ^{19}F peaks at ca. δ –79 and –215 ppm and a ^{1}H peak at ca. δ 6.5 ppm which could be attributed to 2H-perfluoropropane **(22)**. This compound could be produced either by proton abstraction by the highly basic perfluoroisopropyl anion or by reaction of HF, from fluoride ion attack on an alkyl chain, with HFP.

The reaction was repeated using a much smaller quantity of CsF to try and minimise the quantity of free base in the system (Scheme 3.22).



(22)

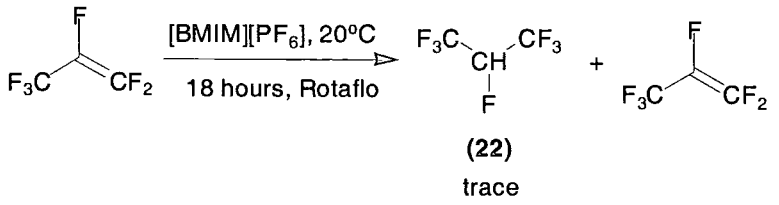
4% isolated yield

Scheme 3.22 Reaction of HFP with catalytic caesium fluoride

After reaction, the appearance of the liquid phase was a dark red/brown viscous liquid. Freezing of the tube in liquid nitrogen again caused the formation of a white deposit above the level of the liquid layer, indicating the presence of volatile material. The volatile components were removed under vacuum to yield 2-H-perfluoropropane **(22)** in 4% yield. As before, the hexafluoroisopropyl anion deprotonated the RTIL (presumably on the butyl side chain), but this time no HFP dimer was detected. This indicates that the deprotonation of the RTIL **(13)** proceeded at a significantly higher rate than the expected dimerisation reaction and that the lower concentration of anion in this reaction was not enough to allow significant dimerisation to occur.

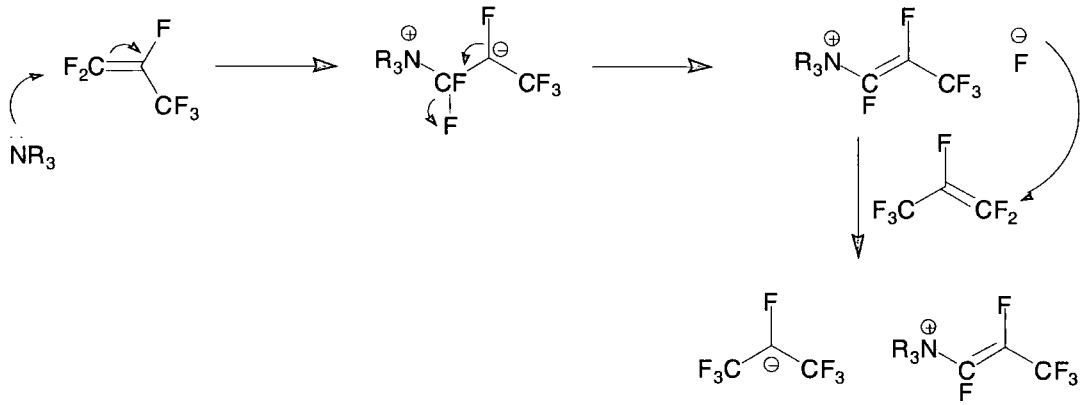
As the CsF had clearly been consumed and no HFP was transferred, it was assumed that some fluorinated material must remain in the reaction mixture in some form, possibly as a perfluoroalkyl anion. Methyl iodide was therefore added to trap any nucleophilic species that may be present. 75% of the methyl iodide was recovered by vacuum transfer and no fluorinated products were observed in the NMR of the volatile fractions. The residue from the reaction, which was a deep brown/red colour, was examined by ^{19}F NMR but unfortunately it was impossible to observe anything other than extremely weak non-PF_6^- resonances due to the high concentration of hexafluorophosphate in the sample.

D.2 Control reaction of HFP with [BMIM][PF_6]



Scheme 3.23 Control reaction of HFP with **(13)**

As a control reaction, HFP was transferred to a Rotaflo tube charged with RTIL **(13)** (Scheme 3.23). After 18 hours at ambient temperature, the tube was opened. The volatile fractions were found to contain unreacted HFP with a trace amount of **(22)**. The ionic liquid was recovered essentially unchanged. It is almost certain that the presence of trace quantities of N-methylimidazole or N-butylimidazole in the **(13)** acted as promoting agents for the release of fluoride ion from HFP (Scheme 3.24). This would have allowed formation of the perfluoroisopropyl anion which then abstracted a proton from the **(13)**.[39]



Scheme 3.24 Amine initiated formation of a carbanion from HFP

3.6.4 Recycling of [BMIM][PF_6]

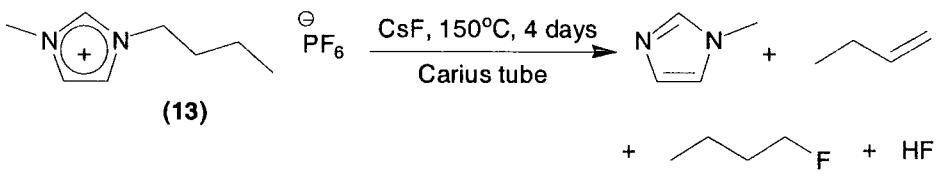
To enable the reuse of **(13)**, a recycling procedure was developed that enabled the solvent to be used for approximately five to seven cycles before decomposition

became a serious problem. The RTIL reaction residue was dissolved in DCM to reduce the viscosity and then shaken with several portions of water to remove any water soluble inorganic materials or amine-based decomposition products. The organic phase was then filtered through a fine glass frit under reduced pressure to remove any residual solid particles (e.g. CsBr) before the solvent was removed and the RTIL **(13)** dried under high vacuum at elevated temperature. The material was then assayed by ^{1}H and ^{19}F NMR before being reused. Although this process was not able to remove high molecular weight water-insoluble impurities (e.g. heavy organic decomposition products), it was found to be suitable for the reactions conducted in the study. Unfortunately, this process could not be completed without introducing an organic solvent as a viscosity modifier, as **(13)** was too viscous to be filtered effectively.

3.6.5 Decomposition of Imidazolium-Based RTILs with Alkali Metal Fluorides

After **(13)** had been used several times and recycled, it was noted that the colour appeared to be rapidly darkening with each additional use. Careful observation revealed that the point at which the most significant change occurred was during reactions performed at elevated temperature and during the vacuum transfer of material. The most likely explanation for this is that the RTIL was unstable in the presence of highly basic fluoride ion at elevated temperatures and the following reactions were carried out to ascertain if this hypothesis was correct. NMR spectra of the heavily used **(13)** clearly revealed the existence of other species; the ^{19}F NMR spectrum contained two overlapping doublets, the more intense of the two due to PF_6^-, the smaller most likely due to another fluorinated phosphorus species.

3.6.5.A Reaction of [BMIM][PF_6] with CsF or KF at 150°C

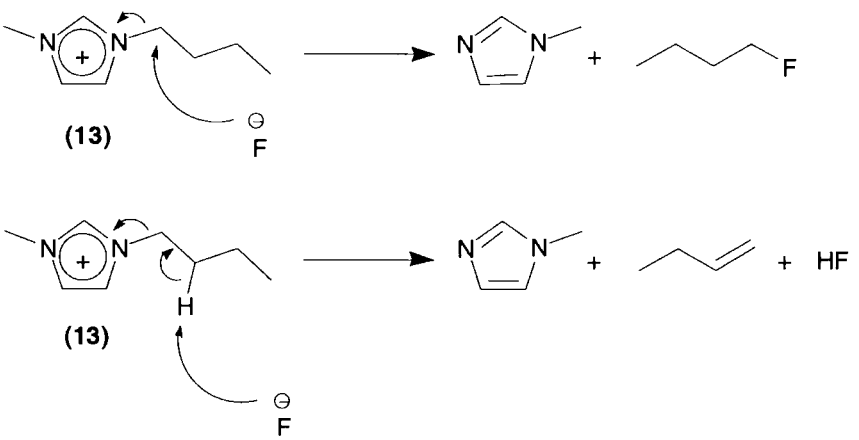


(13)

Scheme 3.25 Decomposition of (13) in the presence of caesium fluoride

In order to mimic the most severe conditions likely to be encountered in a fluorination process (strong heating during vacuum transfer of a high boiling product/substrate mixture), **(13)** was subjected to the action of CsF at high temperature (Scheme 3.25). The reaction was conducted in a Carius tube at 150°C for four days. Under these rather forcing conditions, the RTIL decomposed to a brown solid mass and several volatile components, as evidenced by the distinct smell of amine upon opening the tube. The volatile fractions were collected in a cold trap and analysed by NMR and GC-MS. Clear evidence was obtained for the formation of fluorobutane, butene and N-methylimidazole. Evidently the quaternary centre bearing the butyl side-chain is susceptible to both nucleophilic displacement by fluoride ion and Hoffmann elimination (Scheme 3.26). This is not surprising when it is noted that R'-NR_3^+ (which is essentially the group present in the imidazolium moiety) can function as a synthetically useful electrophile via loss of NR_3.

A similar reaction was attempted with the less basic and nucleophilic KF, although this reaction was run for a shorter period of time. Again, decomposition was noted indicating that the RTIL system is not stable even with a considerably milder fluorinating agent.



Scheme 3.26 Decomposition routes for alkylimidazolium cations in the presence of fluoride

Figure 3.5 [BMIM][PF_6] and caesium fluoride in Carius tube prior to heating

Figure 3.6 [BMIM][PF6] and caesium fluoride in Carius tube after heating

The above photographs show a mixture of two molar equivalents of anhydrous CsF and **(13)** before (Figure 3.5) and after (Figure 3.6) heating to 150°C for 20 hours. Note that **(13)** was almost colourless prior to the preparation of the Carius tube: The sample was degassed under dynamic vacuum for 30 minutes, causing significant phase mixing to occur, and even during this short time at ambient temperature, the RTIL mixture became noticeably more yellow in colour. During heating, **(13)** clearly underwent extensive decomposition and, after cooling, material could be frozen out on the inside of the Carius tube, demonstrating the production of volatile compounds.

3.7 Introduction to Phase Transfer Catalysis in Nucleophilic Displacement Reactions

During the course of the above work, it was realised that RTILs are fundamentally similar to many phase transfer catalysts. They are, in many cases, salts containing a quaternary nitrogen atom, and indeed certain alkylpyridinium halides (amongst others) have been used as phase transfer catalysts (PTCs). A set of reactions was therefore carried out with the aim of screening RTIL **(13)**, [BMIM][BF_4] and their immediate precursor, [BMIM][Cl], for PTC activity versus a range of known

PTCs. [BMIM][BF_4] was included in the study as it is miscible with water, and this was seen as potentially beneficial in reactions containing wet metal fluorides.

Phase transfer catalysis is a method which is used to increase the concentration of an active species in a particular phase as part of a multiphase reaction system.[40, 41] The reaction mixture may be comprised of any combination of solid, liquid and gaseous phases, although liquid-liquid and solid-liquid phase transfer catalysis are the most common types. The technique is generally employed when a reagent (e.g. a source of a nucleophile, such as KF)[36] has low solubility in the phase containing the substrate. Perhaps the classic example is the oxidation of an organic substrate using potassium permanganate in a biphasic water/organic solvent system (Figure 3.7).[42, 43] The PTC used in this case is usually a crown ether, 18-crown-6. The purpose of this catalyst is to strongly coordinate to the potassium ions and thus surround them with an organic or lipophilic shell. This greatly enhances the solubility of the permanganate in the organic phase, allowing reaction to occur in the organic phase rather than just at the phase boundary.

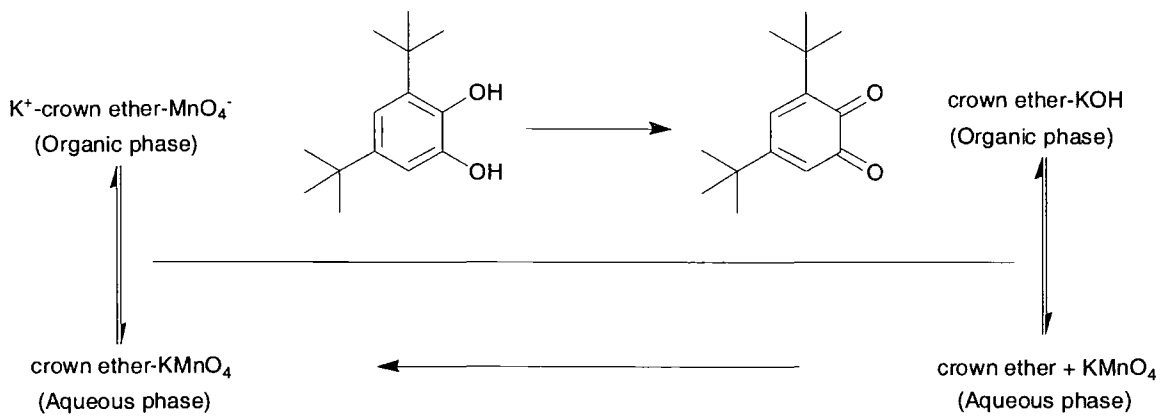


Figure 3.7 Illustration of the PTC concept

One of the other advantages of this technique is that the inorganic byproducts (or materials otherwise insoluble in the organic phase) are usually kept separate from the phase containing the desired product.

Phase transfer catalysis has been used to increase the efficacy of metal fluoride-based fluorination processes for some time. A variety of approaches have been used including solid-liquid PTC[36, 44] (solid MF and an organic solvent) and

liquid-liquid PTC[45] (aqueous solution of MF and an organic solvent). Generally the aqueous liquid-liquid systems are less desirable, both due to the very high energy of solvation of fluoride ion (essentially binding the fluoride in the aqueous phase)[46] and the potential lack of suitability for moisture sensitive substrates. Even so, high yields have been seen for both approaches and the technique is now widely accepted as a useful enhancement to nucleophilic fluorination methodology. Phase transfer catalysts in use for these systems include crown ethers, quaternary ammonium salts and polyethylene glycols.

3.8 Results and Discussion

The project was designed to evaluate the three [BMIM] compounds as potential PTCs in MeCN solvent with KF, KF*, CsF, CsF* and CaF_2 as the sources of fluoride ion. The aim was to increase the yield of fluorination relative to CsF/MeCN only and to quantify the effect of the various PTC systems in relation to each other. The studied reaction was the fluorination of 1-bromooctane, thus the purpose of the PTC was to transfer fluoride ion from the solid to the liquid phase via the *in-situ* formation of a soluble fluoride (for example, Figure 3.8).

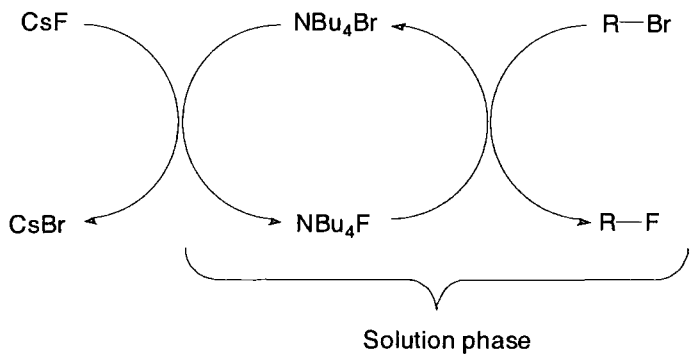


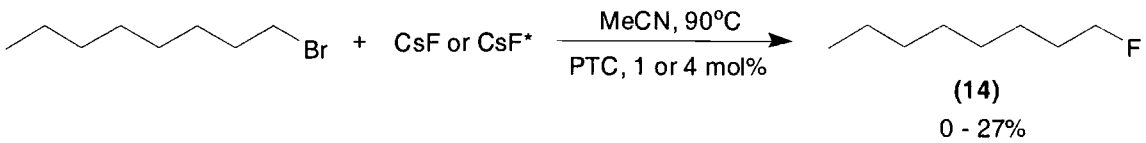
Figure 3.8 Schematic representation of PTC with a fluoride/alkyl ammonium system

A secondary aim of the study was to enable nucleophilic fluorination to occur more readily in MeCN, a solvent which is in general rather poor for conducting metal fluoride reaction processes due to the low solubility of the fluoride in the solvent. It has an inherent advantage over the standard dipolar aprotic solvents, however, in that

it is very easy to work with. In particular, it is relatively non-toxic (compared with DMF for example) and very volatile, thus facilitating easy product removal and purification. A common problem of standard nucleophilic fluorination reactions is that they are conducted in very high boiling solvents which are difficult in the extreme to remove entirely from the product (DMF, NMP and, in particular, sulfolane). The use of MeCN as a solvent negates these problems almost entirely.

Control reactions containing no PTC were also carried out to obtain reference yields for comparison. The catalyst screens were carried out on a small scale using a Radley's 12-station Carousel Reactor with 5mL of solvent in each tube. Dry metal fluorides were loaded in an argon atmosphere glove box and yields were assessed by quantitative ^{19}F NMR of the reaction mixture. For the purposes of this study, yields of elimination products were not quantified so as to facilitate more rapid screening.

3.8.1 Phase Transfer Catalyst Screen



Scheme 3.27 Screening of PTC systems

Initially a PTC loading of 1 mol% was used for the screen, although after very low initial yields this was increased to 4 mol%. Reactions that had been run with the lower quantity of PTC were repeated for CsF* only, as this was generally the highest yielding fluorinating agent (Scheme 3.27, Table 3.9). Reactions were run overnight for approximately 14 hours.

Table 3.9 Results of PTC system screening

PTC	PTC Loading/mol %	Yield (14)/% with fluorinating agent shown: KF, KF*, CaF_2	CsF	CsF*
Blank (no PTC)	*0*		*6*	*6*
PBu_4Br	1	0	12	13
	4			27
NBu_4Br	1	0	8	7
	4			22
$N(Oct)_4Br$	4	0	12	19
NMe_4Br	1	0	13	12
	4			9
[BMIM][Cl]	4		9	11
$[BMIM][BF_4]$	4	0 (KF*, CaF_2 only)	6	8
$[BMIM][PF_6]$	1	0	7	5
	4			7
PPh_4Br	4	0	7	7

* As with CsF*, KF* indicates that the material has been used as received from the suppliers without drying of any kind.

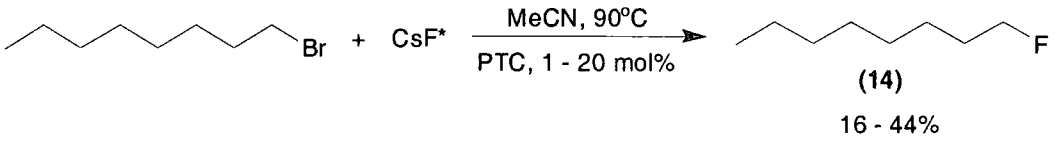
As can be seen from the table, PBu_4Br, NBu_4Br, $N(Oct)_4Br$, NMe_4Br and [BMIM][Cl] all improve the yield of 1-fluorooctane **(14)** by some degree. That the highest yield obtained is 27% is something of a disappointment, representing the difficulty observed in conducting this type of fluorination in MeCN. It would appear that the PTCs employed were only moderately successful in transporting fluoride into the organic phase in a synthetically useful form. As seen in section **3.9.1**, higher catalyst loadings do increase the yield markedly but this is not practical.

Interestingly, fluorination only occurs with CsF and CsF* and in general the yields are fairly similar. In all cases, reactions with KF, KF* and CaF_2 failed to

produce any fluorinated products, thus highlighting the greater reactivity of the CsF system. The fact that this is due mostly to the lower lattice energy of CsF (thus facilitating relatively easy dissolution and hence higher reactivity) is particularly relevant to this study.

With regard to the RTIL-type systems, phase transfer activity seems to be minimal, although there is the possibility of some discrepancy between the BF_4/PF_6 and chloride systems. This is perhaps due to the smaller size of chloride thus allowing an easier metathesis process to take place with fluoride ion. It is likely that the larger anions are more difficult to incorporate into the CsF lattice, thereby slowing the metathesis process.

3.8.2 Phase Transfer Catalyst Loading Study



Scheme 3.28 PTC loading study

PBu_4Br was chosen as the PTC for this study as it gave the highest yields in the screen reactions carried out previously (Scheme 3.28). As can be seen from the results below (Table 3.10, Figure 3.9), the quantity of catalyst present in the reaction mixture has a considerable effect on the yield of 1-fluorooctane **(14)**. Although it would appear that it is a simple exercise to raise the yields of fluoroalkane to 50% or more under the same conditions by using a high catalyst loading, due to the high molecular weight of the catalyst species this is not a practical solution. These results compare poorly with those seen using KF/18-crown-6 in MeCN, [36] indicating that even though the PBu_4Br/CsF system is the highest yielding out of those studied here, it is still not as active as a so-called "naked" fluoride ion source.

Table 3.10 Results of PTC loading study

MF /mmol	R-Br /mmol	PTC /mmol	PTC /mol%	MeCN /mL	Time /h	Temp /°C	(14) /%
CsF* /10	5	PBu_4Br /0.05	1	5	15	90	16
CsF* /10	5	PBu_4Br /0.1	2	5	15	90	17
CsF* /10	5	PBu_4Br /0.2	4	5	15	90	27
CsF* /10	5	PBu_4Br /0.3	6	5	15	90	27
CsF* /10	5	PBu_4Br /0.5	10	5	15	90	35
CsF* /10	5	PBu_4Br /1.0	20	5	15	90	44

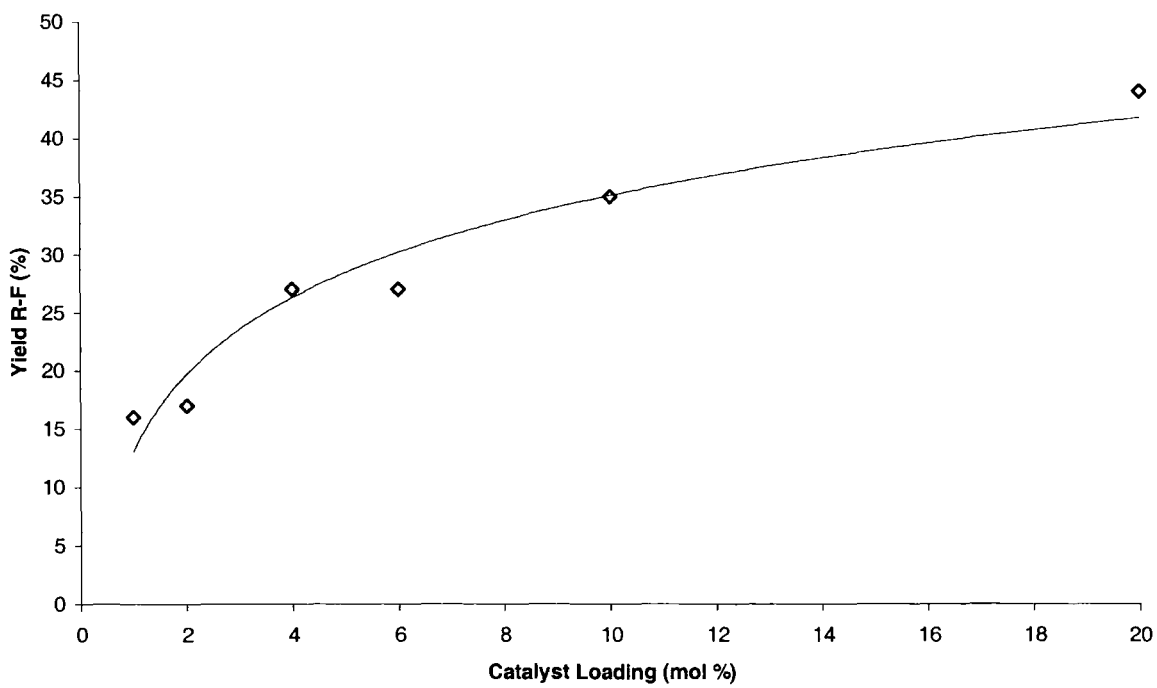
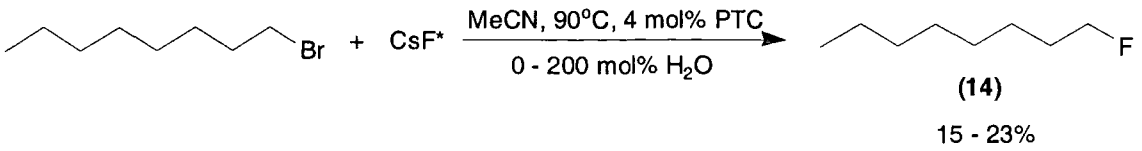


Figure 3.9 Effect of PTC loading on yield of 1-fluorooctane

3.8.3 Water Loading Study



Scheme 3.29 Water loading study

A communication published recently by Chi (see discussion in section **3.9**) highlighted the fact that the behaviour of water in reactions with nucleophilic displacement by fluoride ion is still poorly understood.[47] A study of the effect of water concentration on the known PTC PBu_4Br was made (Scheme 3.29); as can be seen from the data below (Table 3.11, Figure 3.10), the activity of the system does decrease with increasing water content as expected. However, it is worth commenting on the fact that even with two molar equivalents of water the fluorinating ability of the system is still moderate. Clearly the common arguments regarding aqueous solvation shells around fluoride and their effects on its nucleophilicity are incomplete as at least partially solvated fluoride ion is still able to act as a reasonable nucleophile.

Table 3.11 Results of water loading study

MF /mmol	R-Br /mmol	PTC /mmol	H_20 /mmol	H_2O /mol%	MeCN /mL	Time /h	Temp /°C	(14) /%
CsF /10	5	PBu_4Br /0.2	0	0	5	17	90	23
CsF /10	5	PBu_4Br /0.2	0.1	2	5	17	90	20
CsF /10	5	PBu_4Br /0.2	0.5	10	5	17	90	21
CsF /10	5	PBu_4Br /0.2	1	20	5	17	90	19
CsF /10	5	PBu_4Br /0.2	2.5	50	5	16	90	23
CsF /10	5	PBu_4Br /0.2	5	100	5	17	90	15
CsF /10	5	PBu_4Br /0.2	7.5	150	5	16	90	13
CsF /10	5	PBu_4Br /0.2	10	200	5	17	90	15

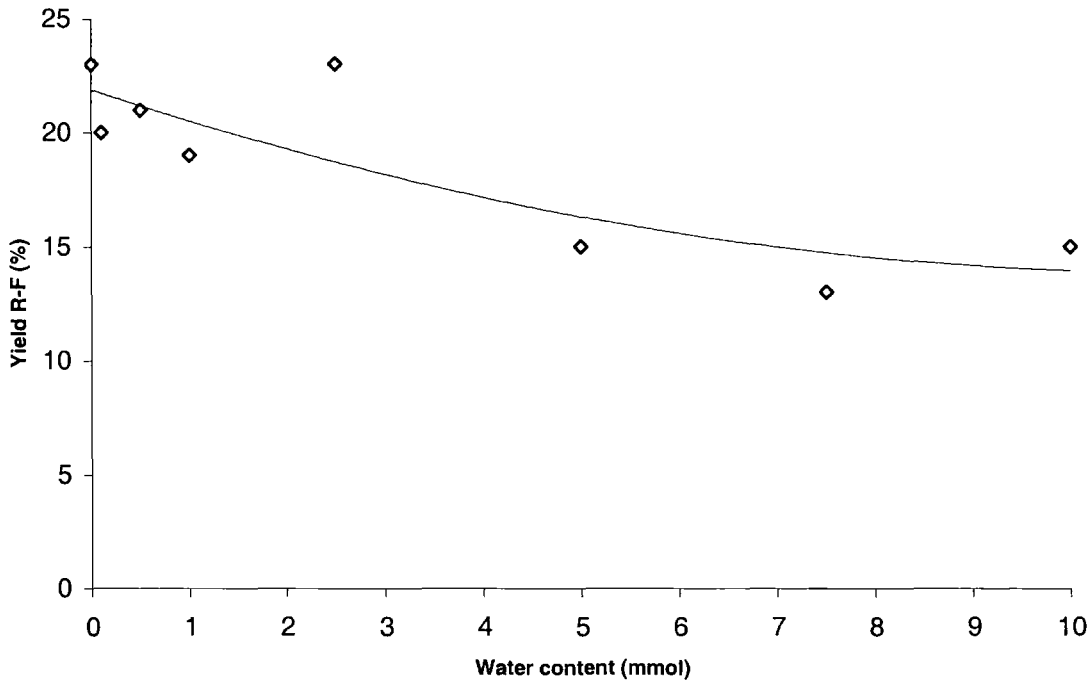


Figure 3.10 Effect of water content on yield of 1-fluorooctane (5mmol substrate)

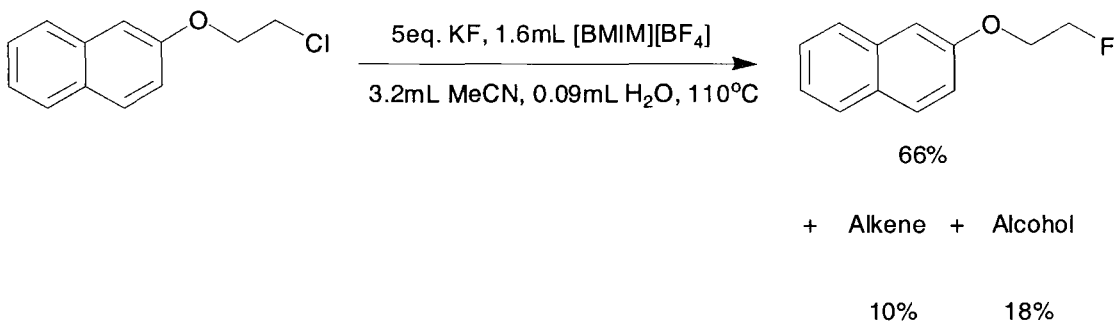
3.9 Conclusion

From the work presented in this chapter it can be seen that [BMIM][PF_6] **(13)** is applicable to the fluorination of electrophilic substrates in the absence of conventional organic solvents. CsF was the only fluorinating agent to be studied that showed any effect on the less reactive substrates, although KF has shown promise in similar systems with reactive substrates.[47, 48] The yields obtained are moderate, most likely due to the low solubility of CsF in **(13)** and coating of the CsF particles with inert bromide or chloride. Side reactions are also encountered and these reduce the efficiency of the system further. Although the reaction system allows for the easy isolation of volatile products from the reaction mixture, the moderate yields and high expense of **(13)** preclude its use for this type of process if it is desirable or necessary to recycle the solvent.

The inability to recycle RTIL **(13)** over a significant number of cycles is a serious drawback, and work has shown that this is due to the inherent instability of the dialkylimidazolium cation in the presence of fluoride ion. It is possible that the

incorporation of hindered alkyl groups with no β-protons would stop the decomposition, but this would also be highly likely to raise the melting point to well above room temperature, thus reducing the utility of the system.

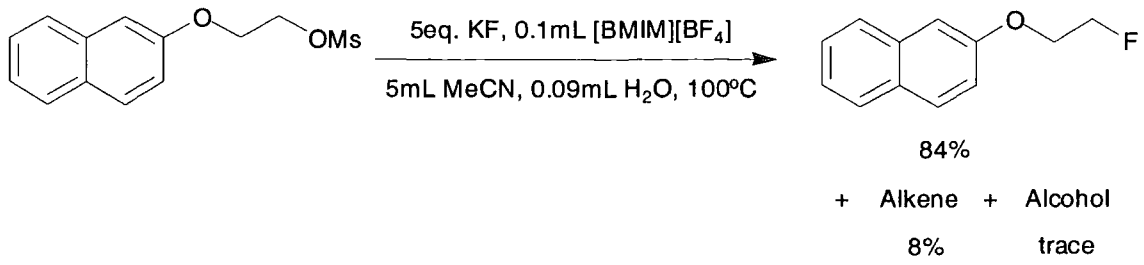
The use of imidazolium based RTILs as PTCs for nucleophilic fluorination processes in MeCN solution has also been investigated. Although a large body of results has been obtained, these suggest that such systems are inferior to well known and widely applicable systems such as KF/18-crown-6.



Scheme 3.30 Use of RTIL as solvent and co-solvent in nucleophilic fluorination

Following the above research on fluorination in RTIL **(13)**, a Korean group published a communication reporting the use of [BMIM][BF_4] as a solvent and also co-solvent in conjunction with acetonitrile, water and water-acetonitrile mixtures (Scheme 3.30).[47] Other RTILs and co-solvents were screened for efficacy, but [BMIM][BF_4]/MeCN provided the best results in the model system used for optimisation. KF was used as the fluoride ion source with a range of reactive substrates such as benzyl systems or molecules which were able to provide anchimeric assistance for nucleophilic displacement.

The presence of an appreciable quantity of water in the reactions detailed in the paper is contrary to established nucleophilic fluorination methodology but it does appear to be quite beneficial in this system. A similar result was observed with CsF in the work presented in this chapter (see sections **3.6.3.A** and **3.8.3**).



Scheme 3.31 Apparent use of RTIL as PTC in nucleophilic fluorination

The same group have now published a full paper detailing their research on these systems as solvents and phase transfer catalysts (Scheme 3.31),[48] an area which is very similar to the work discussed above.

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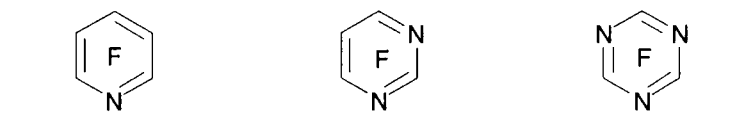
4. *in-situ* Generation of Fluoride Ion from the Interaction of an Aromatic Amine with a Highly Fluorinated Heterocycle

As discussed in the first chapter, many synthetically useful sources of nucleophilic fluorine contain covalently bound "active" fluorine, for example DAST. Many of these reagents are hazardous to handle and rather expensive. A safer, more affordable source of fluoride ion is always desirable, and it was realised that the generation of fluoride *in-situ* from a covalent fluorine-containing precursor could be a valuable synthetic tool. Such a precursor is pentafluoropyridine (although other highly fluorinated heterocycles have been considered – see below), a material which is both relatively cheap and relatively safe. The interaction of a suitable nucleophilic species, such as a tertiary amine, with this compound can result in the elimination of fluoride ion, which may then be used for nucleophilic displacement processes.

Given the reliance on perfluorinated heterocyclic compounds for this technique, it is both useful and necessary to review some of their basic chemistry.

4.1 Introduction to Perfluoroheterocycles

The work presented in this chapter is an extension to the large body of published work concerning highly fluorinated azaheterocycles. A key foundation of much of the work is the fundamental chemistry of several of the principal perfluorinated heterocyclic compounds: Pentafluoropyridine, tetrafluoropyrimidine and trifluoro-*s*-triazine (Figure 1.4).



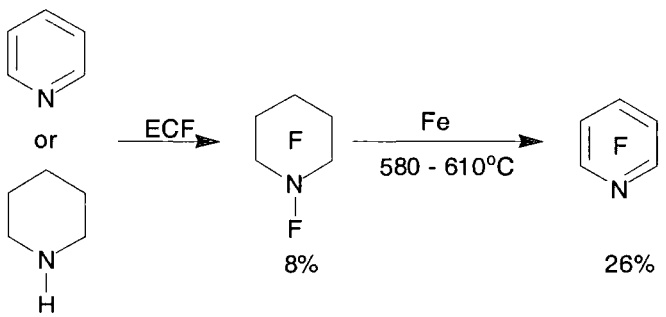
pentafluoropyridine tetrafluoropyrimidine trifluoro-*s*-triazine

Figure 4.1 Perfluorinated azaheterocycles

Because of this, it will be useful to review the properties of such materials with respect to their synthesis and reactivity, and indeed several comprehensive reviews of highly fluorinated aromatic compounds have been published.[1-3]

4.1.1 Synthesis of Perfluorinated Azaheterocycles

Perfluorinated azaheterocycles have been known since the 1960s, when the first examples were synthesised. Substitution of hydrogen by fluorine would be an ideal way to synthesise these compounds, but so far no generally satisfactory route has been developed. Pentafluoropyridine was first obtained by defluorination of perfluoropiperidine over iron,[4] although the yield was rather low (Scheme 4.1). The perfluoropiperidine itself was synthesised by the electrochemical fluorination (ECF) of pyridine or piperidine with anhydrous hydrogen fluoride.

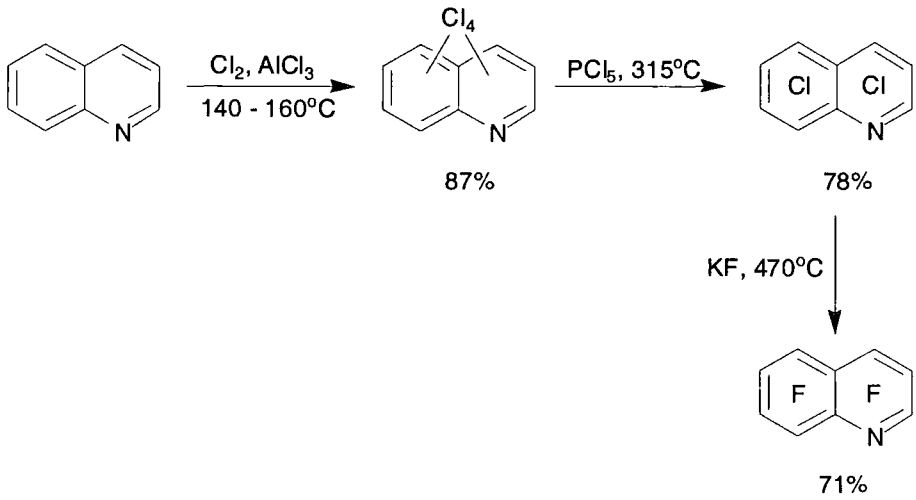


Scheme 4.1 Synthesis of PFP

The most effective route to highly fluorinated heterocyclic compounds is that of halogen exchange, the so-called Halex reaction. This process utilises the nucleophilic substitution of chlorine by fluoride ion in chlorinated heterocyclic species.[5-7] Generally, a chlorinated heterocycle is first prepared by electrophilic substitution of the parent heterocycle with chlorine and aluminium chloride. This is then converted to the perchlorinated compound by reaction with phosphorus pentachloride under forcing conditions. In the classic version of this methodology, the perchlorinated heterocycle is then heated with a suitable source of fluoride ion, such

as CsF, in a dipolar aprotic solvent such as sulfolane or DMF. This method suffers from problems caused by the high temperatures necessarily employed to effect fluorination; in particular, the thermal stability of the solvent is often a limiting factor. An advantage of this method is that it is sometimes possible to run the reaction under conditions that allow for the continuous distillation of the product from the reaction mixture as it is formed, allowing for easy product separation and purification.

A development of this method is to react a metal fluoride and the perchlorinated heterocycle in an autoclave at high temperature in the absence of solvent.[7]

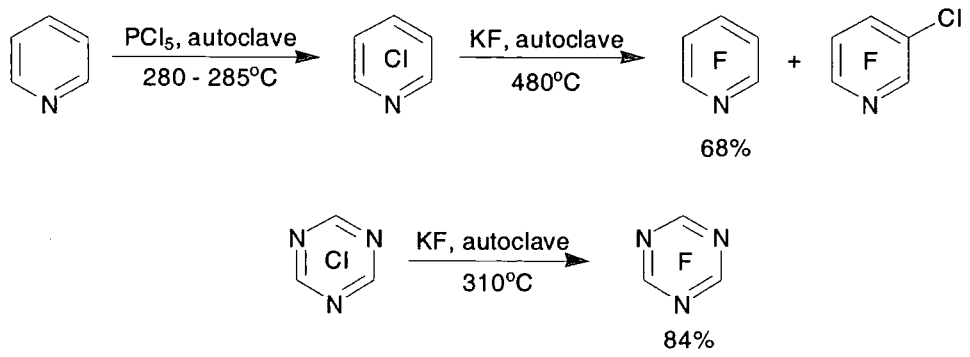


Scheme 4.2 Synthesis of perfluoroquinoline using solvent-free Halex methodology

This method is highly effective for a significant number of compounds, and as with the conventional solvent-containing route, potassium fluoride can often be used in place of the more expensive and hygroscopic caesium fluoride. The extent of fluorination depends upon the conditions employed and the reactivity of the heterocycle; it is often possible to isolate partially fluorinated products. Other similar methodology includes the reaction of the perchlorinated precursor with anhydrous HF in a suitable vessel.[8] This method can give high yields, but there are obvious procedural and safety disadvantages.

Trifluoro-*s*-triazine, tetrafluoropyrimidine and pentafluoropyridine are all readily synthesised using the above solvent-free methodology. The triazine and

pyridine systems are commercially available, although the triazine is rather expensive. Unsurprisingly, the ease with which the perchlorinated precursors can be fully fluorinated increases with the number of nitrogen atoms present in the ring (for a full discussion of this, see section **4.1.3**). Thus, with potassium fluoride, pentachloropyridine requires extremely harsh conditions (480°C) to give a mixture of pentafluoropyridine and 3-chlorotetrafluoropyridine,[2] whereas fluorination of trichloro-*s*-triazine to the trifluoride proceeds under relatively mild conditions (310°) in higher yield (Scheme 4.3).



Scheme 4.3 Comparison of Halex conditions required for perfluorination of pentachloropyridine and trichloro-*s*-triazine

4.1.2 Properties of Perfluorinated Azaheterocycles

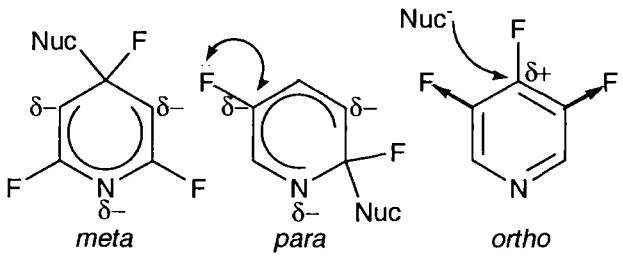
Pentafluoropyridine, tetrafluoropyrimidine and trifluoro-*s*-triazine are all mobile, colourless liquids with high vapour pressure. The reactivity, and hence toxicity and sensitivity to moisture, increase with the number of nitrogen atoms in the system: trifluoro-*s*-triazine is very much more electrophilic than pentafluoropyridine, and can react violently with strong nucleophiles (e.g. ammonia in methanol).

The presence of the ring nitrogen atom(s) significantly alters the electronic character, and hence the reactivity, of these heterocycles. As nitrogen is rather electronegative, the electron density present in the ring π-system is greatly reduced when compared to the parent hydrocarbon. This reduces the susceptibility to electrophilic attack and conversely increases the reactivity of the system towards nucleophiles. Thus it can be seen that when highly fluorinated, such compounds are

significantly more electrophilic than the corresponding perfluorinated carbocyclic aromatics. A further point is that the presence of several fluorine atoms bonded to ring carbon significantly reduces the basicity of the ring nitrogen. Pentafluoropyridine is not protonated by concentrated hydrochloric acid; the production of pyridinium salts requires the use of super acids.[9]

4.1.3 Susceptibility of Perfluorinated Azaheterocycles to Nucleophilic Attack

As mentioned above, perfluorinated azaheterocycles are very susceptible to nucleophilic attack. This is due to both the highly electron deficient ring system, the stabilising influences of both nitrogen and fluorine on the intermediate σ-complexes and the ability of fluoride ion to act as a good leaving group. In general terms, the activating effect of fluorine in nucleophilic aromatic substitution is as follows: *Ortho* > *meta* >> *para*, *i.e.* a fluorine atom *ortho* to the site of attack has the greatest activating influence, followed by *meta* and then *para*.[10]



unnecessary fluorine atoms omitted for clarity

Figure 4.2 Illustration of the effects of *ortho*, *meta* and *para* fluorine atoms on the reactivity of PFP towards nucleophilic attack

In the case of *meta* fluorine, with the transition state shown (Figure 4.2), we can see that there will be a ⁻C-C-F type system. It is well known[11] that fluorine in this position stabilises the carbanion species formed (Figure 4.3).

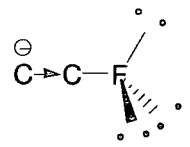


Figure 4.3 Stabilisation of carbanion due to β-fluorine atoms

With *para* fluorine, there is a $^{-}$C-F interaction (Figure 4.2), and this is known to be destabilising due to electron pair repulsion between the fluorine lone pairs and carbon (considerably more so with trigonal than tetrahedral hybridised carbon species, Figure 4.4).[11]

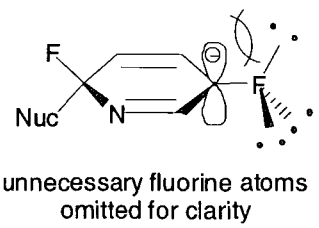


Figure 4.4 Destabilisation of planar carbanion due to α-fluorine atom

However, a problem is encountered when trying to explain the effect of *ortho* fluorine using these arguments. Using the same transition state stabilisation ideas as above actually leads to the prediction that *ortho* fluorine will deactivate the system to nucleophilic attack. It is likely that the observed activation is due to an effect in which the *ortho* fluorine atoms withdraw electron density from the carbon in the initial state, thus making it more electrophilic (Figure 4.2), and therefore more susceptible to nucleophilic attack.[10]

Quantitatively, the approximate activating effect of a ring fluorine on a pyridine system is shown in the table below (Table 4.1). If hydrogen is assigned a value of one (i.e. essentially neutral for our purposes), then we can clearly see the activating effects of *ortho* and *meta* fluorine and the pronounced deactivating effect of a *para* fluorine atom. The values shown are the reactivity enhancement shown by a pyridine containing the indicated fluorine atom relative to the unsubstituted pyridine (i.e. with hydrogen in the indicated position).

Table 4.1 Relative rate enhancement observed in nucleophilic attack on PFP relative to hydrogen at the indicated position

Reactivity enhancement of fluorine relative to hydrogen		
ortho	***meta***	***para***
31	23	0.26

It is worth noting that the inclusion of chlorine atoms in a fluoropyridine system has the same effect as fluorine, i.e. activating effect decreases along the series *ortho* > *meta* > *para*,[12] although the effect is more pronounced due to the lesser ability of chlorine to provide electronic repulsion to α-carbanions

For pentafluoropyridine, we can use the above information to predict the most likely site(s) of nucleophilic attack (Figure 4.5). This does of course ignore other effects such as steric requirements of attacking nucleophile and the influence of the solvent (which can be significant).

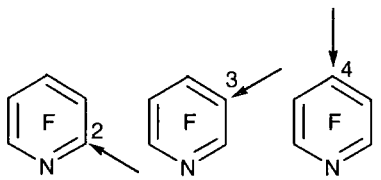


Figure 4.5 Positions of nucleophilic attack on PFP

Table 4.2 Summary of fluorine atoms relative to attacking site on PFP

Position of attack on pentafluoropyridine	***ortho* fluorine atoms**	***meta* fluorine atoms**	***para* fluorine atoms**
2	1	2	1
3	2	1	1
4	2	2	0

From the table above (Table 4.2), we can see that the 4-position is the most susceptible towards nucleophilic attack and that the 2-position is also reactive, but less so than the 4-position. The 3-position would appear to be more activated than the 2-position, but it is important to bear in mind that the ring nitrogen strongly deactivates this position to nucleophilic attack. Experimentally, mono-substitution in pentafluoropyridine occurs almost exclusively at the 4-position,[2] with attack at the 2-position being reserved for bulky nucleophiles[1, 13] or species with other mitigating factors, such as those shown below.

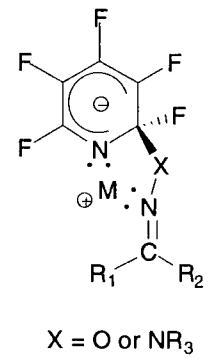


Figure 4.6 Preferential attack at the 2-position of PFP due to coordination of the nucleophile to ring nitrogen

Work carried out on fluorinated pyridine systems with alkali-metal oximate nucleophiles resulted in substitution almost exclusively at the 2-position (Figure 4.6).[14, 15] It is likely that this occurs due to the metal cation co-ordinating to the ring nitrogen, thus directing attack to the 2-position. This effect is a little unexpected, as measurements have shown pentafluoropyridine to be almost entirely non-basic,[9] but the same effect has been highlighted in other work.[16] Polysubstitution of pentafluoropyridine is therefore expected to follow the pattern of 4- then 2- then 6-substitution, with the potential for further attack at the 3,5-positions under certain conditions.[17]

Interestingly, substitution at the 3-position is sometimes observed in apparent preference to other products, usually with compounds which have already been attacked at the 4-position. This is due to fluoride-ion catalysed rearrangement, and can

occur when the 4-substituent (i.e. the *ortho* substituent to the site of attack) is able to exhibit a significant stabilising influence on the Meisenheimer complex.[18] The diagram below (Figure 4.7) illustrates that this is due to the significant difference in carbanion stabilising ability between $^{-}$C-F and $^{-}$C-C-F. Attack at the three position for perfluoro(4-isopropylpyridine) is possible due to the stabilising influence of the perfluoroalkyl group. Attack at the same position on pentafluoropyridine results in a destabilising $^{-}$C-F interaction at the 4-position.

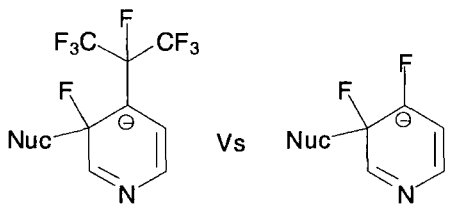


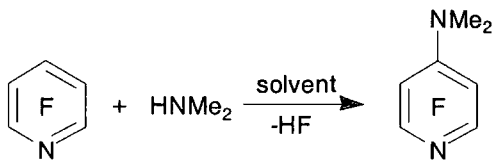
Figure 4.7 Stabilisation of negative charge by 4-substituent allows for attack at 3-position

The above rules can be applied qualitatively to the other two heterocycles of interest, tetrafluoropyrimidine and trifluoro-*s*-triazine. Clearly, the dominating effect is the increase in the number of nitrogen atoms in the ring. This leads to a more electron deficient system with a greater ability to stabilise the intermediate complexes resulting from nucleophilic substitution processes. For the pyrimidine system, the nitrogen exhibits a significant effect both in terms of the reactivity of the compound and the orientation of substitution. The reactivity is significantly higher than pentafluoropyridine and attack generally occurs preferentially at the 4- and 6-positions, *para* to the nitrogen atoms;[2] further attack occurs at the 2- and then 5-positions. With regard to trifluoro-*s*-triazine, due to the symmetry of the system, the only conclusion to be drawn is that the system will show markedly higher reactivity towards nucleophiles than tetrafluoropyrimidine.[2]

4.1.4 Reactions of Amines with Perfluorinated Azaheterocycles

4.1.4.1 Ammonia, Primary and Secondary Amines

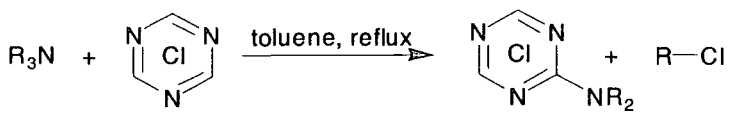
The reactions of perfluorinated azaheterocycles, particularly of pentafluoropyridine and trifluoro-*s*-triazine (due to its use in the synthesis of fibre reactive dyes) with amines have been well studied for ammonia, primary and secondary amines only.[2] There is very little published literature on the reactions of such systems with tertiary amines. Reaction with ammonia, primary or secondary amines proceeds readily *via* nucleophilic attack followed by elimination of HF to yield the expected amine, alkylamine or dialkylamine respectively (Scheme 4.4).



Scheme 4.4 Representative reaction of a non-tertiary amine with PFP

4.1.4.2 Tertiary Amines

Reactions of perfluorinated azaheterocycles with tertiary amines have only been reported in a few publications, and the products are generally poorly characterised. Probably the first publication on the subject was a paper in 1962 by Kober, demonstrating the reaction of tertiary amines with chloro- and fluoropyrimidines and chloro- and fluoro-*s*-triazines.[19] A more recent publication by Elias covered similar ground demonstrating dealkylation of tertiary amines with trichloro-*s*-triazine only (Scheme 4.5).[20]

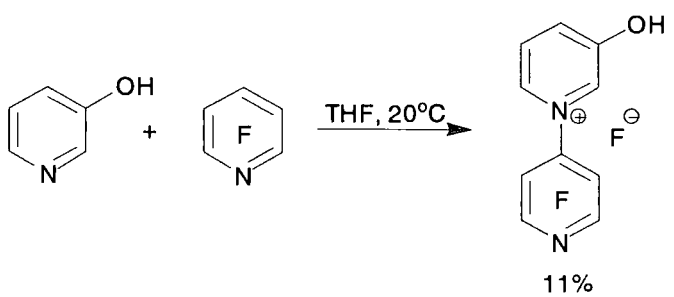


Scheme 4.5 Reaction of a tertiary amine with trichloro-*s*-triazine with resultant dealkylation

Reactions of triethylamine with trichloro-*s*-triazine were interesting in that they led to the corresponding dialkylamine-substituted products, thus indicating a quaternary ammonium species as an intermediate product.[19, 20] Curiously, reaction of the same amines with trifluoro-*s*-triazine allowed the claimed isolation of a quaternary ammonium fluoride in certain cases.[19] Reaction with tri-*n*-butylamine yielded a stable material which was purified by distillation. Clearly the fluoride salts are more stable than their chloride containing counterparts, and this may be explained in part by the use of toluene as the reaction medium, a solvent in which fluoride ion is unlikely to be a particularly strong nucleophile or base due to the non-polar nature of the solvent.

A further publication by Chambers[21] on reactions of pyridine with pentachloropyridine (resulting in the formation of pyridinium chlorides) briefly touched on the analogous reaction with pentafluoropyridine, tentatively reporting the formation of pyridinium fluoride salts, but no further details were given.

The only early paper regarding attack of a tertiary amine on pentafluoropyridine in which adequate product characterisation was carried out was published by Katritzky in 1979 (Scheme 4.6).[22]



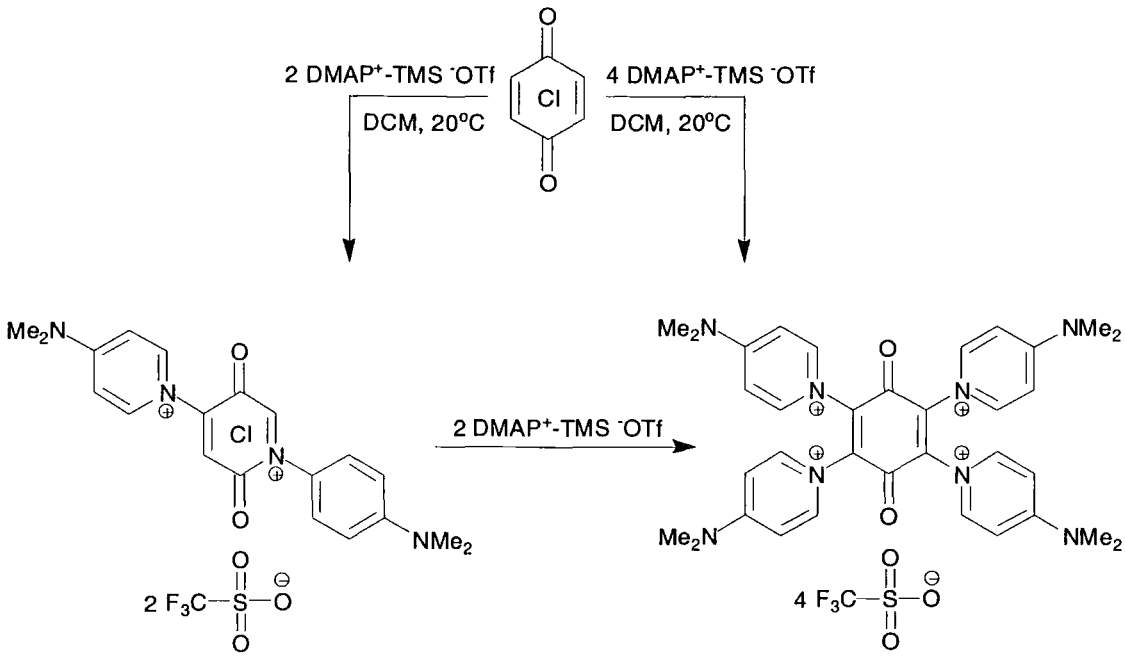
Scheme 4.6 Synthesis of an isolable (pyridinium)perfluoropyridine

Reaction of 3-hydroxy pyridine with pentafluoropyridine led to the formation of the expected fluoride salt in 11% yield as a dark brown amorphous solid.

4.1.5 Reactions of Amines with Halogenated Electron Deficient Species

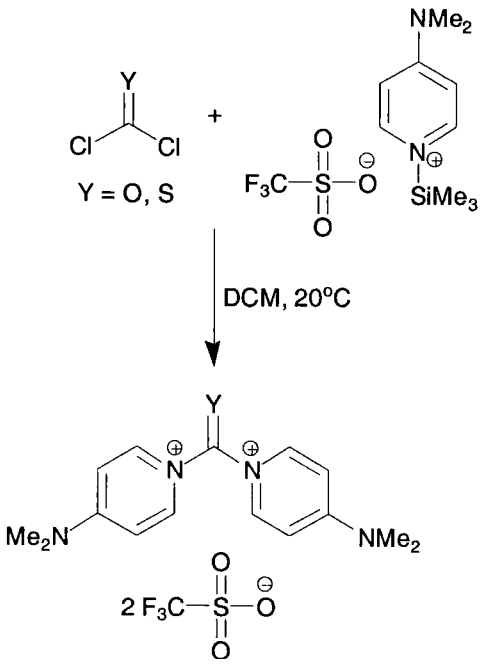
Obviously, the above section does not furnish us with much information; broadening the scope of enquiry results in a more useful range of publications. A study of the reactions of tertiary amines with perchloroheterocycles, perfluorinated carbocyclic aromatics and similarly electron deficient compounds provides several papers of interest that are relevant to the research reported in this chapter. One feature that quickly becomes apparent is that a large number of papers use 4-dimethylaminopyridine (DMAP) as the nucleophilic amine. This compound has been described as a "hyper-nucleophile" and has found many uses due to its high nucleophilicity.[23] When reviewing relevant work pertaining to the reaction of DMAP with halogenated electron deficient compounds, the works of Weiss and Streitwieser are particularly useful and significant in relation to the current topic of research.

Considerable progress has been made in parallel areas (although with mostly different aims) regarding the isolation of (poly)cationic pyridine-containing species. A variety of electrophilic substrates has been utilised, resulting in the synthesis of a number of stable compounds. In 1986, Weiss reported the preparation of oxidising agents similar to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) via the reaction of N-trimethylsilyl-4-dimethylaminopyridinium triflate with perchloroquinone.[24] An important synthetic step here is the formation of volatile chlorotrimethylsilane as the driving force for the reaction. This was the first reported preparation of poly-onio-substituted quinones (i.e. quinones substituted by multiple positively charged species, Scheme 4.7). The 2,5-disubstituted and 2,3,5,6-tetrasubstituted triflate salts were isolated and characterised.



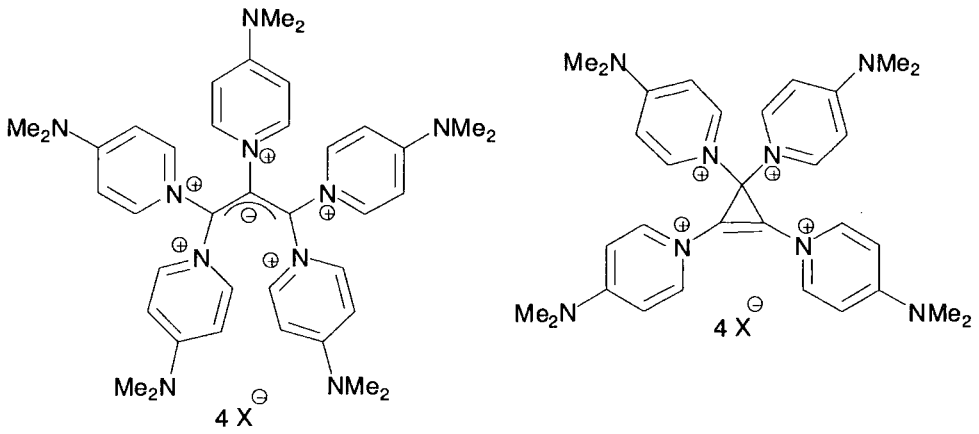
Scheme 4.7 First reported synthesis of poly-onio-quinones

Shortly after this report, the same group published a similar paper detailing the reaction of DMAP with several highly electrophilic trigonal carbon centres including phosgene and thiophosgene.[25] The same methodology as above was employed, resulting in the formation of geminal bis-onio substituted species (Scheme 4.8).



Scheme 4.8 Synthesis of geminal bis-onio substituted compounds

In the same year, the Streitwieser group claimed the synthesis of the first "pyridiniumcarbons," i.e. compounds in which all available positions are substituted by pyridinium groups (Figure 4.8).[26] Preparation of these compounds was by addition of DMAP to the appropriate electrophilic perchlorinated precursors. Substitution of anions was affected by simple metathesis processes.

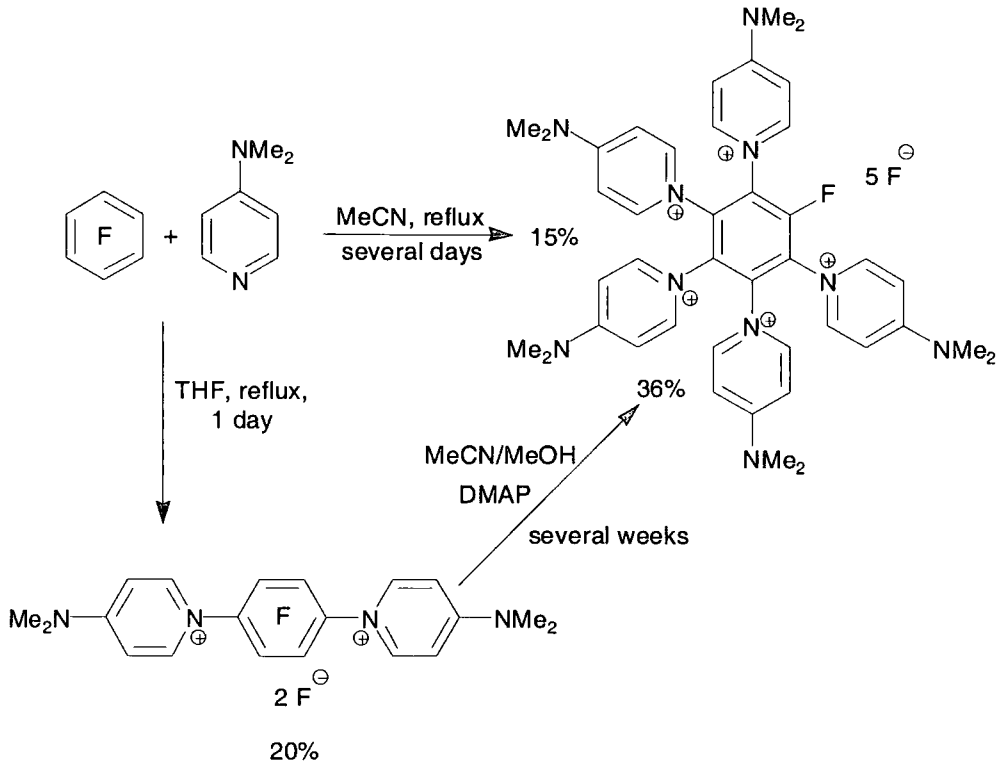


X = Cl, Br, I, AsF_6, PF_6, BF_4

Figure 4.8 Examples of isolated "pyridiniumcarbons"

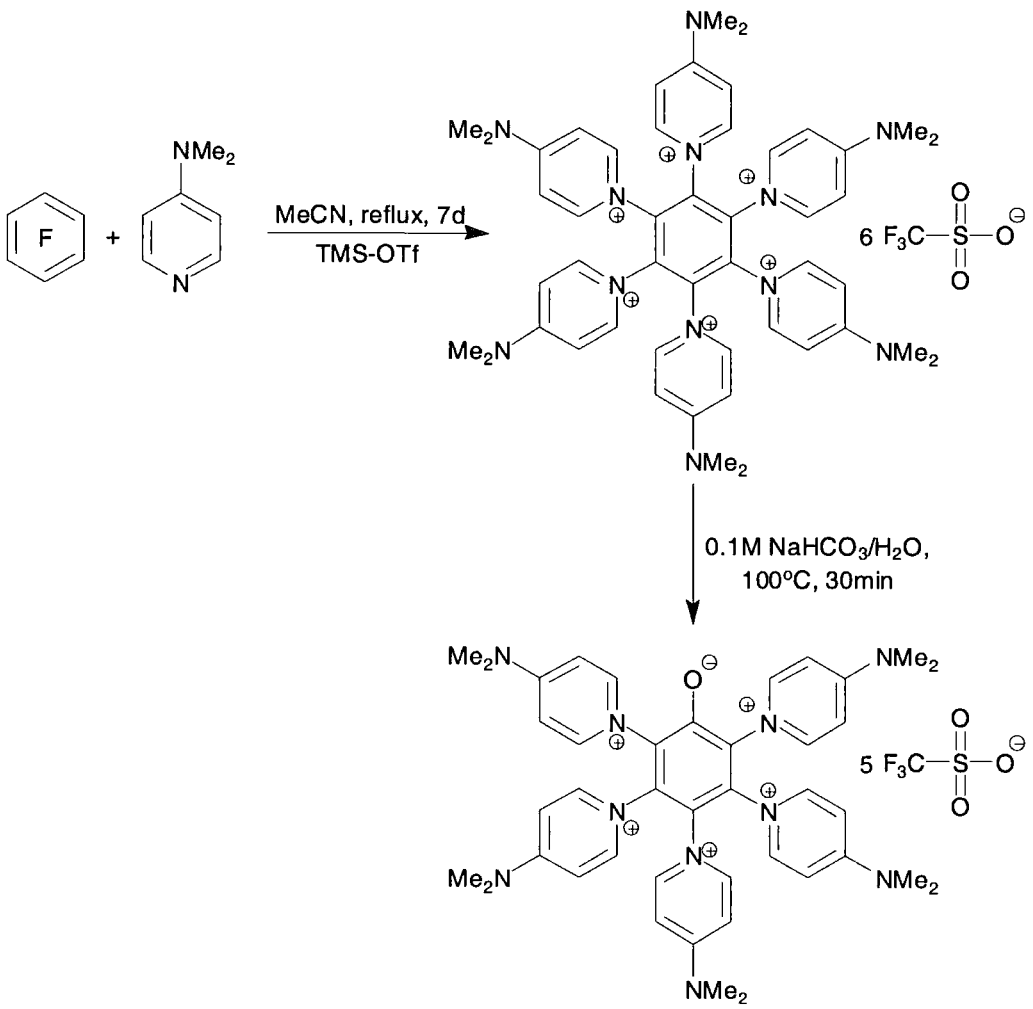
Further publications have explored the chemistry of these systems with regard to nucleophilic substitution, generally resulting in ring opening or exchange of a DMAP moiety with the nucleophile.[27, 28]

Perhaps more relevant are the publications, again by Streitwieser and Weiss, on the reactions of DMAP with hexafluorobenzene. Refluxing hexafluorobenzene with five equivalents of DMAP in THF gave the *para*-substituted dipyridinium salt, although reaction times of longer than one day gave significant quantities of more highly substituted products (Scheme 4.9).[29] Reaction in more polar media led to significantly higher rates of reaction and an increase in the proportion of polysubstituted products. With refluxing acetonitrile as the solvent, hexafluorobenzene with DMAP gave the pentasubstituted compound in low yield after reaction for several days. The dipyridinium compound above could also be converted to the pentapyridinium species somewhat more cleanly by allowing it to stand in an acetonitrile/MeOH solution of DMAP over several months. Unfortunately, the last remaining fluorine could not be substituted, even after reaction at elevated pressure (15 Kbar). Attempted reaction in NMP or similar solvents led to complex product mixtures with a high degree of polysubstitution. An X-ray structure of the dipyridinium tetrafluoroborate salt was obtained from crystals produced by addition of the difluoride to an excess of sodium tetrafluoroborate in acetonitrile/water.



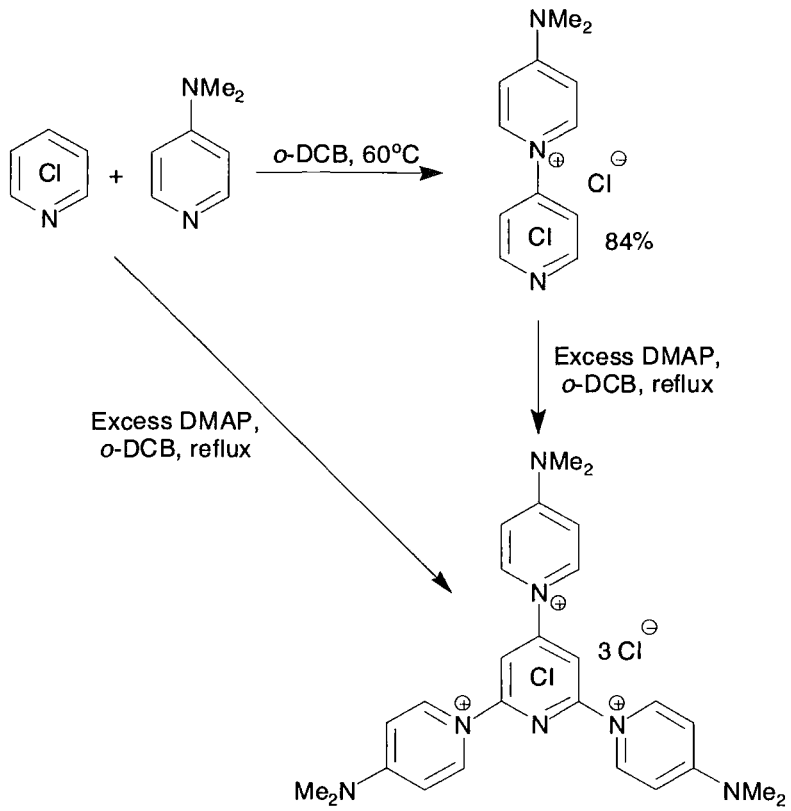
Scheme 4.9 Reaction of DMAP with hexafluorobenzene

Weiss took this methodology a step further[30] by conducting the reaction of hexafluorobenzene and DMAP in MeCN in the presence of TMS-triflate, an extremely active silylating agent. This aided the reaction via formation of stable TMS-fluoride, rendering the reaction irreversible. Interestingly, reaction of the three starting materials in an equimolar ratio yielded the per-onio substituted benzene as the only product, indicating that the DMAP moiety is activating the benzene ring to further nucleophilic attack (Scheme 4.10). Recrystallisation of the product from water yielded crystals suitable for X-ray crystallography, although the material was hydrolysed to the pentakis-substituted phenolate derivative by reaction with sodium hydrogencarbonate in water.

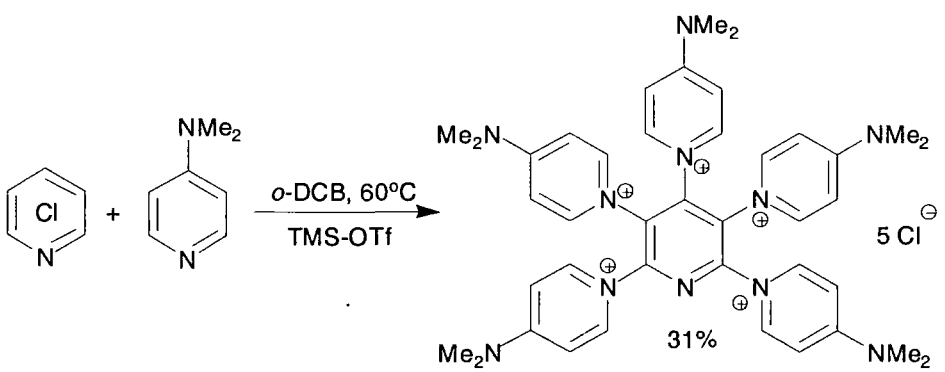


Scheme 4.10 Synthesis of per-onio-substituted benzene

The most relevant publications to the current field of work are those in which the electrophile is a highly halogenated azaheterocycle. In 2002, Schmidt reported the reaction of DMAP with pentachloropyridine as a method to produce highly substituted pyridine systems (Scheme 4.11).[31] Isolation of 4-, 2,4,6- and pentasubstituted pyridine species was observed, depending on conditions, with TMS-triflate being required to convert pentachloropyridine to the pentasubstituted system in the presence of DMAP (Scheme 4.12).

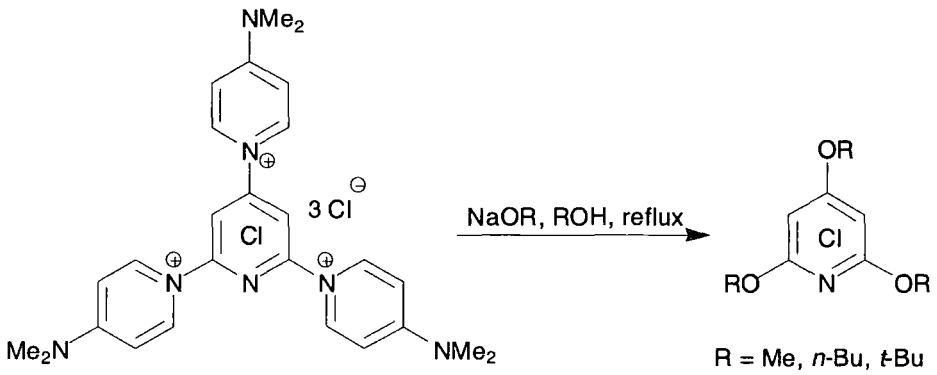


Scheme 4.11 Reaction of DMAP with pentachloropyridine



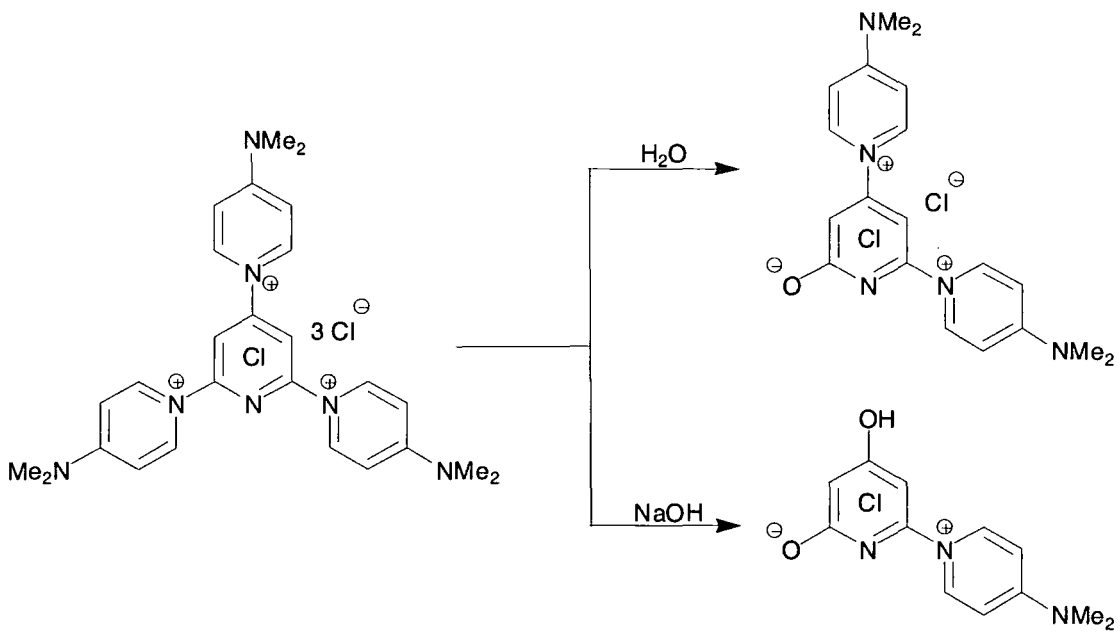
Scheme 4.12 Further substitution aided by use of TMS triflate

Further reactions were investigated with the mono and trisubstituted pyridine systems. The monosubstituted compound could be converted cleanly to the trisubstituted pyridine with excess DMAP. Reaction of the trisubstituted pyridine with various sodium alkoxide species in the parent alcohol resulted in the formation of 2,4,6-trialkoxydichloropyridines in high yields (Scheme 4.13).



Scheme 4.13 Synthesis of 2,4,6-trialkoxy-dichloropyridines

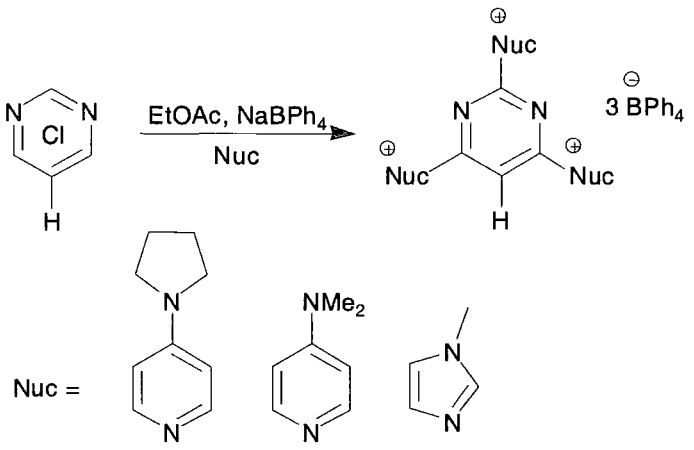
Hydrolysis of the trisubstituted compound was also demonstrated, yielding 2-hydroxy and 2,4-dihydroxy zwitterionic species with water and sodium hydroxide respectively (Scheme 4.14). The indicated site of protonation in the case of reaction with sodium hydroxide could not be accurately determined.



Scheme 4.14 Hydrolysis of cationic pyridine species

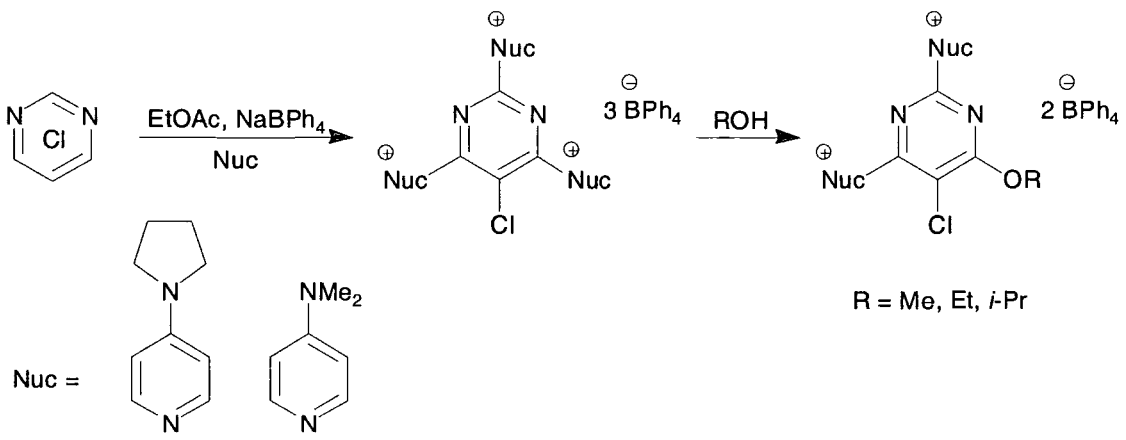
Schmidt also reported similar reactions with 2,4,6-trichloropyrimidine in two papers (Scheme 4.15).[32, 33] Reaction with DMAP, 1-methylimidazole or 4-

(pyrrolidin-1-yl)pyridine yielded 2,4,6-trisubstituted tricationic species. The chlorides thus synthesised were hygroscopic and unstable even in the solid state, although metathesis with sodium tetraphenylborate allowed isolation of stable analogues.



Scheme 4.15 Synthesis of onio-substituted pyrimidines

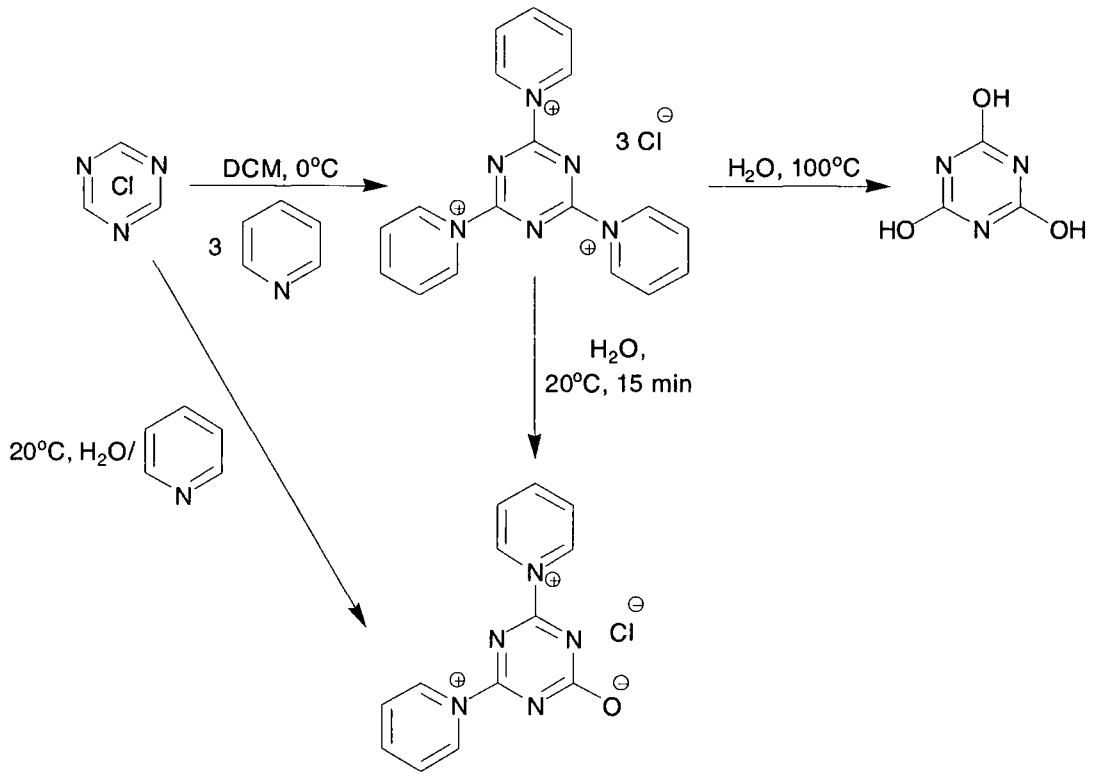
Analogous reactions of tetrachloropyrimidine gave 2,4,6-trisubstituted tricationic species also, although these were highly reactive and underwent nucleophilic attack with an alcohol at the 6-position to yield dicationic species (Scheme 4.16).



Scheme 4.16 Synthesis and alcoholysis of onio-substituted chloropyrimidines

In 1990, Murakami reported the reaction of trichloro-*s*-triazine with three equivalents of pyridine to yield 2,4,6-trispyridinium-*s*-triazine trichloride as an

unstable yellow solid,[34] but because of the handling difficulties associated with this material, characterisation was effected by IR spectroscopy only. Reaction of this material with water for a short period at ambient temperature produced a zwitterionic hydrolysis product, also synthesised via reaction of trichloro-*s*-triazine with aqueous pyridine. Reaction of the trispyridinium salt with boiling water resulted in the synthesis of cyanuric acid via displacement of pyridine (Scheme 4.17).



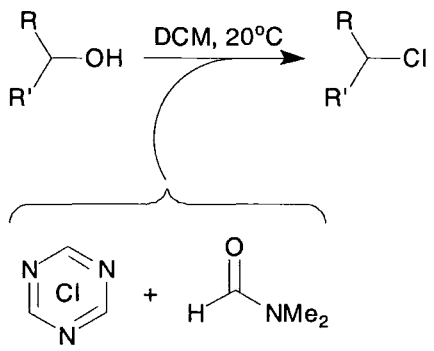
Scheme 4.17 Reported reaction of trichloro-*s*-triazine with pyridine

It should be noted that the possibility of nucleophilic halogenation was mentioned in only two of these publications.[19, 20] It is plainto see that halide ions are generated in the above reaction schemes, but as the publications have not been directed towards effecting selective halogenation, the generation of such species is incidental.

4.1.6 Nucleophilic Chlorination and Fluorination via Halogenated Azaheterocycles

In the current literature, there are few examples demonstrating the use of halogenated azaheterocycles as sources of nucleophilic chlorine and fluorine. The systems described tend to use triazine-based precursors; unfortunately, whereas trichloro-*s*-triazine is relatively stable, the corresponding trifluoro compound is highly moisture sensitive. Although this may seem to place such methodology in the same class as some of the materials mentioned in chapter one (i.e. rather hazardous or difficult to use), it is directly relevant to the current research and will therefore be discussed. The logical step from these systems is to attempt to replace the highly reactive triazine with a rather less reactive material, such as pentafluoropyridine, and this forms the basis for much of the research reported here.

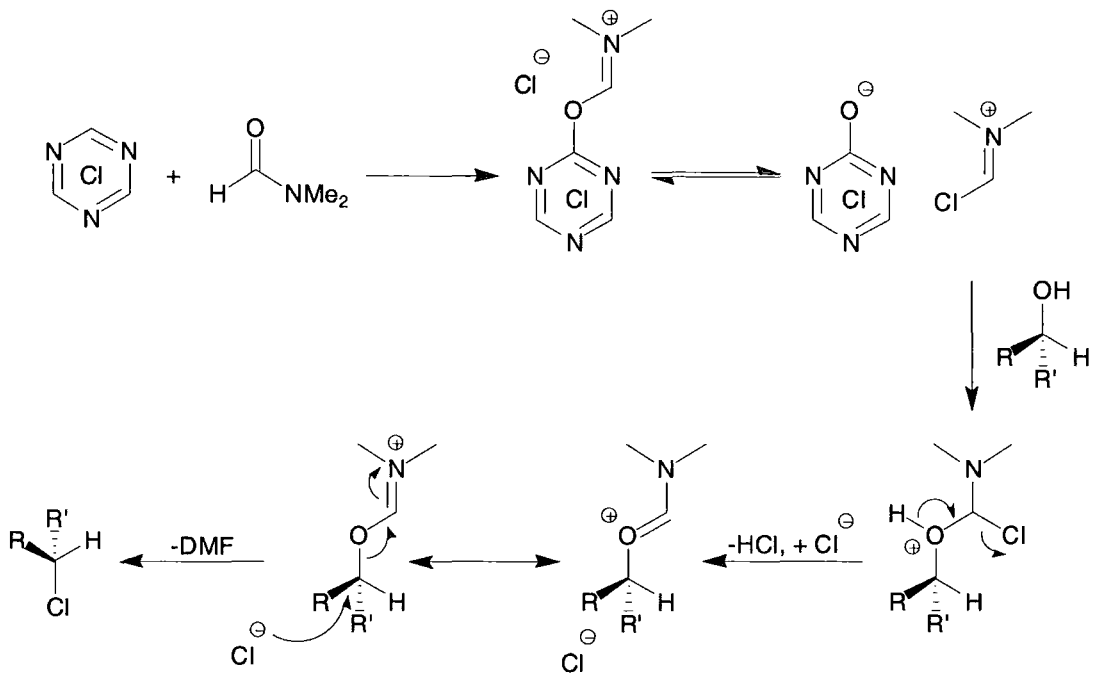
s-Triazine-based halogenating systems have been studied for both carbon-chlorine and carbon-fluorine bond-forming processes. Giacomelli reported the use of a DMF-trichloro-*s*-triazine system for the efficient chlorination of alcohols and β-amino alcohols to the corresponding chlorides via a Vilsmeier-Haack type process (Scheme 4.18).[35]



Scheme 4.18 Vilsmeier-Haack type chlorination of an alcohol

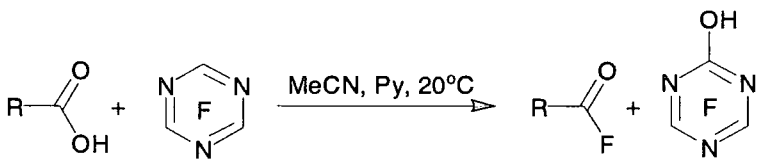
The postulated mechanism for this process involves attack of DMF on the triazine to displace chloride ion, followed by reaction of the alcohol with the activated immonium intermediate. Back-side attack of displaced chloride ion completes the

process, demonstrating classical S_N2 stereochemical inversion at the centre of attack (Scheme 4.19).



Scheme 4.19 Mechanism of chlorination reaction

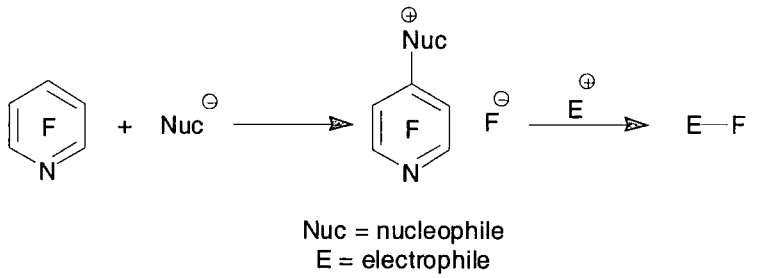
Olah demonstrated the use of trifluoro-*s*-triazine as a reagent for the fluorination of carboxylic acids under mild conditions.[8] Reaction of a carboxylic acid with pyridine led to the formation of a nucleophilic carboxylate anion, which then reacted with the triazine to yield a σ-complex with a pyridinium species as the cation. Decomposition of this complex led to the elimination of the desired acid fluoride, regeneration of pyridine and formation of a difluoro-*s*-triazinol as a byproduct (Scheme 4.20). From the ratios of reactants and yields stated, it would appear that all of the triazine fluorine atoms are used in the process, resulting in high atom efficiency.



Scheme 4.20 Use of TFT as a fluorinating agent

4.2 Results and Discussion

A more general approach than those discussed above would be to produce fluoride ion *in-situ* via the reaction of a perfluorinated azaheterocycle with an appropriate nucleophile, such as an aromatic amine, and then allow the fluoride ion thus formed to react with an electrophile (Scheme 4.21). Reaction of this *in-situ* fluorination reagent with a carbon-centred electrophile should lead to the selective formation of a carbon-fluorine bond. The use of pentafluoropyridine as the fluoride ion source and DMAP as the nucleophile were on the basis of cost, safety and availability of materials.

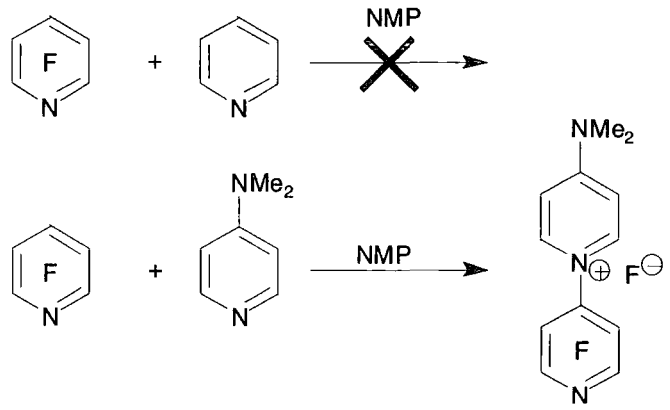


Scheme 4.21 General scheme for fluorination

As with the previous chapters, initial studies focussed on proof of concept. In this case, the proposed methodology was the generation of fluoride ion from pentafluoropyridine with an appropriate nucleophile, followed by the trial fluorination of benzyl bromide. Studies were conducted initially to verify the utility of this technique over a range of conditions.

4.2.1 Reactivity and Fluorination Studies

4.2.1.1 Initial Reactions of Pentafluoropyridine with DMAP



Scheme 4.22 Initial reactions of PFP with nucleophilic pyridines

In order to probe the initial reactivity of the pentafluoropyridine system, reactions were conducted with both DMAP and pyridine as nucleophiles to facilitate the release of fluoride ion. In the literature on this subject, DMAP has been used exclusively as a nucleophilic species with various electrophiles. An attempt was made to use pyridine as a cheaper, less toxic and easier to handle starting material (Scheme 4.22). NMP was employed as the solvent to increase the reactivity of the system when compared to the literature procedures run in THF or MeCN. Although some interaction occurred as evidenced by a distinct green colouration in the reaction mixture, no chemical change could be detected by ^{19}F NMR; this was almost certainly due to the poor nucleophilicity of pyridine.

An analogous reaction involving DMAP instead of pyridine resulted in the production of a yellow/white precipitate, which appeared to be non-uniform in character. The ^{19}F NMR spectrum of this intermediate product, taken from the reaction mixture, is worthy of comment. The DMAP was added in 1/3 molar equivalent portions to the pentafluoropyridine and it was expected that attack would occur at the most highly activated 4-position with some minor reaction at the 2-position.

The NMR spectrum of the reaction mixture showed an increasing amount of the 4-substituted product along with a corresponding decrease in the amount of pentafluoropyridine with each portion of DMAP added. Distinction should be made between the precipitated products and those seen in solution. The pyridinium fluoride adduct is only moderately soluble in MeCN and NMR analysis of the reaction solution therefore emphasises the presence of the minor products that are present. As with the literature reactions with hexafluorobenzene, the use of NMP was found to promote side reactions and so MeCN was chosen as the general reaction solvent (see section 4.2.2.2).

4.2.1.2 ^{19}F NMR of the Adduct and the Monitoring of Reactions

Pentafluoropyridine and a large number of 4-substituted tetrafluoropyridines have been fully characterised, furnishing a significant quantity of comparative data for assessment. Thus, reaction of DMAP with pentafluoropyridine produced the expected 4-substituted species as the major product.

Table 4.3 Comparison of ^{19}F NMR shifts for PFP and (**23**)

Fluorine atom position	**Chemical shift/ppm**	
	Pentafluoropyridine	Adduct (**23**)[a]
2,6	-86.7	-88.7
3,5	-160.8	-147.0
4	-132.7	

a.) ^{19}F NMR shifts of the tetrafluoroborate analogue (**23**) are given here

Comparison with the ^{19}F NMR spectrum of the parent pentafluoropyridine shows the very obvious disappearance of the 4-F peak, and a distinct shift in the positions of the resonances corresponding to the 2,6- and 3,5-F atoms (Table 4.3). The data indicates that the 3,5-fluorine atoms are significantly deshielded in the adduct, relative to PFP. This can be attributed to the adjacent positively charged nitrogen centre and the lack of any lone electron pairs on this centre for donation into the ring

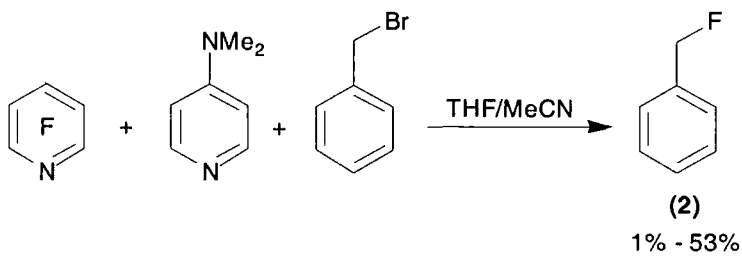
π-system. The 2,6-fluorine atoms are slightly more shielded when compared to pentafluoropyridine, although the effect is relatively small.

Table 4.4 Comparison of ^{19}F NMR shifts for **(23)** and product species from fluorination reactions

Compound	Approximate chemical shift in MeCN/ppm
1,4-Difluorobenzene	-119
Adduct 2,6-F **(23)**	-89
Adduct 3,5-F **(23)**	-147
1-Fluorooctane **(14)**	-217
2-Fluorooctane **(16)**	-171
Benzyl fluoride **(2)**	-204
Benzoyl fluoride **(12)**	18
1,4-Dinitrofluorobenzene **(17)**	-108

Reaction monitoring was accomplished by using ^{19}F NMR techniques also, as the chemical shifts of product monofluorinated compounds (Table 4.4) were appreciably removed from those attributed to the adduct.

4.2.1.3 Effect of the Order of Addition of Reagents on the Yield of Fluorination



Scheme 4.23 Varying the order of reagent addition

In order to determine the ideal order for the addition of reagents, three reactions were performed as indicated in the table below (Scheme 4.23, Table 4.5). The reaction mixtures were refluxed after the addition of the first two reagents and then cooled except in the case of entry **A**, where excessive decomposition was noted

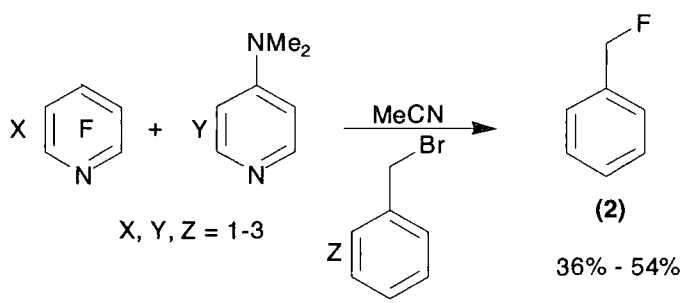
and the initial reaction was repeated at 20°C. The fluorination reactions were run at 20°C for approximately one hour before being sampled for ^{19}F NMR, followed by reflux for a further hour before final analysis.

Table 4.5 Results of varying the order of reagent addition

	Order of addition (solvent)	Yield of (2) at 20°C/%	Yield of (2) at high T/%
A.	PFP + DMAP then benzyl bromide (MeCN)	53	43/65°C
B.	PFP + benzyl bromide then DMAP (THF)	low concentration	7/reflux
C.	Benzyl bromide + DMAP, then PFP (THF)	trace	~1/reflux

Reaction **A** gave the highest yield of **(2)** by far due to pre-formation of the fluoride adduct resulting in a much higher available quantity of fluoride ion in the system. In reactions **B** and **C**, the yields of **(2)** were very low, indicating that reaction of benzyl bromide with DMAP is rapid and essentially irreversible under the conditions employed. Clearly, the most desirable methodology is to pre-mix the amine and perfluoro heterocycle prior to addition of the electrophilic substrate.

4.2.1.4 Effect of the Ratio of Reagents on the Yield of Fluorination



Scheme 4.24 Varying the ratio of reagents

Table 4.6 Results of varying the ratios of reagents

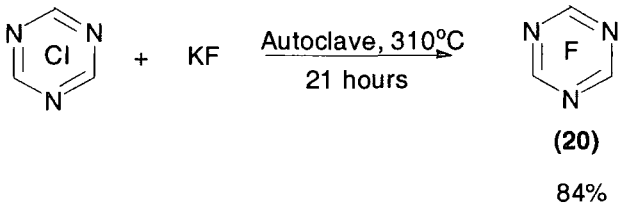
	Reagent/molar equivalents			
	Benzyl bromide	**DMAP**	**PFP**	**Yield of (2)/%**
A.	1	1	1	48
B.	1	2	1	42[a]
C.	1	3	1	42
D.	1	2	2	54

a.) The DMAP/pentafluoropyridine/acetonitrile mixture was heated to reflux and then cooled before addition of benzyl bromide.

In order to determine whether additional fluorine atoms on the pentafluoropyridine ring could be utilised for fluorination, attempts were made to generate polysubstitution products with excess DMAP (Scheme 4.24). Benzyl bromide was added to a mixture of various ratios of DMAP and pentafluoropyridine. Clearly the predominant effect was that of reaction of the excess DMAP with the substrate rather than with PFP. Even with pre-heating so as to encourage reaction of the starting materials to go to completion (see above table, entry 2), enough DMAP remained to reduce the overall yield. Unfortunately, as these results show, the fluorination method was not particularly atom-efficient in terms of its use of potentially "active" fluorine in the starting materials. The only increase in the yield of **(2)** was noted with an overall excess of fluorinating agent, reducing the cost-benefits of the system still further (Table 4.6).

It was worrying that the concentration of **(2)** decreased with time in the first set of reactions, however, as this pointed to one of two major problems: Either **(2)** was inherently unstable at the higher temperature or enough free DMAP was being generated by attack of bromide or residual fluoride on the adduct to react with the product or substrate. Because of this and other similar indications 1-bromooctane was subsequently used as the test substrate as the product 1-fluorooctane **(14)** is considerably more stable.

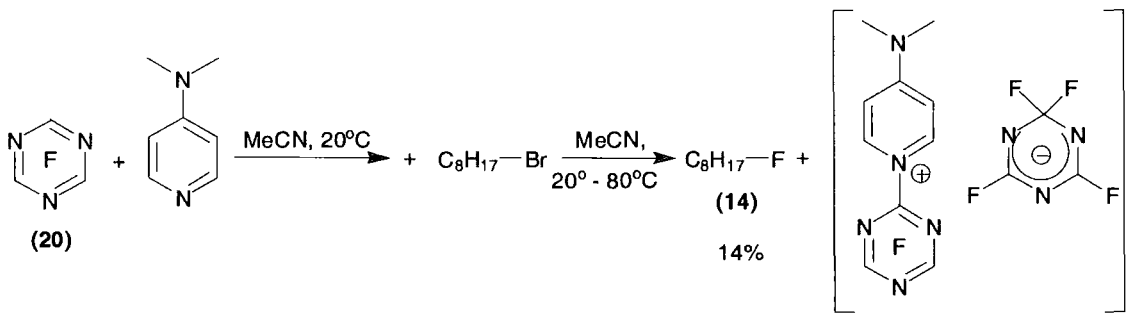
As PFP was unreactive towards further substitution under the employed conditions, the much more reactive TFT **(20)** was synthesised by a Halex reaction (Scheme 4.25):



Scheme 4.25 Synthesis of **(20)**

The synthesis was carried out on a moderate scale due to the relatively high cost of the fluorinated triazine and the ease of synthesis via a method previously developed by the Chambers group. With suitable precautions, the volatile products were transferred out of the hot, pressurised autoclave into evacuated traps cooled in liquid nitrogen. A colourless liquid containing some metal contaminants was isolated. Following further vacuum transfer, the expected product **(20)** was isolated pure in 84% yield, which compares well with previous results.

This reactive fluoroheterocycle was then employed in place of PFP in the hope that the proportion of "active" fluorine utilised for fluorination could be increased (Scheme 4.26).



Scheme 4.26 Use of a more reactive fluoroheterocycle as a fluoride ion source

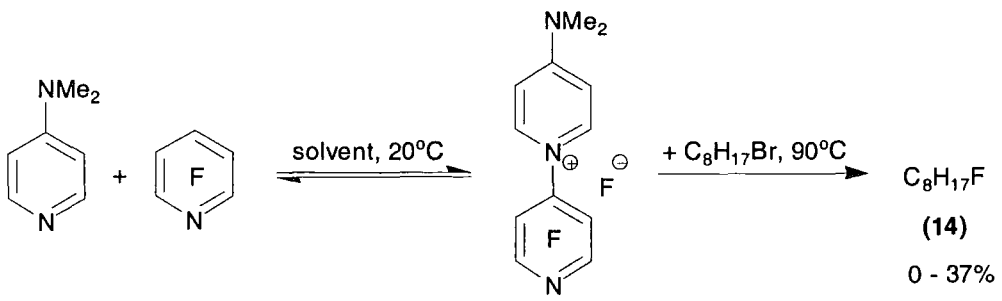
Table 4.7 Results of using a more reactive fluoroheterocycle

Reagent/molar equivalents			
1-Bromooctane	**DMAP**	**TFT**	**Yield of (14)/%**
1	1	1	14
1	3	1	10

No fluorination was observed at 20°C with one equivalent of DMAP, although rapid formation of a precipitate was noted upon the addition of **(20)** to the DMAP solution. ^{19}F NMR measurements confirmed the presence of fluorine shifts in the δ –5 to –10ppm range, thus indicating the formation of a stable σ-complex between fluoride ion and **(20)**.[36] This was present both before and after the fluorination reaction, and therefore clearly acted as a sink for fluoride ion in the system due to the fluorophilicity of the triazine, even above 60°C, the reported temperature for the onset of decomposition of the σ-complex (Table 4.7).[36] Reaction with three equivalents of DMAP gave a corresponding increase in intensity for the σ-complex peaks. As the previous reaction had shown, the σ-complex had a limited ability to donate fluoride ion and the reaction was stopped after 10 hours. This was shorter than the previous reaction, but long enough for any indicative increase in the yield of fluoroalkane **(14)** to have occurred.

4.2.2 Optimisation of Reaction Conditions

4.2.2.1 Solvent Screen



Scheme 4.27 Reaction for screening of solvents

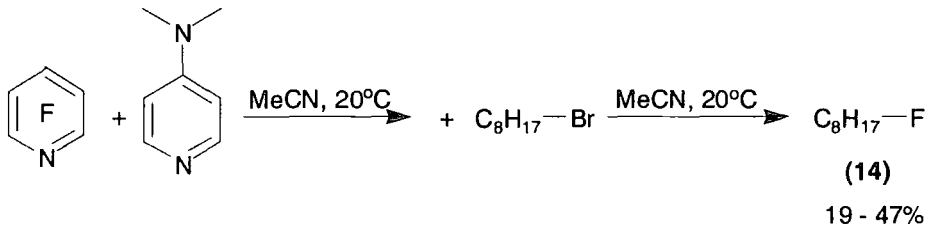
Table 4.8 Results of solvent screen

Solvent	Yield (14)/%
Ethylene glycol	0
DCM	19
THF	23
Toluene	24
MeCN	31
DMF	37

In order to optimise the reaction conditions, perhaps the most important factor is the choice of reaction medium. A screen was conducted using a Radleys 6-station Carousel reactor, equipped with a -10°C capable glycol/water cryostat for the condenser to allow the use of highly volatile solvents. DMAP was added to the solvent and stirred until dissolution was complete, at which point the PFP was added (Scheme 4.27). The reaction mixtures were stirred for a further five minutes to allow adduct formation, reaction being indicated in all of the solvents except ethylene glycol by the formation of the expected orange/yellow colouration.

An equimolar quantity of 1-bromooctane was then added rapidly to each vessel via a syringe and the Carousel heated to 90°C for eight hours. The reaction mixtures were allowed to cool and the stirring was stopped to allow any precipitate to settle before samples were withdrawn for quantitative ^{19}F NMR. The results showed that DMF and MeCN were the most effective solvents for fluorination, with the rest of the solvents significantly less well suited to the reaction (Table 4.8). As this research was directed towards to finding a methodology for fluorination in which product isolation was easy and environmental impact was minimised, use of DMF was ruled out. MeCN is significantly more volatile and it is much easier to isolate products from MeCN than DMF; it is also rather less toxic. For these reasons, MeCN was chosen as the most suitable solvent for these studies as it had produced an acceptable yield of fluorinated product compared to the other solvents.

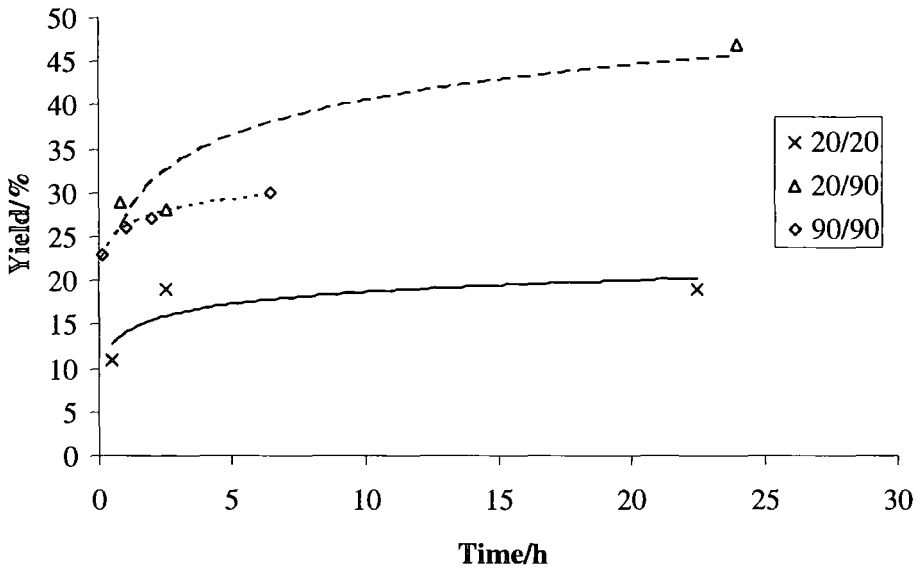
4.2.2.2 Effect of Temperature during Adduct Formation and Fluorination



Scheme 4.28 Effect of temperature during different reaction stages

Table 4.9 Results of changing temperature during different reaction stages

Temperature during:					
Adduct formation/°C	**Fluorination/°C**	**Yield of (14) (%)/time (h)**			
20	20	11/0.5	19/2.5	19/22.5	
20	90	29/50min	28/2.5	47/24	
90	90	23/10min	26/1	27/2	30/6.5

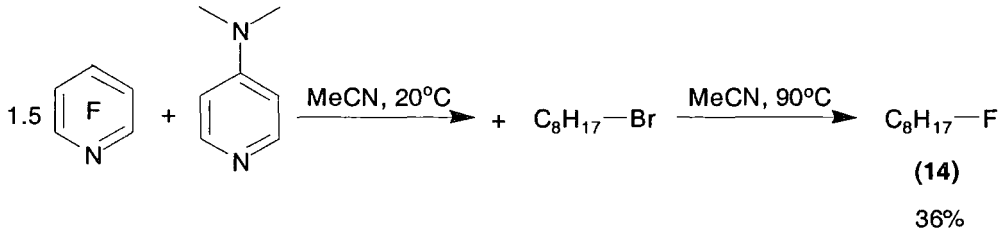


Scheme 4.9 Effect of varying temperature over different reaction stages on the yield of **(14)**

DMAP was dissolved in anhydrous MeCN as before and pentafluoropyridine was then added, causing the immediate formation of a pale yellow precipitate. After approximately five minutes, 1-bromooctane was added and the mixture left to stir at the appropriate temperature. At various times during the reaction, an aliquot of solution was transferred to an NMR tube equipped with a Young's tap as above for quantitative ^{19}F NMR. The time given is the time starting from the addition of the substrate, i.e. 1-bromooctane (Scheme 4.28).

As noted above (section **4.2.1.3**), reflux during the adduct formation stage resulted in excessive decomposition, causing the reaction mixture to turn a deep brown/black colour and ultimately significantly reducing the yield of **(14)**. Clearly, the best strategy was to pre-form the adduct at ambient temperature and then heat the reaction mixture to reflux upon the addition of the substrate. Attempts to increase the concentration of fluoride ion in the system by using two equivalents of DMAP and pentafluoropyridine relative to the substrate did not result in increased yields of fluorinated product (Table 4.9, Figure 4.9).

One further reaction was conducted with the aim of minimising the initial concentration of free DMAP in the reaction mixture by using an excess of PFP.



Scheme 4.29 Use of an excess of PFP

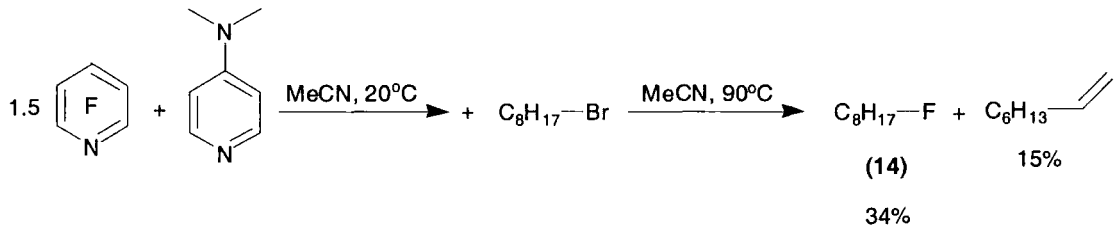
Table 4.10 Results of using an excess of PFP

Temperature during:		Yield of (14) (%)/time (h)	
Adduct formation/°C	Fluorination/°C		
20	90	22/1h 20min	36/25

An excess of pentafluoropyridine was used to ensure consumption of the available DMAP by negating evaporation losses of PFP (Scheme 4.29), but no appreciable difference in yield was observed (Table 4.10).

4.2.2.3 Difficulties Encountered During Fluorination Reactions

A. Alkene Formation

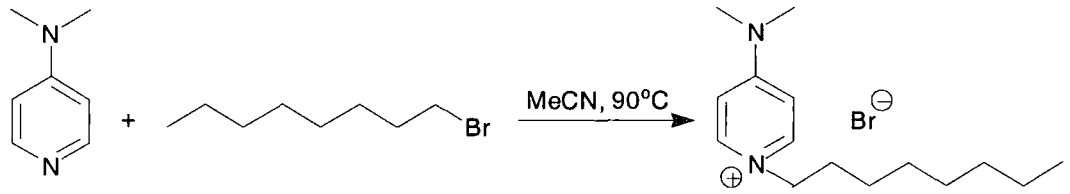


Scheme 4.30 Elimination process observed during fluorination reactions

A larger scale reaction was set up with the aim of isolating pure compounds as a proof of principle and to quantify the elimination products that were likely to be produced in the reaction (Scheme 4.30). Unfortunately due to the large quantity of solvent relative to the quantity of products, it was not possible to isolate the product materials free from solvent without incurring appreciable losses. As the yield of **(14)** could be deduced from quantitative ^{19}F NMR, the yield of octene and recovery of 1-bromooctane were calculated by reference to GC-MS analysis. Accordingly, the volatile materials were vacuum transferred and analysed. This revealed elimination to be a major factor with a 15% yield of alkene, comparable to Halex fluorination with metal fluorides.

B. Alkylation of DMAP

In order to further understand the lower than expected yields of fluorination resulting from the use of the DMAP-pentafluoropyridine adduct system as a source of soluble fluoride ion, a set of control reactions was carried out. It was believed that DMAP was nucleophilic enough to react rapidly with the electrophilic substrates. The hope was that all of the DMAP had been consumed in the initial adduct formation reaction, but attack of fluoride or bromide ion on the adduct could regenerate free DMAP.



(24)

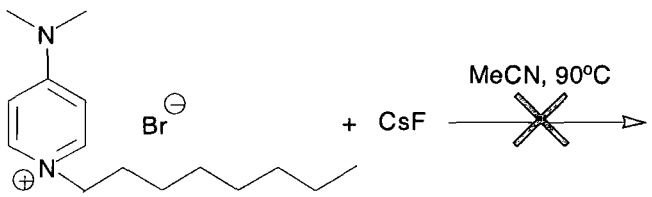
100%

Scheme 4.31 Alkylation of DMAP by electrophilic substrate

A reaction was performed to determine the extent of attack on the substrates by DMAP. The reaction went to complete conversion and the expected product, 4-

(dimethylamino)-1-octylpyridinium bromide (**24**), was isolated in 100% yield as a white solid (Scheme 4.31).[37]

C. Attempted Fluorination of 4-(Dimethylamino)-1-octylpyridinium Bromide



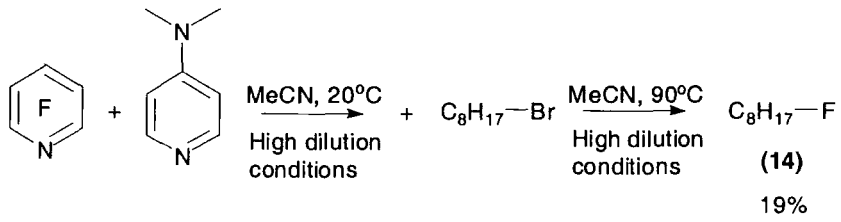
(24)

Scheme 4.32 Attempted fluorination of **(24)**

The adduct **(24)** from the above reaction was reacted with roughly one equivalent of CsF (ie an active source of fluoride ion) under similar conditions to those found in a typical fluorination reaction with the DMAP-pentafluoropyridine adduct (Scheme 4.32). It was hoped that as the C_8 chain was equipped with a suitable leaving group (the 4-(dimethylamino)pyridinium cation), S_N2 attack of fluoride would take place to yield 1-fluorooctane **(14)**, DMAP and CsBr. Unfortunately even after 24 hours at 90°C, no fluorination of the bromide **(24)** was detected. The ^{19}F NMR spectrum contained no resonances at all, indicating that elimination was not occurring to any great extent as no HF or pyridine-HF signals were detected. GC analysis of the vacuum-transferred volatile fractions confirmed this – no peaks were seen which corresponded to **(14)** or octene.

This result would seem to provide a convenient explanation for the poor yields obtained in the fluorinations with the DMAP-pentafluoropyridine adduct: Any residual DMAP present (or generated through equilibrium processes) in the reaction mixture has the effect of removing the substrate from the reaction as an inert pyridinium salt, thus lowering the overall yield of fluorinated product.

4.2.2.4 Effect of Dilution on Yield of Fluorination



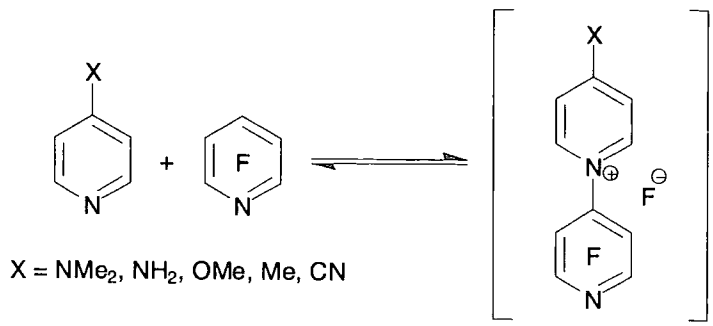
Scheme 4.33 Effect of high dilution conditions on the yield of **(14)**

More dilute reaction conditions (0.125M as opposed to 0.25M or 0.5M) were also investigated to enable to complete dissolution of the adduct (Scheme 4.33). In the previous reactions, the adduct had been present as a partially soluble precipitate, and it was hoped that the increased quantity of fluoride ion in solution, coupled with the driving force of the known lower solubility of the pyridinium bromide would force fluorination to occur. The yield of **(14)** here was disappointing as it was less than half the amount observed in section **4.2.2.2** after 24 hours; clearly the only effect of dilution is that of reduced reaction rate due to the lower concentrations of reagents.

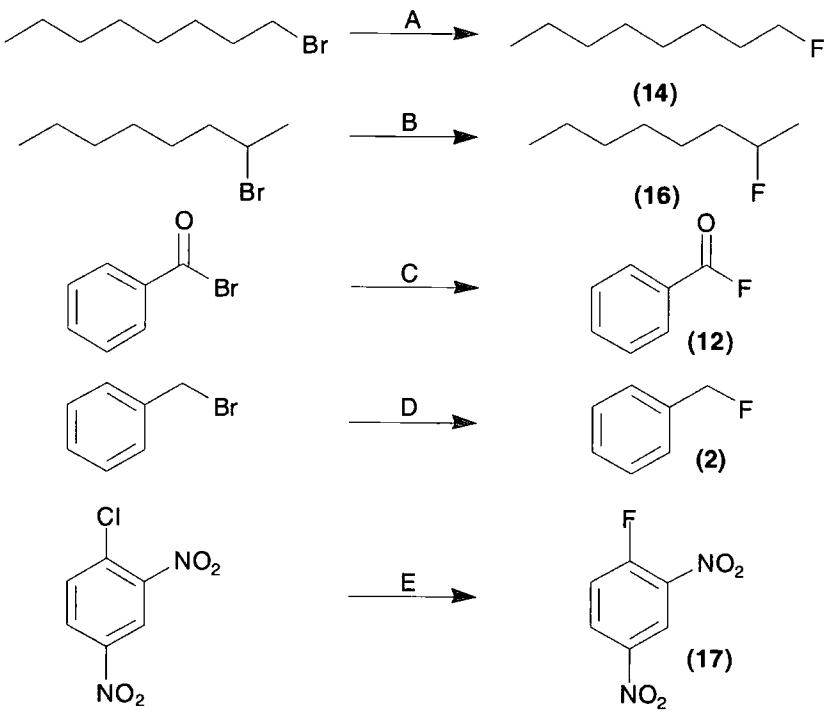
4.2.3 Fluorination System Screening

Having established that DMAP was at best only partially suitable as a nucleophile for the generation of fluoride ion from pentafluoropyridine, attention was turned to other pyridine systems. A screening program was set up, allowing the *in-situ* reactions of various pyridines with pentafluoropyridine. These adducts were then reacted with a range of electrophiles, thus broadening the scope of the work. This allowed for the optimisation of reagents as well as the conditions, as established previously.

4.2.3.1 Yields Produced by Different Fluorination Systems



Scheme 4.34 Reaction used for fluorination system screening



Scheme 4.35 Substrates and products generated by the various screens

Table 4.11 Results of fluorination system screening

Reaction	Amine 4-substituent time (h)/temp (°C)						
	NMe_2 18/20	NMe_2 23/90	NMe_2 17/90*	NH_2 16/90	MeO 19/90	Me 17/90	CN 19/90
A (14)/%	12	25	20	0	2	0	0
B (16)/%	0	8	10	0	0	0	0
C (12)/%	30	35	57	65	9	12	0
D (2)/%	33	34	13	3	<1	0	0
E (17)/%	72	71	64	6	74	15	0

*Reaction was heated upon addition of PFP, substrates added when temperature reached 90°C

The bulk of the optimisation work regarding reagents rather than conditions was carried out in a Radley's six station Carousel reactor, allowing (for these screens) five inert-atmosphere reactions to be carried out simultaneously under almost identical conditions. The reactions were all run using the same methodology, in that a solution of amine was made in MeCN, followed by addition of the fluoroheterocycle (Scheme 4.34). After stirring for approximately five minutes, the electrophilic substrate (Scheme 4.35) was added, the reaction mixture was heated to 90°C, and the reaction run overnight.

Precipitation was observed in many cases and so after cooling the stirring was stopped to allow any solids to settle out. A known volume of sample was then taken and added to a Young's-tap NMR tube. The tube was weighed and a known mass of 1,4-difluorobenzene added as a quantitative reference. Yields were then calculated from the ^{19}F NMR spectrum as the 1,4-difluorobenzene peak was distinct from any of the other peaks in the reactions (Table 4.11).

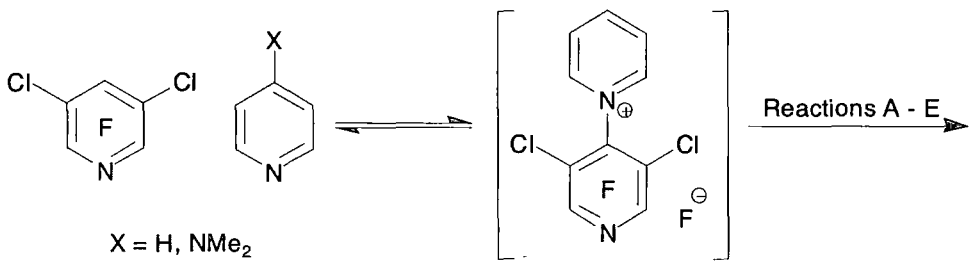
As seen above, problems were encountered in the reaction of an electrophilic substrate with the DMAP-PFP adduct due to alkylation of the free DMAP. Studies were conducted involving various substrates with a range of different 4-substituted pyridine nucleophiles. DMAP was the most highly nucleophilic of these, whilst 4-cyanopyridine was the least. It was hoped that for the less reactive electrophiles it

would be possible to find a pyridine system which was sufficiently active to react with the highly electrophilic pentafluoropyridine but not appreciably with the substrates.

Unsurprisingly, it appears that the DMAP/PFP system behaves as a stronger fluorinating agent at higher temperature. There is a general trend of decreasing reactivity with decreasing pyridine nucleophilicity as expected, but there are discrepancies. Yields of fluorooctanes are low or zero, but the yields of the more reactive systems are variable.

It was expected that the more highly reactive benzoyl, benzyl and chlorodinitrobenzene systems would give moderate yields even with the less reactive systems. However with the 4-NH_2 and 4-OMe systems there are inexplicable results for the benzoyl and dinitrobenzene systems. One would expect them to produce roughly comparable quantities in each case, but this is not observed.

Reactions with 3,5-Dichloro-2,4,6-trifluoropyridine



Scheme 4.36 Use of the more reactive 3,5-dichloro-2,4,6-trifluoropyridine as a fluoride ion source

Table 4.12 Results of using a more reactive, non-σ-complex forming fluoride ion source

System	A (14)/%	B (16)/%	C (12)/%	D (2)/%	E (17)/%
Pyridine	0				
DMAP	0	0	44	<1	24

A further attempt was made to decrease the formation of alkylated pyridine species by using the more reactive 3,5-dichloro-2,4,6-trifluoropyridine instead of PFP to allow the use of the less nucleophilic pyridine (Scheme 4.36). Unfortunately even with reaction for 17 hours at 90°C no fluorination of the 1-bromooctane substrate was

seen (Table 4.12). Use of DMAP for 17 hours at 90°C produced results much as before, with no fluorination of the less reactive substrates, an unexpectedly low yield of benzyl fluoride (**2**) and moderate yields for the benzoyl and dinitrobenzene systems.

4.2.3.2 Effect of Time Allowed for Adduct Formation

Table 4.13 Results of varying time between PFP and substrate addition

Time between PFP and substrate addition/min	1	3	10	15	30
Yield (14)/%	22	24	29	34	28

As the formation of the adduct between PFP and DMAP takes a finite length of time, an investigation was conducted into the effect of the length of time between PFP addition and substrate addition in the Carousel reactor. A reaction was run for 17½ hours at 90°C with 1-bromooctane as the electrophile. As can be seen from the results (Table 4.13), there is a definite trend, indicating that the adduct takes around 15 minutes to form and that prior to this time some remaining DMAP is able to react with the substrate. The drop in yield of (**14**) at 30 minutes is perhaps indicative of decomposition of the adduct.

4.2.4 Phase Transfer Catalysis Reactions

4.2.4.1 Use of DMAP Adduct as PTC

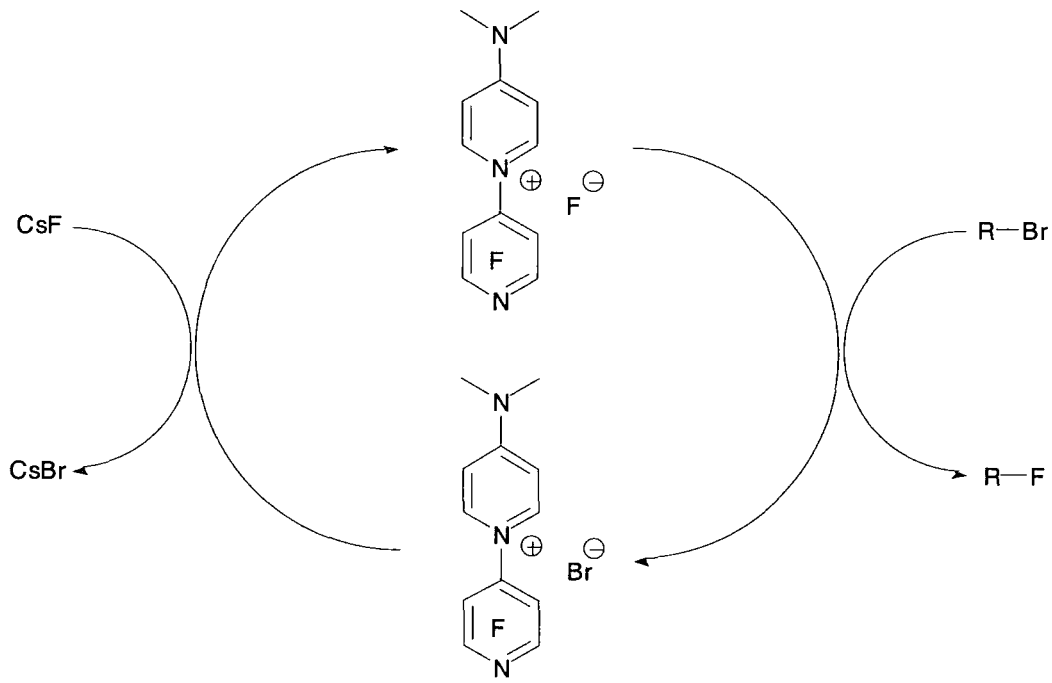
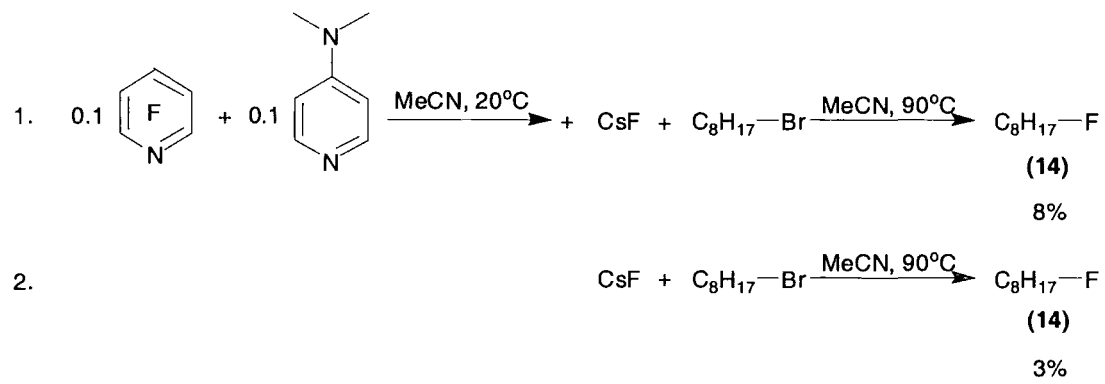


Figure 4.10 Proposed PTC pathway for pyridinium system

An attempt was made to encourage the catalytic cycle shown above (Figure 4.10) by using CsF as the fluoride source and a small quantity of the pre-formed adduct as a PTC (Scheme 4.3).



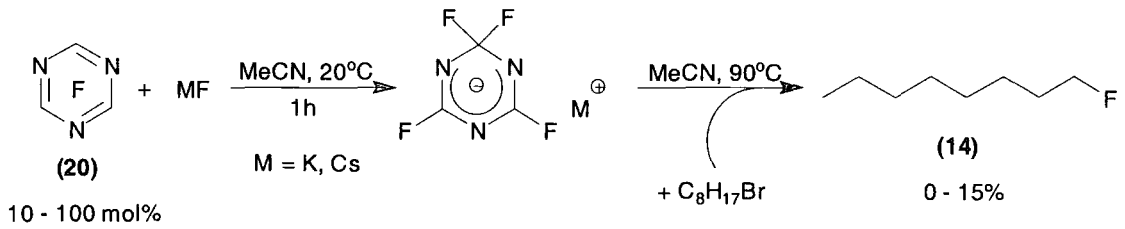
Scheme 4.37 Attempted use of a catalytic quantity of the adduct as a PTC with caesium fluoride

Table 4.14 Results of the use of the adduct as a PTC with caesium fluoride

Time/h	Yield (14) without PTC/%	Yield (14) with PTC/%
17 (20°C)	0	0
5 (90°C)	3	8

Two reactions were set up in a Carousel reactor with CsF in MeCN as the fluorinating agent and 1-bromooctane as the substrate. One of the reaction vessels had a small quantity of DMAP and pentafluoropyridine added (10 mol %) prior to the addition of CsF. 1-Bromooctane was then added and the reactions run for 17 hours at 20°C followed by 5 hours at reflux. The adduct showed some minor effect but this was so small as to be insignificant and possibly due to fluorination by the adduct itself (Table 4.14).

4.2.4.2 Use of Fluoroheterocycles as PTCs

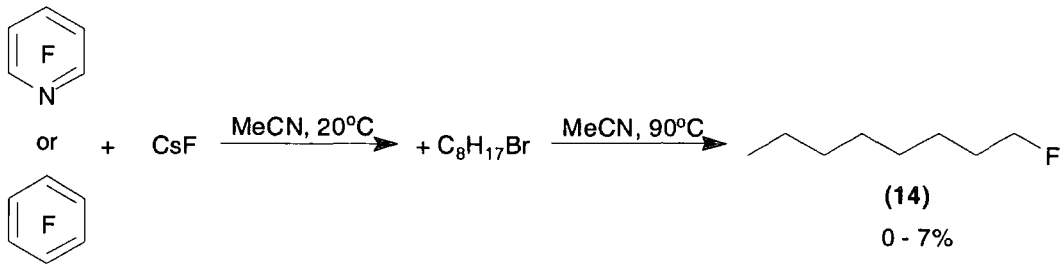


Scheme 4.38 Attempted use of **(20)** as PTC

Table 4.15 Results of using **(20)** as a PTC

Time(h)/temperature(°C)	Yield of (14) under conditions shown (%)		
	MF/mol% TFT		
	KF/100	CsF/10	CsF/100
16½/20	0		0
4/60	0		0
3/90	0		4
47/90		1.5	
116/90	0		15

Following work conducted above (section **4.2.1.4**) with TFT and DMAP, in which the free fluoride ion reacted with residual TFT to form a σ-complex,[36] it was decided to investigate whether this property could be used to enhance the solubility of fluoride ions from a conventional source. Experiments were conducted with either KF or CsF as the fluorinating agent, 1-bromooctane as the substrate and varying amounts of TFT as a phase transfer catalyst (Scheme 4.38). The TFT and metal fluoride were stirred together for one hour at 20°C prior to 1-bromooctane addition. NMR analysis showed formation of the expected σ-complex for CsF only; the solution with KF exhibited the same ^{19}F NMR spectrum as TFT. The only reactions in which fluorination occurred were those with CsF, and the yield of the fluoroalkane **(14)** was highly dependent on the quantity of TFT present. The reaction with 10mol% TFT had produced less **(14)** in 47 hours than the reaction with 100mol% TFT had produced in three hours at 90°C (Table 4.15). Clearly the major active fluorinating agent was the decomposing σ-complex rather than residual CsF, although yields are very low.



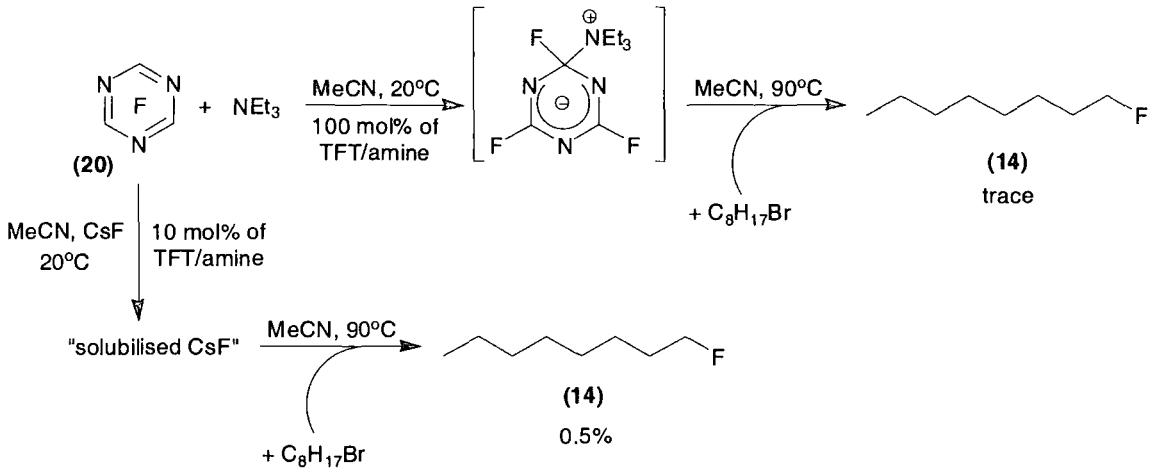
Scheme 4.39 Attempted use of less reactive fluoroheterocycles as PTCs

Table 4.16 Results of using less reactive perfluoroheterocycles as PTCs

Time(h)/temperature(°C)	**Yield of (14) under conditions shown/%**	
	Heterocycle/mol%	
	PFP/100	Hexafluorobenzene/100
18/20	0	0
71/90	7	5

One possible reason for the lack of fluorination is that the σ-complex was too stable, i.e. it forms as soon as any fluoride is dissolved and then reaction with the substrate is dependent entirely on the decomposition of the potentially very stable σ-complex. It was decided to use the considerably less fluorophilic heterocycles PFP and hexafluorobenzene to test this hypothesis (Scheme 4.39). It should be noted that these species are not known to form relatively stable σ-complexes with fluoride ion and so in these cases CsF was used with 100mol% of the potential PTC. With these reactions it is difficult to tell whether the heterocycle is having any effect as the yields are similar in each case to those expected from the control reaction with CsF alone. Indeed, heating 1-bromooctane together with CsF in NMP for 31h gave a 14% yield of **(14)**. Clearly these systems are rather ineffective as phase transfer catalysts, although they do not appear to retard fluorination in the way that the σ-complex forming TFT does when present in 10mol% quantities.

4.2.4.3 Use of Fluoroheterocycle-tertiary Aliphatic Amines as PTC or Fluoride Ion Source



Scheme 4.40 Attempted use of a **(20)**/aliphatic amine adduct as a PTC or fluoride ion source

Table 4.17 Results of using a **(20)**/aliphatic amine adduct as a PTC or fluoride ion source

Time (h)/temperature (°C)	Yield of (14) under conditions shown/%	
	TFT/NEt_3 (10mol%) as PTC for CsF	TFT/NEt_3 (100mol%) as fluorinating agent
16/20	0	0
8/90	0.5	trace

A further approach taken was the use of a tertiary aliphatic amine, triethylamine, employed both as a fluoride release agent analogous to DMAP and as a PTC in conjunction with TFT and CsF (Scheme 4.40). Similarly to above, reactions were conducted in MeCN with either 100mol% TFT/NEt_3 as the fluorinating agent or with 10mol% of TFT/NEt_3 as the PTC and 100mol% CsF as the fluorinating agent.

Unfortunately, although some fluorination was observed in both cases after reaction at high temperature, the yields of **(14)** were very small (Table 4.17). The 0.5% seen for the PTC case is less than that seen for the control reaction with CsF alone in MeCN (3%/5h, 6%/14h, see sections **4.2.4.1** and **3.8.1** respectively), hence the TFT system is acting as a retarding agent once again, even in the presence of an

equimolar quantity of amine which should cause the formation of a less fluorophilic triazine σ-complex capable of fluoride ion exchange. In the reaction with TFT/NEt_3 as the only source of fluoride ion, only a trace of fluorination was seen, indicating that the σ-complex is very stable.

4.3 Synthetic Studies – Isolation of Amine-fluoroheterocycle Adducts

Following the fluorination studies conducted above, the scope of the project was altered slightly to include the synthesis and characterisation of several of the amine fluoroheterocycle adducts. As reported above, very few publications have been made in this area, and there is only one report of an isolated and characterised adduct of pentafluoropyridine with a pyridine species.[22] Attempts were therefore made to synthesise a range of different adducts based on the reaction of pentafluoropyridine, tetrafluoropyrimidine and trifluoro-*s*-triazine with various nucleophilic amines.

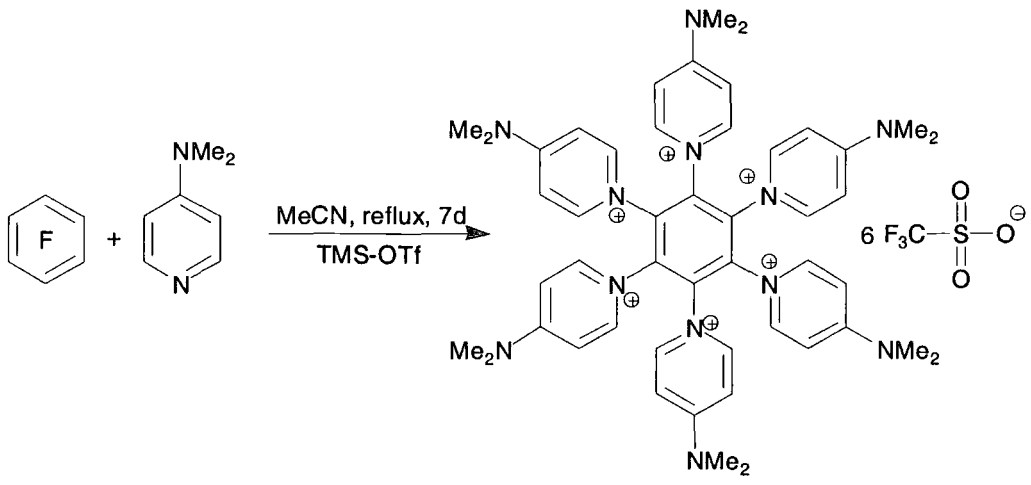
4.3.1 General Points

A variety of syntheses was attempted before a good set of synthetic methods was obtained, as outlined below. The successful general methods will be presented first, together with illustrative examples of the compounds isolated by the respective methods. Following this section, there will be a more general report on the various other routes that were attempted and were either unsuccessful or only partially successful.

4.3.1.1 Fluoride Salt Isolation and Decomposition – Reasons for Pursuing More Stable Analogues

Initial isolation studies focussed on the DMAP/PFP adduct, i.e. the fluoride salt. Although it was possible to isolate crude samples of this material as a pale yellow solid, purification was not successful as decomposition always occurred. It is likely that hydrolysis occurred, aided by the hygroscopic nature of fluoride ion to yield oxygen-containing functionalities on the fluoropyridine ring system, thus giving rise to a variety of products. Because of this discouraging result, it was decided to use a

more stabilising anion such as tetrafluoroborate or triflate, as had been demonstrated for the corresponding published fluorobenzene/DMAP adducts (Scheme 4.41).[30, 31] In this case the fluoride is removed from the system, thus removing the possibility of re-attack, by conversion to the gaseous fluorotrimethylsilane.



Scheme 4.41 Example of the use of triflate anions to allow for the isolation of more stable products

Apart from the higher stability of such systems (less susceptible to hydrolysis, bulky non-nucleophilic anion), the likelihood of obtaining high quality crystals suitable for X-ray diffraction is much improved due to the larger size of the anion and the less hygroscopic nature of the resulting compounds.

4.3.1.2 Difficulties Encountered in Synthesis, Purification and Characterisation.

The synthetic side of this project encountered a significant problem which was not fully overcome. The purification and characterisation of the reaction mixtures were extremely challenging. Initial analysis of the crude reaction products (which were often sparingly soluble amorphous solids) was in most cases limited to NMR. This was complicated by the fact that many of the materials were insoluble in most common deuterated solvents (for example chloroform and benzene) and often reacted with those that they dissolved in (dimethylsulfoxide, methanol and water).

Product mixtures were almost always obtained, rendering conventional MS techniques unsuitable, although use was made of electrospray ionisation in isolated

cases. This allowed molecular ion peaks to be observed in some materials, although as seen below it often produced rather complex spectra, perhaps indicative of rearrangement or reaction within the mass spectrometer. Elemental analysis was used occasionally to poor effect on the crude product mixtures where other techniques indicated that a sample might be relatively pure. Unfortunately, the samples were frequently very hygroscopic, necessitating the use of a glove box for sample preparation. The few samples which gave acceptable elemental analysis results were fairly stable towards atmospheric moisture, and no successful analysis of any of the intermediate fluoride salts was obtained despite repeated attempts to purify and characterise them.

However, even though the array of spectroscopic techniques usually applicable to a synthetic project was diminished, appropriate information was still obtainable from NMR studies. Several characteristics of the various species allowed accurate interpretation of many of the product mixtures. Specifically, the ^{19}F NMR signals of the fluorinated pyridine system allowed rapid assignment of substitution patterns around the ring. Also, the ring protons of the DMAP moieties exhibited distinct, well resolved and often well separated shifts even with small differences in local environment.

Product purification was also rather challenging as many of the impurities were similar to the desired products, i.e. mono- or polycationic species containing the same (or similar) functional groups. Normally, separation of such species would be undertaken by column chromatography but this was not generally applicable for such systems. Attempts to run TLC analysis of various product mixtures led to the discovery of two problems: Firstly, the general lack of solubility in suitable solvents at ambient temperature, as noted above. MeCN was one of the few solvents that dissolved reasonable quantities of the adducts without reacting with them. Secondly, on performing the TLC analysis for the DMAP/PFP tetrafluoroborate adduct **(23)**, it was found that the vast majority of the material stayed on the baseline. Only a very small quantity of material eluted, and this was used as the basis of a last resort preparative scale TLC of a non-ionic reaction product (section **4.3.3.1**). Another group had previously reported purification of the analogous fluorinated benzene adducts via a laborious multi-stage precipitation procedure using various solvents.[29] It would

appear that the fluorobenzene adducts are both easier to purify and more resistant to hydrolysis.

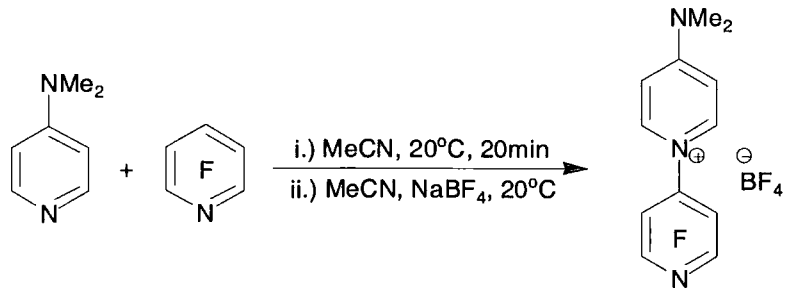
Purification was therefore generally carried out by various different methods of recrystallisation. Again, the choice of solvents was limited but pure compounds were isolated in several cases. Once pure compounds had been obtained, characterisation was relatively straightforward. NMR, MS and elemental analysis techniques (generally for the non-hygroscopic species) gave the expected results, and attempts were made to obtain crystals suitable for XRD in all cases, although only three compounds yielded suitable crystals.

4.3.2 Synthetic Routes

4.3.2.1 Metathesis with Sodium Tetrafluoroborate

Perhaps the most obvious technique for replacing the fluoride ion of the "straight" adducts is that of metathesis with a suitable species.[33]

4.3.2.1.A Synthesis of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Tetrafluoroborate



(23)
17%

Scheme 4.42 Synthesis of **(23)**

In this case, sodium tetrafluoroborate was used successfully to prepare the first appreciably stable, fully characterised quaternary nitrogen species bonded to a perfluoropyridine moiety (Scheme 4.42). The fluoride salt was prepared by adding an

equimolar quantity of PFP to a solution of DMAP in MeCN. After stirring for 20 minutes, the pale yellow solid was isolated by filtration under reduced pressure using Schlenk techniques and washed with cold MeCN.

The solid was redissolved in MeCN to form a slurry and one equivalent of $NaBF_4$ was added. After stirring overnight, a clear bright yellow solution had formed with a fine white precipitate that was assumed to be sodium fluoride. The solution was filtered through a fine frit and the solvent was removed *in-vaccuo*. The yellow solid thus obtained was then recrystallised several times from MeCN to yield the expected product **(23)** as a white crystalline solid in 17% yield.

Single crystals of this material were grown from the bright yellow MeCN solution by slow evaporation at ambient temperature (over approximately three weeks). These were colourless and gave excellent elemental analysis results. Submission for XRD produced the data shown below, with an interesting head-to-tail packing arrangement seen for the cations (Figures 4.11, 4.12). The orthogonality of the rings is presumably due to repulsion between the 3,5-ring fluorine atoms and the pyridine hydrogen atoms. This allows the material to crystallise in a manner which causes the formation of continuous stacks of alternating tetrafluoropyridine rings and tetrafluoroborate ions, essentially creating fluorous domains within the structure.

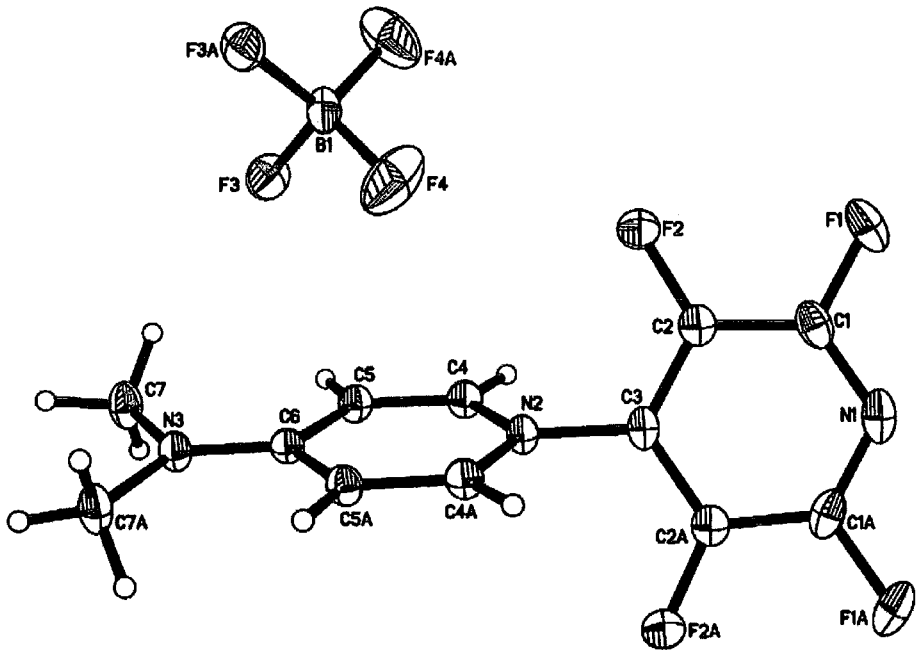


Figure 4.11 Molecular structure of (23)

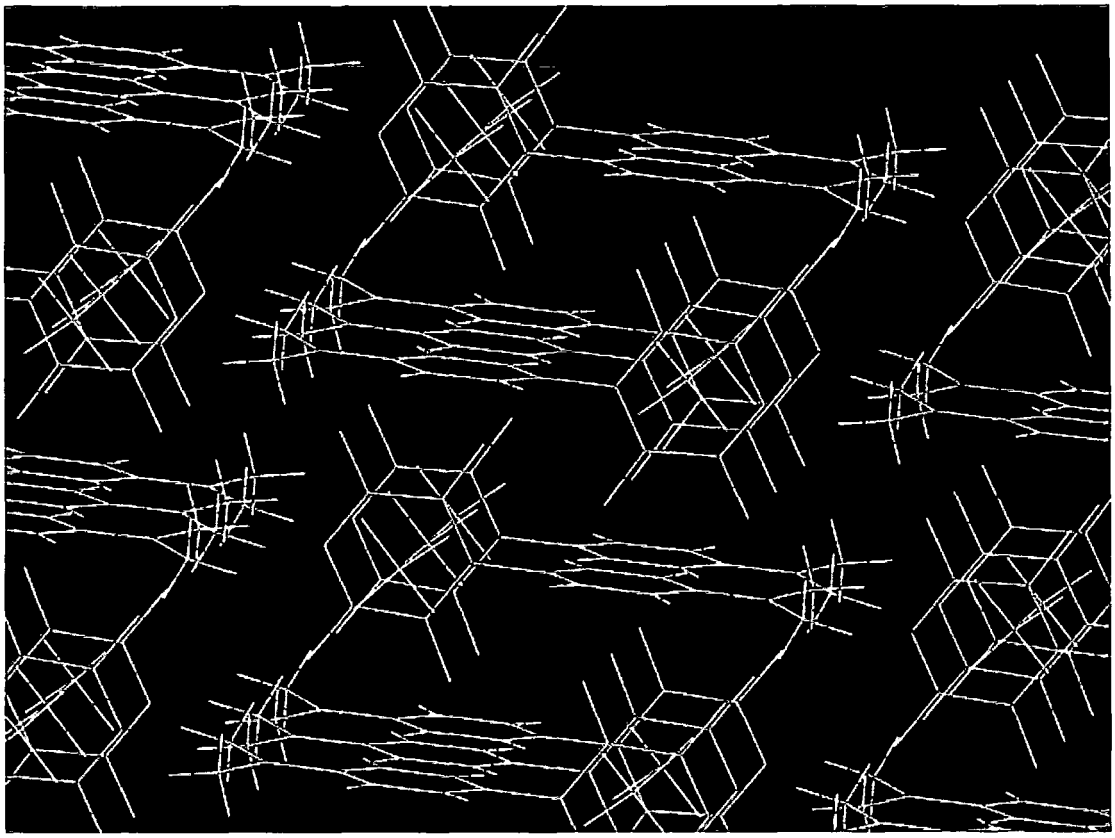
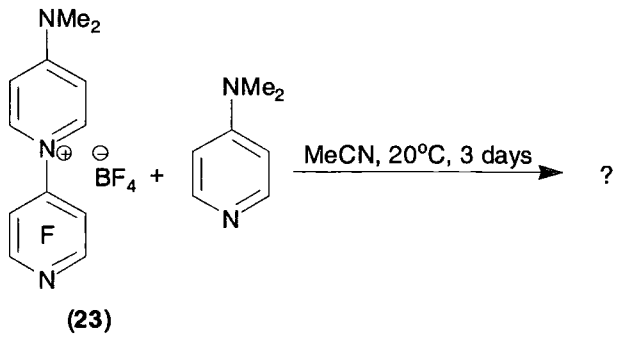


Figure 4.12 Crystal structure of **(23)**

4.3.2.1.B Reactions of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Tetrafluoroborate with a Range of Nucleophiles

Once suitable synthetic methodology for the production of the DMAP/PFP adduct had been established, the synthesis was scaled up to allow the chemistry of **(23)** to be probed. Reactions were undertaken with a small selection of nucleophiles, although results in this somewhat limited study were not entirely conclusive.

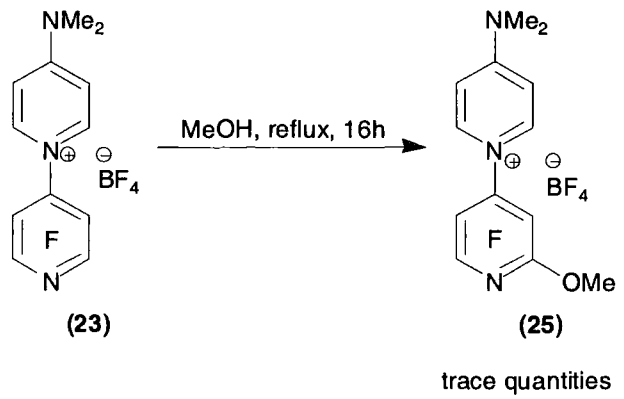
Reaction of Adduct with DMAP



Scheme 4.43 Reaction of **(23)** with DAMP

Reaction of **(23)** with a molar equivalent of DMAP produced a variety of peaks in the ^{19}F NMR after 1 3/4 hours at 20°C (Scheme 4.43). After one day, only a small quantity of starting material was left; after three days no further change was seen and the reaction mixture was poured into water and extracted with DCM. Only 0.022g of an off-white solid (16% mass recovery) was isolated due to the hydrophilicity of the materials involved. Analysis of the product was inconclusive, and neither NMR nor MS techniques yielded enough information to allow identification of the products.

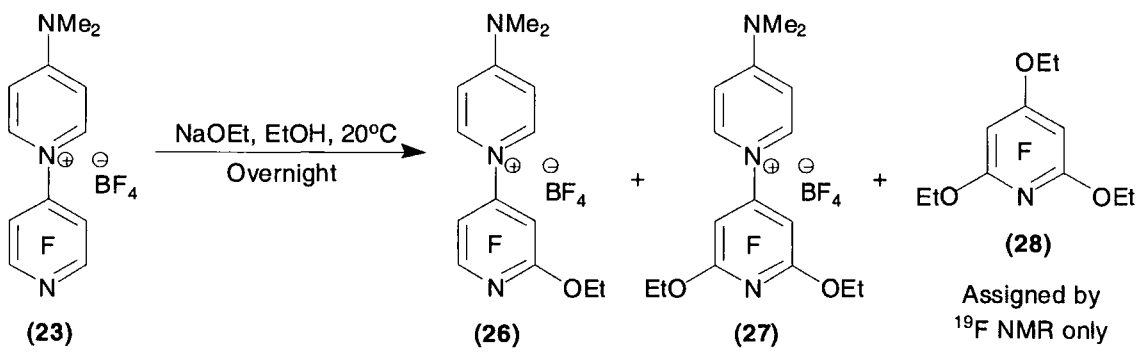
Reaction of Adduct with Methanol



Scheme 4.44 Reaction of **(23)** with methanol

As part of the purification procedure, an attempt was made to recrystallise adduct **(23)** from methanol, owing to the large solubility difference observed with hot and cold methanol. To test the stability of **(23)** in hot methanol, the material was refluxed in methanol overnight (Scheme 4.44). After removal of the solvent, ^{19}F and ^{1}H NMR measurements of the recovered white solid showed it to be identical to the starting material, although MS-ES^{+} showed a small peak at *m/z* 284 in addition to the starting material, demonstrating that reaction with methanol had taken place to a small extent to yield the 2-methoxypyridine **(25)**.

Reaction of Adduct with Sodium Ethoxide

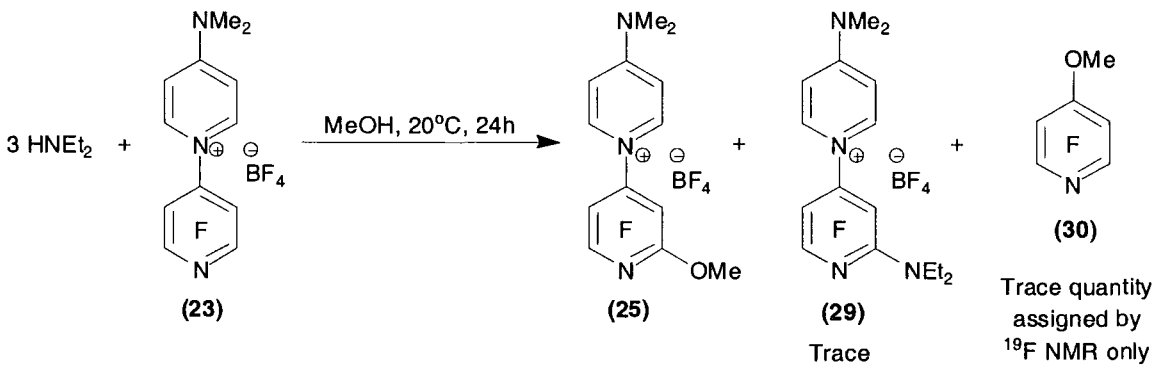


Scheme 4.45 Reaction of **(23)** with sodium ethoxide

Reaction of adduct **(23)** with one equivalent of freshly prepared sodium ethoxide in ethanol solution gave rise to an immediate yellow colouration at ambient temperature (Scheme 4.45). A white precipitate was formed overnight and the solution was then filtered and the solvent removed. A pale yellow solid (mass recovery 93% based on the expected product) was isolated, and shown to be a mixture of the 2-ethoxy **(26)** (major) and 2,6-diethoxy **(27)** (minor) substituted adduct species by ^{1}H and ^{19}F NMR and MS techniques.

A further reaction, with purification by preparative scale TLC in 6 : 1 hexane : DCM, gave three products, only one of which contained enough material for analysis. This middle spot was shown by ^{19}F NMR to be a 2,4-disubstituted-3,5,6-trifluoropyridine. From comparison with a known sample, and the fact that this material moved up the pate, whereas the ionic adduct species did not, the spot was tentatively identified as 2,4-diethoxy-3,5,6-trifluoropyridine **(28)**. This material was present in the reaction mixtures of both reactions.

Reaction of Adduct with Diethylamine in Methanol



Scheme 4.46 Reaction of **(23)** with diethylamine in methanol

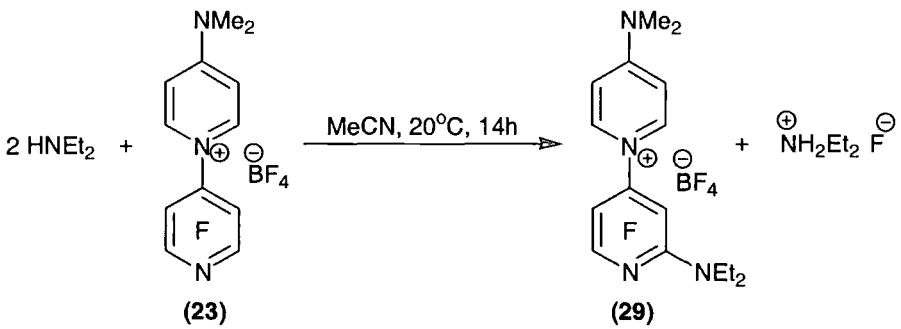
Addition of $HNEt_2$ to a MeOH suspension of adduct **(23)** at 20°C led to approximately 50% conversion of starting material in two hours (Scheme 4.46). Further conversion was unlikely due to formation of diethylammonium fluoride and so, with monitoring by ^{19}F NMR, two further equivalents of the amine were added over the next 24 hours. Addition of the second equivalent raised the conversion to approximately 80%, whilst the third equivalent had very little effect on the reaction.

The volatile fractions were then removed to yield a sticky pale yellow solid which was soluble in DMSO.

Analysis of this material by NMR showed it to contain the 2-methoxy substituted adduct (**25**) as the main product, with appreciable contamination by N-ethyl containing impurities. The MS-ES$^+$ spectrum showed that in addition to (**25**), approximately 10% of the 2-diethylamino substituted adduct (**29**) was present in the crude product. The volatile fraction showed very weak ^{19}F resonances at δ -92.78 and -160.57ppm, indicating attack had also occurred at the 4-position resulting in the displacement of the DMAP moiety and the formation of a volatile species, probably 4-methoxytetrafluoropyridine (**30**). Clearly the adduct is reactive towards nucleophilic species, but the $HNEt_2$ reacted more rapidly with the methanol to produce methoxide.

Recrystallisation of the solid from methanol, followed by repeated washing with methanol led to the isolation of a small quantity of a white solid. Analysis of this material by NMR and MS-ES$^+$ showed it to be a relatively pure sample of (**25**), although satisfactory elemental analysis results were not obtained.

Reaction of Adduct with Diethylamine in MeCN

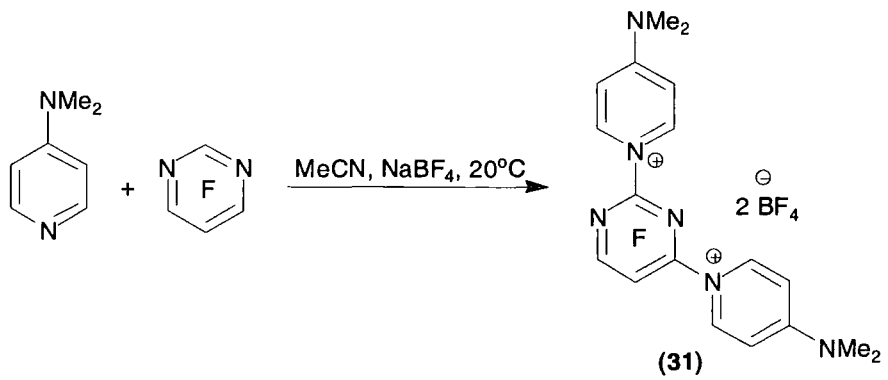


Scheme 4.47 Reaction of (**23**) with diethylamine in acetonitrile

Reaction of adduct (**23**) with two equivalents of diethylamine in MeCN gave 100% conversion after 14 hours at 20°C (Scheme 4.47). Isolation of the product by removal of the volatile material under vacuum yielded a brown oil (93% total mass recovery, but 114% recovery based on the expected product. In other words the desired product was significantly contaminated with other material), which was

shown to be the 2-diethylamino substituted adduct (**29**) contaminated with diethylammonium fluoride.

4.3.2.1.C Synthesis of 4-Dimethylamino-1-[2-(4-dimethylaminopyridinium)-5,6-difluoro-pyrimidin-4-yl]-pyridinium Tetrafluoroborate



Scheme 4.48 Synthesis of (**31**)

This compound was synthesised using a variation of the sodium tetrafluoroborate metathesis technique, in which sodium tetrafluoroborate was present during the initial adduct formation (Scheme 4.48). A pale orange solid precipitated on cooling after several days at 20°C and, after several recrystallisations, a very small quantity of pure product was isolated and determined to be the 2,4-diadduct of DMAP and tetrafluoropyrimidine (**31**). This unexpected substitution pattern can be explained by fluoride-ion catalysed rearrangement processes,[18, 38] in which the initially formed expected 4,6-adduct is isomerised to the observed 2,4-adduct (**31**). Purification and analysis of the material was difficult and this caused many problems. Eventually, crystals suitable for XRD were obtained and a poor quality X-ray structure determined (Figure 4.13). The structure was highly disordered, due to the dimethylamino and tetrafluoroborate groups assuming several different configurations in the lattice. The tetrafluoroborate groups are omitted for clarity in the structure shown below.

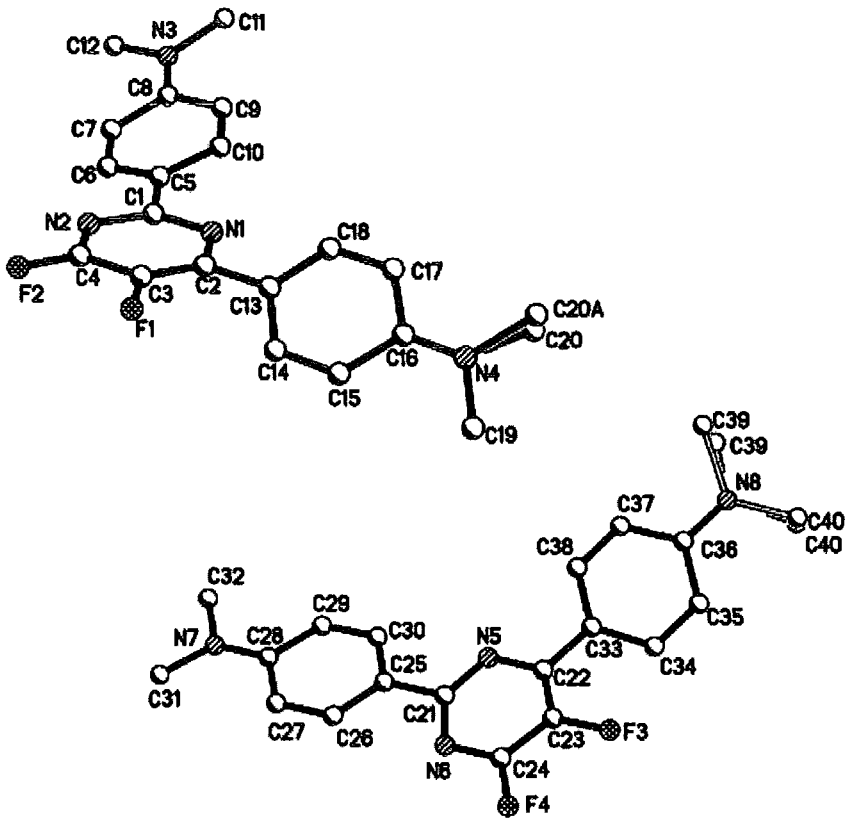


Figure 4.13 Partial molecular structure of **(31)**. Note disorder of methyl groups

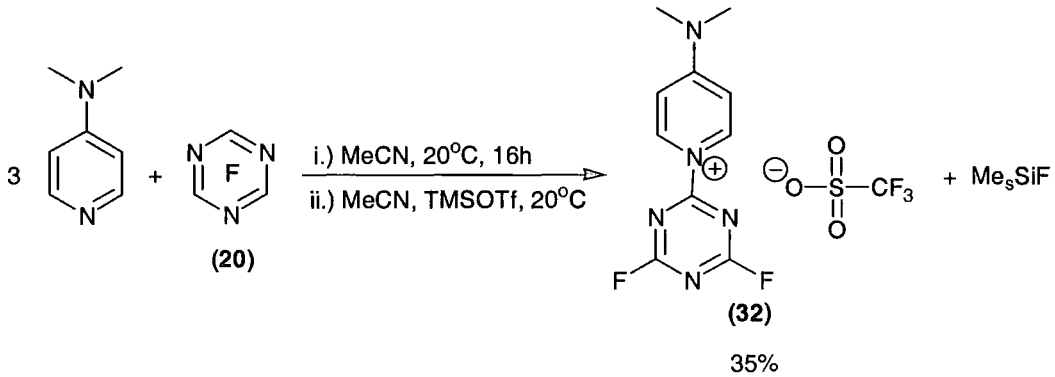
If we consider the two other isolated DMAP-fluoroheterocycle cations, the *s*-triazine-centred compound **(32)** (section **4.3.2.2.A**) would clearly be susceptible to nucleophilic attack by fluoride ion. However, this process would result in the formation of a stable σ-complex[36] as seen in the fluorination experiments above, thus trapping the fluoride ion. Conversely, the DMAP adduct containing a tetrafluoropyridine core **(23)** (section **4.3.2.1.A**) is necessarily the least reactive and does not form a detectable σ-complex; some degree of reverse reaction due to nucleophilic fluoride ion would therefore be expected (and indeed was demonstrated in the fluorination screen reactions above). Because of this behaviour, both of these adducts are unlikely to be suitable for PTC-type fluorination with a fluoride ion source.

The fluoropyrimidine adduct **(31)** is expected to possess intermediate behaviour in that it should have higher reactivity than the corresponding pyridine

analogue, whilst avoiding the complications associated with stable σ-complex formation as observed for the triazine analogue. It would seem likely that this adduct would be the most susceptible of all the isolated adducts to reversible attack of fluoride ion, and may therefore be the most preferable system for PTC fluorination, i.e. as a "solubilising" agent for fluoride ion from another source (e.g. CsF).

4.3.2.2 Metathesis with Trimethylsilyl Trifluoromethanesulfonate[30]

4.3.2.2.A Synthesis of 1-(4,6-Difluoro-1,3,5-triazin-2-yl)-4-(dimethylamino)pyridinium Trifluoromethanesulfonate



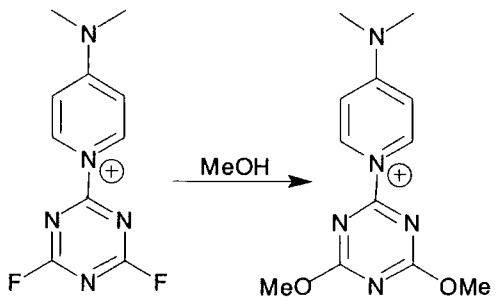
Scheme 4.49 Synthesis of **(32)**

Following a literature procedure for the preparation of stabilised polycationic species utilising trimethylsilyl trifluoromethanesulfonate (TMS-OTf) to drive the reaction through loss of volatile trimethylsilyl fluoride,[30] an analogous process was attempted. TFT **(20)** was reacted with three equivalents of DMAP to produce a white precipitate (Scheme 4.49). This was filtered and washed under an inert atmosphere using Schlenk techniques before being slurried in MeCN and treated with TMS-OTf.

Following the addition of TMS-OTf, the reaction mixture was stirred at room temperature and argon was passed through the headspace of the reaction to remove TMS-F. Cloudy white fumes were observed exiting the bubbler from the reaction, indicating either trimethylsilyl fluoride evolution or else the release of excess TMS-OTf. The resulting pink solution, containing a white solid, was filtered and washed

under an inert atmosphere to yield the mono-substituted *s*-triazine **(32)** as a white powder in 35% yield.

During characterisation of this compound, the high reactivity of the fluorine atoms on the triazine ring was demonstrated in the mass spectrum of the product. The spectrum was run using electrospray ionisation in MeCN solvent, but with methanol as a dilutant. The product reacted with the methanol to produce a non-fluorinated di-methoxy compound in the mass spectrometer (Scheme 4.50):



Scheme 4.50 Reaction of **(32)** with methanol inside the mass spectrometer

A sample of **(32)** was carefully recrystallised by slow evaporation of its MeCN solution to yield a crystalline material that was suitable for single crystal X-ray diffraction, with the structure shown below (Figure 4.14). Again, head to tail packing was observed although an overall "herring-bone" configuration was seen also (Figure 4.15). The crystal structure obtained was rather different to that seen for **(23)** (see section **4.3.2.1.A**), as the pyridine and fluoropyridine rings are coplanar. In this compound, there are no 3,5-fluorine atoms on the fluoroheterocyclic ring to cause repulsion of the pyridine ring system.

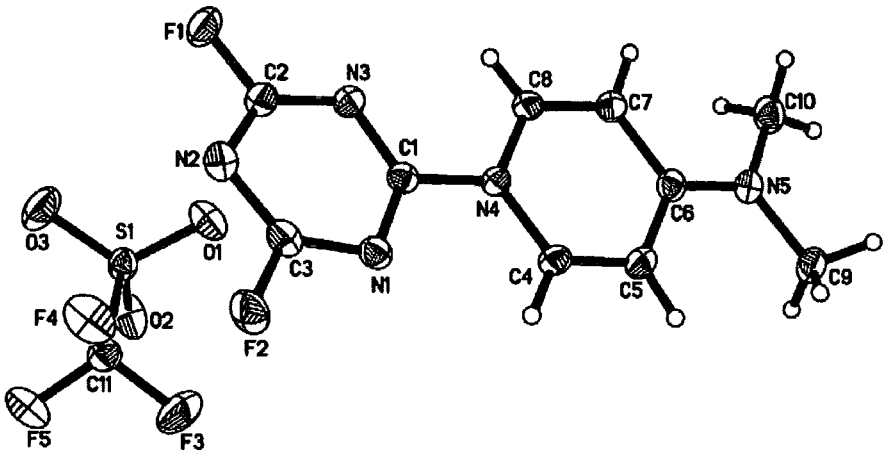


Figure 4.14 Molecular structure of **(32)**

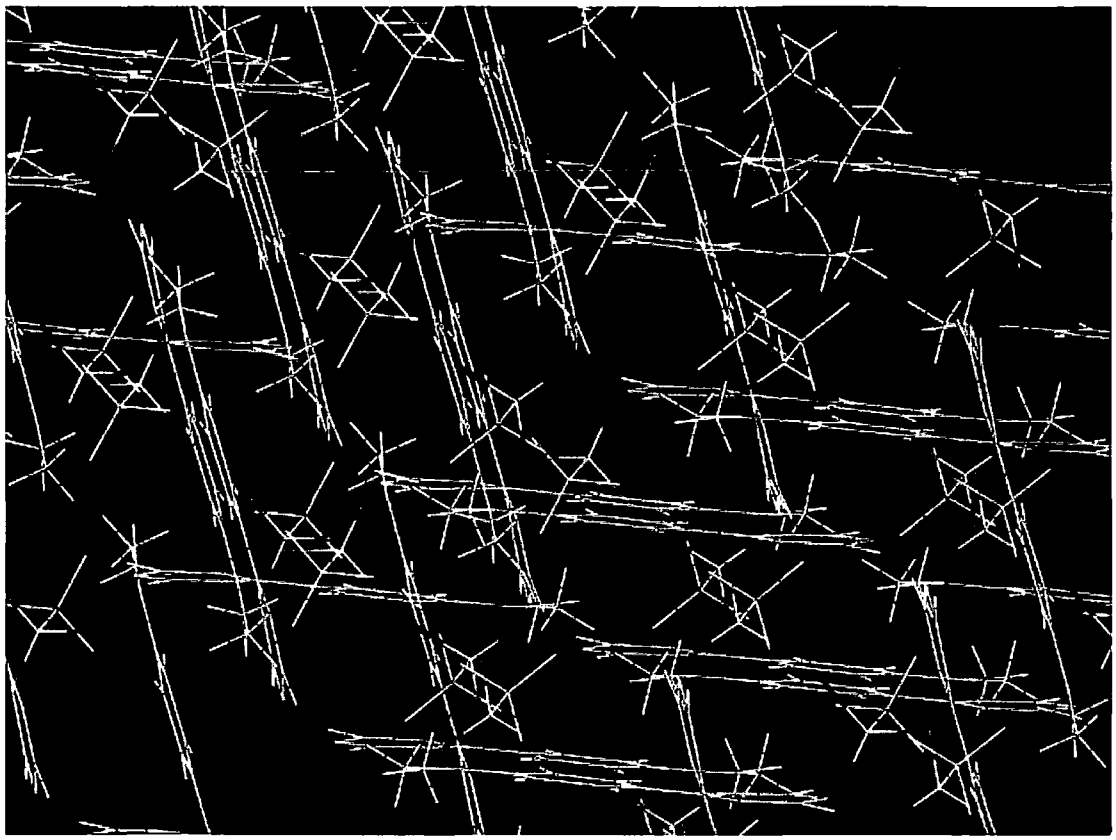
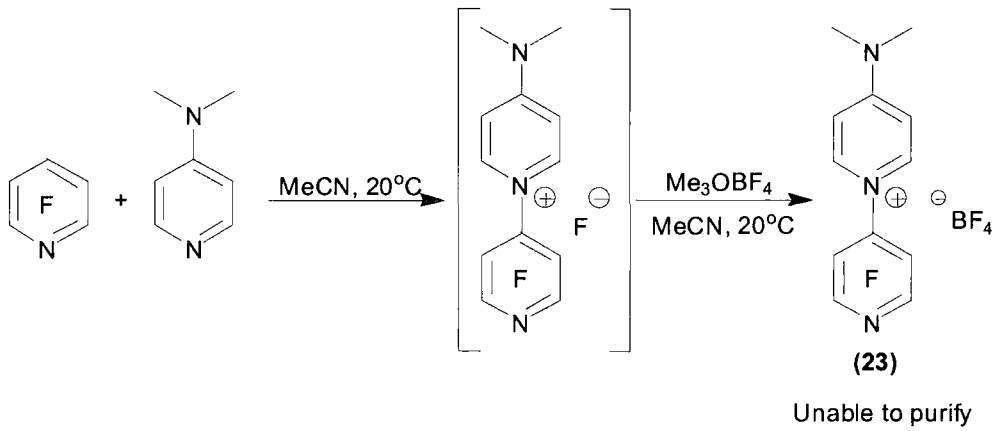


Figure 4.15 Crystal structure of **(32)**

4.3.2.3 Metathesis with Trimethyloxonium Tetrafluoroborate

4.3.2.3.A Synthesis of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Tetrafluoroborate



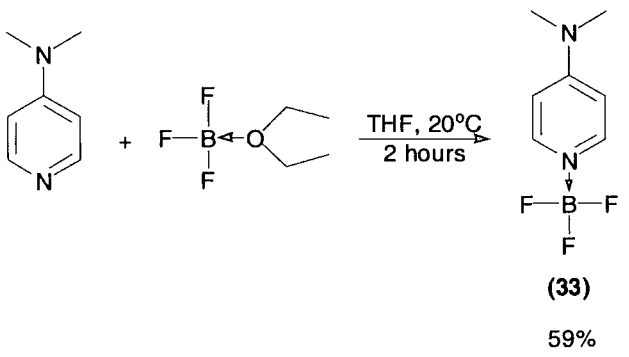
Scheme 4.51 Synthesis of **(23)** via use of trimethyloxonium tetrafluoroborate

A further attempt was made to develop a direct synthetic pathway to the more stable tetrafluoroborate salts. Reaction of DMAP with pentafluoropyridine as above, followed by addition of trimethyloxonium tetrafluoroborate after 15 minutes was expected to lead to the previously isolated dimethylamino-2',3',5',6'-tetrafluoro-[1,4']bipyridinyl-1-ylium tetrafluoroborate (**23**) via elimination of fluoromethane and dimethyl ether (Scheme 4.51). Examination of the reaction mixture by ^{19}F NMR showed approximately 30% conversion, probably due to the formation of a methylated DMAP salt. On recrystallisation of the washed precipitate two crops of crystals were isolated, one of which was strongly fluorescent; unfortunately isolation and characterisation of the fluorescent impurity was unsuccessful.

The second crop of crystals corresponded to the desired product (**23**) but there were considerable impurities present. Recrystallisation from MeCN yielded a sample of (**23**) that was approximately 60% pure, identified by its NMR spectrum. The isolation of the pure compound was not successful. The difficulty in obtaining a pure product, coupled with the hazard in handling Me_3OBF_4 (an exceptionally potent methylating agent) mean that this route is not ideal.

4.3.2.4 Synthesis via DMAP-Boron Trifluoride Complex

Synthesis of DMAP-boron Trifluoride Complex



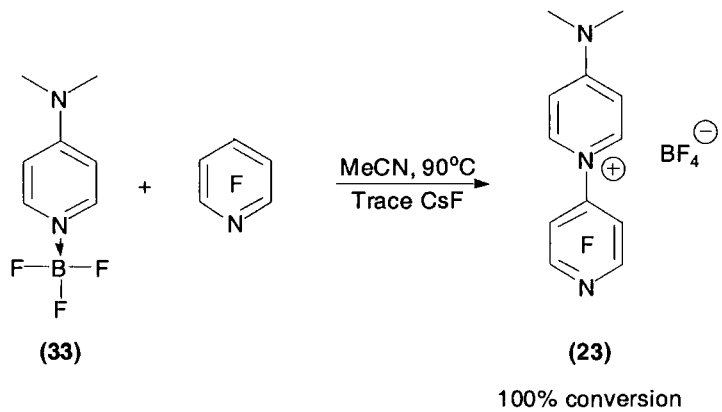
(33)

59%

Scheme 4.52 Synthesis of (**33**)

As above, an attempt to develop a faster, less complicated route to tetrafluoroborate salts of polyfluoroheterocycle-DMAP adducts was made. Following the work of Marder *et al*,[39] the stable complex of DMAP and boron trifluoride **(33)** was prepared (scheme 4.52). The synthesis was simple, although the product was difficult to handle due to its tendency to accumulate static electricity and adhere to any glass surface.

4.3.2.4.A Synthesis of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Tetrafluoroborate

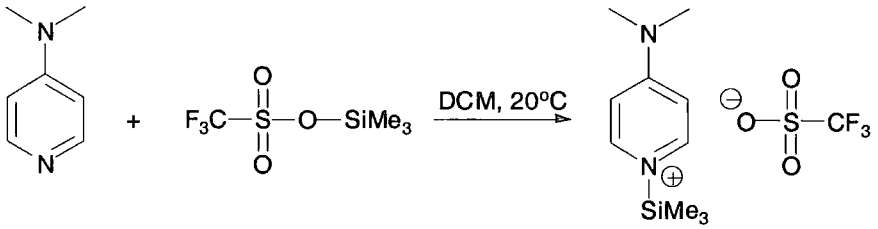


Scheme 4.53 Synthesis of **(23)** via use of **(33)**

The complex **(33)** was reacted with pentafluoropyridine in MeCN (Scheme 4.53) in order to produce adduct **(23)**. No reaction was observed at 20°C or 90°C, even after the addition of a trace quantity of DMAP to act as a fluoride ion source via reaction with pentafluoropyridine. Addition of a trace quantity of CsF to displace the BF_3 from **(33)** as tetrafluoroborate resulted in the immediate formation of a yellow solution, and NMR analysis showed that the reaction had gone to 100% conversion. It should be noted that product purification was more difficult than with the preparation using sodium tetrafluoroborate in section **4.3.2.1**. Four successive recrystallisations were required to remove a troublesome as-yet unidentified fluorescent byproduct which appeared to be similar if not identical to that seen in section **4.3.2.3**.

4.3.2.5 Synthesis via DMAP-trimethylsilyl Triflate

Synthesis of 4-Dimethylamino-1-trimethylsilyl-pyridinium Trifluoromethanesulfonate



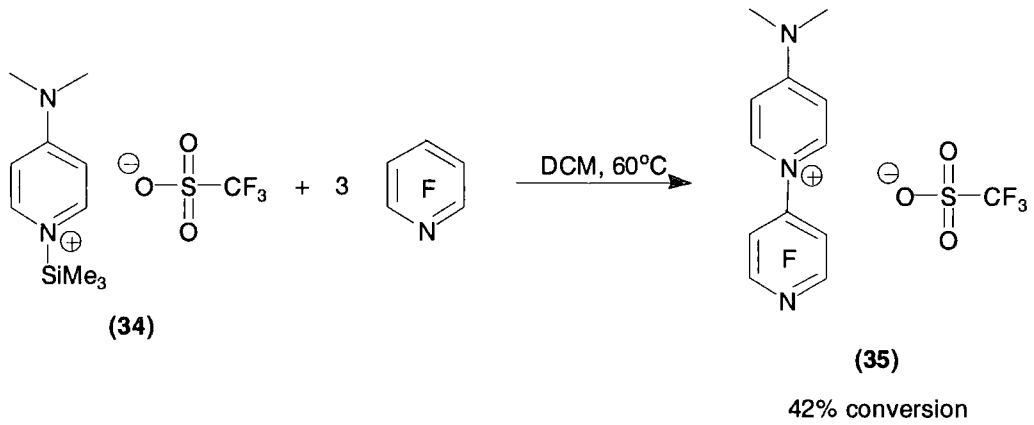
(34)

97%

Scheme 4.54 Synthesis of **(34)**

Following the method of Weiss *et al*,[24] the adduct formed by the reaction of TMS-triflate and DMAP **(34)** was synthesised with the aim of developing a one-step reaction for the synthesis of triflate salts of DMAP adducts (Scheme 4.54). The paper gave details of the *in situ* formation of **(34)**, along with some characterisation indicating that the adduct had been isolated. Synthesis in DCM gave **(34)** pure in 97% yield, but the product decomposed rapidly on standing, allowing only a ^{1}H NMR spectrum to be obtained. The material was used immediately in the next reaction.

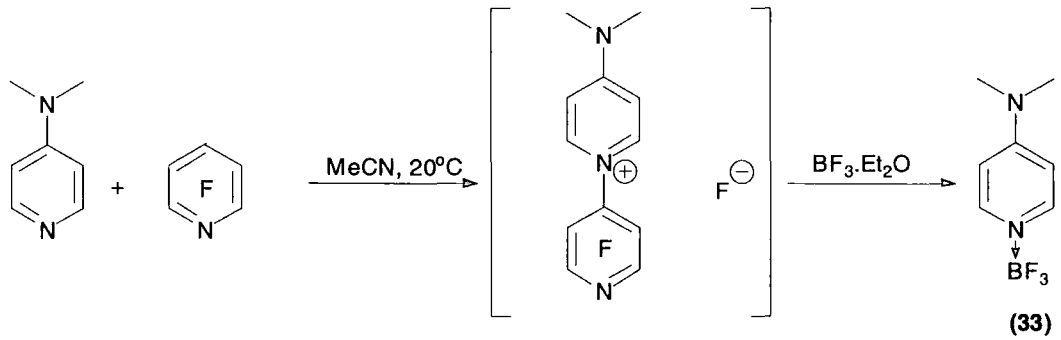
4.3.2.5.A Synthesis of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Trifluoromethanesulfonate



Scheme 4.55 Synthesis of **(35)** via use of **(34)**

In order to simplify the preparation of the $CF_3SO_3^-$ stabilised compounds, the silylated DMAP **(34)** was reacted with pentafluoropyridine in DCM (Scheme 4.55). A white precipitate was observed within five minutes and the reaction was left overnight. Analysis of the precipitate by ^{19}F NMR showed low conversion to the product triflate **(35)**. Raising the temperature to 60°C and adding an excess of pentafluoropyridine only raised the conversion to 42% as shown by NMR. It is likely that this was due to decomposition of reagent **(34)**. As the conversion could not be raised, development of the method was halted.

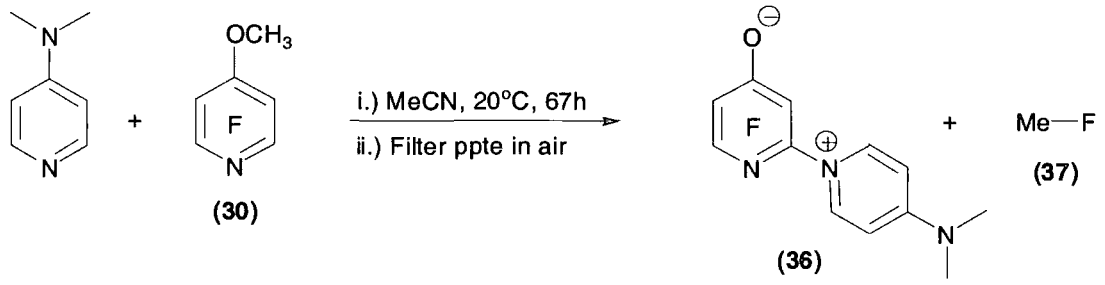
4.3.2.6 Attempted Synthesis of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Tetrafluoroborate via Addition of Boron Trifluoride Etherate



Scheme 4.56 Attempted synthesis of **(23)** via use of boron trifluoride diethyl etherate

The above reaction was attempted in order to assess its potential as a general method for the synthesis of a variety of tetrafluoroborate salts (Scheme 4.56). Upon slow addition of boron trifluoride etherate, the reaction mixture changed rapidly from pale yellow to a deep brown colouration. The sole identifiable product was the adduct of DMAP and boron trifluoride **(33)**, and this was the only species detectable in the ^{1}H and ^{19}F NMR spectra of the recovered solid after the reaction. It seems likely that following reaction between DMAP and BF_3, ring opening of the fluoropyridine moiety occurred.

4.3.3 Synthesis of Demethylation Product of 4-Methoxytetrafluoropyridine



Scheme 4.57 Synthesis of **(36)**

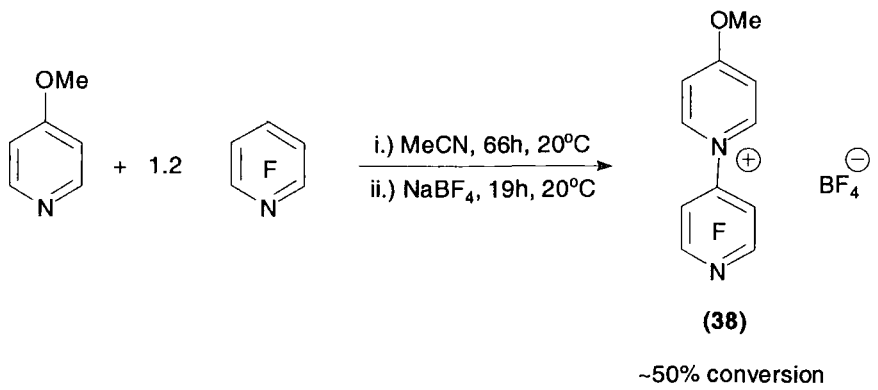
Prior to the establishment of the stabilised cation syntheses shown above, work was underway to isolate fluoride ion containing adducts. An attempt to produce a product with a pyridinium moiety at the 2-position was undertaken with 4-methoxytetrafluoropyridine (Scheme 4.57). The expected substitution at the 2-position took place, but it was accompanied by de-methylation at the 4-methoxy group; fluoromethane (**37**) was detected in the reaction mixture by its distinctive ^{19}F NMR quartet at δ -266ppm. Similar demethylation has been noted within the research group during work with 4-methoxyfluoropyridines.

There are two possible products based on the data available: Either the cation containing a hydroxyl group at the 4-position with either a fluoride or hydroxide anion, or a zwitterion bearing a deprotonated hydroxyl group at the 4-position (**36**). The elemental analysis data, whilst still indicative of an impure compound, is significantly closer to the calculated values for the zwitterionic compound, and the material is tentatively assigned as such. The MS-ES$^+$ spectrum shows significant clustering of molecules and the formation of sodium complexes, furthering the likelihood of a system bearing both positive and negative charges.

Exhaustive attempts were undertaken to grow a suitable crystal for single-crystal X-ray diffraction, but only amorphous product or microcrystals resulted. An impure, intractable deep red by-product obtained from the filtered reaction solution proved impossible to identify and attempts to recrystallise this material were also unsuccessful.

4.3.4 Reactions of Different Amines

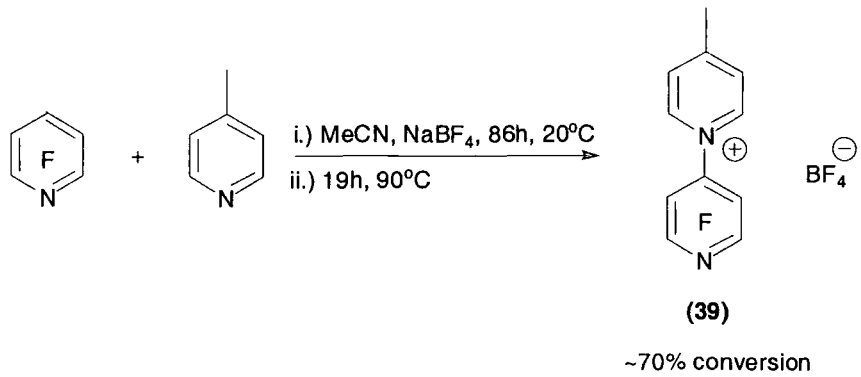
4-Methoxypyridine



Scheme 4.58 Synthesis of **(38)**

As expected, reaction of 4-methoxypyridine with pentafluoropyridine led to attack at the 4-position at a lower rate than with DMAP, with very little reaction observed until after the addition of sodium tetrafluoroborate (Scheme 4.58). This suggests either an extremely slow reaction in the absence of tetrafluoroborate or a significant amount of fluoride attack at the 4-position of the fluoropyridine ring. The crude product was isolated as a solid containing considerable amounts of 4-methoxypyridine and inorganic material, and attempts to further purify the material by recrystallisation were unsuccessful. Characterisation of the product **(38)** was by ^{1}H and ^{19}F NMR only.

4-Methylpyridine



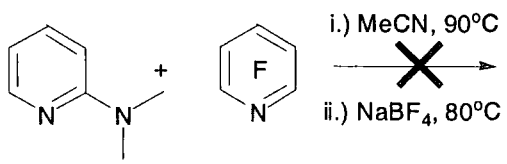
(39)

~70% conversion

Scheme 4.59 Synthesis of **(39)**

In an attempt to examine the limits of the substitution reaction, a pyridine with a non π-donating substituent at the 4-position was utilised as the nucleophile (Scheme 4.59). Previous work had shown that pyridine was not sufficiently reactive to attack pentafluoropyridine and it was expected that a π-donating substituent would be required to provide sufficient reactivity. However, the reaction scheme above clearly shows that 4-methylpyridine is reactive enough to attack the 4-position of pentafluoropyridine. The reaction was much slower than with DMAP, but a crude solid product was isolated and NMR analysis appeared to confirm the scheme shown above. Examination of the product by MS-ES$^+$ showed the desired adduct **(39)** as the only visible product. Unfortunately the intensely coloured material decomposed on standing after extensive attempts at purification and recrystallisation failed.

2-Dimethylaminopyridine

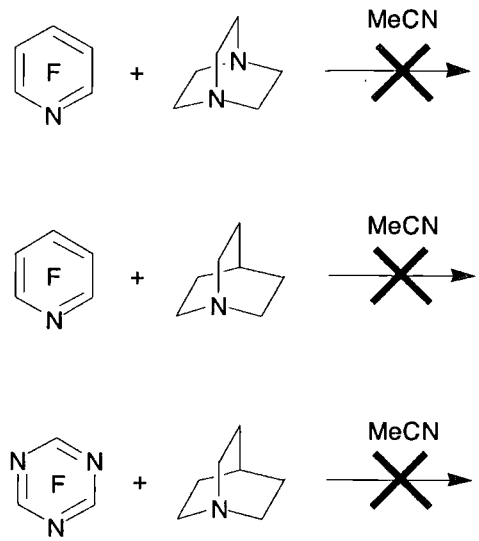


Scheme 4.60 Attempted reaction of PFP with 2-(dimethylamino)pyridine

An attempt was made to utilise 2-dimethylaminopyridine as a model compound for the formation of adducts with chiral alkylamino groups adjacent to the

quaternary nitrogen centre (Scheme 4.60). Unfortunately no reaction occurred, even after extended heating. Sodium tetrafluoroborate was added to disrupt any equilibrium reaction in case the back reaction was favoured, but no effect was observed.

DABCO and Quinuclidine



Scheme 4.61 Attempted reaction of perfluorinated azaheterocycles with non-aromatic polycyclic amines

Attempts were made to react pentafluoropyridine and TFT with the non-aromatic bicyclic amines DABCO and quinuclidine (Scheme 4.61). All attempts, regardless of the conditions employed, led to degradation of the amine and no products were isolated. This process was almost certainly due to fluoride ion mediated deprotonation and ring opening of the bicyclic amines.

4.5 Other Reactions: Studies of Perfluorinated Azaheterocycles with Aliphatic Tertiary Amines

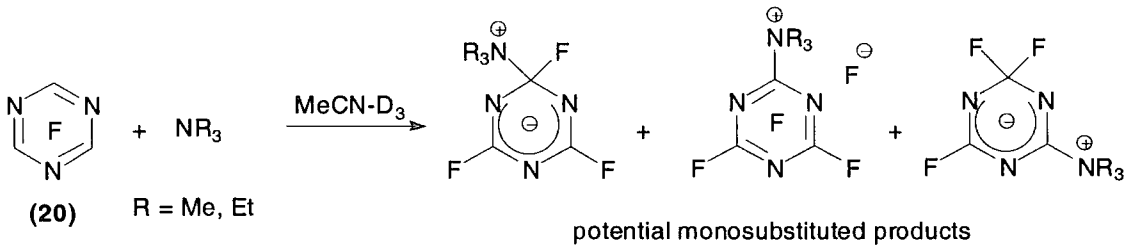
4.5.1 Reactions with Trifluoro-*s*-triazine

As has been observed above, the σ-complexes formed by TFT **(20)** are clearly rather stable, and in several cases they have inhibited fluorination processes by the

sequestration of fluoride ion. It is known that addition of CsF to a solution of TFT in sulfolane leads to the formation of a precipitate.[36] Isolation of this solid, followed by addition of fresh solvent results in a solution with an identical ^{19}F NMR spectrum to the initial solution. Furthermore, addition of boron trifluoride etherate (a very powerful fluorophile) results in the regeneration of trifluoro-*s*-triazine. Clearly, these species exhibit significant stability. As a further probe of these systems, and as an extension to the above methodology, the reactions between trifluoro-*s*-triazine and two aliphatic amines (trimethylamine and triethylamine) were studied.

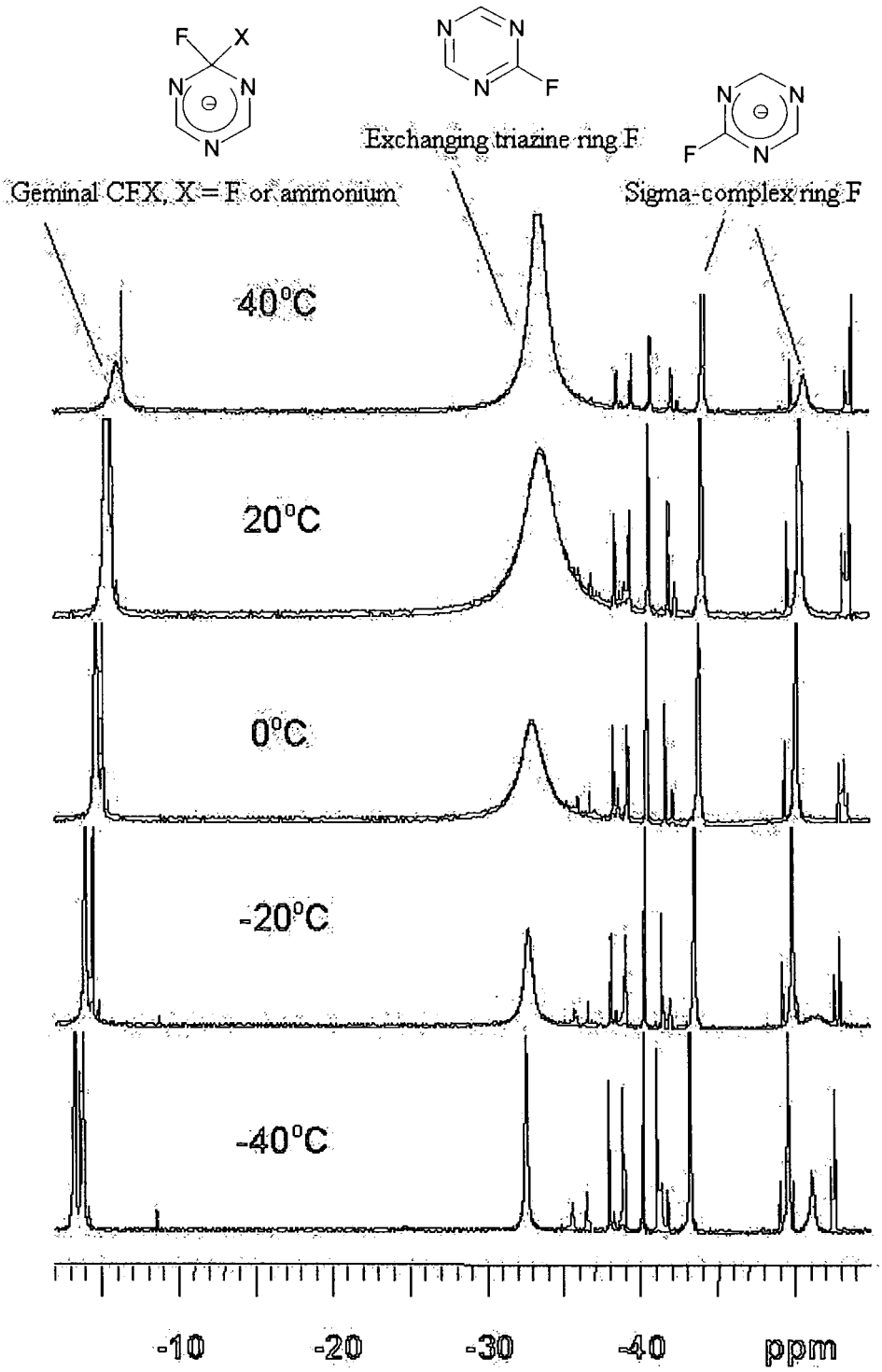
The initial hope was that a stable σ-complex or discrete fluoride ion ammonium salt would be produced as an isolable solid as above. This would allow XRD studies to be made of the bonding in such a species for the first time.

4.5.1.1 Reactions of Trifluoro-*s*-triazine with Trimethylamine and Triethylamine: VT-NMR Studies



Scheme 4.62 Some possible monosubstituted products from the reaction of **(20)** with a trialkyl amine

In an attempt to isolate a discrete σ-complex, the reaction of trimethyl- and triethylamine with the triazine **(20)** was studied by variable temperature (VT) ^{19}F NMR (Scheme 4.62). It was hoped that the σ-complex would be observed as the only species present, allowing possible product isolation by removal of the solvent under vacuum, or cooling of a concentrated solution.



VT-NMR plot of TFT + triethylamine

Figure 4.16 VT ^{19}F NMR study of **(20)** and triethylamine in MeCN-d_3

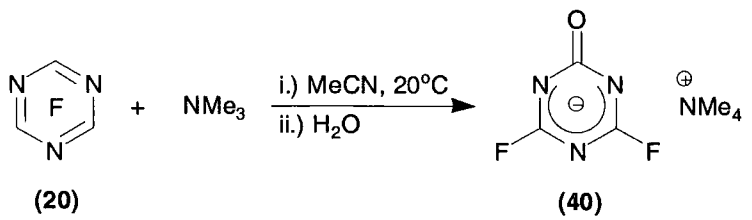
Unfortunately, the reaction proved to be considerably more complex than expected. Shown above is the VT NMR plot for the ^{19}F spectra exhibited by the reaction between **(20)** and triethylamine (the corresponding spectra for trimethylamine

were similar). Several species were observed in the ^{19}F NMR spectrum, and these species behaved differently under VT conditions in that their exchange profiles showed different exchange temperatures. Consequently, on cooling the solution, certain species exhibited peak broadening (particularly apparent in the trimethylamine spectra) whereas others started to produce sharper, more distinct resonances.

Exchange is clearly seen between the geminal CFX group and the σ-complex ring fluorine signals at δ -5 and -50ppm respectively. At high temperatures, a broad set of peaks are observed, which clearly sharpen to two major sets of resonances at higher temperature. These signals most likely correspond to σ-complexes containing geminal CF_2 and $CFNEt_3$, although complete assignment is not possible. A further exchange pattern seems to be between the triazine ring peak at δ -32ppm and one of the σ-complex fluorine peaks at δ -51ppm. Deconvolution analyses were performed on several of these peaks to attempt a more accurate measurement of the peak integral to enable a more complete assignment of the spectra; unfortunately, this approach was not successful. Clearly these assignments are somewhat arbitrary given the nature of the system and the number of possible products.

A further problem was that the material decomposed in the NMR tubes over several days (even though the tubes were dried and equipped with Young's taps, and the samples were prepared in a glove box), indicating reaction with the glass of the tube. This prevented the acquisition of ^{13}C NMR spectra of appropriate quality.

4.5.1.2 Isolation and Characterisation of the Tetramethylammonium Salt of 1-Keto-3,5-difluoro-*s*-triazine



(20) (40)

Scheme 4.63 Synthesis of **(40)**

During one of the VT NMR experiments with (20) and Me_3N in MeCN-d_3, it was noticed that the signal strength was dropping off at lower temperatures. On removing the cooled NMR tube from the spectrometer, a small quantity of colourless solid was seen in the bottom of the tube (Scheme 4.63). A repeat of the reaction on a larger scale in a fritted Schlenk tube yielded large plate-like crystals and these were filtered and transferred to the glove box. Although the material appeared to decompose quickly on loss of solvent, NMR, MS-ES^+, MS-ES^- and XRD data were obtained.

At no time was the material exposed to atmospheric moisture or other contamination as an NMR tube fitted with a Young's tap was employed, and the sample was prepared in the glove box. In the reaction mixture, the classic σ-complex ^{19}F NMR spectrum was observed. The CFX peak and the triazine ring fluorine peak displayed equal intensities whilst the σ-complex ring fluorine peak had an intensity roughly half as large. This equates to a one to one mixture of a σ-complex bearing a difluoromethylene and a trimethylammonium group, and a triazine bearing a trimethylammonium group as the fluoride salt.

Analysis of the crystalline solid was rather more difficult, as differences appeared in the spectra whenever there was a delay between supposedly confirmatory analyses. The low resolution ^{19}F NMR spectrum taken immediately after product isolation showed three major peaks: A sharp CF_2 singlet at δ -5ppm, a slightly broad ring C-F at δ -36ppm and a sharp singlet at δ -49ppm. The σ-complex peaks had small peaks to their right indicating the presence of another σ-complex, presumably containing geminal fluorine and trimethylammonium.

The high resolution spectrum, taken seven days later, showed no triazine ring fluorine peak and a succession of six sharp singlets of varying intensity between δ -38 and -51ppm. In addition there was a broad peak, almost certainly due to HF, at δ -168ppm accounting for the vast majority of the peak area of the spectrum as well as a further sharp singlet at δ -184ppm. The only reasonable conclusion is that the material is either inherently unstable, or else is reacting slowly with the solvent (DMSO) or the glass wall of the NMR tube.

The only recognisable peaks in the ^1H spectrum were those attributable to NMe_3 and NMe_4^+, although there were several small multiplets present. ^{13}C NMR

proved very difficult to interpret, as the only signals present in any magnitude were those due to $RNMe_3^+$ and NMe_4^+. Other carbon signals were extremely weak and obscured by the baseline, even after extended acquisition times (which also resulted in sample decomposition).

Mass spectrometry was rather more helpful, however. Samples were prepared in anhydrous MeCN in the glove box and sealed in air-tight septa-capped vials. Positive ion mode electrospray showed the presence of isocyanuric acid as the major product, providing more evidence for the ability of the material to lose HF on contact with glass. Minor products detected are shown below, although this may indicate rearrangement or reaction in the mass spectrometer (Figure 4.17).

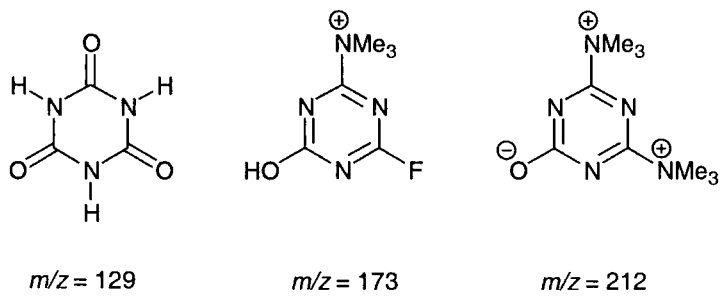
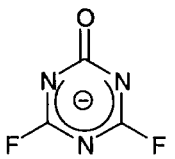


Figure 4.17 Major identifiable peaks observed in MS-ES$^+$ spectrum of **(40)**

Negative ion mode electrospray gave a very different picture; the only material present in any quantity corresponded to a difluoroketotriazine system with *m/z* = 132 (Figure 4.18).



(40)

Figure 4.18 Major identifiable peaks observed in MS-ES$^-$ spectrum of **(40)**

Further, final analysis by XRD techniques confirmed the isolated product to be the tetramethyl ammonium salt of 1-keto-3,5-difluoro-*s*-triazine **(40)** (Figure 4.19).

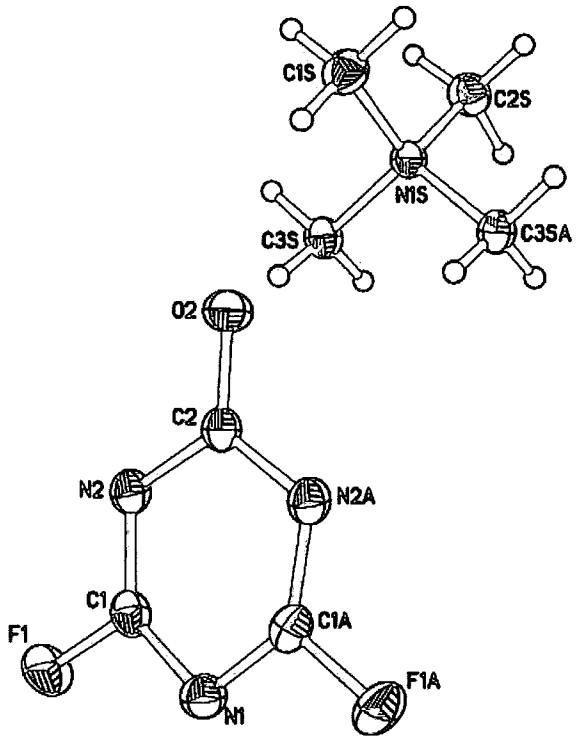


Figure 4.19 Molecular structure of **(40)**

Very distinct ring-stacking can be seen in the X-ray crystal structure (Figure 4.20), and from bond-length data it is clear that a significant proportion of the negative charge is localised on the ring, as the C-O and C-N bond lengths correspond to those expected for a carbonyl-containing structure. The C-O bond is short at 1.233A, whilst the ring C-N bonds show a slight alternating character with the shorter bonds in the 2,3 and 5,6 positions, indicating some double bond character in conjugation with the carbonyl group.

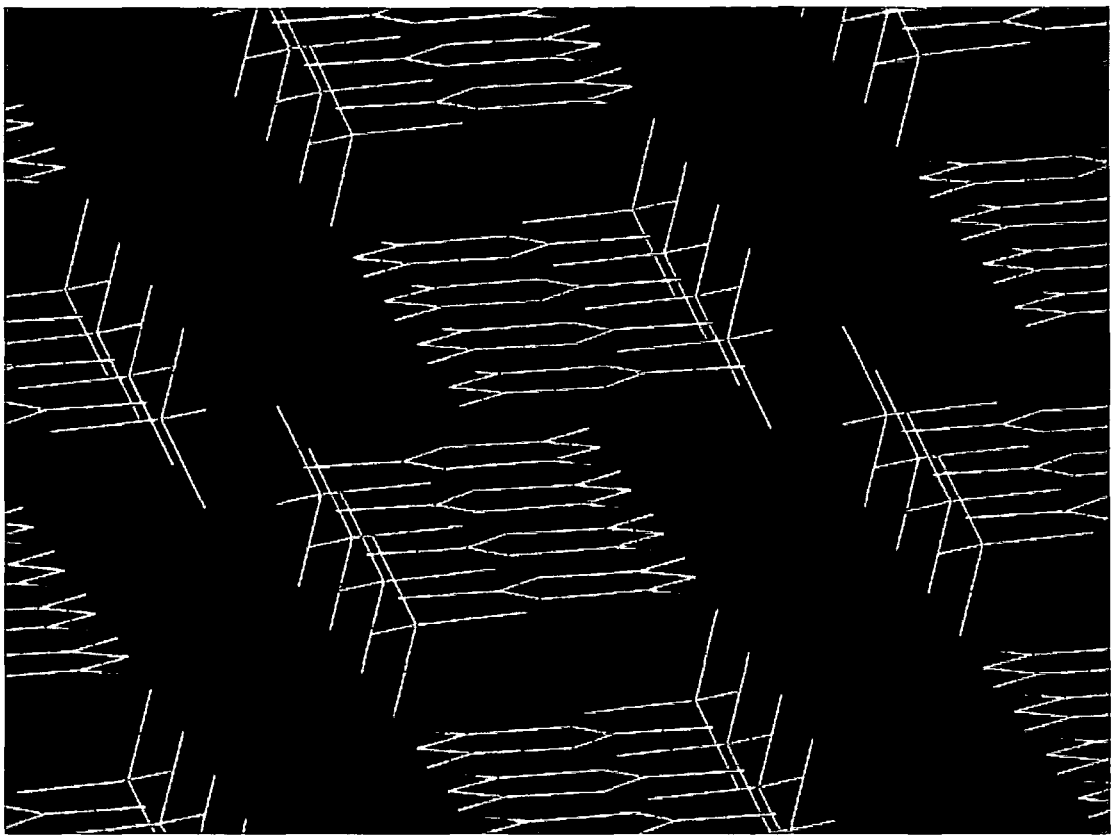
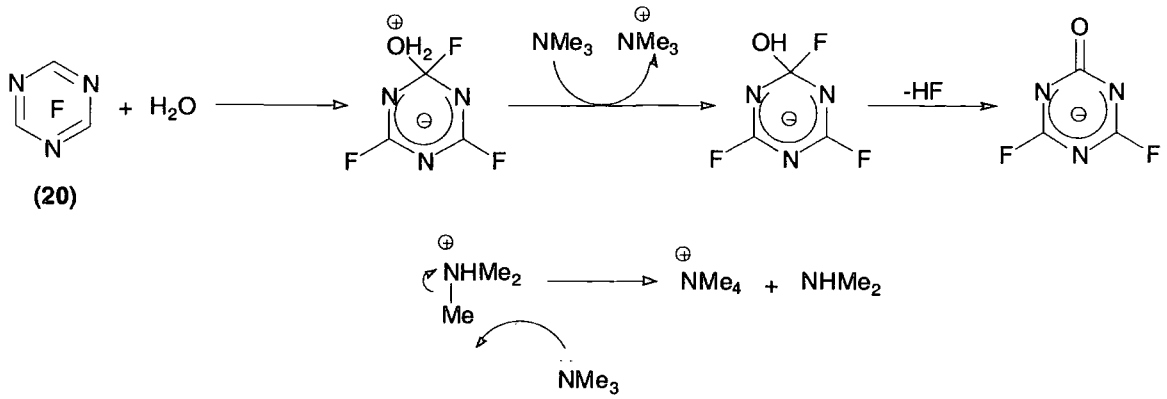


Figure 4.20 Crystal structure of **(40)**

From consideration of the somewhat contradictory data presented above, it is fairly certain that **(40)** was not the initial isolated product. It is likely that this material formed on hydrolysis of another material, perhaps a sigma complex, on contact with glass or in contact with air during crystal mounting (even though significant precautions were taken to avoid exposure to atmospheric moisture during this step).



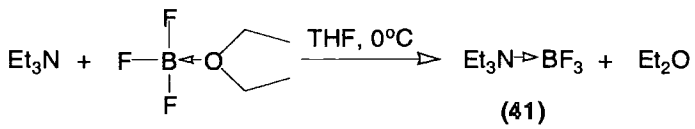
Scheme 4.64 Detail of the proposed steps in the synthesis of **(40)**

Formation of compound **(40)** is accounted for simply by the scheme shown (Scheme 4.64). Hydrolysis of either the parent triazine or a trimethylammonium adduct yields a 1,1-fluorohydroxy-*s*-triazine after initial deprotonation. Loss of HF across these geminal groups results in the formation of the carbonyl. If the deprotonation is carried out by trimethylamine, then this sets up a quaternary centre for nucleophilic displacement via methyl loss to another molecule of trimethylamine.

4.5.2 Reaction of Trifluoro-*s*-triazine with Triethylamine-boron Trifluoride Adduct

Synthesis of Triethylamine-boron Trifluoride Adduct

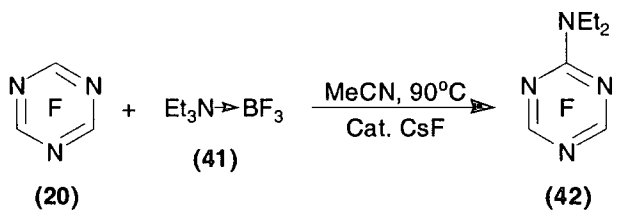
Following the unsuccessful attempts to prepare isolatable σ-complexes and related compounds, attention was turned to the synthesis of tetrafluoroborate systems containing quaternary aliphatic nitrogen centres. Analogously to the preparation of DMAP-BF_3, the complex between DMAP and NEt_3 was also prepared following a Russian paper reporting the synthesis of a variety of such complexes (Scheme 4.65).[40]



Scheme 4.65 Synthesis of **(41)**

The slow addition of $BF_3.Et_2O$ in THF to an ice cold solution of NEt_3 in THF, followed by fractional distillation yielded the desired product (41) as a colourless liquid/low melting solid in 91% purity and high yield; the only impurity was $BF_3.Et_2O$. This compound was used as a starting material for the attempted synthesis of tetrafluoroborate-stabilised aliphatic quaternary ammonium adducts. The potential advantage of this route is that it avoids the generation of significant quantities of basic fluoride ion, which could lead to Hoffmann elimination from the alkyl groups on the ammonium centre.

Reaction with Trifluoro-*s*-triazine



Scheme 4.66 Synthesis of **(42)** involving a dealkylation step

Reaction of **(41)** with **(20)** proceeded readily once the appropriate conditions had been attained (Scheme 4.66). No reaction was seen until CsF was added, at which time a small quantity of a peak at δ -5.8ppm corresponding to a σ-complex CF_2 was observed and approximately 60% of the NEt_3-BF_3 had been converted to tetrafluoroborate. Following overnight reflux, the σ-complex disappeared, leaving only a singlet at the same position as the parent triazine (δ -33.1 ppm), a singlet of moderate intensity at δ -40.5 ppm and a peak corresponding to tetrafluoroborate at δ -150.4 ppm. As an aside, this illustrates the markedly higher fluorophilicity of boron trifluoride when compared to the still strongly fluorophilic trifluoro-*s*-triazine.

The resulting orange solution was placed on a rotary evaporator until most of the volatile material had been removed, yielding a deep orange liquid and an orange precipitate. This was heated until the precipitate dissolved and then slowly cooled to allow recrystallisation to occur, resulting in the formation of large needle-like crystals. After drying under vacuum, NMR analysis in DMSO showed only two major peaks in the ^{19}F spectrum: Ring fluorine at δ -39.7ppm and BF_4^-. The proton spectrum confirmed the presence of an ethyl group, although some significant proton-containing impurities were detected.

Analysis of the solid by electrospray MS in the positive ion mode gave some very interesting information. The major detected product was an *s*-triazine containing both a diethylamine group and a triethylamino moiety, and bis(diethylamino)fluoro-*s*-triazine was also present as a minor product. A wide range of other species, shown below, were detected although these were only present in small amounts (Figure 4.21).

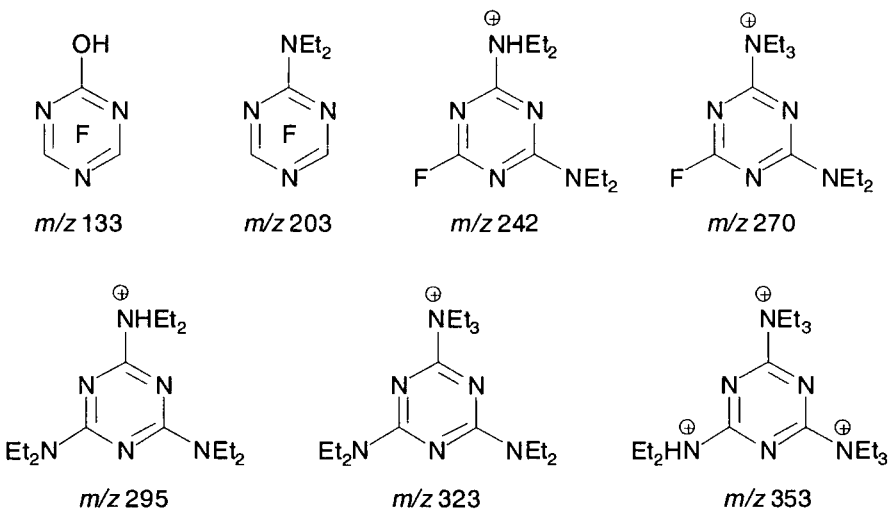


Figure 4.21 Species observed in the MS-ES$^+$ spectrum of **(42)**

A non-amino containing product, difluoro-*s*-triazinol (or its tautomer) was also formed, presumably via formation and subsequent hydrolysis of trifluoro-*s*-triazine in the mass spectrometer. Finally, a successful XRD analysis was carried out, showing the major crystalline product to be 2,4-difluoro-6-diethylamino-*s*-triazine **(42)** (Figure 4.22).

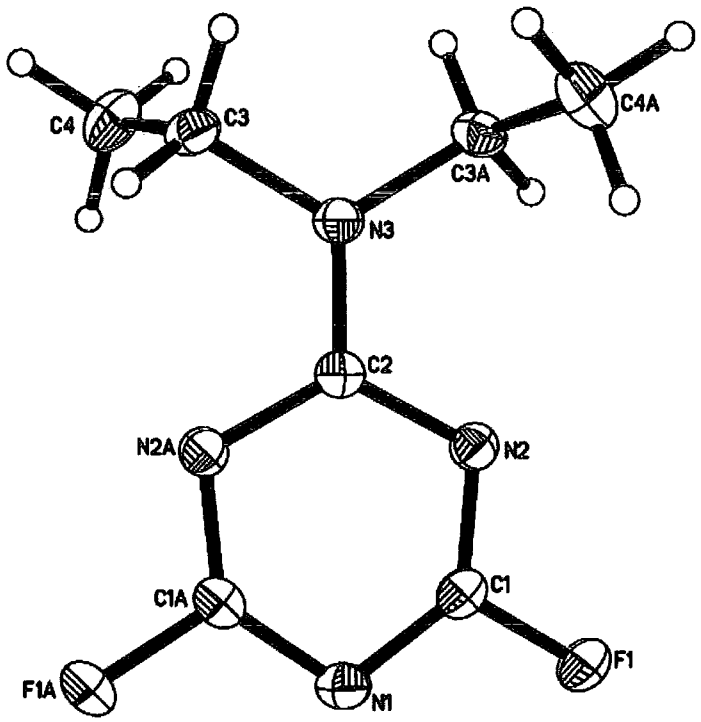
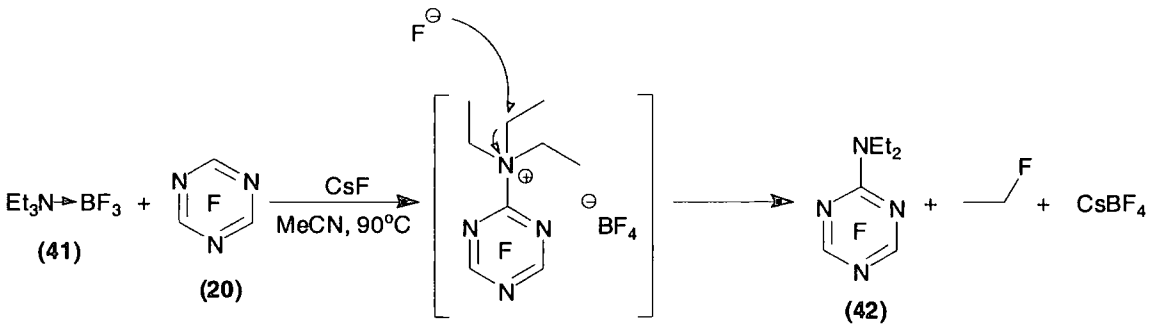


Figure 4.22 Molecular structure of **(42)**

It would appear that the majority of the products seen in the mass spectrometer were due to exchange processes occurring within the instrument.

The formation of this product raises an obvious question: What was the cause of the dealkylation process to produce the dialkylamino group? There are two options: The CsF added to catalyse Et_3N-BF_3 decomposition or the nascent fluoride ion produced during attack of the newly generated amine (Scheme 4.67).



Scheme 4.67 Synthetic steps involved in the synthesis of (**42**)

There have only been a very small number of papers published concerning the reaction between tertiary amines and trihalo-*s*-triazines. A report made in 1962[19] claimed that the reaction of (**20**) with triethylamine occurred in very low yield to furnish a dealkylated (i.e. diethylamino-containing) difluoro-*s*-triazine (**42**).

4.6 Conclusion

Clearly, there are many conclusions that can be drawn from this research. The initial aim of the project was to develop a system for nucleophilic fluorination from a covalently bound fluorine containing precursor. A range of fluorine sources and nucleophilic "fluoride release agents" were screened against a variety of substrates. Fluorination in general proceeded in moderate yield, although product recovery was simplified by the insoluble nature of the bromide or chloride containing pyridinium byproducts. Fluorination was demonstrated in MeCN to a synthetically useful degree.

Side-reactions, particularly the alkylation of the nucleophilic amine by the substrate, were a significant limiting factor, and limited attempts to circumvent this by balancing the reactivities of the components of the fluoride ion source were unsuccessful. The most useful system, therefore, was comprised of DMAP and PFP with premixing of the reagents in MeCN at 20°C for a finite period. Addition of the substrate, followed by refluxing for several hours generally gave acceptable yields of products. Phase transfer reactions involving similar systems were generally unsuccessful, possibly due to the fluorinated solubilising agents employed exhibiting an affinity to fluoride ion which was either too high or too low.

Further to the fluorination studies, a wide range of reactions were investigated with the aim of isolating and characterising amine-fluoroheterocycle adducts. Extreme difficulty was encountered in product isolation and purification, but nonetheless several new materials were unambiguously identified. The reactivity of one such compound, the DMAP-PFP tetrafluoroborate adduct (**23**), with a variety of nucleophiles was studied and the adduct was found to be of similar reactivity to pentafluoropyridine under the conditions employed. Interestingly, the quaternary amine group exhibited quite limited lability, with DMAP loss being observed only rarely.

Finally, investigations into the chemistry of trifluoro-*s*-triazine (**20**) and aliphatic tertiary amines proved to be rather complicated. The only new isolated material was a novel hydrolysis product (**40**), and accurate reaction data for the anhydrous system could not be obtained due to complex exchange processes and reactivity with the glass vessel. The chemistry of these systems is clearly interesting, as several processes were observed by ^{19}F NMR. Combination of the metathesis methodology applied to stabilisation of the isolated adducts with these systems hints at an interesting possibility: A general methodology for the preparation of highly reactive stabilised fluoroheterocycles bearing a quaternary amine group, an as yet unexplored class of materials.

4.7 References to Chapter 4

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5. Experimental

5.1 Instrumentation and Reagents

Gas-Liquid Chromatography

Analyses were performed on a Fisons Trio 1000 spectrometer linked to a Hewlett Packard 5890 Series II gas liquid chromatograph, equipped with a 25m cross-linked methyl silicone capillary column. All GLC-MS spectra were generated by Electron Impact.

Preparative-scale gas chromatography was carried out on a Shimadzu GC-8A fitted with an SE30 non-polar column.

Elemental Analysis

Elemental analyses were obtained on a Carlo Erba Elemental Analyser.

NMR Spectra

NMR spectra were recorded in deuterio-chloroform unless otherwise stated on either Varian Mercury 200, Varian Unity 300, Varian Mercury 400, Bruker Avance 400, Varian Unity Inova 500 or Varian Unity Inova AS500 spectrometers with tetramethylsilane, trichlorofluoromethane or residual deuterated solvent proton peaks as internal standards. In ^{19}F NMR spectra, low frequency shifts are quoted as negative. Coupling constants (J) are given in Hz.

Mass Spectra

Mass spectra were recorded on either a VG 7070E spectrometer, a Thermo-Finnigan Trace GC-MS or a Fisons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Electrospray MS were recorded on a Micromass LCT.

Column Chromatography

Column chromatography was performed on silica gel (Merck no. 1-09385) and TLC analysis was performed on silica gel TLC plates (Merck).

Distillation

Fractional distillation of product mixtures was carried out using either Vigreux columns or a Fischer Spaltrohr MMS255 small concentric tube apparatus.

Melting and Boiling Points

Melting and boiling points were recorded at atmospheric pressure using a Gallenkamp apparatus, and are uncorrected.

Reagents and Solvents

All starting materials were either obtained commercially (Aldrich, Lancaster, Fluorochem) or prepared using literature procedures. Solvents and, where appropriate, reagents were purified by literature procedures. Unless explicitly stated, experimental procedures were conducted in dry apparatus under an argon or nitrogen atmosphere. Where appropriate, an argon atmosphere glove box or standard inert atmosphere techniques were used.

5.2 Refurbishment of Glove Box

Due to the high moisture sensitivity of the adduct salts formed (chapter 4), and the difficulty in conducting truly anhydrous reactions with CsF, it was desirable to obtain a glove box to allow for the rigorous exclusion of moisture during sample manipulation. As the box would only be needed for these projects, and as even a very cheap commercial system would cost several thousand pounds this seemed unfeasible. Fortunately an old glove box "shell" was being scrapped by another research group and this was obtained for refurbishment.

The box was constructed of welded steel and fitted with a plastic window, two ports and various breakthroughs for services. The seals on all breakthroughs except the ports were degraded, although the general condition was adequate. The box had to allow for the synthesis, isolation and preparation of samples for characterisation. To this end, an electrical system was required for a stirrer and balance and the gas handling system had to be able to cope with volatile materials which were likely to be flammable and/or toxic. It was also considered advantageous to have some ability to remove solvents or volatile materials under reduced pressure. Of course, all operations and transfers had to be compatible with the integrity of the box regarding the exclusion of moisture. As a safety issue, the decision was made to run the box as an inert atmosphere system (rather than with a dry air atmosphere) due to the fire or explosion risk from flammable solvents in close proximity to the electrical items in the box. The following is a breakdown of the steps that were required to complete the refurbishment project.

- Box integrity and siting

All breakthroughs, port covers and seals were pressure tested and silicone sealant was applied to all fittings due to numerous pinhole leaks. The electrical breakthrough was fitting replaced due to degradation of the rubber seals and internal sockets. Service outlets (water, vacuum, natural gas, argon) were removed from a lab bench and a steel open-frame stand was constructed to support the box at a suitable level for work. This had the added effect of permitting the gas handling equipment to be sited underneath the box, significantly reducing the

overall footprint. The box was placed close to a fume hood to allow the exhaust to vent safely.

- Vacuum system

To enable the application of high vacuum inside the box, a further access point was made into the box. An external double-trap vacuum system was then connected via Swagelok fittings to an emergency shut-off quarter-turn ball valve inside the box. A small vacuum manifold was then connected inside the box to allow for reduced pressure work and the use of the mini port.

- Gas handling

After consultation with various other glove box users, it was decided that the gas handling system needed to accomplish three things; the removal of moisture, the removal of volatile organic materials and the recirculation of inert gas to minimise gas usage. It is relatively simple to construct a "single pass" box, whereby a constant flow of fresh gas is fed to the box and exhausted, thus maintaining a dry uncontaminated atmosphere. However, this is tremendously wasteful and unnecessary, although a small gas flow was needed to maintain the refurbished box at positive pressure. A recirculating system with appropriate scrubbing devices is a much more efficient and cost effective way of ensuring the integrity of the system.

Swagelok connections and metal tubing and components were highly desirable for the gas handling parts of the box. However flexible PVC tubing was used instead due to time and financial constraints, requiring replacement after perhaps a year of use. All gas lines were equipped with bubblers where appropriate to indicate gas flow. Lines from gas supply or to exhaust were run above the false ceiling of the laboratory so as to minimise the impact of the installation on the laboratory environment. The gas handling system comprised three discrete sections:

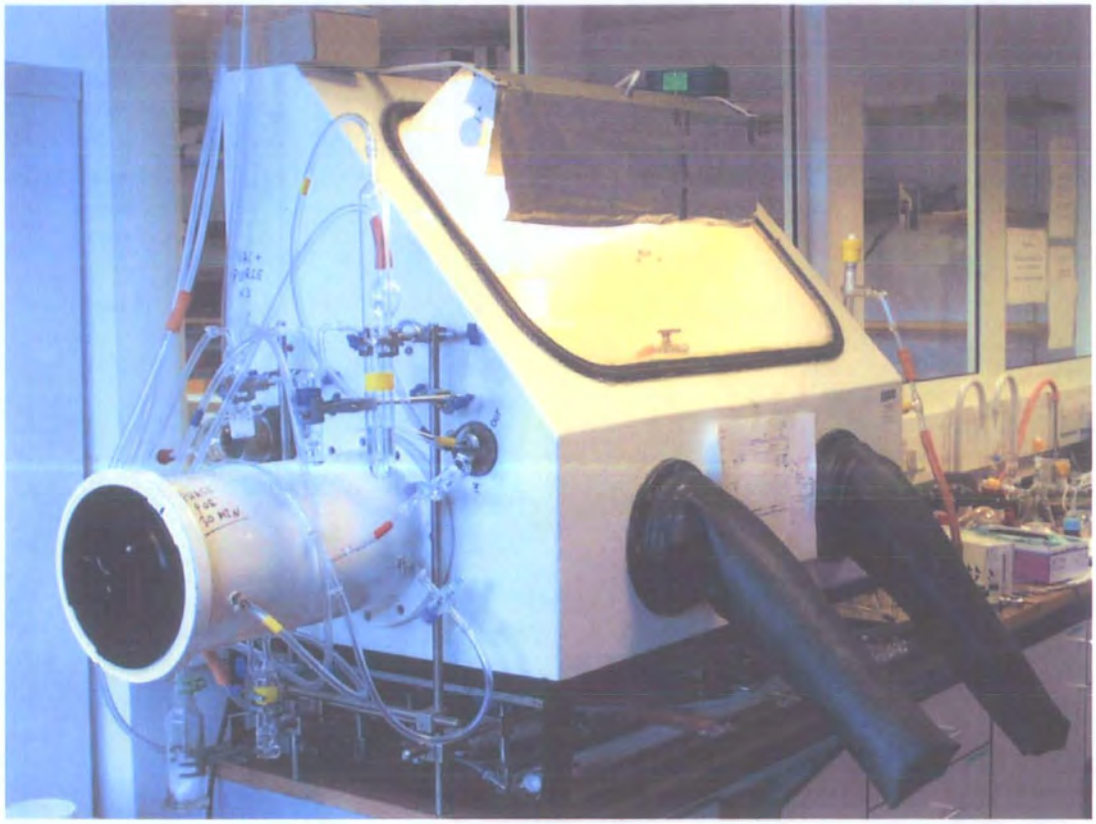
i.) The gas inlet, equipped with a 4Å molecular sieve column and branches to the box and large port with appropriate control valves.

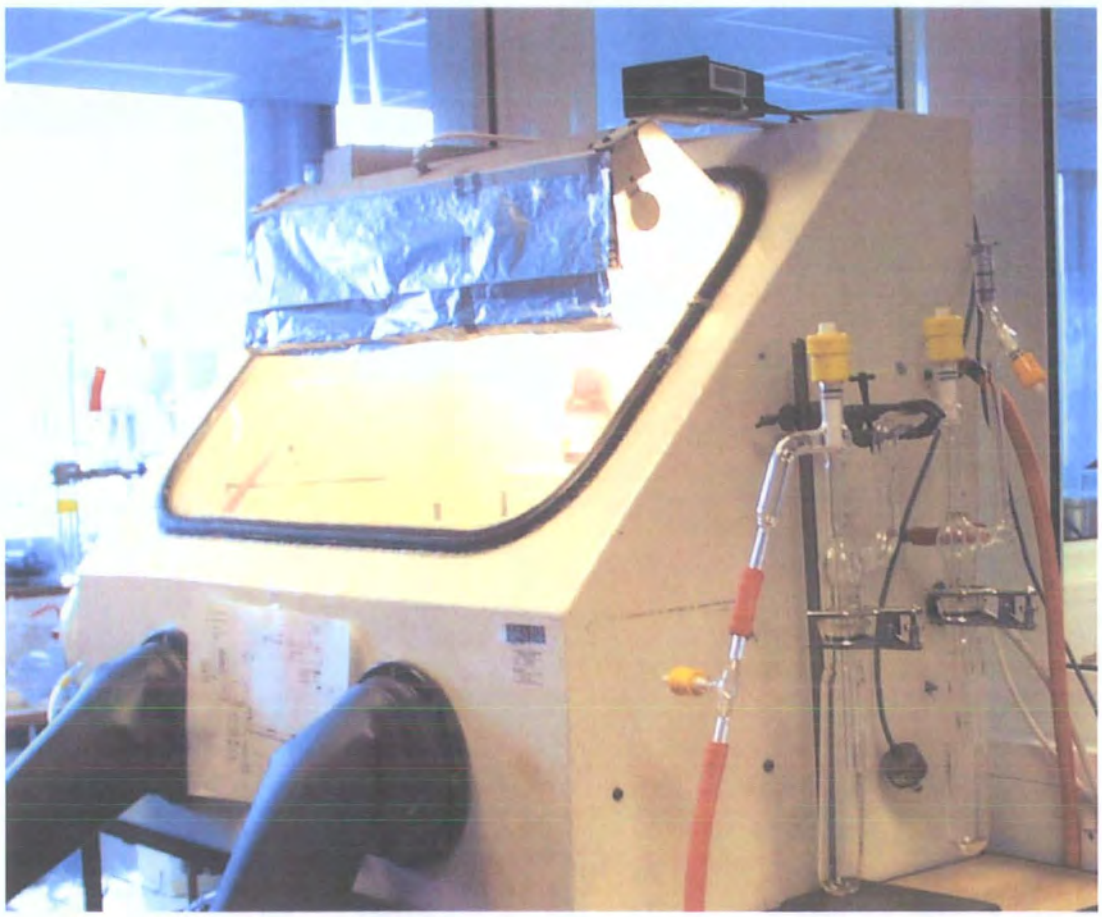
ii.) The gas exhaust, with branches from the main box and main port, each fitted with a separate pressure regulation device (lute). The mini port was exhausted to the vacuum system.

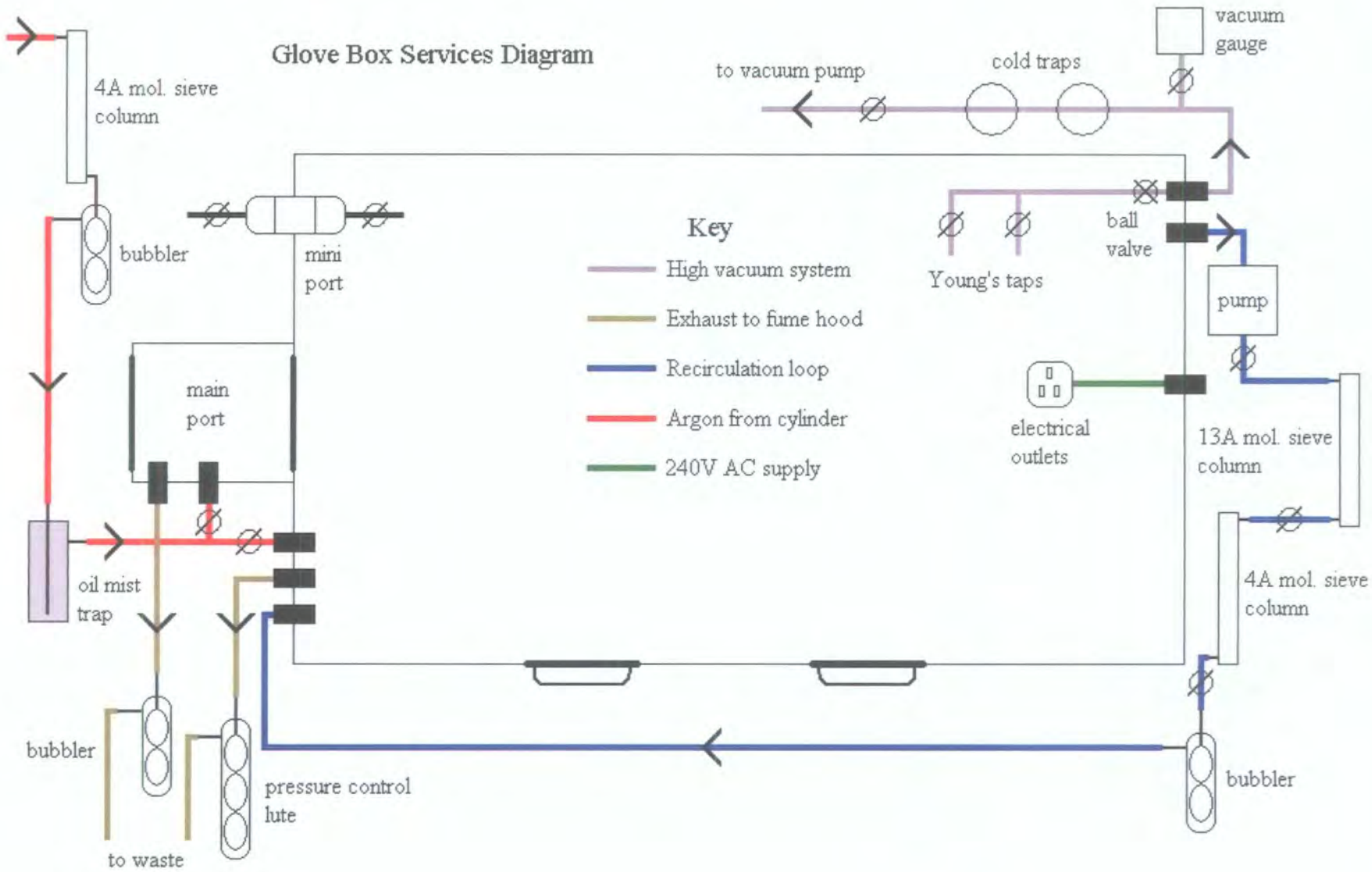
iii.) The gas recirculation system, based around a small air-pump, placed outside the box as close to the recirculation outlet as possible. This minimized the portion of the recirculation circuit operating in negative pressure mode, thereby reducing the likelihood of introducing air into the box. The gas was passed through 4Å and 13Å molecular sieve scrubbing columns to remove moisture and volatile organics, before being passed back into the box. The design allows the isolation of a column to change the molecular sieves without significantly compromising the integrity of the box. This solution is appreciably simpler from a design perspective than the use of heaters for column regeneration.

Although it would have been desirable to quantify the moisture content of the box (and the recirculation system downstream from the scrubber columns), the prohibitive cost of a hygrometer capable of measuring to less than 0.1% (1000ppm) moisture meant that this was not possible.

Prior to first use, the box was connected to a dedicated argon supply and purged continuously for two days. A slow stream of argon (~20mL/minute) was then maintained through the box and P_2O_5 filled drying trays were used to bring the residual moisture levels down as far as possible prior to activation of the recirculation system. Just before use, a qualitative test with a solution of $TiCl_4$ in DCM showed only very slight fuming inside the box, compared to considerable fuming in the lab atmosphere. As $TiCl_4$ starts to fume appreciably at approximately 20ppm atmospheric moisture content, the atmosphere in the box appeared to be very dry.






Glove Box Services Diagram
4A mol. sieve column
bubbler
mini port
main port
oil mist trap
bubbler
to waste
pressure control lute
to vacuum pump
cold traps
vacuum gauge
Young's taps
ball valve
pump
electrical outlets
13A mol. sieve column
4A mol. sieve column
bubbler
Key
High vacuum system
Exhaust to fume hood
Recirculation loop
Argon from cylinder
240V AC supply

5.3 Experimental to Chapter 2

Synthesis of Starting Materials

Synthesis of Hexane-1-trifluoromethanesulfonate (6)

A solution of hexan-1-ol (2.06g, 20mmol) and pyridine (1.62ml, 20mmol) in DCM (5ml) was added dropwise with stirring, over a 60 minute period, to a solution of trifluoromethanesulfonic anhydride (6.60g, 23mmol) in DCM (20ml) at 0°C. An inert atmosphere was maintained throughout. After an additional 15 minutes, the solution was washed with water, dried (magnesium sulfate) and the solvent was removed under vacuum. The crude product was isolated as a pale yellow oil (3.95g). The crude product was cautiously distilled through a Vigreux column under high vacuum and collected in a receiver cooled in a dry ice/acetone bath. The distillate, obtained as a colourless oil, was identified as *hexane-1-trifluoromethanesulfonate* **(6)** (3.1g, 66%); δ_H 0.81 (3H, t, $^3J_{HH}$ 6.4, CH_3), 1.26 (6H, m, CH_3-CH_2-CH_2-CH_2), 1.74 (2H, pent, $^3J_{HH}$ 6.4, CH_2-CH_2-OSO_2CF_3), 4.45 (2H, t, $^3J_{HH}$ 6.4, CH_2-OSO_2CF_3); δ_F – 75.3 (s, CF_3); δ_C 14.0 (s, *C*H_3), 22.6 (s, CH_3-*C*H_2), 24.9 (s, CH_3-CH_2-*C*H_2), 29.4 (s, *C*H_2-CH_2-CH_2-OSO_2CF_3), 31.2 (s, *C*H_2-CH_2-OSO_2CF_3), 78.0 (s, *C*H_2-OSO_2CF_3), 118.9 (d, $^1J_{CF}$ 319.5, *C*F_3).

Synthesis of 2,2-Dimethylpropane-1-trifluoromethanesulfonate (8)

As above, but with (1.72g, 19.5mmol) 2,2-dimethylpropan-1-ol. The crude product was isolated as a dark brown oil (3.59g). The crude product was cautiously distilled through a Vigreux column under high vacuum and collected in a receiver cooled in a dry ice/acetone bath. The distillate, obtained as a colourless oil, was identified as *2,2-dimethylpropane-1-trifluoromethanesulfonate* **(8)** (2.48g, 85%); δ_H 1.04 (9H, s, (CH_3)$_3$C), 4.19 (2H, s, CH_2-OSO_2CF_3); δ_F –75.1 (s, *C*F_3); δ_C 25.7 (s, (*C*H_3)$_3$C), 32.1 (s, (CH3)$_3$*C*), 86.0 (s, *C*H_2-OSO_2CF_3), 118.7 (d, $^1J_{CF}$ 319.5, *C*F_3).

Synthesis of Cyclohexyl Tosylate (10)

Cyclohexanol (2.01g, 20mmol) was dissolved in ethanol-free chloroform (20ml) in a round bottom flask equipped with a magnetic stirrer and $CaCl_2$ drying tube, and cooled in an ice bath. Pyridine (3.18g, 40mmol) was added, followed by the addition of *p*-toluenesulfonyl chloride (5.75g, 30mmol) in small portions. The reaction was monitored by TLC until no further change could be detected. Ether (100ml) and water (20ml) were added and the organic layer washed successively with 2M HCl, saturated aqueous $NaHCO_3$ and water before being dried over $MgSO_4$. The ether was removed on a rotary evaporator to give a crude product as white crystals (5.56g). The crude product was purified by column chromatography (pet ether 40° – 60°C/2% ether) to yield *cyclohexyl tosylate* **(10)** (2.18g, 42%) as a tan powder; spectral data were consistent with the literature.[1]

Synthesis of Diacetone-*d*-glucose Trifluoromethanesulfonate (11)

A solution of diacetone-*d*-glucose (1.84g, 7mmol) and pyridine (2.6mL, 32mmol) in DCM (50mL) was cooled to 0°C in an ice bath under an inert atmosphere. To this was added trifluoromethanesulfonic anhydride (5.1g, 18mmol) dropwise with stirring. The resulting pale yellow solution was stirred at <5°C for 20 minutes and then washed with ice-cold dilute hydrochloric acid and water. The organic layer was dried (magnesium sulfate) and the solvent was removed on a rotary evaporator at room temperature under vacuum. The product was obtained as an off-white powder (2.55g, 92%) and used immediately. The product was shown to be *diacetone-d-glucose trifluoromethanesulfonate* **(11)**; δ_H 1.34 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.53 (3H, s, CH_3), 3.99 (H, m, C*H*), 4.20 (3H, br m), 4.77 (d, $^3J_{HH}$ 3.8, C*H*), 5.27 (H, s, C*H*), 6.00 (H, d, $^3J_{HH}$ 3.6, C*H*); δ_F –75.0 (s, CF_3) by comparison with literature data.[2]

General Procedure for Reaction of Electrophiles with Caesium Fluoride

Caesium fluoride was dried by heating in an oven at 180°C with periodic grinding over two days. After ensuring that any lumps were broken up, the solid was

transferred to a round bottom flask with a large, heavy stir bar. The flask was evacuated and heated to 200°C with rapid stirring for two days. The solid was periodically removed from the flask and ground under a dry argon atmosphere. The dry CsF was then stored under argon until needed.

Reaction of Benzyl Bromide with Caesium Fluoride

A two-necked round bottom flask was equipped with a condenser, magnetic stir-bar and septa under an inert atmosphere. Caesium fluoride (8.93g, 58.6mmol) in NMP (50ml) was heated to 65°C followed by the rapid addition of benzyl bromide (10.0g, 58.5mmol) with vigorous stirring. The appearance of the reaction mixture was of a colourless liquid with white suspended solid. Over 31 hours a distinct cream coloured precipitate formed and quantitative ^{19}F NMR showed the presence of *benzyl fluoride* **(2)** as the only product (44%); δ_F (NMP) –205.5 (t, $^2J_{HF}$ 47.4, CH_2F).

Typical Preparation of Perfluoro(2-methylpentan-2-yl)caesium (1)

A double-Schlenk apparatus equipped with a fine glass frit was charged with dry caesium fluoride (16.1g, 106mmol), DMF (40ml) and perfluoro(2-methylpent-2-ene) (16.9g, 56.3mmol) and stirred vigorously at 20°C. The reaction was monitored by ^{19}F NMR until complete conversion to the carbanion was achieved (approximately three days). The solution was filtered through the frit to remove residual CsF and a transparent deep red solution was obtained. ^{19}F NMR with 1,4-difluorobenzene as a quantitative reference showed *(perfluoro-2-methylpentan-2-yl)caesium* **(1)**,[3] present at a concentration of 1.36M; δ_F (DMF) –40.6 (6F, br s, $(CF_3)_2C$), -79.9 (3F, br s, CF_3), -91.5 (2F, br s, C-CF_2), -125.0 (2F, br s, CF_2CF_3). The anion solution was then transferred via a double-ended needle to a storage flask fitted with a Young's tap.

Reaction with Benzyl Bromide

A flask was charged with a solution of perfluoro(2-methylpentan-2-yl)caesium **(1)** in DMF (20ml, 20mmol) and heated to 65°C with stirring. A small amount of white precipitate appeared on heating, indicating decomposition of the carbanion to

HFP dimer and caesium fluoride. Benzyl bromide (3.20g, 20.7mmol) was added via a syringe and the reaction followed by ^{19}F NMR. When no remaining carbanion could be detected (two days), the reaction mixture was cooled to room temperature. ^{19}F NMR showed the presence of *[(perfluoro-2-methylpentan-2-yl)methyl]benzene* **(3)** (87%); and *benzyl fluoride* **(2)** (13%). Water (40ml) was added and the mixture stirred overnight. Continuous extraction into Flutec PP2 yielded *[(perfluoro-2-methylpentan-2-yl)methyl]benzene* **(3)** (2.80g, 34%) as a pale yellow liquid; bp 196°C (Siwoloboff) (Found: C, 38.4; H, 1.8. $C_{13}H_7F_{13}$ requires C, 38.1; H, 1.7%); δ_H ($CDCl_3$) 3.56 (2H, s, PhCH_2), 7.32 (5H, m, C_6H_5); δ_F –62.7 (6F, m, $(CF_3)_2C$), -80.5 (3F, t, $^3J_{FF}$ 13, CF_3), -106.4 (2F, m, C-CF_2), -123.4 (2F, m, CF_2CF_3); δ_C {^1H} 32.7 (s, Ar-CH_2), 63.5 (m, $C(CF_3)_2$), 110.0 (tq, $^1J_{CF}$ 272, $^2J_{CF}$ 38.1, CF_2CF_3), 114.8 (tt, $^1J_{CF}$ 270, $^2J_{CF}$ 33.2, C-CF_2), 117.7 (qt, $^1J_{CF}$ 290, $^2J_{CF}$ 34.4, CF_3), 122.1 (q, $^1J_{CF}$ 291, $(CF_3)_2C$), 128.1 (s, Ar 4-C), 128.2 (s, Ar 3,5-C), 130.9 (s, Ar 1-C), 131.5 (s, Ar 2,6-C); *m/z* (EI^+) 410 (M^+, 6.4%), 91 ($C_7H_7^+$, 100%).

Reaction with 1-Bromohexane

As above, except after three days at 20°C there was little reaction and the mixture was heated to 65°C. ^{19}F NMR after three days showed no remaining anion, and the main products were *4,4-di(trifluoromethyl)-1,1,1,2,2,3,3-heptafluorodecane* **(5)** (21%), *HF*; δ_F –178.5 (1F, s, broad) and *1-fluorohexane* **(4)** (5%); δ_F –217.9 (F, m, CH_2F). Water (40ml) was added and the mixture extracted into Flutec PP2. Preparative scale GC at 140°C (with column stripping at 280°C between injections) yielded a pure sample of *4,4-di(trifluoromethyl)-1,1,1,2,2,3,3-heptafluorodecane* **(5)** as a yellow oil; (Found: C, 35.7; H, 3.0. $C_{12}H_{13}F_{13}$ requires C, 35.6; H, 3.2%); δ_H 0.90 (3H, m, CH_3), 1.31 (6H, m, broad, $CH_3CH_2CH_2CH_2$), 1.62 (2H, m, broad, $R_FCH_2CH_2$), 2.13 (2H, t, $^3J_{HH}$ 8.8, R_FCH_2); δ_F –64.3 (6F, m, $(CF_3)_2C$), -80.7 (3F, t, $^3J_{FF}$ 13.9, CF_3), -108.0 (2F, m, C-CF_2), -123.7 (2F, m, CF_2CF_3); δ_C {^1H} 13.90 (s, CH_3), 22.5 (s, CH_2), 23.5 (s, CCH_2CH_2), 27.8 (s, C-CH_2), 29.9 (s, CH_2), 31.1 (s, CH_2), 60.6 (m, $C(CF_3)_2$), 109.6 (tq, $^1J_{CF}$ 272, $^2J_{CF}$ 37.7, CF_2CF_3), 115.2 (tt, $^1J_{CF}$ 270, $^2J_{CF}$ 33.6, C-CF_2), 117.7 (qt, $^1J_{CF}$ 290, $^2J_{CF}$ 34.0, CF_3), 122.3 (q, $^1J_{CF}$ 290, $(CF_3)_2C$); *m/z* (EI^+) 404 (M^+, 0.3%), 85 ($C_6H_{13}^+$, 6.3%).

Reaction with Hexane-1-trifluoromethanesulfonate (6)

As above, except the reaction was stirred at 20°C. The solution darkened rapidly to an orange/yellow colour and solid material was visible on the walls of the flask. ^{19}F NMR after 135 minutes showed no remaining carbanion. The fluorinated products were *1,1,1,2,2,3,3,5,5,5-decafluoro-4-(trifluoromethyl)pentane* (7) (~48%), *4,4-di(trifluoromethyl)-1,1,1,2,2,3,3-heptafluorodecane* (5), *1-fluorohexane* (4) (~10%) and *HF* (~10%).

The volatile fractions were removed by vacuum transfer to yield a colourless liquid. This was shown by NMR to consist of *NMP* (36%); δ_H 2.01 (2H, m, $CH_2CH_2CH_2$), 2.36 (2H, t, $^3J_{HH}$ 8.2, CH_2CO), 2.83 (3H, s, N-CH_3), 3.37 (2H, t, $^3J_{HH}$ 7.2, CH_2N), *1-fluorohexane* (4) (8%); δ_H 0.89 (3H, t, $^3J_{HH}$ 6.6, CH_3), 1.30 (6H, br m, $CH_3CH_2CH_2CH_2$), 1.60 (2H, m, CH_2CH_2F), 4.41 (2H, dt, $^2J_{HF}$ 47.4, $^3J_{HH}$ 6.2, CH_2F); δ_F –218.5 (sep, $^2J_{HF}$ 25, CH_2F); *1,1,1,2,2,3,3,5,5,5-decafluoro-4-(trifluoromethyl)pentane* (7) (45%); δ_H 3.96 (m, C-*H*); δ_F –62.1 (6F, m, $(CF_3)_2C$), -80.7 (3F, t, $^3J_{FF}$ 12.1, CF_3), -112.5 (2F, m, C-CF_2), -125.9 (2F, t, $^3J_{FF}$ 3.8, CF_2CF_3); and *4,4-di(trifluoromethyl)-1,1,1,2,2,3,3-heptafluorodecane* (5) (11%).

Reaction with 2,2-Dimethylpropane-1-trifluoromethanesulfonate (8)

As above, except no reaction was detected by ^{19}F NMR after 75 minutes at 20°C and the temperature was raised to 65°C. ^{19}F NMR after a further 45 minutes showed no remaining carbanion. The only fluorinated product present was *1,1,1,2,2,3,3,5,5,5-decafluoro-4-(trifluoromethyl)pentane* (7). The volatile fractions were removed by vacuum transfer to yield a colourless liquid. This was shown to consist of *NMP* (0.6%); δ_H 2.01 (2H, m, CH_2-CH_2-CH_2), 2.37 (2H, t, $^3J_{HH}$ 8.2, CH_2-CO), 2.83 (3H, s, N-CH_3), 3.37 (2H, t, $^3J_{HH}$ 7.0, CH_2-N); *1,1,1,2,2,3,3,5,5,5-decafluoro-4-(trifluoromethyl)pentane* (7) (64%), *2-methylbut-2-ene* (23%);[4] δ_H 1.57 (3H, d, $^3J_{HH}$ 6.6, $CHCH_3$), 1.61 (3H, s, CH_3C=), 1.69 (3H, s, CH_3C=), 5.20 (H, m, =C*H*); *m/z* (EI^+) 70 (M^+, 12%); *2-methylbut-1-ene* (12%);[4] δ_H 1.04 (3H, t, $^3J_{HH}$ 7.4, CH_3CH_2), 1.74 (3H, s, CH_3-C=), 2.03 (2H, q, $^3J_{HH}$ 7.4, CH_3CH_2), 4.69 (2H, s, =CH_2).

Reaction with 1-Chloroprop-2-yne

As above, except the mixture was left to stir at 20°C and the reaction was monitored by ^{19}F NMR. After 24 hours, no change was detected and the temperature was raised to 65°C. NMR after a further 18 hours showed the conversion to be 49%. The volatile components were removed by vacuum transfer. The residue was shown by ^{19}F NMR to contain *[(perfluoro-2-methylpentan-2-yl)caesium]* **(1)** as the major fluorinated component; δ_F (NMP) –41.1 (6F, m, $(CF_3)_2C$), -79.7 (3F, m, CF_3), -91.8 (2F, broad s, C-CF_2), -125.1 (2F, s, CF_2CF_3). The volatile fraction was shown by NMR to contain *5,5,6,6,7,7,7-heptafluoro-4,4-bis(trifluoromethyl)hept-1-yne* **(9)** as the major fluorinated component. Preparative scale GC at 80°C (with column stripping at 200°C every four injections) yielded a pure sample of *5,5,6,6,7,7,7-heptafluoro-4,4-bis(trifluoromethyl)hept-1-yne* **(9)** as a volatile colourless liquid; (Found: C, 30.0; H, 0.8. $C_9H_3F_{13}$ requires C, 30.2; H, 0.8%); δ_H 2.20 (H, t, $^4J_{HH}$ 2.8, CH), 3.14 (2H, d, $^4J_{HH}$ 2.4, CH_2); δ_F –64.8 (6F, m, $(CF_3)_2C$), -80.6 (3F, t, $^3J_{FF}$ 13.5, CF_3), -108.5 (2F, q, $^4J_{FF}$ 10.9, C-CF_2), -123.4 (2F, m, CF_2CF_3); δ_C {^1H} 18.0 (m, CH_2), 60.0 (m, $C(CF_3)_2$), 73.1 (s, CH), 73.2 (s, HC≡*C*), 109.4 (tq, $^1J_{CF}$ 271, $^2J_{CF}$ 38, CF_2CF_3), 114.4 (tt, ^1J, 271, $^2J_{CF}$ 32, C-CF_2), 117.5 (qt, $^1J_{CF}$ 290, $^2J_{CF}$ 34, CF_3), 121.5 (q, $^1J_{CF}$ 291, $(CF_3)_2C$); *m/z* (EI$^+$) 358 (M^+, 61%), 289 (M^+ - CF_3, 47%), 39 ($C_3H_3^+$, 91%).

Reaction with 2-Bromo-2-methylbutane

As above, except no reaction was observed at 20°C and so the reaction was heated to 65°C. After 24 hours, ^{19}F NMR showed that all of the carbanion had been consumed, and that the major species present was a (perfluoro-2-methylpentan-2-yl) substituted system. No HF was detected. The volatile components were removed by vacuum transfer to yield a colourless volatile liquid, which was examined by NMR and GC-MS. The major components were found to be *perfluoro(2-methylpent-2-ene)* (30%); δ_F –57.2 (3F, m, C-CF_3), -59.6 (3F, m, C-CF_3), -82.7 (3F, m, CF_3), -97.2 (F, m, CF), -116.6 (2F, m, CF_2); *1,1,1,2,2,3,3,5,5,5-decafluoro-4-(trifluoromethyl)pentane* **(7)** (70%), *2-methyl-but-1-ene* (14%); δ_H 1.06 (3H, m, CH_2CH_3), 1.75 (3H, m, CH_3), 2.04 (2H, m, CH_3CH_2), 4.65 (1H, m, =CH_2); *m/z* (EI$^+$)

70 (M^+, 100%) and *2-methyl-but-2-ene* (18%); δ_H 1.58 (3H, m, CH_3), 1.75 (6H, m, $(CH_3)_2C$), 5.20 (1H, m, =C*H*); *m/z* (EI^+) 70 (M^+, 100%).

Reaction with Cyclohexyl Tosylate (10)

As above, except the solution was heated to 50°C with stirring. To this was added 1ml of anion solution in DMF (0.75mmol). The reaction was followed by ^{19}F NMR, and after two days at 50°C no anion could be detected in the reaction mixture. The ^{19}F NMR showed (amongst other peaks) a broad resonance at δ –180 ppm due to HF. The volatile fractions were then vacuum transferred and examined by ^{19}F NMR; the peak at δ –180 ppm was only present in the residue. The only fluorinated material contained in the volatile fractions was *1,1,1,2,2,3,3,5,5,5-decafluoro-4-(trifluoromethyl)pentane* (7).

Reaction with Diacetone-*d*-glucose trifluoromethanesulfonate (11)

As above, except the reaction was stirred at 20°C; ^{19}F NMR after one hour showed no reaction and the flask was heated to 65°C. An NMR sample was taken after a further hour at this temperature showing the presence of *1,1,1,2,2,3,3,5,5,5-decafluoro-4-(trifluoromethyl)pentane* (7) along with other minor fluorinated components. An unidentified small multiplet at δ_F -133.4 may be due to the fluorinated sugar. The volatile components were removed by vacuum transfer to yield a colourless liquid. Examination of this liquid by ^{19}F NMR showed it to be a mixture of *1,1,1,2,2,3,3,5,5,5-decafluoro-4-(trifluoromethyl)pentane* (7) (34%) and *perfluoro-2-methylpent-2-ene* (62%) and *NMP* (4%). The suspected fluorinated sugar (δ_F – 133.4) remained in the residue from the vacuum transfer; attempts to extract this very small quantity of product were unsuccessful.

Reaction with Benzoyl Chloride

As above, except the mixture was left to stir at 20°C and the reaction was monitored by ^{19}F NMR. A white precipitate formed immediately on addition of benzoyl chloride. After two hours, the solution had changed from deep red to pale

brown and a large quantity of precipitate was present. A sample was taken and a quantitative ^{19}F NMR was run using 1,4-difluorobenzene as a reference. The major product was *benzoyl fluoride* **(12)** (80%); δ_F (sulfolane) 18.4 (s, ArCOF).

Reaction with Benzoyl Chloride at –40°C

A flask was charged with a solution of carbanion **(1)** in NMP (11ml, 8.9mmol) and cooled in an acetonitrile/dry ice slush bath. This was followed by the addition of freshly distilled benzoyl chloride (1.23g, 8.9mmol) via a syringe. The mixture was left to stir at -40°C for *ca.* 30 minutes, and then removed from the bath and allowed to warm to room temperature for 30 minutes. The volatile material was removed by vacuum transfer, and on examination two layers were found to be present. NMR confirmed the upper layer to be *benzoyl fluoride* **(12)** dissolved in NMP; δ_F 17.6 (s, ArCOF). The lower layer was shown to be *perfluoro(2-methylpent-2-ene)* with a trace of *1,1,1,2,2,3,3,5,5,5-decafluoro-4-(trifluoromethyl)pentane* **(7)**.

Attempted Reaction with Carbon Dioxide

A two-necked flask was equipped with a magnetic stir-bar, a septum and a condenser and charged with a solution of carbanion **(1)** in NMP (20.5ml, 16.6mmol). An inert atmosphere was maintained by allowing a low flow-rate of nitrogen through a needle in the septum. Carbon dioxide was provided by filling a thick-walled conical flask with dry ice and connecting to the gas inlet, and a wide-bore needle was used to allow excess gas to escape. The carbon dioxide was introduced below the liquid level and the solution was stirred vigorously. The carbon dioxide was bubbled through for seven hours whilst maintaining the temperature at 20°C, causing the formation of a white precipitate. The solvent and volatiles were removed by vacuum transfer to leave a red and white solid that coated the flask. It was not possible to interpret the highly complex ^{19}F NMR of this material, the only recognisable peak being due to a small quantity of HF.

The solid material was dissolved in water and added to 8% hydrochloric acid. The aqueous components were then removed under vacuum to yield a pale green solution and eventually a pale green solid, which was assumed to be a mixture of the

carboxylic acid, caesium chloride and metal salt contamination from acidic corrosion of the gas-inlet needle. Vacuum sublimation of the solid at < 50°C yielded a small quantity of pale orange crystals. These were observed to be both volatile and extremely deliquescent. Universal indicator paper showed the material to have a pH of less than one, but due to volatility or decomposition no analytical data could be obtained.

5.4 Experimental to Chapter 3

Synthesis of Starting Materials

Synthesis of [BMIM][PF_6] (13)

A two-necked round bottom flask was equipped with a condenser, magnetic stir-bar and septa under an inert atmosphere. Freshly distilled N-methylimidazole (58.5g, 712mmol) and 1-chlorobutane (74.1mL, 800mmol) were added and heated to 80°C with vigorous stirring. After three days a viscous colourless liquid was observed in the flask, along with a very small amount of a brown liquid impurity floating on the reaction mixture. The product was washed with ethyl acetate (3 x 60mL) and residual ethyl acetate was removed by vacuum transfer at 80°C to yield a colourless liquid, which gave a white solid on cooling. This was shown to be *[BMIM][Cl]* (82%); δ_H (DMSO-d_6) 0.89 (3H, t, $^3J_{HH}$ 7.2, CH_2CH_3), 1.25 (2H, sex, $^3J_{HH}$ 7.6, CH_2CH_3), 1.76 (2H, pent, $^3J_{HH}$ 7.4, N-CH_2CH_2), 3.86 (3H, s, N-CH_3), 4.18 (2H, t, $^3J_{HH}$ 7.2, N-CH_2), 7.75 (1H, s, N-CHCH), 7.83 (1H, s, N-CHCH), 9.36 (1H, s, N-CH-N); δ_C {^{1}H} (DMSO-d_6) 13.2 (CH_2CH_3), 18.7 (CH_2CH_3), 31.3 (NCH_2CH_2), 35.7 (N-CH_3), 48.4 (N-CH_2).

The [BMIM][Cl] intermediate was dissolved in warm water (320mL) and poured into a PTFE reactor equipped with an overhead stirrer and an ice/salt bath. Hexafluorophosphoric acid (65%) (166mL, 837mmol) was added via a polythene dropping funnel over the course of one hour and the reaction stirred for a further hour. On opening the reactor a pale red lower layer was observed. The aqueous upper layer was decanted off and the lower layer poured into a beaker. The crude [BMIM][PF_6]

was washed with successive portions of deionised water (750mL) with high-speed stirring until the aqueous phase was neutral to Universal Indicator paper.

After a further wash with two portions of deionised water, the lower colourless liquid layer was collected and placed into a single-neck round-bottom flask equipped with a Dean-Stark apparatus. The [BMIM][PF_6] was then azeotropically dried with benzene before heating under high vacuum to remove the last traces of volatile impurities. The product was obtained as a pale straw coloured viscous liquid which was shown to be *N,N-butylmethylimidazolium hexafluorophosphate* **(13)**;[5] (Found: C, 33.7; H, 5.3; N, 9.8. $C_8H_{15}F_6N_2P$ requires C, 33.8; H, 5.3; N, 9.9); δ_H 0.90 (3H, t, $^3J_{HH}$ 7, CH_3), 1.26 (2H, sex, $^3J_{HH}$ 7.6, CH_2CH_3), 1.77 (2H, pent, $^3J_{HH}$ 7.2, N-CH_2CH_2), 3.84 (3H, s, N-CH_3), 4.16 (2H, t, $^3J_{HH}$ 7.2, N-CH_2), 7.67 (1H, t, $^3J_{HH}$ 2, N-CHCH), 7.74 (1H, t, $^3J_{HH}$ 2, N-CHCH), 9.08 (1H, s, N-CH-N); δ_F –70.6 (d, $^2J_{FF}$ 778, PF_6^-); δ_C {^{1}H} (CD_3CN) 13.7 (CH_2CH_3), 19.56 (CH_2CH_3), 32.6 (N-CH_2CH_2), 36.8 (N-CH_2), 50.3 (N-CH_3), 123.3 (N-CHCH), 124.7 (N-CHCH), 136.9 (N-CH-N).

Synthesis of 1-Triflatooctane (15)

A three-necked round bottom flask was equipped with a condenser, magnetic stir-bar, septum and pressure equalised dropping funnel with septum. The flask was charged with DCM (48mL) and trifluoromethanesulfonic anhydride (20.31g, 72mmol) and cooled in an ice/water bath. The dropping funnel was charged with DCM (12mL), pyridine (4.85mL, 60mmol) and octan-1-ol (9.44mL, 60mmol). The contents of the dropping funnel were added to the flask over a 45-minute period with stirring during which time the colour of the reaction turned deep red. The reaction was then stirred at 0°C for a further 30 minutes. The reaction mixture was washed with water three times before being dried ($MgSO_4$) and filtered. The solvent was removed on a rotary evaporator to yield the crude product as a dark blue oil (13.24g, 84%).

The crude product was distilled under high vacuum through a Vigreux column into a dry-ice cooled receiver and the product distilled over between 31°C and 48°C. The wide range is likely due to the first portion of the product merely diffusing through the apparatus rather than actually boiling and condensing in the column. The product was *1-triflatooctane* **(15)** (4.82g, 31%), isolated as a colourless oil; δ_H 0.89 (3H, m, CH_3), 1.35 (10H, br m, $CH_3CH_2CH_2CH_2CH_2CH_2$), 1.83 (2H, pent, $^3J_{HH}$ 7.6,

$CH_2CH_2OSO_2CF_3$), 4.53 (2H, t, $^3J_{HH}$ 6.6, $CH_2OSO_2CF_3$); δ_F –75.4 (s, CF_3); δ_C 14.2 (s, CH_3), 22.7 (s, CH_3CH_2), 25.2 (s, $CH_3CH_2CH_2$), 29.0 (s, $CH_3CH_2CH_2CH_2$), 29.1 (s, $CH_2CH_2CH_2CH_2O$), 29.4 (s, $CH_2CH_2CH_2O$), 31.8 (s, CH_2CH_2O), 78.0 (s, CH_2O), 118.8 (q, $^1J_{CF}$ 320, $CF_3SO_3CH_2$). The product was stored briefly at -20°C before being used.

Trial Fluorination of Benzyl Bromide

A single-necked round bottom flask equipped with a magnetic stir-bar was charged with CsF (1.45g, 9.5mmol) and [BMIM][PF_6] (**13**) (10mL) and degassed under high vacuum to aid the mixing of the components. The CsF did not dissolve appreciably. After replenishing the atmosphere with dry nitrogen, benzyl bromide (0.88g, 5.1mmol) was added and the reaction stirred vigorously at 20° C. After one hour, the volatile fractions were removed by vacuum transfer to yield a colourless liquid (0.5g). Analysis of the liquid by NMR, referenced to a known mass of reference compound, identified it as a mixture of *benzyl fluoride* (**2**) (0.26g, 47%, 66% conversion); δ_H 5.41 (2H, d, $^2J_{HF}$ 48, CH_2F), 7.42 (5H, br s, Ar-H); δ_F –207.2 (t, $^2J_{HF}$ 47, CH_2F); *m/z* (EI^+) 110 (M^+, 70%) and *benzyl bromide* (0.24g); δ_H 4.53 (2H, s, CH_2Br), 7.42 (5H, br s, Ar-H); *m/z* (EI^+) 172 (M^++1, 56%). The total recovery of organic components was 75% by mass.

Fluorination Reactions Using Metal Fluorides in [BMIM][PF_6] at Atmospheric Pressure

General Procedure:

A two-necked round bottom flask was equipped with a condenser, magnetic stir-bar and septa under an inert atmosphere. The flask was charged with CsF (4.93g, 32mmol) and [BMIM][PF_6] (**13**) (20mL) and then degassed for 10 minutes to allow distribution of the CsF in the liquid media. 1-Bromooctane (6.22g, 32mmol) was added and the mixture stirred vigorously at 20°C. After 16 ½ hours the volatile fractions were removed by vacuum transfer to yield a colourless liquid (5.40g) which was analysed by quantitative NMR and GC-MS and identified as a mixture of *1-*

fluorooctane (14) (12%); δ_H 4.44 (2H, dt, $^2J_{HF}$ 47, $^3J_{HH}$ 6.2, CH_2F), all other peaks overlap with 1-bromooctane peaks; δ_F -218.4 (m, $^2J_{HF}$ 47, CH_2F); *m/z* (EI^+) 132 (M^+, 4%), *1-bromooctane* (78%); δ_H 0.89 (3H, t, $^3J_{HH}$ 6.6, CH_3), 1.29 (10H, br m, $CH_3CH_2CH_2CH_2CH_2CH_2$), 1.86 (2H, pent, $^3J_{HH}$ 7.2, CH_2CH_2Br), 3.41 (2H, t, $^3J_{HH}$ 6.8, CH_2Br); *m/z* (EI^+) 192 (M^+, 6%) and *oct-1-ene* (3%); δ_H 4.97 (2H, br m, $CH=CH_2$), 5.82 (H, br m, $CH=CH_2$), all other peaks overlap with 1-bromooctane peaks; *m/z* (EI^+) 112 (M^+, 6%). This gave a recovery of 93% and a conversion of 17%.

Fluorination of 1-Triflatooctane with CsF in [BMIM][PF_6] in a Carius Tube

A Carius tube was charged with CsF (2.13g, 13.8mmol) and [BMIM][PF_6] **(13)** (10mL) in a glove bag under an argon atmosphere. The tube was degassed under high vacuum to cause foaming of the RTIL and thus allow efficient mixing of the reactants. The argon atmosphere was replenished and 1-triflatooctane **(15)** (1.80g, 6.7mmol) was added. The tube was frozen in liquid nitrogen and evacuated before being sealed with a flame. The Carius tube was then placed in a steel sheath and attached to a rotating arm at ambient temperature. After four days the tube was frozen in liquid nitrogen and opened before being quickly connected to an evacuated trap cooled in liquid nitrogen. The product mixture was isolated as a colourless liquid (1.01g). This was shown, by comparison with reference samples and NMR and GC-MS reference data to be comprised of *1-fluorooctane* **(14)** (11%); *1-triflatooctane* **(15)** (8%), *oct-1-ene* (5%)[6] and *cis/trans-oct-2-ene* (13%).[6] This gave a recovery of 37% and a conversion of 78%.

Fluorination of Trichloro-*s*-triazine with CsF in a Carius Tube

A Carius tube was charged with CsF (4.39g, 28.5mmol) in a glove bag under an argon atmosphere followed by the addition of trichloro-*s*-triazine (1.70g, 9.2mmol) and [BMIM][PF_6] **(13)** (5mL). The tube was degassed under high vacuum to cause foaming of the RTIL and thus allow efficient mixing of the reactants. The tube was frozen in liquid nitrogen, evacuated, sealed and placed in a steel sheath. The reaction was then placed in a furnace at 80°C. After 19 hours the Carius tube was frozen and

opened. The volatile fractions were removed by vacuum transfer to yield a colourless liquid (0.39g) and a white solid (0.10g). Analysis of the material by NMR and GC-MS, compared with reference samples and literature data,[7, 8] showed it to be composed of *trifluoro-s-triazine* **(20)** (10%); δ_F –30.4 (s, N-C*F*-N); *m/z* (EI^+) 135 (M^+, 100%), *chlorodifluoro-s-triazine* **(19)** (11%); δ_F -32.4 (s, N-C*F*-N); *m/z* (EI^+) 151 (M^+, 100%) and *dichlorofluoro-s-triazine* **(18)** (3.4%); δ_F -34.3 (s, N-C*F*-N); *m/z* (EI^+) 167 (M^+, 100%) along with a trace of *trichloro-s-triazine*; *m/z* (EI^+) 183 (M^+, 100%). This gave a recovery of 24.5%. Conversion could not be calculated as starting material was observed subliming inside the Carius tube during vacuum transfer and this material could not be accurately quantified.

Reactions of HFP with CsF in [BMIM][PF_6]

A Carius tube was charged with CsF (4.18g, 27.1mmol) and [BMIM][PF_6] **(13)** (5.5mL) in a glove bag under an argon atmosphere. The tube was degassed under high vacuum to cause foaming of the RTIL and thus allow efficient mixing of the reactants. The argon atmosphere was replenished and hexafluoropropene (3.75g, 25mmol) was vacuum transferred into the Carius tube from a Rotaflo vessel. The tube was frozen in liquid nitrogen and evacuated before being sealed with a flame. The Carius tube was then placed in a steel sheath and attached to a rotating arm at ambient temperature. After four days, the tube was taken out of the sheath and frozen in liquid nitrogen.

The tube contained a dark red/brown solid; no liquid material was present and on freezing a white crystalline solid collected on the walls of the tube, indicating the presence of a gas. The volatile material was removed via vacuum transfer and collected to yield 3.31g of a white solid at -196°C or a colourless liquid on slight warming. The material appeared to be gaseous at room temperature and so a sample was vacuum transferred to a quartz NMR tube which was then sealed with a flame. As the NMR was run in the absence of solvent, locking signal or reference, the data acquired was only roughly accurate in terms of NMR chemical shift and coupling. The volatile fractions were shown to be comprised of *perfluoro-4-methylpent-2-ene* **(21)**; δ_F (neat) –70 (3F, CF_3), -77 (6F, (CF_3)$_2$CF), -157 (1F, CF_3C*F*), -159 (F,

$CF_3CF{=}CF$), -188 (F, $(CF_3)_2CFCF$); and *2H-heptafluoropropane* **(22)**; δ_H (neat) 6.5 (br m, C*H*); δ_F (neat) –77 (6F, $(CF_3)_2CHF$), -215 (F, $(CF_3)_2CFH$).

Reaction of HFP with 0.1CsF in [BMIM][PF_6]

A Rotaflo vessel was charged with CsF (0.47g, 3.1mmol) and [BMIM][PF_6] **(13)** (5.5mL) as above. The argon atmosphere was replenished and hexafluoropropene (3.85g, 25.7mmol) was vacuum transferred into the Rotaflo from another Rotaflo vessel. The reaction was run as above. The volatile material was removed via vacuum transfer and collected to yield a white solid (0.17g) at -196°C or a colourless liquid on slight warming. The material appeared to be gaseous at room temperature and so a sample was transferred by vacuum transfer to a quartz NMR tube and shown to be only *2H-heptafluoropropane* **(22)**.

To the residue in the Rotaflo (a red/brown liquid) was added a molar equivalent of iodomethane (based on the initial quantity of hexafluoropropene) (3.54g, 25mmol). The Rotaflo was replaced on the rotating arm and allowed to rotate at room temperature for ca. 18 hours. The volatile fractions were vacuum transferred to a cooled receiver and 2.91g of a colourless liquid was isolated. This was shown by NMR to be predominantly *iodomethane*; δ_H 2.15 (s, CH_3I). Approximately 75% of the iodomethane was recovered and no fluorination was observed in the volatile fractions. Analysis of the residue by NMR showed essentially pure [BMIM][PF_6]. Any other products, whether fluorinated or not, were masked by the [BMIM][PF_6] ^1H and ^{19}F resonances.

Control Reaction of HFP with [BMIM][PF_6]

A Rotaflo tube was charged with [BMIM][PF_6] **(13)** (2.1mL, 10mmol) and then evacuated and frozen. Hexafluoropropene (1.45g, 9.7mmol) was vacuum transferred into the Rotaflo from another Rotaflo vessel. The Rotaflo was then frozen in liquid nitrogen and evacuated before being placed in a steel sheath and attached to a rotating arm in an explosion proof cubicle. The tube was allowed to warm to ambient temperature and was then rotated for 18 hours. On examination, the tube appeared to contain (visually) unchanged [BMIM][PF_6]. The tube was frozen in liquid nitrogen

and the volatile fractions transferred to a Rotaflo vessel under vacuum to give a colourless gas (1.38g). This was transferred under vacuum into a quartz NMR tube and shown by ^{19}F and ^{1}H NMR to be composed of *hexafluoropropene*; δ_F (neat, $CFCl_3$ ext. ref.) –72.0 (3F, m, CF_3), -96.7 (F, m, C=C*F*F), -110.0 (F, m, C=C*F*F), 195.8 (F, m, C*F*=C) and *2H-pentafluoropropane* (**22**); δ_H (neat, $CFCl_3$ ext. ref.) 5.00 (d sept, $^2J_{HF}$ 44, $^3J_{HF}$ 6.0; δ_F (neat, $CFCl_3$ ext. ref.) –79.3 (6F, m, $(CF_3)_2C$), -216.8 (F, m, C*F*H).

Reaction of [BMIM][PF_6] with 1.5 CsF at 150°C in a Carius Tube

A dry Carius tube was charged with anhydrous CsF (3.60g, 23.4mmol) and [BMIM][PF_6] (**13**) (31.mL, 15mmol) in a glove bag under argon. The tube was then evacuated, frozen in liquid nitrogen and sealed with a flame before being placed in a metal sheath and heated to 150°C in an oven for four days. On cooling and examination, the material in the tube consisted of a deep red/brown solid indicating decomposition. The tube was opened and the volatile materials isolated by vacuum transfer. A small quantity of colourless liquid was collected in the trap, the residue in the Carius tube being a deep brown/yellow colour.

Analysis of the volatile fractions by NMR showed the presence of an alkyl fluoride other than fluoromethane as there was a distinctive CH_2CH_2F peak. Presumably this was *1-fluorobutane*; δ_H 4.41 (dt, $^2J_{HF}$ 47, $^3J_{HH}$ 6.0, CH_2F); δ_F –218.1 (sep, $^2J_{HF}$ 47, CH_2F). No alkene CH or $=CH_2$ peaks were visible, but there were three weak peaks in the region of the imidazolium ring protons (δ_H 6.87, 7.00, 7.42) and a large singlet (δ_H 3.41) in the region expected for the N-methyl in N-methylimidazole although the integrals are different from those expected for this material.

A portion of the volatile fraction was vacuum transferred to a sample vessel fitted with a Young's tap and septum so that a sample could be withdrawn for GC-MS analysis. The sample was very dilute (the quantity of recovered sample was such that at the vacuum transfer pressure of ~0.1 mbar, the majority of the transferred material was air), but the following products were detected: *But-1-ene*; *m/z* (EI^+) 56 (M^+, 87%), *1-fluorobutane*; *m/z* (EI^+) 75 (M^+-1, 1.5 %), 56 (M^+- HF, 100%), 47 ($CH_2CH_2F^+$, 15%), 33 (CH_2F^+, 55%) and *N-methylimidazole*; *m/z* (EI^+) 81 (M^+-1,

2%), 56 (N-CH-N-CH_3^+, 13%), 55 (CH-CH-N-CH_3^+, 8%), 42 (CH-N-CH_3^+, 9%), 40 (N-CH-CH^+, 92%), 41 (N-CH-N^+, 100%), 28 (N-CH_3^+, 22%).

Reaction of [BMIM][PF_6] with 2KF at 150°C in a Carius Tube

A dry Carius tube was charged with KF (0.58g, 10mmol) and [BMIM][PF_6] **(13)** (1.15g, 4mmol) in a glove box. The tube was then evacuated, frozen in liquid nitrogen and sealed with a flame before being placed in a metal sheath and heated to 150°C in an oven overnight. After cooling and removal of the sheath, visual examination indicated that the [BMIM][PF_6] had decomposed due to its increased viscosity and deep yellow/brown colour. No further analysis was conducted.

General Procedure for Phase Transfer Fluorination Reactions

Dry CsF:

A dry Radley's Carousel reaction tube equipped with a magnetic stir-bar was quickly charged with tetraoctylammonium bromide (0.109g, 0.2mmol), flushed with argon and transferred to a glove box. Caesium fluoride (1.55g, 10mmol) was added and the tube was then sealed and transferred to the carousel reactor. MeCN (5mL) and 1-bromooctane (0.9mL, 5mmol) were added and the reaction tube was heated for 15 hours at 90°C. The reaction mixture was allowed to cool and a sample was withdrawn for quantitative NMR analysis, identifying the product as *1-fluorooctane* **(14)** (12%).

Wet CsF:

A dry Radley's Carousel reaction tube equipped with a magnetic stir-bar was charged with as-received caesium fluoride (1.54g, 10mmol) and tetrabutylphosphonium bromide (0.017g, 0.05mmol. The tube was sealed and transferred to the Carousel reactor and MeCN (5mL) and 1-bromooctane (0.9mL, 5mmol) were added. The reaction tube was then heated for 15 hours at 90°C. The reaction mixture was allowed to cool and a sample was withdrawn for quantitative NMR analysis, identifying the product as *1-fluorooctane* **(14)** (16%).

General Method for Water Loading Study

A dry Radley's Carousel reaction tube equipped with a magnetic stir-bar was transferred to a glove box and charged with tetrabutylphosphonium bromide (0.07g, 0.2mmol) and caesium fluoride (1.57g, 10mmol). The tube was then sealed and transferred to the carousel reactor. MeCN (5mL) was added, followed by water (0.0018mL, 0.1mmol) via a micro-syringe. 1-Bromooctane (0.9mL, 5mmol) was then added and the carousel was heated for 17 hours at 90°C. The reaction mixture was then allowed to cool and a sample was withdrawn for quantitative NMR analysis. The yield of *1-fluorooctane* **(14)** was 20%.

5.5 Experimental to Chapter 4

Synthesis of Starting Materials

Synthesis of Trifluoro-*s*-triazine (20)

Finely ground, flame-dried potassium fluoride (110g, 1.9mol) and trichloro-*s*-triazine (33g, 180mmol) were mixed under argon in a flask before being transferred to a dry preconditioned 500mL stainless steel autoclave. An autoclave without a pressure gauge or bursting disk was used so as to avoid fouling with trichloro-*s*-triazine, which tends to coat surfaces. This necessitated the use of a large safety margin for the difference between the maximum pressure obtained during the reaction and the maximum working pressure of the autoclave. The autoclave was evacuated, sealed and heated to 310°C for 21 hours before being cooled to 130°C. With suitable precautions, the product was cautiously distilled out of the autoclave into an evacuated double trap system cooled with liquid nitrogen. A colourless fluid was observed passing into the traps for several minutes and after the flow had visibly ceased the apparatus was put under dynamic vacuum for a further hour. The isolated liquid contained some metal contamination, and so further purification by vacuum transfer yielded *trifluoro-s-triazine* **(20)** (20.4g, 84%); δ_F –30.2 (s, $(CFN)_3$); NMR and GC-MS analysis was identical to that of a reference sample.

General Procedure for Fluorination Reactions

A two-necked round-bottom flask was equipped with a magnetic stir bar, septa, condenser and an inert gas inlet. The flask was charged with DMAP (1.20g, 9.80mmol) and MeCN (20mL). When the DMAP had dissolved, pentafluoropyridine (1.65g, 9.80mmol) was added via a syringe and the mixture was left to stir for five minutes. A yellow solution formed immediately on mixing and within the five-minute period a thick yellow precipitate had formed. 1-Bromooctane (1.93g, 10mmol) was then added via a syringe and the reaction was stirred at 20°C for 22 ½ hours. Quantitative ^{19}F NMR using 1,4-difluorobenzene as a reference yielded the following results (by comparison to a reference sample): Yield of *1-fluorooctane* (**14**)/time, 11%/0.5h, 19%/2.5h, 19%/22.5h.

Effect of the Ratio of Reagents on the Yield of Fluorination – Reactions of Trifluoro-*s*-triazine (20)

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (0.62g, 5mmol) and MeCN (10mL), followed by trifluoro-*s*-triazine (**20**) (0.72g, 5.3mmol) when the DMAP had fully dissolved. An immediate white precipitate formed with the solution remaining colourless. 1-Bromooctane was added and the reaction stirred at 20°C for 2 ¼ hours after which time no fluorination was observed by ^{19}F NMR. The only signals observed were due to a *σ-complex*; δ_F -4.4 (s, CFX), -4.9 (s, CFX), -7.8 (s, CFX), -49.5 (s, NCF), -51.2 (br s, NCF), where X = $DMAP^+$ or F. The reaction was heated to 80°C for a further 74 hours after which time analysis of the reaction mixture by ^{19}F NMR showed the yield of *1-fluorooctane* (**14**) to be 14%.

Solvent Screen

A six-station Radley's Carousel reactor was purged with argon and five of the flasks were charged with DMAP (10mmol, 1.22g), followed by the appropriate solvent (40mL). The condenser head was connected to a glycol/water recirculating cryostat at -10°C. When the DMAP had dissolved and the head had cooled (-8°C

indicated), pentafluoropyridine (10mmol, 1.1mL) was added, and the reaction mixture was stirred rapidly for five minutes. All reactions showed the expected yellow/orange colouration, except for the flask containing ethylene glycol which remained colourless. 1-Bromooctane (10mmol, 1.8mL) was added and the carousel was heated to 90°C for 20 ½ hours. Analysis by quantitative NMR, using 1,4-difluorobenzene as the reference, gave the following yields of *1-fluorooctane* **(14)** (Table 5.1):

Table 5.1 Yield of **(14)** in solvent screen reactions

Solvent	Yield (14)
Ethylene glycol	0
DCM	19
THF	23
Toluene	24
MeCN	31
DMF	37

Difficulties Encountered in Fluorination Reactions

Alkene Formation

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (2.46g, 20mmol) and MeCN (40mL), followed by pentafluoropyridine (5.07g, 30mmol) when the DMAP had fully dissolved. After stirring for 25 minutes at 20°C, 1-bromooctane (3.86g, 20mmol) was added and the temperature was raised to 90°C. Analysis of the reaction mixture by ^{19}F NMR after 14 ½ hours gave the yield of 1-fluorooctane **(14)** to be 34%. The volatile fractions were removed by vacuum transfer and the resulting colourless liquid analysed by GC-MS. This showed the liquid to be composed of *MeCN*, *1-bromooctane* (13%); *m/z* (EI^+) 192 (M^+, 4%); *1-fluorooctane* **(14)** (34%); *m/z* (EI^+) 132 (M^+, 1%), 112 (M^+ - HF, 2%); *oct-1-ene* (15%); *m/z* (EI^+) 112 (M^+, 18%) and *pentafluoropyridine*; *m/z* (EI^+) 169 (M^+, 100%); by comparison with reference compounds.

Reaction of DMAP with 1-Bromooctane

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (1.22g, 10mmol) and MeCN (10mL) followed by 1-bromooctane (1.8mL, 10mmol) when the DMAP had fully dissolved. The temperature was raised to 90^{0}C and the reaction was left to stir for 15 hours. Removal of the solvent on a rotary evaporator yielded the crude product as a very pale yellow hygroscopic solid (3.15g, 100%). Analysis by standard techniques and comparison with literature data showed the material to be *4-(dimethylamino)-1-octylpyridinium bromide* **(24)**; δ_H 0.83 (3H, t, $^3J_{HH}$ 7.0, CH_3), 1.23 (10H, m, $CH_3CH_2CH_2CH_2CH_2CH_2$), 1.84 (2H, m, $^3J_{HH}$ 7.0, $N^+CH_2CH_2$), 3.25 (6H, s, $N(CH_3)_2$), 4.31 (2H, t, $^3J_{HH}$ 7.5, N^+CH_2), 7.03 (2H, d, $^3J_{HH}$ 7.5, $N(CH_3)_2CH$), 8.46 (2H, d, $^3J_{HH}$ 8.0, N^+CH); (Found: C, 56.8; H, 8.5; N, 9.1. $C_{12}H_{27}BrN_2$ requires C, 57.1; H, 8.6; N, 8.9); *m/z* (ES^+) 235 (M^+, 100%).

Reaction of 4-(Dimethylamino)-1-octylpyridinium Bromide (24) with Caesium Fluoride at 90°C

A two necked flask was charged with 4-(dimethylamino)-1-octylpyridinium bromide **(24)** (2.70g, 8.6mmol) and dry CsF (1.45g, 9.5mmol) in a glove box. The flask was removed from the glove box and a condenser and inert gas inlet were attached. MeCN (10mL) was added and the flask was stirred at 20°C. A pale yellow solution resulted and, after stirring overnight, ^{19}F NMR showed that no reaction had occurred. The reaction was heated to 90°C for 23 hours and then a further sample was taken for NMR analysis. No 1-fluorooctane **(14)** or HF could be detected and the volatile materials were removed by vacuum transfer to yield a colourless liquid. Analysis of this material by GC showed it to contain only MeCN.

Effect of Dilution on Yield of Fluorination

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (0.31g, 2.5mmol) and MeCN (20mL),

followed by pentafluoropyridine (0.42g, 2.5mmol) when the DMAP had fully dissolved. No precipitate was produced under these higher dilution conditions. 1-bromooctane (0.48g, 2.5mmol) was added after 30 minutes and the reaction was then heated to 90°C for 16 hours. The appearance of the reaction solution after this time was of a dark orange solution and ^{19}F NMR showed the yield of *1-fluorooctane* (**14**) to be 19%.

Fluorination System Screening – General Procedure

The six-station carousel reactor was purged with argon and five of the flasks were charged with DMAP (1.22g, 10mmol) followed by the MeCN (40mL). The condenser head was connected to a glycol/water recirculating cryostat at -10°C. When the DMAP had dissolved and the head had cooled (-8°C indicated), pentafluoropyridine (1.10mL, 10mmol) was added, and the reaction mixture was stirred rapidly for five minutes. 1-Bromooctane (1.80mL, 10mmol), 2-bromooctane (1.80mL, 10mmol), benzoyl bromide (1.29mL, 10mmol), benzyl bromide (1.15mL, 10mmol) and 2,4-dinitrochlorobenzene (1.99g, 10mmol) were added to the reaction flasks rapidly in turn and the carousel was heated to 90°C for 20 ½ hours. Analysis by quantitative NMR, using 1,4-difluorobenzene as the reference, gave *1-fluorooctane* (**14, A**), *2-fluorooctane* (**16, B**), *benzoyl fluoride* (**12, C**), *benzyl fluoride* (**2, D**) and *2,4-dinitrofluorobenzene* (**17, E**) in the yields shown below (Table 5.2):

Table 5.2 Results of fluorination system screening

	Amine 4-substituent Time (h)/temp (°C)						
Reaction	NMe_2	NMe_2	NMe_2	NH_2	MeO	Me	CN
	18/20	23/90	17/90*	16/90	19/90	17/90	19/90
A (14)/%	12	25	20	0	2	0	0
B (16)/%	0	8	10	0	0	0	0
C (12)/%	30	35	57	65	9	12	0
D (2)/%	33	34	13	3	<1	0	0
E (17)/%	72	71	64	6	74	15	0

*Reaction was heated upon addition of PFP, substrates added when temperature reached 90°C

Effect of Time Allowed for Adduct Formation

The six-station carousel reactor was purged with argon and five of the flasks were charged with DMAP (1.22g, 10mmol) followed by the MeCN (40mL). The condenser head was connected to a glycol/water recirculating cryostat at -10°C. When the DMAP had dissolved and the head had cooled (-8°C indicated), pentafluoropyridine (1.10mL, 10mmol) was added to each flask in turn at times of 0 min, 15 min, 25 min, 28 min and 29 min. After a further minute, 1-bromooctane (1.80mL, 10mmol) was added simultaneously to all the flasks and the carousel was heated to 90°C for 17 ½ hours. Analysis by quantitative NMR, using 1,4-difluorobenzene as the reference, gave *1-fluorooctane* **(14)** in the yields shown below (Table 5.3):

Table 5.3 Results of variable time study

Time between PFP and substrate addition/min	1	3	10	15	30
Yield/%	22	24	29	34	28

Use of DMAP Adduct as PTC

Two carousel reactor tubes from the 12-station carousel were charged with MeCN (10mL). The first tube was then charged with CsF (0.33g, 2.14mmol) and 1-bromooctane (0.40g, 2.09mmol). The second tube was charged with DMAP (0.31g, 0.25mmol), pentafluoropyridine (0.03mL, 0.25mmol) and, after a 10-minute delay, CsF (0.38g, 2.49mmol) and 1-bromooctane (0.48g, 2.49mmol). The reactions were left to stir at 20°C for 17 hours after which time ^{19}F NMR showed that no reaction had occurred. The reactions were then heated to 90°C for 5 hours after which time the yields of *1-fluorooctane* **(14)** were found to be 3% and 8% for tubes one and two respectively.

Use of Fluoroheterocycles as PTCs – General Procedure

A two-neck round bottom flask was charged with KF (0.58g, 10mmol) in a glove box and equipped with a condenser, magnetic stir-bar, septa and inert gas inlet. After transferring to an oil bath, MeCN (20mL) and trifluoro-*s*-triazine **(20)** (1.0mL, 10mmol) were added and the whole stirred for one hour at 20°C. An NMR sample taken after this time showed no resonances apart from trifluoro-*s*-triazine in the ^{19}F spectrum. 1-Bromooctane (1.80mL, 10mmol) was then added and the reaction left stirring at 20°C overnight. NMR analysis the following morning again showed no fluorination to have occurred. After heating to 60°C for four hours, 90°C for three hours and then for a further 116 hours NMR samples were also taken. In no case could any fluorination of the starting material be detected.

Use of Fluoroheterocycle-tertiary Aliphatic Amines as PTC or Fluoride Ion Source

TFT (20)/Et_3N as Fluoride Source

A two-neck round bottom flask was equipped with a condenser, magnetic stir-bar, septa and inert gas inlet and charged with MeCN (20mL) and Et_3N (1.4mL,

10mmol). Trifluoro-*s*-triazine (**20**) (1.0mL, 10mmol) was then added cautiously (excessive fuming noted due to vapour-phase reaction in the headspace) and the mixture stirred for five minutes at 20°C. 1-Bromooctane (1.80mL, 10mmol) was added and the reaction left stirring at 20°C overnight. Analysis by ^{19}F NMR showed that no fluorination had occurred. The reaction was then heated to 90°C for a further eight hours and a further sample taken for analysis. Only a trace (< 1%) of *1-fluorooctane* (**14**) was detected.

TFT (20)/Et_3N as PTC

A two-neck round bottom flask was equipped with a condenser, magnetic stir-bar, septa and inert gas inlet and charged with MeCN (20mL), CsF (1.54g, 10mmol) and Et_3N (0.14mL, 1.0mmol). Trifluoro-*s*-triazine (**20**) (0.1mL, 1.0mmol) was then added cautiously and the mixture stirred for five minutes at 20°C. 1-Bromooctane (1.80mL, 10mmol) was added and the reaction left stirring at 20°C overnight. Analysis by ^{19}F NMR showed that no fluorination had occurred. The reaction was then heated to 90°C for a further eight hours and a further sample taken for analysis. Quantitative ^{19}F NMR showed a trace of *1-fluorooctane* (**14**) (0.5%).

Metathesis with Sodium Tetrafluoroborate

Synthesis of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Tetrafluoroborate (23)

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (2.41g, 20mmol) and MeCN (40mL), followed by pentafluoropyridine (3.38g, 20mmol) when the DMAP had fully dissolved. After stirring for 20 minutes at 20°C, a pale yellow solution and thick light yellow precipitate had formed. The reaction mixture was filtered using Schlenk techniques and washed twice with portions of cold MeCN. A pale yellow solid was isolated and slurried with MeCN (40mL). Sodium tetrafluoroborate (2.20g, 20mmol) was added, resulting in the almost immediate dissolution of the pale yellow solid to form a yellow solution. After stirring overnight, the fine white precipitate of sodium

fluoride was filtered off through a fine frit and the solvent was removed on a rotary evaporator to yield the crude product as a yellow solid (2.68g). This was dissolved in MeCN (15mL) at reflux and allowed to slowly cool. The crystals thus formed were isolated and the solution cooled further to produce a second crop of crystals. The product was isolated as an off-white solid (1.22g, 17%). A small sample was recrystallised further to yield a colourless solid, shown to be *4-(dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium tetrafluoroborate* **(23)**; mp >250°C; δ_H (DMSO) 3.34 (6H, s, N(CH_3)$_2$), 7.35 (2H, d, $^3J_{HH}$ 4.0, Ar-H), 8.39 (2H, d, $^3J_{HH}$ 7.6, Ar-H); δ_F (DMSO) –88.7 (2F, m, 2,6-*F*), -147.0 (2F, m, 3,5-*F*), -148.7 (4F, s, BF_4^-); δ_C (DMSO) 40.6 (s, N(CH_3)$_2$), 108.6 (s, (NMe_2)C-*C*), 131.0 (m, N^+-*C*-CF), 137.8 (dd, $^1J_{CF}$ 263, $^3J_{CF}$ 38, N^+-C-*C*F), 141.2 (s, N^+-*C*H), 142.8 (dt, $^1J_{CF}$ 245, $^3J_{CF}$ 16, N-*C*F), 156.6 (s, N-*C*-CH); (Found: C, 39.7; H, 2.8; N, 11.4. $C_{12}H_{10}BF_8N_3$ requires C, 40.1; H, 2.8; N, 11.7%); *m/z* (EI^+) 272 (M^+, 100%). Suitable crystals were obtained for X-Ray diffraction by slow evaporation of their MeCN solution.

Reaction of Adduct (23) with DMAP

A two-necked round bottom flask was equipped with a condenser, magnetic stir-bar, inert gas inlet and septa. The flask was charged with DMAP (0.032g, 0.28mmol) and MeCN (5mL). When the DMAP had dissolved, DMAP-PFP BF_4 adduct **(23)** (0.1g, 0.28mmol) was added and the reaction mixture stirred at 20°C. A pale yellow colour developed in 30 minutes, and ^{19}F NMR of the reaction mixture at various points showed a large number of peaks from -68.6ppm to -169ppm. After three days, no further change was noted and the reaction mixture was poured into water and extracted with DCM. After removal of the solvent on a rotary evaporator, an off white solid was obtained (0.022g), which could not be identified with any degree of certainty by NMR or MS techniques.

Reaction of Adduct (23) with Methanol

A two-necked round bottom flask was equipped with a condenser, magnetic stir-bar, inert gas inlet and septa. DMAP-PFP BF_4 adduct **(23)** (0.5g, 1.4mmol) was added, followed by MeOH (20mL). The reaction was then heated to reflux overnight,

causing the solid to dissolve. Removal of the solvent from a sample of the reaction mixture and analysis by NMR and MS-ES$^+$ showed the major product to be the starting material, contaminated by a small quantity of *4-dimethylamino-3',5',6'-trifluoro-2'-methoxy-[1,4']bipyridinyl-1-ylium tetrafluoroborate* (**25**); *m/z* (ES$^+$) 284 (M^+, 4%).

Reaction of Adduct (23) with Sodium Ethoxide

A two-necked round bottom flask was equipped with a condenser, magnetic stir-bar, inert gas inlet and septa. EtOH (20mL) was added to the flask, followed by freshly cut sodium (0.032g, 1.4mmol), When the sodium had reacted, DMAP-PFP BF_4 adduct (**23**) (0.5g, 1.4mmol) was added and the reaction stirred at 20°C. A yellow colouration developed immediately on adding the adduct. A white precipitate appeared on stirring overnight which was filtered off and the volatile components were then removed on a rotary evaporator. The crude product was a pale yellow solid (0.431g) and was shown to be a mixture of *4-dimethylamino-2'-ethoxy-3',5',6'-trifluoro-[1,4']bipyridinyl-1-ylium tetrafluoroborate* (**26**) (major); δ_H (DMSO) 1.32 (3H, t $^3J_{HH}$ 7.0, CH_3), 4.47 (2H, q $^3J_{HH}$ 7.0, CH_2), other peaks obscured; δ_F (DMSO) -90.9 (F, dd $^3J_{FF}$ 28, $^5J_{FF}$ 24, 6-*F*), -147.8 (4F, s, BF_4^-) -148.5 (F, dd $^3J_{FF}$ 28, $^4J_{FF}$ 6.4, 5-*F*), -158.4 (F, dd $^5J_{FF}$ 24, $^4J_{FF}$ 6.4, 3-*F*); *m/z* (ES$^+$) 298 (M^+, 55%), and *4-dimethylamino-2',6'-diethoxy-3',5'-difluoro-[1,4']bipyridinyl-1-ylium tetrafluoroborate* (**27**) (minor); δ_H (DMSO) 1.39 (3H, t $^3J_{HH}$ 7.0, CH_3), 4.30 (2H, q, $^3J_{HH}$ 7.0, CH_2), other peaks obscured; δ_F (DMSO) -147.8 (4F, s, BF_4^-) -159.3 (2F, s, 3,5-*F*); *m/z* (ES$^+$) 324 (M^+, 100%), as well as other impurities. Separation of these materials could not be achieved.

A further reaction on a 0.28mmol scale yielded an off white solid after aqueous work-up and extraction into DCM. Purification by preparative scale TLC in 6 : 1 hexane : DCM gave three spots. The majority of the material stayed on the baseline, and both the top and bottom spots contained so little material that they could not be identified. The middle spot contained just enough product to run a dilute ^{19}F NMR spectrum, identifying it as a 2,4-disubstituted-3,5,6-trifluoropyridine. From comparison with a known sample, and as the product eluted up the TLC plate (unlike the ionic adducts), this material was most likely *2,4-diethoxy-3,5,6-trifluoropyridine*

(28); δ_F (DMSO) -93.9 (1F, t $^3J_{FF}$ 25, 6-F), -159.1 (1F, d $^3J_{FF}$ 25, 5F), -166.5 (1F, d $^3J_{FF}$ 25, 3F).

Reaction of Adduct (23) with Diethylamine in Methanol

A two-necked round bottom flask was equipped with a condenser, magnetic stir-bar, inert gas inlet and septa. DMAP-PFP BF_4 adduct **(23)** (0.46g, 1.3mmol) was added, followed by MeOH (20mL). With stirring at 20°C, three equivalents of $HNEt_2$ (0.39mL, 3.9mmol) were added in equimolar portions over 24 hours. The solvent was removed from the resultant pale yellow solution on a rotary evaporator to yield a colourless liquid and a sticky pale yellow solid. Analysis of the volatile fractions by ^{19}F NMR showed the presence of a *4-substituted tetrafluoropyridine*, presumably *4-methoxytetrafluoropyridine* **(30)**; δ_F (CH_3OH) -92.8 (F, m, 6-F), -160.6 (2F, m, 3,5-F). The solid material was recrystallised from hot methanol and washed several times with cold methanol to yield a small quantity of a white solid. Analysis showed that this material that contained *4-dimethylamino-3',5',6'-trifluoro-2'-methoxy-[1,4']bipyridinyl-1-ylium tetrafluoroborate* **(25)**; δ_H (DMSO) 3.31 (6H, s, $N(CH_3)_2$), 4.01 (3H, s, OCH_3), 7.30 (2H, d, $^3J_{HH}$ 8.1, N^+CHCH), 8.41 (2H, d, $^3J_{HH}$ 8.1, N^+CH); δ_F -91.1 (F, dd $^3J_{FF}$ 28, $^5J_{FF}$ 23, 6-*F*), -147.8 (4F, s, BF_4^-), -148.7 (F, dd $^3J_{FF}$ 28, $^4J_{FF}$ 6.4, 5-*F*), -152.2 (F, dd $^5J_{FF}$ 23, $^4J_{FF}$ 6.4, 3-*F*); *m/z* (ES^+) 284 (M^+, 100%).

Reaction of Adduct (23) with Diethylamine in MeCN

A two-necked round bottom flask was equipped with a condenser, magnetic stir-bar, inert gas inlet and septa. DMAP-PFP BF_4 adduct **(23)** (0.50g, 1.4mmol) was added, followed by MeCN (20mL). With stirring at 20°C, two equivalents of $HNEt_2$ (0.29mL, 3.0mmol) were added resulting in the immediate formation of a yellow/brown colour. The solvent was removed from the reaction mixture on a rotary evaporator to yield a brown oil (0.66g), which was then further purified by placing under high vacuum. Analysis of the product showed it to be comprised mainly of *2'-diethylamino-4-dimethylamino-3',5',6'-trifluoro-[1,4']bipyridinyl-1-ylium tetrafluoroborate* **(29)**; δ_H (DMSO) 1.169 (6H, t, $^3J_{HH}$ 6.9, $N(CH_2CH_3)_2$), 3.31 (6H, s, $N(CH_3)_2$), 3.49 (4H, q, $^3J_{HH}$ 6.9, $N(CH_2CH_3)_2$), 7.28 (2H, d, $^3J_{HH}$ 7.8, N^+CHCH), 8.46

(2H, d, $^3J_{HH}$ 6.9, N^+CH); δ_F (DMSO) -88.3 (1F, m, 6-*F*), -145.1 (F, dd $^3J_{FF}$ 20, $^4J_{FF}$ 6, 5-*F*), -166.0 (F, dd $^5J_{FF}$ 17, $^4J_{FF}$ 6, 3-*F*); *m/z* (ES^+) 325 (M^+, 100%).

Synthesis of 4-Dimethylamino-1-[2-(4-dimethylaminopyridinium)-5,6-difluoro-pyrimidin-4-yl]-pyridinium Tetrafluoroborate (31)

A three-necked flask equipped with a condenser, magnetic stir-bar, septa, pressure-equalising dropping funnel and inert gas inlet was charged with freshly distilled tetrafluoropyrimidine (1.09g, 7mmol), MeCN (10mL) and sodium tetrafluoroborate (0.66g, 6mmol). A solution of DMAP (0.80g, 6.5mmol) in MeCN (15mL) was made up and cannulated into the dropping funnel. The DMAP solution was added with stirring at 20°C over one hour, causing the formation of a white precipitate and bright orange solution over the course of two days. On disturbing the flask, a large quantity of precipitate suddenly appeared from solution. This was filtered off using Schlenk techniques to yield a pale yellow solid (0.16g), which was transferred to a glove box. Analysis of this material by NMR showed it to be comprised of sodium tetrafluoroborate and a small quantity of DMAP-containing products. Whilst this analysis was being carried out, more material started to precipitate from the solution and the reaction mixture was cooled and then filtered using Schlenk techniques to yield the crude product as a pale orange solid (1.51g).

This solid was found to contain at five different DMAP environments and so recrystallisation was attempted using a variety of techniques. A small number of crystals were successfully grown from an MeCN solution of the material using vapour diffusion with DCM as the second component. Analysis of the isolated crystals showed the product to be *4-Dimethylamino-1-[2-(4-dimethylaminopyridinium)-5,6-difluoro-pyrimidin-4-yl]-pyridinium tetrafluoroborate* **(31)**; δ_H (DMSO) 3.31 (6H, s, $N(CH_3)_2$), 3.31 (6H, s, $N(CH_3)_2$), 7.13 (2H, d $^3J_{HH}$ 8.4, NCC*H*), 7.18 (2H, d $^3J_{HH}$ 7.8, NCC*H*), 8.66 (2H, d $^3J_{HH}$ 6.9, N^+CH), 9.11 (2H, d $^3J_{HH}$ 8.1, N^+CH); δ_F -71.1 (F, d $^3J_{FF}$ 23, 5-*F*), -152.1 (4F, s, BF_4^-), -157.1 (F, d $^3J_{FF}$ 23, 6-*F*); *m/z* (ES^+) 255 (4-(4-dimethylaminopyridinium)-2,5,6-trifluoropyrimidine, 100%), 355 (4-Dimethylamino-1-[2-(4-dimethylaminopyridinium)-5-fluoro-pyrimidin-4-yl-6-olate]-pyridinium, 82%). Crystals suitable for XRD were grown, and confirmed the 2,4-disubstitution pattern.

Metathesis with Trimethylsilyl Trifluoromethanesulfonate

Synthesis of 1-(4,6-Difluoro-1,3,5-triazin-2-yl)-4-(dimethylamino)pyridinium Trifluoromethanesulfonate (32)

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (3.69g, 30mmol) and MeCN (20mL), followed by trifluoro-*s*-triazine (**20**) (1.36g, 10mmol) when the DMAP had fully dissolved. An immediate yellow precipitate formed on addition of the triazine and the reaction was left to stir overnight. The solid material was isolated and washed twice with MeCN using Schlenk-type techniques before being treated with TMS-OTf (6.67g, 30mmol) in MeCN (20ml). The reaction was left to stir at 20°C with a gentle flow of argon over the reaction mixture via a pass-through bubbler fitted to the condenser. A precipitate was isolated and washed twice as above before being dried *in-vacuo* to give the crude product as a white solid (1.36g, 35%). The product was recrystallised from MeCN and shown to be *1-(4,6-difluoro-1,3,5-triazin-2-yl)-4-(dimethylamino)pyridinium trifluoromethanesulfonate* (**32**); δ_H (DMSO) 3.44 (6H, s, $N(CH_3)_2$), 7.27 (2H, d, $^3J_{HH}$ 8, CHC-$N(CH_3)_2$), 9.07 (2H, d, $^3J_{HH}$ 8, CH-N^+); δ_F (DMSO) –34.2 (2F, s, CF-N), -77.3 (3F, s, CF_3); ^{13}C NMR was unsuccessful as the material reacted with the solvent before a suitable spectrum could be obtained; (Found: C, 34.2; H, 2.6; N, 18.3. $C_{11}H_{10}F_5N_5O_3S$ requires C, 34.1; H, 2.6; N, 18.1%); *m/z* (ES^+) 262 (M^+ + 24, 4,6-di-methoxy compound from reaction with MeOH dilutant, 100%). A crystal was grown from MeCN and successfully submitted for X-ray diffraction.

Metathesis with Trimethyloxonium Tetrafluoroborate

Synthesis of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Tetrafluoroborate (23)

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (1.22g, 10mmol) and MeCN (15mL), followed by pentafluoropyridine (1.1mL, 10mmol) when the DMAP had fully

dissolved. After 15 minutes, a thick pale yellow precipitate had formed and trimethyloxonium tetrafluoroborate (1.29g, 9mmol) was added to the reaction mixture quickly in several portions. Effervescence was observed and an orange solution formed within two minutes of addition followed by an orange/brown solution and precipitate after stirring overnight. The reaction mixture was filtered and the solvent removed under reduced pressure to yield a pale brown solid. Analysis of a portion of the crude product by NMR in DMSO showed it to contain the desired product, *dimethylamino-2',3',5',6'-tetrafluoro-[1,4']bipyridinyl-1-ylium tetrafluoroborate* (**23**). The solid was dissolved in the minimum volume of hot MeCN and successive cooling produced two crops of crystals. The first crop was pale yellow and strongly fluorescent. Various attempts at recrystallisation and characterisation were unsuccessful. The second crop of crystals were recrystallised from hot MeCN and then washed with cold MeCN to yield a brown solid. ^{1}H and ^{19}F NMR spectra of the material corresponded to that of the desired product, *dimethylamino-2',3',5',6'-tetrafluoro-[1,4']bipyridinyl-1-ylium tetrafluoroborate* (**23**) in approximately 60% purity. A pure sample could not be obtained from this crude product.

Synthesis via DMAP-Boron Trifluoride Complex

Synthesis of DMAP-boron Trifluoride Complex (33)

A two-necked flask equipped with a condenser, magnetic stir-bar, pressure equalising dropping funnel with septa and inert gas inlet was charged with DMAP (3.03g, 24.6mmol) and THF (30mL), followed by dropwise addition of a solution of boron trifluoride etherate (3.81mL, 30mmol) in THF (30mL). The reaction was stirred at room temperature for two hours, which resulted in the formation of a white precipitate. The reaction flask was cooled and the precipitate was filtered off under reduced pressure to yield the expected product, *DMAP-boron trifluoride adduct* (**33**) as a white solid (2.74g, 59%); δ_H 3.17 (6H, s, $N(CH_3)_2$), 6.62 (2H, dd $^{3}J_{HH}$ 7.6, NCHC*H*), 8.10 (2H, br m, NC*H*); δ_F -152.4 (m, BF_3); δ_C 156.6 (s, $N(CH_3)_2C$), 142.1 (s, N*C*H), 106.4 (s, NCH*C*H), 39.8 (s, $N(CH_3)_2$); (Found: C, 43.7; H, 5.3; N, 14.5. $C_7H_{10}BF_3N_2$ requires C, 44.3; H, 5.3; N, 14.8%) by comparison with literature data.[9]

Synthesis of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Tetrafluoroborate (23)

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with boron trifluoride-DMAP adduct **(33)** (0.66g, 3.5mmol) and MeCN (10mL) followed by pentafluoropyridine (0.43mL, 4.2mmol). After stirring for 17 hours at 20°C, analysis by ^{19}F NMR showed that no reaction had occurred. A trace quantity of DMAP was added to initiate the reaction but no effect was observed even on heating to 90°C. Addition of trace CsF led immediately to the formation of a pale yellow solution, which was left to reflux over the weekend. Analysis of the reaction solution by ^{19}F NMR showed the main product of the reaction to be consistent with *4-Dimethylamino-2',3',5',6'-tetrafluoro-[1,4']bipyridinyl-1-ylium tetrafluoroborate* **(23)**. No residual DMAP-BF_3 or pentafluoropyridine 4-F peaks were observed by ^{19}F NMR, indicating complete conversion. Removal of the solvent on a rotary evaporator gave the crude product as a pale yellow solid. This was dissolved in the minimum volume of MeCN and filtered through a 0.1μM syringe filter to remove residual CsF. Four successive recrystallisations from MeCN removed an unidentified fluorescent impurity and yielded a small quantity of the expected product, *4-Dimethylamino-2',3',5',6'-tetrafluoro-[1,4']bipyridinyl-1-ylium tetrafluoroborate* **(23)** as a white solid, characterised by comparison with a known sample.

Synthesis via DMAP-Trimethylsilyl Triflate

Synthesis of 4-Dimethylamino-1-trimethylsilylpyridinium Trifluoromethanesulfonate (34)

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (0.94g, 7.7mmol) and DCM (10mL), followed by dropwise addition of TMS-triflate (1.40mL, 7.7mmol) when the DMAP had fully dissolved. The reaction was left to stir at 20°C for 17h after which time the volatile materials were removed by vacuum transfer to leave a white solid. This was

identified as *4-(dimethylamino)-1-(trimethylsilyl)pyridinium trifluoromethanesulfonate* **(34)** (2.58g, 97%); δ_H 0.59 (9H, s, Si(CH_3)$_3$), 3.23 (6H, s, N(CH_3)$_2$), 6.94 (2H, d, $^3J_{HH}$ 8, Ar-*H*), 8.06 (2H, d, $^3J_{HH}$ 8, Ar-*H*) by comparison with literature data.[10] The sample was used immediately following reaction due to its rapid decomposition.

Synthesis of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Trifluoromethanesulfonate (35)

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet with a pass-through bubbler was charged with 4-(dimethylamino)-1-(trimethylsilyl)pyridinium trifluoromethanesulfonate **(34)** (1.72g, 5mmol) and DCM (10mL) giving a yellow suspension, followed by pentafluoropyridine (0.85g, 5mmol). A white precipitate formed within five minutes of the addition of the pentafluoropyridine and the reaction was left to stir overnight. Analysis of the precipitate by NMR showed the conversion to be 22%. The temperature was raised to 60°C and the precipitate analysed again after 2 ¾ hours, the conversion at this time being 33%. An excess of pentafluoropyridine was added (1mL, 9mmol) and the reaction stirred for a further 1 ¾ hours. The final conversion to *4-(dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium trifluoromethanesulfonate* **(35)** was 42%, as confirmed by NMR analysis of the precipitated product; δ_H (DMSO) 3.35 (6H, s, N(CH_3)$_2$), 7.35 (2H, d $^3J_{HH}$ 8, NCHC*H*), 8.41 (2H, d, $^3J_{HH}$ 8, NC*H*); δ_F -77.3 (3F, s, CF_3), -88.7 (2F, m, 2,6-*F*), -147.2 (2F, m, 3,5-*F*).

Attempted Synthesis of 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Tetrafluoroborate (23) via Addition of Boron Trifluoride Etherate

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (1.23g, 10mmol) and MeCN (20mL), followed by pentafluoropyridine (1.1mL, 10mmol) when the DMAP had fully dissolved. The reaction was stirred for 15 minutes and then boron trifluoride etherate (1.42g, 10mmol) was added. The reaction mixture changed instantly to a deep orange solution and was left to stir for 16 hours. A sample taken for ^{19}F NMR showed the

absence of the expected product resonances, and there were several unidentifiable broad peaks. The solvent was removed on a rotary evaporator and a brown solid was obtained. Analysis of this material by NMR showed it to be *DMAP-boron trifluoride* **(33)** as shown by comparison with a reference sample of the material. Attempted recrystallisation to recover any dimethylamino-2',3',5',6'-tetrafluoro-[1,4']bipyridinyl-1-ylium tetrafluoroborate that had formed in the reaction was unsuccessful.

Synthesis of Demethylation Product of 4-Methoxytetrafluoropyridine (36)

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (1.22g, 10mmol) and MeCN (10mL), followed by 4-methoxytetrafluoropyridine **(30)** (2.17g, 12mmol) when the DMAP had fully dissolved. The reaction turned yellow almost immediately and proceeded to produce a thick green precipitate over the next 67 hours. ^{19}F NMR of the reaction mixture showed the presence of *fluoromethane* **(37)**; δ_F -266.8 (1F, q, $^2J_{HF}$ 46, CH_3F) The precipitate was rapidly filtered in air, causing it to turn brown, before being dried under vacuum (0.29g). Analysis of the precipitate by NMR showed it to contain a 2,4-disubstituted trifluoropyridine and one other unidentified major product. Other minor byproducts were also present. The solid material was recrystallised from MeCN to yield a yellow solid, which after repeated washing with MeCN gave an off-white moisture-sensitive product, tentatively assigned as *4-(dimethylamino)-1-(3,5,6-trifluoro-4-hydroxy-2-pyridinyl)pyridinium* **(36)** as the deprotonated zwitterion; δ_H (DMSO) 3.27 (6H, s, $N(CH_3)_2$), 7.10 (2H, d, $^3J_{HH}$ 8.0, C*H*-C-$N(CH_3)_2$), 8.44 (2H, d, $^3J_{HH}$ 6.2, N^+-C*H*); δ_F (DMSO) –98.6 (1F, dd, $^3J_{FF}$ 25, $^5J_{FF}$ 17, 6-*F*), -156.4 (1F, dd, $^3J_{FF}$ 28, $^4J_{FF}$ 17, 5-*F*), -167.7 (1F, dd, $^4J_{FF}$ 28, $^5J_{FF}$ 25, 3-*F*); δ_C 108.3 (s, NMe_2CCH), 141.9 (s, N^+C), 157.3 (NMe_2C); (Found: C, 53.0; H, 3.5; N, 16.0. $C_{12}H_{10}F_3N_3O$ requires C, 53.5; H, 3.7; N, 15.6%); *m/z* (ES^+) 270 (M^+ + H, 22%), 292 (M^+ + Na, 100%), 561 ($2M^+$ + Na, 50%), 830 ($3M^+$ + Na, 1%). Attempts to grow suitable single crystals via solvent evaporation, layer diffusion or vapour diffusion, both in open atmosphere and in a glove box were unsuccessful.

Reactions of Different Amines

4-Methoxypyridine

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with 4-methoxypyridine (1.10g, 10mmol) and MeCN (10mL), followed by pentafluoropyridine (1.32mL, 12mmol). The reaction mixture turned a deep red/brown in less than one minute. After 66 hours, the appearance was of a red/brown solution with a pale brown precipitate. Sodium tetrafluoroborate (1.21g, 11mmol) was added and the reaction left to stir at 20°C. Analysis by ^{19}F NMR after six hours showed that the conversion was 53% and so the precipitate was filtered off and dried under vacuum to yield the crude product as a pale brown solid. Analysis of this partially soluble mixture by NMR showed it to consist of the expected product, *4-methoxy-1-(2,3,5,6-tetrafluoro-4-pyridinyl)pyridinium tetrafluoroborate* **(38)**; δ_H 4.27 (3H, s, CH_3), 8.00 (2H, d $^3J_{HH}$ 7.2, N^+CHCH), 9.09 (2H, d $^3J_{HH}$ 6.8, N^+CH); δ_F -87.9 (2F, m, 2,6-*F*), 145.7 (2F, m, 3,5-*F*), and unreacted 4-methoxy pyridine in a roughly 2:1 ratio as well as a substantial quantity of sodium tetrafluoroborate and sodium fluoride. Attempts to recrystallise the material for further analysis were unsuccessful.

4-Methylpyridine

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with 4-methylpyridine (0.94g, 10mmol), sodium tetrafluoroborate (1.11g, 10mmol) and MeCN (15mL), followed by pentafluoropyridine (1.1mL, 10mmol). The reaction mixture immediately started to change colour from colourless to yellow, then red and finally deep purple. Analysis of the solution by ^{19}F NMR showed a reduction in the relative intensity of the 4-F peak of the pentafluoropyridine. After 86 hours at 20°C, the conversion was 63%. The temperature was raised to 50°C for 24 hours and the conversion rose very slightly, and the reaction was refluxed at 90°C for a further 19 hours. The final conversion was 71%. The flask was transferred to a glove box and the volatile materials were

removed under vacuum to yield a dark red solid (2.22g). Analysis of the crude material by NMR showed it to be composed of the expected 4-substituted product, *4-methyl-1-(2,3,5,6-tetrafluoro-4-pyridinyl)pyridinium tetrafluoroborate* (**39**); δ_H (DMSO) 2.80 (3H, s, CH_3), 8.39 (2H, d, $^3J_{HH}$ 6.6, CH_3CCH), 9.20 (2H, d, $^3J_{HH}$ 6.8, N^+CH); δ_F (DMSO) –87.6 (2F, m, 2,6-*F*), -145.5 (2F, m, 3,5-*F*), -147.8 (4F, s, BF_4^-); *m/z* (ES^+) 243 (M^+, 100%), as well as some residual sodium tetrafluoroborate, 4-methylpyridine and other minor contaminants. Exhaustive attempts were made to recrystallise the crude product, but no further purification could be effected and the material decomposed on standing to a black tarry substance.

2-Dimethylaminopyridine

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with 2-dimethylaminopyridine (1.22g, 10mmol) and MeCN (15mL) followed by pentafluoropyridine (1.32mL, 12mmol). Analysis of the reaction mixture by NMR after three days showed that no reaction had taken place. The temperature was raised to 90°C and the reaction was stirred for a further three days by which time a brown solution had formed. NMR analysis again showed that no reaction had occurred. The reaction mixture was cooled to room temperature and sodium tetrafluoroborate (1.13g, 10.2mmol) was added. After stirring for 24 hours a cloudy orange solution had formed, but no detectable reaction had occurred and the reaction was heated to 80°C. No appreciable reaction could be detected after a further seven hours and the experiment was stopped.

Reactions of Trifluoro-*s*-triazine (20) with Trimethylamine and Triethylamine: VT-NMR Studies

A solution of trifluoro-*s*-triazine (**20**) (0.0375mL, 0.375mmol) and triethylamine (0.052mL, 0.374mmol) in MeCN-d_3 (0.75mL) was made up under anhydrous conditions. The solution was rapidly transferred to a dry, argon-flushed NMR tube equipped with a Young's tap. NMR measurements were then taken on a ^1H 500MHz spectrometer at temperatures of 40, 20, 10, 0, -10, -20, -30 and -40°C with ^{19}F as the target nucleus. Acquisition of ^{13}C $\{^1H\}$ data was attempted at the same

temperatures, but reaction of the solution with the glass of the NMR tube precluded the collection of suitable data. The spectra collected are shown graphically in section **4.5.1.1**.

A similar procedure was adopted for the corresponding reaction with trimethylamine: Trimethylamine (0.06g, 1.02mmol) was vacuum transferred into a Rotaflo vessel frozen in liquid nitrogen. The vessel was allowed to warm to -78°C under argon and MeCN-d_3 (1.5mL), followed by trifluoro-*s*-triazine (**20**) (0.1mL, 1.0mmol) were added. On slow warming to ambient temperature, minimal gas evolution was observed and 0.75mL of the solution was transferred to an NMR tube as above. The spectra collected were very similar to those observed in the reaction with triethylamine.

Isolation and Characterisation of the Tetramethyl Ammonium Salt of 1-Keto-3,5-difluoro-*s*-triazine (40)

A dry Schlenk tube was equipped with a fine frit and a stir-bar. Trifluoro-*s*-triazine (**20**) (2.07g, 15.3mmol) was vacuum transferred to the vessel and allowed to warm to ambient temperature under argon. MeCN (22.5mL), rigorously dried over CaH_2 to avoid any traces of acid, was then added to the Schlenk. Finally the Schlenk was cooled in liquid nitrogen and evacuated and trimethylamine (0.95g, 16.2mmol) was vacuum transferred to the vessel. After warming to ambient temperature under argon, the reaction mixture was stirred for one hour before being analysed by ^{19}F NMR. The spectrum displayed the following peaks; δ_F -5.4 (2F, m, C*F*X) (X = F or NMe_y, y = 2 or 3), -37.3 (2F, br s, triazine NC*F*), -50.1 (1F, s, σ-complex NC*F*). The relative peak intensities given equate to a 1:1 mixture of a σ-complex with a difluoromethylene group and a trimethylammonium moiety, and a trimethylammonium substituted triazine as the fluoride salt, although this was somewhat ambiguous. Other smaller peaks were also observed in the spectrum. The Schlenk tube was then placed in the freezer until large (10mm per side) colourless plate crystals appeared. These crystals were carefully filtered off under argon and retained in the Schlenk tube. This was rapidly transferred to a glove box and the crystals isolated from the reaction vessel. The crystals were soluble in DMSO, allowing the collection of NMR data, although they required careful handling in that

they appeared to decompose rapidly once the acetonitrile reaction solvent was removed.

Analysis by NMR showed an interesting phenomenon – the material still exhibited a spectrum characteristic of an exchanging fluoro-*s*-triazine species. The only difference between this spectrum and the previous was that small peaks could be seen to the right of the C*F*X and σ-complex NC*F* peaks, indicating the presence of another σ-complex (presumably one containing geminal fluorine and trimethylammonium groups). The ^{1}H NMR spectrum showed two proton environments at δ_H 3.34 and 3.40ppm, although the peaks were broad and overlapped. This would again correlate with a species containing two trimethylammonium groups in different environments. Unfortunately, after several days the NMR spectra of the material changed markedly. The triazine ring fluorine peak disappeared completely, to be replaced by a series of sharp singlets between δ_F -38 and -50ppm. The majority of the fluorine integration resulted from a new broad peak at δ_F -168ppm, most likely due to trimethylammonium hydrofluoride, and there was also a small peak at δ_F -184ppm. The ^{1}H spectrum exhibited a new singlet at δ_H 2.76ppm, responsible for almost 50% of the signal integration, in the region for NMe_4^+. Numerous other weaker signals including a singlet at δ_H 2.07ppm due to trimethylamine were also present. The ^{13}C spectrum showed signals in the region for $RNMe_3^+$ or NMe_4^+ at δ_C -52.74 and -44.11ppm. Analysis by MS was more successful; *m/z* (ES^+) 129 (M^+ cyanuric acid, 100%), 173 (M^+ 2-fluoro-4-hydroxy-6-(trimethylammonium)-*s*-triazine, 30%), 212 (M^+, bis-(trimethylammonium)-*s*-triazinolate, 12%); *m/z* (ES^-) 132 (M^+ 1-keto-3,5-difluoro-*s*-triazine, 100%). After several attempts, a crystal was successfully mounted for X-ray diffraction and the final structure was confirmed as the *tetramethylammonium salt of 1-keto-3,5-difluoro-s-triazine* **(40)**.

Reaction of Trifluoro-*s*-triazine (20) with Triethylamine-boron Trifluoride Adduct (41)

Preparation of Boron Trifluoride-triethylamine Adduct (41)

A Schlenk tube was equipped with a stir-bar and a pressure-equalising dropping funnel. A solution of NEt_3 (3.42mL, 24.5mmol) in THF (20mL) was added to the tube and the mixture was cooled in an ice bath under an inert atmosphere. Once the solution had cooled, $BF_3.Et_2O$ (3.81mL, 30mmol) in THF (20mL) was added over 25 minutes with stirring. A pale yellow solution formed which was left at room temperature overnight. The volatile materials were removed under vacuum to yield a pale brown oil. Fractional distillation of this material through a Vigreux column under reduced pressure yielded *boron trifluoride-triethylamine* **(41)** (3.02g) as a colourless liquid in 91% purity, the balance being composed of unreacted $BF_3.Et_2O$; δ_H 1.23 (9H, tq, $^3J_{HH}$ 7.5, J_{HF} 0.9, CH_3), 3.27 (6H, q $^3J_{HH}$ 7.2, CH_2); δ_F -150.4 (m, BF_3); δ_C 8.6 (s, CH_3), 48.0 (s, CH_2); *m/z* (EI^+) 150 (M^+ - F^-, 1.4%), 101 (NEt_3^+, 16%), 86 ($Et_2NCH_2^+$, 100%), 49 (BF_2^+, 18%).

Reaction with Trifluoro-*s*-triazine (20)

A two-necked round bottom flask equipped with a stir-bar, septa, condenser and gas inlet was charged with MeCN (10mL) and boron trifluoride-triethylamine **(41)** (1.43g, 8.5mmol), followed by trifluoro-*s*-triazine **(20)** (1.0mL, 10mmol) at 20°C. The reaction was run as above, and no significant reaction was seen at 20°C or reflux without CsF. One small spatula of dry CsF was added resulting in the detection of a small quantity of σ-complex, and the conversion of approximately 50% of the Et_3N-BF_3 to BF_4^- after four hours at 20°C. The reaction was heated to reflux overnight, resulting in an orange solution, after which time ^{19}F NMR showed the only boron containing species to be BF_4^-. Surprisingly, the spectrum in the triazine ring fluorine region appeared relatively unchanged, with only a slight increase in the concentration of σ-complex. Removal of most of the solvent on a rotary evaporator resulted in the formation of an orange solid. The mixture was heated and slowly cooled, before placing in a freezer to yield the product as a small quantity of orange

needle-like crystals and semi-crystalline solid material. A small sample of the needle crystals was dried under vacuum and shown to be *2,4-difluoro-6-(diethylamino)-s-triazine* (**42**); δ_H (DMSO) 1.15 (6H, t $^3J_{HH}$ 7.0, $N(CH_2CH_3)_2$), 3.58 (4H, q $^3J_{HH}$ 7.0, $N(CH_2CH_3)_2$); δ_F (DMSO) -39.7 (s, NC*F*); *m/z* (ES^+) 203 (M^+ , 0.1%), 242 (2-(diethylamino)-4-(diethylammonium)-6-fluoro-*s*-triazine, 72%). A crystal structure was obtained, confirming the isolated solid to be *2,4-difluoro-6-(diethylamino)-s-triazine* (**42**).

5.6 References to Chapter 5

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6. Appendix 1: X-Ray Diffraction Data

Crystals suitable for diffraction were grown by the author and all experimental work, analysis and data manipulation involved in collecting and interpreting the diffraction patterns was performed by Dr D S Yufit.

6.1 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium Tetrafluoroborate (23)

Table 1. Crystal data and structure refinement for 02srv112.

Identification code	s112	
Empirical formula	$C_{12} H_{10} B F_8 N_3$	
Formula weight	359.04	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 7.9938(8) Å	α= 90°.
	b = 22.540(2) Å	β= 103.46(4)°.
	c = 7.8484(8) Å	γ = 90°.
Volume	1375.3(2) $Å^3$	
Z	4	
Density (calculated)	1.734 Mg/m^3	
Absorption coefficient	0.181 mm^{-1}	
F(000)	720	
Crystal size	0.58 x 0.14 x 0.11 mm^3	
Theta range for data collection	1.81 to 27.50°.	
Index ranges	-10<=h<=10, -28<=k<=29, -10<=l<=10	
Reflections collected	4976	
Independent reflections	1568 [R(int) = 0.0229]	
Completeness to theta = 27.50°	98.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1568 / 0 / 132	
Goodness-of-fit on F^2	1.065	
Final R indices [I>2sigma(I)]	R1 = 0.0416, wR2 = 0.1138	
R indices (all data)	R1 = 0.0474, wR2 = 0.1201	
Largest diff. peak and hole	0.445 and -0.270 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 02srv112. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
F(1)	4616(1)	4281(1)	258(1)	32(1)
F(2)	4542(1)	3082(1)	367(1)	26(1)
F(3)	3881(1)	1116(1)	1310(1)	29(1)
F(4)	5947(2)	1825(1)	1618(2)	55(1)
N(1)	5000	4274(1)	-2500	26(1)
N(2)	5000	2409(1)	-2500	18(1)
N(3)	5000	581(1)	-2500	20(1)
B(1)	5000	1473(1)	2500	24(1)
C(1)	4794(2)	3972(1)	-1141(2)	24(1)
C(2)	4771(2)	3359(1)	-1064(2)	21(1)
C(3)	5000	3043(1)	-2500	19(1)
C(4)	3539(2)	2107(1)	-2400(2)	20(1)
C(5)	3509(2)	1506(1)	-2397(2)	19(1)
C(6)	5000	1173(1)	-2500	18(1)
C(7)	3514(2)	243(1)	-2236(2)	25(1)

Table 3. Bond lengths [Å] and angles [°] for 02srv112.

F(1)-C(1)	1.336(2)	N(2)-C(4)	1.369(2)	C(1)-C(2)	1.383(2)
F(2)-C(2)	1.336(2)	N(2)-C(3)	1.430(2)	C(2)-C(3)	1.381(2)
F(3)-B(1)	1.389(2)	N(3)-C(6)	1.334(2)	C(4)-C(5)	1.355(2)
F(4)-B(1)	1.388(2)	N(3)-C(7)	1.466(2)	C(5)-C(6)	1.427(2)
N(1)-C(1)	1.307(2)				

C(1)#1-N(1)-C(1)	117.26(18)	N(1)-C(1)-C(2)	124.13(14)
C(4)-N(2)-C(4)#1	120.43(17)	F(1)-C(1)-C(2)	118.66(14)
C(4)-N(2)-C(3)	119.78(8)	F(2)-C(2)-C(3)	120.95(13)
C(6)-N(3)-C(7)	121.31(8)	F(2)-C(2)-C(1)	120.73(13)
C(7)-N(3)-C(7)#1	117.39(16)	C(3)-C(2)-C(1)	118.32(14)
F(4)-B(1)-F(4)#2	110.2(2)	C(2)-C(3)-C(2)#1	117.82(18)
F(4)-B(1)-F(3)	109.62(7)	C(2)-C(3)-N(2)	121.09(9)
F(4)#2-B(1)-F(3)	109.00(7)	C(5)-C(4)-N(2)	120.85(13)
F(4)#2-B(1)-F(3)#2	109.62(7)	C(4)-C(5)-C(6)	120.68(13)
F(3)-B(1)-F(3)#2	109.37(17)	N(3)-C(6)-C(5)	121.75(9)
N(1)-C(1)-F(1)	117.20(14)	C(5)#1-C(6)-C(5)	116.51(18)

Symmetry transformations used to generate equivalent atoms: #1 -x+1,y,-z-1/2 #2 -x+1,y,-z+1/2

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 02srv112. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	29(1)	25(1)	43(1)	-15(1)	11(1)	-1(1)
F(2)	28(1)	27(1)	25(1)	0(1)	10(1)	0(1)
F(3)	29(1)	26(1)	29(1)	0(1)	0(1)	-9(1)
F(4)	50(1)	54(1)	53(1)	20(1)	-7(1)	-31(1)
N(1)	18(1)	16(1)	44(1)	0	7(1)	0
N(2)	18(1)	14(1)	23(1)	0	6(1)	0
N(3)	19(1)	16(1)	26(1)	0	7(1)	0
B(1)	23(1)	17(1)	29(1)	0	-1(1)	0
C(1)	17(1)	20(1)	34(1)	-7(1)	6(1)	0(1)
C(2)	17(1)	21(1)	25(1)	0(1)	5(1)	0(1)
C(3)	15(1)	14(1)	26(1)	0	3(1)	0
C(4)	17(1)	19(1)	24(1)	0(1)	7(1)	0(1)
C(5)	16(1)	18(1)	24(1)	0(1)	6(1)	-2(1)
C(6)	20(1)	17(1)	18(1)	0	4(1)	0
C(7)	23(1)	16(1)	39(1)	0(1)	11(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 x\ 10^3$) for 02srv112.

Atom	x	y	z	U(eq)
H(4)	2590(30)	2341(9)	-2340(30)	28(5)
H(5)	2510(20)	1319(9)	-2290(30)	23(5)
H(71)	3840(30)	-174(11)	-1990(30)	40(6)
H(72)	3120(20)	391(9)	-1230(30)	31(5)
H(73)	2600(30)	245(10)	-3260(30)	43(6)

Table 6. Torsion angles [°] for 02srv112.

C(1)#1-N(1)-C(1)-F(1)	178.77(15)	C(4)-N(2)-C(3)-C(2)#1	-115.80(10)
C(1)#1-N(1)-C(1)-C(2)	-0.41(10)	C(4)#1-N(2)-C(3)-C(2)#1	64.20(10)
N(1)-C(1)-C(2)-F(2)	-179.53(11)	C(4)#1-N(2)-C(4)-C(5)	0.04(10)
F(1)-C(1)-C(2)-F(2)	1.3(2)	C(3)-N(2)-C(4)-C(5)	-179.96(10)
N(1)-C(1)-C(2)-C(3)	0.81(19)	N(2)-C(4)-C(5)-C(6)	-0.08(19)
F(1)-C(1)-C(2)-C(3)	-178.36(11)	C(7)-N(3)-C(6)-C(5)#1	174.46(10)
F(2)-C(2)-C(3)-C(2)#1	179.97(15)	C(7)#1-N(3)-C(6)-C(5)#1	-5.54(10)
C(1)-C(2)-C(3)-C(2)#1	-0.37(9)	C(7)-N(3)-C(6)-C(5)	-5.54(10)
F(2)-C(2)-C(3)-N(2)	-0.03(15)	C(7)#1-N(3)-C(6)-C(5)	174.46(10)
C(1)-C(2)-C(3)-N(2)	179.63(9)	C(4)-C(5)-C(6)-N(3)	-179.96(10)
C(4)-N(2)-C(3)-C(2)	64.20(10)	C(4)-C(5)-C(6)-C(5)#1	0.04(10)
C(4)#1-N(2)-C(3)-C(2)	-115.80(10)		

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y,-z-1/2 #2 -x+1,y,-z+1/2

6.2 4-Dimethylamino-1-[2-(4-dimethylaminopyridinium)-5,6-difluoro-pyrimidin-4-yl]-pyridinium Tetrafluoroborate (31)

Table 1. Crystal data and structure refinement for 03srv037.

Identification code	s037	
Empirical formula	$C_{11}\ H_{10}\ B\ F_7\ N_4\ O$	
Formula weight	358.04	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 40.0894(8) Å	α= 90°.
	b = 18.3248(3) Å	β= 102.15(1)°.
	c = 14.7895(3) Å	γ = 90°.
Volume	10621.3(3) $Å^3$	
Z	24	
Density (calculated)	1.343 Mg/m^3	
Absorption coefficient	0.138 mm^{-1}	
F(000)	4320	
Crystal size	0.42 x 0.30 x 0.14 mm^3	
Theta range for data collection	1.04 to 25.00°.	
Index ranges	-47<=h<=47, -21<=k<=21, -17<=l<=17	
Reflections collected	54378	
Independent reflections	9356 [R(int) = 0.0405]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9356 / 0 / 573	
Goodness-of-fit on F^2	2.409	
Final R indices [I>2sigma(I)]	R1 = 0.1917, wR2 = 0.5165	
R indices (all data)	R1 = 0.2382, wR2 = 0.5550	
Largest diff. peak and hole	2.405 and -1.108 $e.Å^{-3}$	

6.3 1-(4,6-Difluoro-1,3,5-triazin-2-yl)-4-(dimethylamino)pyridinium Trifluoromethanesulphonate

Table 1. Crystal data and structure refinement for 02srv115.

Identification code	s115	
Empirical formula	$C_{11} H_{10} F_5 N_5 O_3 S$	
Formula weight	387.30	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 13.4874(3) Å	α= 90°.
	b = 9.7812(2) Å	β= 92.04(1)°.
	c = 22.2499(5) Å	γ = 90°.
Volume	2933.4(1) $Å^3$	
Z	8	
Density (calculated)	1.754 Mg/m^3	
Absorption coefficient	0.305 mm^{-1}	
F(000)	1568	
Crystal size	0.30 x 0.24 x 0.10 mm^3	
Theta range for data collection	1.83 to 30.00°.	
Index ranges	-18<=h<=17, -13<=k<=13, -31<=l<=31	
Reflections collected	14627	
Independent reflections	4267 [R(int) = 0.0492]	
Completeness to theta = 30.00°	99.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4267 / 0 / 266	
Goodness-of-fit on F^2	1.235	
Final R indices [I>2sigma(I)]	R1 = 0.0310, wR2 = 0.0922	
R indices (all data)	R1 = 0.0413, wR2 = 0.0962	
Largest diff. peak and hole	0.397 and -0.507 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 02srv115. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
S(1)	1863(1)	5308(1)	3887(1)	22(1)
F(1)	3749(1)	2114(1)	3313(1)	31(1)
F(2)	911(1)	2078(1)	2236(1)	30(1)
F(3)	434(1)	5318(1)	3066(1)	50(1)
F(4)	724(1)	3344(1)	3458(1)	39(1)
F(5)	-45(1)	4864(1)	3956(1)	36(1)
O(1)	2540(1)	5096(1)	3407(1)	31(1)
O(2)	1645(1)	6720(1)	4011(1)	34(1)
O(3)	2041(1)	4463(1)	4408(1)	42(1)
N(1)	2147(1)	3338(1)	1897(1)	20(1)
N(2)	2316(1)	1999(1)	2789(1)	23(1)
N(3)	3682(1)	3288(1)	2455(1)	20(1)
N(4)	3544(1)	4456(1)	1545(1)	17(1)
N(5)	4891(1)	6796(1)	263(1)	23(1)
C(1)	3098(1)	3655(1)	1986(1)	18(1)
C(2)	3220(1)	2486(1)	2828(1)	22(1)
C(3)	1834(1)	2493(1)	2309(1)	22(1)
C(4)	2992(1)	4979(1)	1067(1)	21(1)
C(5)	3411(1)	5737(1)	636(1)	22(1)
C(6)	4452(1)	6026(1)	665(1)	20(1)
C(7)	5007(1)	5426(1)	1160(1)	21(1)
C(8)	4548(1)	4686(1)	1579(1)	19(1)
C(9)	4340(1)	7409(1)	-251(1)	27(1)
C(10)	5942(1)	7166(1)	342(1)	29(1)
C(11)	684(1)	4676(1)	3575(1)	24(1)

Table 3. Bond lengths [Å] and angles [°] for 02srv115.

S(1)-O(3)	1.4370(9)	N(1)-C(3)	1.316(1)	N(4)-C(1)	1.406(1)
S(1)-O(2)	1.4402(9)	N(1)-C(1)	1.328(1)	N(5)-C(6)	1.326(1)
S(1)-O(1)	1.4445(9)	N(2)-C(2)	1.310(1)	N(5)-C(10)	1.467(2)
S(1)-C(11)	1.820(1)	N(2)-C(3)	1.322(1)	N(5)-C(9)	1.470(1)
F(1)-C(2)	1.322(1)	N(3)-C(2)	1.315(1)	C(4)-C(5)	1.352(2)
F(2)-C(3)	1.313(1)	N(3)-C(1)	1.334(1)	C(5)-C(6)	1.431(2)
F(3)-C(11)	1.328(1)	N(4)-C(8)	1.373(1)	C(6)-C(7)	1.434(4)
F(4)-C(11)	1.331(1)	N(4)-C(4)	1.376(1)	C(7)-C(8)	1.348(2)
F(5)-C(11)	1.334(1)				

O(3)-S(1)-O(2)	115.24(6)	N(2)-C(2)-F(1)	115.39(10)
O(3)-S(1)-O(1)	115.01(6)	N(3)-C(2)-F(1)	115.18(10)
O(2)-S(1)-O(1)	114.69(5)	F(2)-C(3)-N(1)	115.83(9)
O(3)-S(1)-C(11)	103.33(6)	F(2)-C(3)-N(2)	115.05(10)
O(2)-S(1)-C(11)	102.54(6)	N(1)-C(3)-N(2)	129.12(10)
O(1)-S(1)-C(11)	103.59(5)	C(5)-C(4)-N(4)	121.60(10)
C(3)-N(1)-C(1)	112.09(9)	C(4)-C(5)-C(6)	120.73(9)
C(2)-N(2)-C(3)	110.63(9)	N(5)-C(6)-C(5)	122.88(9)
C(2)-N(3)-C(1)	112.04(9)	N(5)-C(6)-C(7)	121.10(10)
C(8)-N(4)-C(4)	119.10(9)	C(5)-C(6)-C(7)	116.01(9)
C(8)-N(4)-C(1)	119.95(8)	C(8)-C(7)-C(6)	120.68(10)
C(4)-N(4)-C(1)	120.90(9)	C(7)-C(8)-N(4)	121.82(9)
C(6)-N(5)-C(10)	120.81(9)	F(3)-C(11)-F(4)	107.86(9)
C(6)-N(5)-C(9)	122.11(10)	F(3)-C(11)-F(5)	107.80(10)
C(10)-N(5)-C(9)	116.90(9)	F(4)-C(11)-F(5)	107.14(10)
N(1)-C(1)-N(3)	126.43(10)	F(3)-C(11)-S(1)	110.90(9)
N(1)-C(1)-N(4)	117.45(8)	F(4)-C(11)-S(1)	111.54(8)
N(3)-C(1)-N(4)	116.13(9)	F(5)-C(11)-S(1)	111.41(8)
N(2)-C(2)-N(3)	129.44(10)		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 02srv115. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	22(1)	23(1)	20(1)	1(1)	0(1)	-4(1)
F(1)	28(1)	41(1)	24(1)	12(1)	-4(1)	-2(1)
F(2)	20(1)	42(1)	28(1)	-1(1)	2(1)	-10(1)
F(3)	45(1)	70(1)	32(1)	16(1)	-15(1)	0(1)
F(4)	35(1)	31(1)	52(1)	-16(1)	5(1)	-8(1)
F(5)	23(1)	41(1)	45(1)	-7(1)	10(1)	-2(1)
O(1)	26(1)	30(1)	40(1)	-3(1)	12(1)	-2(1)
O(2)	42(1)	25(1)	36(1)	-9(1)	15(1)	-9(1)
O(3)	39(1)	54(1)	33(1)	20(1)	-13(1)	-11(1)
N(1)	17(1)	25(1)	20(1)	-2(1)	1(1)	-1(1)
N(2)	25(1)	24(1)	22(1)	0(1)	3(1)	-3(1)
N(3)	19(1)	23(1)	18(1)	1(1)	0(1)	0(1)
N(4)	17(1)	19(1)	16(1)	0(1)	-1(1)	0(1)
N(5)	25(1)	25(1)	18(1)	2(1)	2(1)	0(1)
C(1)	18(1)	18(1)	17(1)	-2(1)	1(1)	1(1)
C(2)	24(1)	24(1)	19(1)	1(1)	0(1)	1(1)
C(3)	19(1)	25(1)	22(1)	-5(1)	3(1)	-3(1)
C(4)	19(1)	25(1)	19(1)	-1(1)	-4(1)	1(1)
C(5)	22(1)	25(1)	18(1)	1(1)	-3(1)	1(1)
C(6)	23(1)	20(1)	17(1)	-2(1)	1(1)	0(1)
C(7)	18(1)	25(1)	20(1)	1(1)	0(1)	0(1)
C(8)	18(1)	23(1)	18(1)	0(1)	-1(1)	1(1)
C(9)	33(1)	28(1)	19(1)	4(1)	1(1)	4(1)
C(10)	26(1)	37(1)	25(1)	4(1)	5(1)	-5(1)
C(11)	23(1)	27(1)	22(1)	0(1)	-1(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 x\ 10^3$) for 02srv115.

Atom	x	y	z	U(eq)
H(4)	2296(12)	4809(15)	1055(7)	29(4)
H(5)	2998(10)	6094(14)	343(6)	24(3)
H(7)	5722(11)	5516(14)	1193(6)	23(3)
H(8)	4872(10)	4303(14)	1882(6)	20(3)
H(91)	3858(12)	6797(16)	-415(7)	31(4)
H(92)	4019(13)	8229(18)	-147(7)	43(5)
H(93)	4822(12)	7564(16)	-575(7)	32(4)
H(101)	6058(13)	7535(16)	722(7)	37(4)
H(102)	6365(14)	6399(18)	286(7)	43(4)
H(103)	6109(14)	7840(20)	84(8)	52(5)

Table 6. Some torsion angles [°] for 02srv115.

N(1)-C(1)-N(4)-C(4)	5.11(14)
C(5)-C(6)-N(5)-C(9)	-0.53(16)

6.4 Tetramethylammonium Salt of 1-Keto-3,5-difluoro-*s*-triazine

Table 1. Crystal data and structure refinement for 03srv060.

Identification code	s060	
Empirical formula	$C_3 N_3 F_2 O \times C_4 H_{12} N$	
Formula weight	206.21	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/m	
Unit cell dimensions	a = 16.4758(9) Å	α= 90°.
	b = 8.8008(5) Å	β= 92.85(2)°.
	c = 6.5815(4) Å	γ = 90°.
Volume	953.14(9) $Å^3$	
Z	4	
Density (calculated)	1.437 Mg/m^3	
Absorption coefficient	0.127 mm^{-1}	
F(000)	432	
Crystal size	0.54 x 0.42 x 0.12 mm^3	
Theta range for data collection	3.10 to 28.99°.	
Index ranges	-22<=h<=22, -11<=k<=11, -8<=l<=7	
Reflections collected	4167	
Independent reflections	1157 [R(int) = 0.1070]	
Completeness to theta = 28.99°	86.2 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1157 / 0 / 99	
Goodness-of-fit on F^2	1.109	
Final R indices [I>2sigma(I)]	R_1 = 0.0507, wR_2 = 0.1457	
R indices (all data)	R_1 = 0.0562, wR_2 = 0.1545	
Largest diff. peak and hole	0.351 and -0.446 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03srv060. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
F(1)	5467(1)	2535(1)	2399(1)	31(1)
O(2)	3106(1)	0	2705(2)	26(1)
N(1)	5518(1)	0	2387(2)	23(1)
N(2)	4273(1)	1371(1)	2585(2)	21(1)
C(1)	5050(1)	1227(2)	2464(2)	21(1)
C(2)	3852(1)	0	2632(3)	19(1)
N(1S)	2025(1)	0	7496(2)	19(1)
C(1S)	1479(1)	0	5603(3)	27(1)
C(2S)	1510(1)	0	9316(3)	26(1)
C(3S)	2552(1)	1385(1)	7529(2)	23(1)

Table 3. Selected bond lengths [Å] and angles [°] for 03srv060.

F(1)-C(1)	1.343(1)	N(2)-C(1)	1.294(2)	N(1S)-C(1S)	1.500(2)
O(2)-C(2)	1.233(2)	N(2)-C(2)	1.392(1)	N(1S)-C(2S)	1.502(2)
N(1)-C(1)	1.330(2)	N(1S)-C(3S)	1.496(2)		

C(1)#1-N(1)-C(1)	108.6(2)	N(2)-C(2)-N(2)#1	120.1(2)
C(1)-N(2)-C(2)	114.3(1)	C(3S)-N(1S)-C(3S)#1	109.0(1)
N(2)-C(1)-N(1)	131.3(1)	C(3S)-N(1S)-C(1S)	109.65(9)
N(2)-C(1)-F(1)	115.4(1)	C(3S)-N(1S)-C(2S)	109.82(9)
N(1)-C(1)-F(1)	113.3(1)	C(1S)-N(1S)-C(2S)	108.8(2)
O(2)-C(2)-N(2)	119.94(8)		

Symmetry transformations used to generate equivalent atoms:

#1 x,-y,z

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03srv060. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	30(1)	21(1)	41(1)	0(1)	2(1)	-10(1)
O(2)	19(1)	22(1)	38(1)	0	2(1)	0
N(1)	21(1)	23(1)	26(1)	0	0(1)	0
N(2)	24(1)	15(1)	25(1)	0(1)	1(1)	-1(1)
C(1)	25(1)	19(1)	20(1)	0(1)	0(1)	-4(1)
C(2)	22(1)	16(1)	20(1)	0	1(1)	0
N(1S)	18(1)	15(1)	22(1)	0	1(1)	0
C(1S)	27(1)	29(1)	24(1)	0	-3(1)	0
C(2S)	26(1)	28(1)	24(1)	0	5(1)	0
C(3S)	24(1)	14(1)	32(1)	0(1)	1(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 x\ 10^3$) for 03srv060.

Atom	x	y	z	U(eq)
H(31)	2200(13)	2250(20)	7460(30)	31(5)
H(11)	1150(11)	890(20)	5600(30)	27(4)
H(32)	2850(14)	1380(20)	8750(30)	32(5)
H(33)	2836(13)	1380(20)	6290(30)	27(5)
H(21)	1189(12)	900(20)	9230(30)	28(4)
H(22)	1911(17)	0	10480(40)	27(6)
H(12)	1836(17)	0	4450(40)	28(6)

6.5 Diethylaminodifluoro-*s*-triazine

Table 1. Crystal data and structure refinement for 03srv118.

Identification code	s118	
Empirical formula	$C_{16} H_{10} F_8 N_4 O_4$	
Formula weight	474.28	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 8.9004(2) Å	α= 90°.
	b = 5.6928(1) Å	β= 102.21(1)°.
	c = 17.4069(4) Å	γ = 90°.
Volume	862.03(3) Å^3	
Z	2	
Density (calculated)	1.827 Mg/m^3	
Absorption coefficient	0.188 mm^{-1}	
F(000)	476	
Crystal size	0.30 x 0.24 x 0.08 mm^3	
Theta range for data collection	2.34 to 25.99°.	
Index ranges	-10<=h<=10, -7<=k<=7, -21<=l<=20	
Reflections collected	6092	
Independent reflections	1674 [R(int) = 0.0162]	
Completeness to theta = 25.99°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9851 and 0.9457	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1674 / 4 / 172	
Goodness-of-fit on F^2	1.054	
Final R indices [I>2sigma(I)]	R_1 = 0.0501, wR_2 = 0.1281	
R indices (all data)	R_1 = 0.0552, wR_2 = 0.1319	
Largest diff. peak and hole	0.725 and -0.600 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03srv118. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	6049(3)	-4551(4)	1719(1)	44(1)
O(2)	7375(3)	-1567(4)	1514(2)	72(1)
O(1')	6732(17)	-3370(30)	2139(6)	62(3)
O(2')	6917(18)	-1950(30)	1028(8)	62(3)
N(1)	757(2)	3105(4)	888(1)	32(1)
N(2)	6173(2)	-2470(4)	1529(1)	41(1)
F(1)	3317(2)	4200(3)	299(1)	43(1)
F(2)	5826(2)	1673(3)	579(1)	45(1)
F(3)	3505(2)	-3545(2)	2122(1)	42(1)
F(4)	1002(2)	-1082(2)	1807(1)	38(1)
C(1)	55(3)	3679(4)	71(2)	34(1)
C(2)	-257(3)	3276(5)	1450(2)	40(1)
C(3)	2045(2)	1705(4)	1046(1)	26(1)
C(4)	3338(3)	2256(4)	742(1)	30(1)
C(5)	4669(3)	961(4)	898(1)	32(1)
C(6)	4784(3)	-1035(4)	1368(1)	31(1)
C(7)	3517(3)	-1639(4)	1676(1)	31(1)
C(8)	2201(2)	-306(4)	1519(1)	28(1)

Table 3. Anisotropic displacement parameters ($Å^2$x 10^3) for 03srv118. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	47(1)	34(1)	48(1)	10(1)	8(1)	15(1)
O(2)	27(1)	35(1)	151(3)	-8(2)	11(2)	2(1)
N(1)	28(1)	36(1)	32(1)	4(1)	6(1)	8(1)
N(2)	33(1)	40(1)	46(1)	-15(1)	2(1)	9(1)
F(1)	42(1)	39(1)	51(1)	17(1)	17(1)	3(1)
F(2)	33(1)	52(1)	54(1)	-6(1)	21(1)	-3(1)
F(3)	51(1)	32(1)	41(1)	9(1)	6(1)	7(1)
F(4)	37(1)	37(1)	42(1)	8(1)	16(1)	-1(1)
C(1)	31(1)	32(1)	35(1)	0(1)	-2(1)	4(1)
C(2)	32(1)	40(2)	51(2)	4(1)	16(1)	7(1)
C(3)	25(1)	29(1)	24(1)	-2(1)	2(1)	1(1)
C(4)	32(1)	29(1)	30(1)	3(1)	7(1)	1(1)
C(5)	26(1)	37(1)	34(1)	-7(1)	10(1)	-2(1)
C(6)	28(1)	31(1)	30(1)	-8(1)	-2(1)	6(1)
C(7)	38(1)	27(1)	23(1)	0(1)	1(1)	4(1)
C(8)	29(1)	31(1)	26(1)	-1(1)	6(1)	-1(1)

Table 4. Selected bond lengths [Å] and angles [°] for 03srv118.

N(1)-C(3)	1.375(3)	F(2)-C(5)	1.332(3)	C(3)-C(4)	1.399(3)
N(1)-C(1)	1.464(3)	F(3)-C(7)	1.335(3)	C(4)-C(5)	1.373(3)
N(1)-C(2)	1.467(3)	F(4)-C(8)	1.347(3)	C(5)-C(6)	1.391(3)
N(2)-C(6)	1.459(3)	C(1)-C(1)#1	1.524(5)	C(6)-C(7)	1.391(3)
F(1)-C(4)	1.347(3)	C(3)-C(8)	1.400(3)	C(7)-C(8)	1.374(3)

C(3)-N(1)-C(1)	119.30(19)	F(2)-C(5)-C(6)	121.8(2)
C(3)-N(1)-C(2)	120.67(19)	C(4)-C(5)-C(6)	120.5(2)
C(1)-N(1)-C(2)	115.8(2)	C(7)-C(6)-C(5)	117.6(2)
N(1)-C(1)-C(1)#1	112.2(3)	C(7)-C(6)-N(2)	120.7(2)
N(1)-C(3)-C(8)	124.4(2)	C(5)-C(6)-N(2)	121.6(2)
N(1)-C(3)-C(4)	120.8(2)	F(3)-C(7)-C(8)	117.0(2)
C(8)-C(3)-C(4)	114.7(2)	F(3)-C(7)-C(6)	122.1(2)
F(1)-C(4)-C(5)	117.5(2)	C(8)-C(7)-C(6)	120.9(2)
F(1)-C(4)-C(3)	119.2(2)	F(4)-C(8)-C(7)	117.0(2)
C(5)-C(4)-C(3)	123.3(2)	F(4)-C(8)-C(3)	120.02(19)
F(2)-C(5)-C(4)	117.7(2)	C(7)-C(8)-C(3)	122.9(2)

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y+1,-z

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for 03srv118.

Atom	x	y	z	U(eq)
H(11)	630(30)	2970(50)	-268(15)	30(6)
H(12)	-930(30)	3000(50)	-48(15)	30(6)
H(21)	380(40)	3190(60)	1964(19)	50(8)
H(22)	-740(30)	4870(60)	1370(17)	45(8)
H(23)	-1020(40)	2020(60)	1337(17)	45(8)